PATHOGENESIS OF GILLES DE LA TOURETTE SYNDROME: CLUES FROM CLINICAL PHENOTYPES

by

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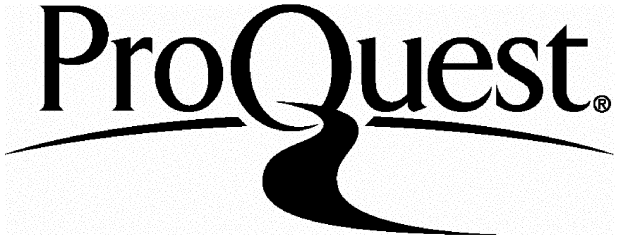

TO MY PARENTS

ABSTRACT

Gilles de la Tourette Syndrome (GTS) is a developmental neuro-psychiatric disorder characterised by multiple motor and vocal tics. More than a century after its original description, there are still controversies about the essential clinical features of GTS, and, the failure as yet to find the putative gene(s) for the disorder may be a reflection of incorrect definition of the phenotypes. In this thesis, genetic data and neuroimaging techniques have been used to elucidate the phenotypic expressions of GTS.

A total of 168 First Degree Relatives (FDRs) ascertained through 40 GTS probands and 66 FDRs ascertained through 20 Obsessive Compulsive Disorder (OCD) probands were studied. Findings from the segregation analyses were consistent with an autosomal dominant gene transmission with high penetrance, and sex dependent differences in the expression of GTS. There was also evidence to suggest the existence of a single major gene in the transmission of OCD. A genomic imprinting study of 437 GTS family members showed that maternally transmitted offsprings had a significantly earlier age at onset.

There was evidence to suggest that Obsessive Compulsive Behaviour (OCB) forms an alternative phenotypic expression of

the putative GTS gene(s). Analysis for GTS and Attention Deficit Hyperactivity Disorder (ADHD) failed to support a similar hypothesis. With regard to tics, it appears that not all cases are genetically related to GTS, and that some may be phenocopies.

Single Photon Emission Tomography (SPET) showed that the affected family members of GTS probands had `hypoperfusion' in the different brain areas. There were no distinctions based on the clinical phenotypes (GTS, Tics or OCB).

Phenomenological analysis revealed differences in the obsessive compulsive symptom profile between GTS and OCD probands, but the familial OCD probands shared a similar profile to that of GTS. Implications of these findings in the aetiology and pathogenesis of GTS are discussed.

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STATEMENT

The collection, collation and analysis of the data presented in this thesis were carried out by the author herself, except in the following areas.

The data for the section on "genomic imprinting" was collected by the author along with five other investigators (Dr Mary M Robertson; Dr Jeremy Stern; Dr Allison Gourdie; Dr Vivienne Schneiden; Dr Gary Jackson) as part of another study on clinical phenomenology and linkage analysis. However, the data used in the analysis reported in this thesis was collated solely by the author. Support for statistical analysis was provided by Dr Jane O'Neill and Dr Hugh Gurling.

For the section on Single Photon Emission Tomography, the author herself carried out the direct clinical examination and collated the data. Dr J Moriarty performed the SPET scanning and Dr DC Costa provided the blind rating.

Dr Mary M Robertson helped in the diagnostic process by providing consensus diagnosis on the GTS probands and First Degree Relatives. The data analyses for the section on phenomenology and the segregation analysis were carried out by the author under the supervision of Dr David Pauls.

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GLOSSARY OF ABBREVIATIONS

ADHD	Attention Deficit Hyperactivity Disorder
CMT	Chronic Motor Tics
CT	Computerised Tomography
FDRs	First Degree Relatives
DZ	Dizygotic
GABA	Gamma Amino Butyric Acid
GTS	Gilles de la Tourette Syndrome
HMPAO	Hexamethyl propylene amine oxime
MOCI	Maudsley Obsessive Compulsive Inventory
MZ	Monozygotic
5HT	5 Hydroxy Tryptamine
LOI	Leyton Obsessional Inventory
LRT	Likelihood Ratio Test
MR	Magnetic Resonance
OC	Obsessive Compulsive
OCB	Obsessive Compulsive Behaviour
OCD	Obsessive Compulsive Disorder
PET	Positron Emission Tomography
rCBF	Regional Cerebral Blood Flow
SPET	Single Photon Emission Tomography
SSRI	Specific Serotonin Reuptake Inhibitor
STAI	State Trait Anxiety Inventory
TTD	Transient Tic Disorder

YBOCS	Yale Brown Obsessive Compulsive Scale
<	Less than
>	More than

SECTION 1

INTRODUCTION

INTRODUCTION

Gilles de la Tourette Syndrome (GTS) is a developmental neuropsychiatric disorder characterised by involuntary movements (e.g. motor tics), vocal tics and a range of behavioural symptoms. GTS is unique in the exciting challenge it poses to clinicians and scientists interested in the relationship between brain and behaviour. It serves as a paradigm for understanding neurological and psychiatric disorders, and bridges the gap between the two disciplines. In GTS there is a familial neurobiological basis, but yet environmental influences may modify the nature and course of the disorder. There is no doubt that GTS will continue to serve as a testing ground for exploring the brain behaviour relationships for years to come.

The hereditary nature of GTS has been recognised from the time of its original description. However, more than a century later, there are still controversies about some fundamental issues including the very basic question, how broadly should the clinical spectrum be defined? Are there alternative ways in which the GTS gene expresses itself? How do we know whether GTS, Tics or Obsessive Compulsive Behaviours (OCB) in a given individual indicate a phenotype or a phenocopy? A phenotype is the physical expression of the underlying genotype. A phenocopy on the other hand, represents similar physical expression as in a phenotype, but is unrelated to the genotype. While definitive

answers to these questions will have to await identification of the gene, in this study, an attempt has been made to address some of these issues. In this thesis, family and phenomenological data as well as neuroimaging techniques have been used to elucidate the clinical expressions of GTS, thereby contributing to a better phenotypic definition and a better understanding of the relationship between GTS and associated conditions.

This thesis will cover three areas of investigation; genetic analysis, neuroimaging and phenomenological analysis. The study was designed to address the following questions:

1. To examine whether or not GTS and primary Obsessive Compulsive Disorder (OCD) have a pattern of inheritance consistent with a genetic aetiology, and if so, whether such patterns of inheritance within families of subjects with primary GTS and primary OCD are consistent with any specific models of genetic transmission.

2. To examine `parent of origin effect' (whether there are any differences between maternally and paternally transmitted cases) on phenotypic expressions (the phenotypic expressions being defined as GTS, TICS and OCB based on the consensus from available literature), as well as on age at onset and age at diagnosis of GTS.

3. To examine the hypothesis that OCB, Tics and Attention Deficit Hyperactivity Disorder (ADHD) are possible alternative phenotypic expressions of GTS.

4. To study the regional cerebral blood flow patterns in GTS probands and their First Degree Relatives (FDRs) using Single Photon Emission Tomography (SPET) and to examine whether specific perfusion patterns were correlated with the different clinical phenotypes (physical expressions of the GTS genotype) such as GTS, Tics and OCB.

5. To examine the phenomenology of OCB occurring in the context of GTS and to compare the Obsessive Compulsive (OC) symptom profile between subjects with primary OCD and those with GTS and OCB.

SECTION 11

REVIEW OF THE LITERATURE

CHAPTER 1

GILLES DE LA TOURETTE SYNDROME

1.1. History

The first medical description of the condition was in 1825 by Itard (Itard 1825) when he described the Marquise de Dampierre. Subsequently, Georges Gilles de la Tourette described nine cases in 1885 and emphasised the clinical triad of involuntary tics, echolalia and coprolalia (Gilles de la Tourette 1885). Until the early 70's only case reports existed, but in the past 20 years there has been an increasing volume of literature especially from North America, the United Kingdom and Europe (Robertson 1989; 1994). The condition has been described world wide and includes reports from Australia (Chee and Sachdev 1994), Brazil (Cardoso et al 1996), China (Lieh Mak et al 1982), India (Chakraborty 1960, Eapen and Srinath 1990), Japan (Kondo & Nomura 1982), Korea (Min and Lee 1986), the Middle East (El-Assra 1987; Robertson and Trimble 1991), New Zealand (Groot and Bardwell 1970), and South America (Eapen & Robertson 1992). The universality of symptoms across all races and cultures indicates the biological nature of the disorder.

1.2. DEFINITION AND CLINICAL PHENOMENOLOGY

Gilles de la Tourette Syndrome (GTS) is characterised by multiple motor and one or more vocal tics, which occur many times a day in bouts, the number, frequency and complexity of which change over time (American Psychiatric Association 1987; World Health Organisation 1992). The diagnosis of GTS as per DSM-111R (Diagnostic and Statistical Manual 111-Revised) criteria include a duration of more than one year, and an age at onset before 21 years [see chapter 4.1.i for details]. DSM-1V (American Psychiatric Association 1994) has incorporated an additional criteria that "the disturbance causes marked distress or significant impairment in social, occupational, or other important areas of functioning"; however, subsequent to the objections raised about the inclusion of this criteria (Comings 1995, Freeman et al 1995), it has been agreed that this may be waived for specific research purposes such as genetic studies (First et al 1995).

The initial manifestations occur in childhood with a mean age at onset around 7 years. Boys are more commonly affected, with a male to female ratio of about 3:1. GTS is found in all social

classes although there is some indication that clinic patients may well underachieve socially (Robertson 1989). Blinking is the most common first symptom (50% to 70%), although any motor or vocal tics and in a few cases, other behaviours such as OCB and ADHD may mark the onset of GTS. As the condition progresses, new tics replace old ones and characteristically takes a waxing and waning course. Symptoms are usually made worse by anxiety, stress and tiredness, while most patients find that relaxation and concentrating on enjoyable tasks alleviates the symptoms. The motor and vocal tics can be voluntarily suppressed for brief periods of time, although at the expense of mounting inner tension. Coprolalia (involuntary and inappropriate swearing) occurs in about 30% of clinic patients. Other features such as copropraxia (the involuntary making of obscene gestures), echophenomenon (copying and imitating behaviours of others), palilalia (repeating one's own words or phrases), palipraxia (repeating one's own actions) and self injurious behaviours (SIB) occur as the syndrome develops into its fullest form (Robertson 1994, Robertson and Eapen 1995).

A variety of subjective symptoms have been reported and include sensory tics (internal sensations that are premonitory to, or causative of a motor or vocal tic), (Shapiro et al 1988), reflex or stimulus induced tics (Eapen et al 1994), premonitory experience such as an inner urge or need that caused them to tic

(Lang 1993), and mental play (Cath et al 1992). Available evidence suggests that 30% to 40% of cases will show remission by late adolescence and an additional 30% will show significant improvement, while the remaining one third will continue to be symptomatic in adulthood (Singer and Walkup 1991).

Several associated symptoms have been reported, of which OCB and ADHD have received most attention. OCB occurs in more than 50% of cases (Robertson 1989), which is significantly higher than in general population (Pauls et al 1994). Family studies have further provided evidence that OCB may be aetiologically related to GTS (Pauls et al 1986a; 1991).

The relationship between GTS and ADHD is more complex, and there are several ways in which this relationship can be viewed. There may be an aetiological link, with common genetic or biochemical mechanisms, while some consider the relationship to be linked to severity, co-morbidity or referral bias in clinic samples (Robertson and Eapen 1992; Towbin and Riddle 1993).

Robertson et al (1988; 1993) reported significantly higher levels of depression in GTS when compared to controls, but suggested that this may be secondary and related to the chronicity and social disability. Anxiety (Coffey et al 1992; Robertson et al 1993) is also prominent, and more so than in

control populations. A variety of psychiatric conditions including conduct problems, aggression and impulsivity, panic attacks, inappropriate sexual behaviours, sleep disorders and eating disorders have been suggested to be associated with GTS (Comings and Comings 1985; 1987; 1990). However, there is considerable controversy as to the true incidence of these problems and whether they can be meaningfully linked to GTS. It has been shown that clinic population may not be representative with regard to co-morbidity as individuals are more likely to attend clinics if he/she has more than one problem (Pauls et al 1986b). Studies that have controlled for these factors have shown that there is no consistent association between GTS and psychiatric disorders in general (Pauls et al 1988a; 1988b, Carter et al 1994).

School related problems have been reported in children with GTS (Erenberg et al 1986; Comings & Comings 1987; Kurlan 1992; Eapen et al 1993) and may be contributed to by psychosocial, biochemical and neurodevelopmental factors. This may include the secondary effects of having a socially disabling condition, the result of associated behaviours such as OCB and ADHD, or a reflection of referral and ascertainment bias.

To date most of the studies on phenomenology have been based on targeted samples such as clinic populations. Such sample

selection bias compromises our understanding of the degree and nature of relationship between GTS and associated disorders. Trying to generalise from a clinic setting, where most cases are severely symptomatic and dysfunctional, to mild cases in the community could be misleading. Individuals ascertained through clinics are more likely to have multiple problems and associated conditions. Thus, the observed patterns in these individuals and their families may be skewed, resulting in wrong interpretations about the aetiological relationship between these conditions. In this regard it is interesting to note that mild cases in the community have been shown to be reasonably well adjusted, unknown to physicians, and not in need of medication (Caine et al 1988, Kurlan et al 1986;87, McMohan et al 1992). Robertson and Gourdie (1990) in a family study reported that mild cases in the community were significantly obsessional, but otherwise did not differ from the general population with regard to psychopathology. As more community based prospective studies are performed and include the milder forms of GTS, there is no doubt that a clearer clinical profile of the disorder will emerge.

1.2.i. **GTS AND TICS**

Tics are involuntary, sudden, repetitive, recurrent, non rhythmic, stereotyped movements (motor tics) or vocalisations (vocal tics) (American Psychiatric Association 1987). A variety

of primary tic disorders have been described based on the pattern and duration of tics. Transient Tic Disorder (TTD) refers to single or multiple motor or vocal tics of less than a year's duration. When tics (motor or vocal but not both) have been present for more than a year, the term Chronic Motor Tics (CMT) is used. When multiple motor and one or more vocal tics have been present for more than a year, the diagnosis of GTS is made.

Tics form the salient clinical feature of GTS. However, despite almost a century of research and writings, it is not clear as to whether all cases of tics represent the GTS clinical spectrum. In addition, the question remains as to what proportion of patients with tics have a disorder genetically related to GTS and whether there is a genetic basis to tics independent of GTS.

The generally accepted prevalence of GTS in childhood populations is 0.5/1000 (Bruun 1984). Childhood tics on the other hand are much more common with a prevalence rate of around 10% (Fallon and Schwab-Stone 1992) to 20% (Mac Farlane et al 1954). Since most individuals with transient or chronic tics do not come to the attention of professionals, this issue can only be addressed by a community based epidemiological study, where all subjects are personally evaluated. Whilst GTS is the most common cause of tics, they may also be due to other neurologic

and physiologic conditions. Some of the other causes of tics are given below (modified from Jankovic 1992).

1. Physiologic tics

Mannerisms

Habits

Gestures

11. Pathologic tics

Primary tic disorders

Chronic motor or vocal tics

Transient motor or vocal tics

Gilles de la Tourette syndrome

Secondary tics

Infections (encephalitis, Creutzfeldt-Jakob disease, Sydenham's chorea)

Drugs (stimulants, anti convulsants, levodopa, dopamine antagonists)

Toxins (carbon monoxide)

Metabolic disorders (phenyl ketonuria, neuroacanthocytosis)

Head injury, vascular accidents/ stroke

Degenerative disorders, Neuro cutaneous syndrome, chromosomal abnormalities

Clinically the distinction between GTS tics and other forms of tics and hyperkinetic movements is extremely difficult. Although most hyperkinetic movements decrease or disappear during sleep, tics in GTS have been demonstrated to be present during all stages of sleep (Jankovic 1992). Although these characteristics are useful in making the diagnosis in the day to day clinical practice, such case definitions based purely on clinical grounds have proved to be far from optimum, especially for genetic and linkage studies.

Family studies have provided evidence that TTD and CMT are aetiologically related to GTS (Pauls et al 1981, Kurlan et al 1986; 1987; 1988). Whilst it is true that in majority of subjects, CMT and TTD represent phenotypic expressions of the putative GTS gene, it cannot be assumed that all cases are part of the same disorder.

1.2.ii. GTS AND ADHD

The hyperactive syndrome of "fidgety Phil" was first described in a children's book by a German physician, Heinrich Hoffman in 1845 (Cantwell 1972). The condition is characterised by an early onset, the combination of over-active, poorly modulated behaviour and marked inattention with lack of persistent task involvement, and pervasiveness of these characteristics over

situations and their persistence over time (World Health Organisation 1992). The DSM-111R classification criteria (American Psychiatric Association 1987) are similar, but the presence over a 6-month period, of at least eight out of fourteen types of behaviours including inattention, impulsivity and overactivity are required, and the age of onset is specified as before 7 years.

The prevalence has been found to vary widely, especially between North America and the UK, with prevalence rates of 0.06 in the UK and 1.2 % in the USA (Taylor 1986). The main reason for this discrepancy is the fact that in the UK, emphasis is given to the pervasive nature of the condition and a diagnosis is not made if the behaviour is situation specific. Boys are three to four times more commonly affected. There is no strong link between social class and the condition (Graham 1991), although higher rates of family disharmony and social disruption is reported in children showing hyperkinetic syndrome and aggressive behaviour (Stewart et al 1980). The role of genetic factors in the aetiology have been demonstrated through adoption studies (Cantwell 1975), as well as twin studies (Goodman and Stevenson 1989) showing a higher concordance rate in monozygotic twins when compared to dizygotic twins.

ADHD has been reported to occur in a substantial proportion of GTS patients with rates ranging from 21% to 90% (Robertson & Eapen 1992). However, the exact relationship between the two disorders remains unclear and has been the subject of much controversy. Stefl (1984), Bornstein et al (1990) and Champion et al (1988) in postal questionnaire surveys, reported that 42% to 74% of GTS subjects had ADHD. In an epidemiological study Caine et al (1988) reported 27% to have ADHD. There have been suggestions that male GTS patients are more likely to have ADHD, that these symptoms often precede the development of tics, and that they are more pronounced in those with a severe form of GTS (Shapiro et al 1978; Comings and Comings 1985; Bornstein et al 1990; Pauls et al 1988). Sverd et al (1988) have suggested that increased severity of GTS symptoms is associated with an earlier age at onset and the occurrence of behavioural problems such as ADHD. Furthermore, it may well be that in clinic samples there is an over-representation of associated problems and in particular ADHD, because of referral and ascertainment bias. It has been shown that those with more severe symptoms and those with multiple problems are more likely to come to professional attention (Pauls et al 1986b).

Furthermore, the developmental course of the two disorders is somewhat different. ADHD, by definition has an age at onset

before seven years. Although these subjects continue to have some attentional impairment into adult life, by and large the symptoms disappear after the early childhood years. GTS on the other hand has an age at onset around seven years, and the symptoms persist into adult life.

The observation that stimulants that are used in the treatment of ADHD, cause, provoke or exacerbate tics/GTS, has led to several possible explanations regarding the relationship between the two disorders. It is known that stimulants release dopamine and norepinephrine from the pre-synaptic nerve terminals (Rudowitz & Klawans 1972). If indeed the hypothesis of increased dopaminergic activity in GTS is correct, it is not surprising that the stimulant induced increase in dopaminergic activity can precipitate the onset or cause exacerbation of GTS symptoms. Other evidence for such a relationship comes from amphetamine induced stereotypic behaviours in animals, as well as the occurrence of tremulousness and tics in patients taking toxic doses of amphetamines (Bonthala & West 1983).

Although dopamine has received most attention in GTS, abnormalities in serotonin, norepinephrine, acetylcholine, Gamma Amino Butyric Acid (GABA) and opioid system have all been implicated in both GTS and ADHD (Baker et al 1995; Robertson 1989). Since many of the synaptic neurotransmitter systems are

inter-related, it is possible that imbalances within different systems may lead to similar group of symptoms either directly or by involving a second messenger system such as the cyclic AMP (Schramm & Selinger 1984).

At a neuroanatomical level, it has been suggested that thalamocortical pathways and frontal lobe - caudate nucleus pathways are related to hyperkinetic symptomatology. Furthermore, a dysfunction in the dopaminergic pathways in the frontal lobe has been postulated in hyperkinesis (Mattes 1980). Interestingly, these are the same areas and the neurotransmitter implicated in GTS as well (Comings and Comings 1987).

Thus there is increasing evidence to suggest a considerable symptomatic, neuroanatomical and biochemical overlap between GTS and ADHD. However, it is not clear whether the association between the two disorders is due to such overlaps in some intermediate or final pathways in the genesis of clinical symptoms, or indeed the result of a shared primary aetiology. If there is indeed a genetic relationship between GTS and ADHD, and ADHD represents an alternative phenotypic expression of the same gene, it would be expected that significantly greater number of relatives of GTS patients will have ADHD. In addition, the morbid risk of ADHD should be the same in relatives of GTS + ADHD probands, as compared to that in relatives of GTS - ADHD

probands. However, if those with GTS and ADHD represent a distinct genetic subentity of GTS, it will be noted that the two conditions co-segregate within families, and that both GTS and ADHD would coexist in a given individual much more than expected by chance alone (Pauls et al 1986b). It has been suggested by Comings and Comings (1984) that the two disorders may share the same underlying genetic mechanism and that ADHD may represent a different manifestation of the GTS diathesis. Others have refuted such an association (Pauls et al 1986b, Pauls et al 1988), followed by debate (Comings and Comings 1988).

Whilst there is general agreement about the increased rate of occurrence of ADHD in patients with GTS (Robertson and Eapen 1992; Towbin and Riddle 1993), findings from available studies are inconsistent as to the exact relationship between the two disorders. There may be several explanations for this disparity. Issues relating to ascertainment and referral bias have already been discussed. In addition, studies using family history data have an inherent problem of misdiagnosis and underdiagnosis and therefore the true rates of illnesses among the relatives may be different, and consequently, the pattern of illnesses within families can be affected by this reporting bias (Orvaschel et al 1982; Pauls et al 1986a). This is particularly relevant in the case of ADHD with an early age of onset, and most subjects reporting about their relatives may be relying on their memories

or other people's account of their behaviour during childhood. The use of multiply affected families in some studies and the fact that most probands had severe form of the disorder, are other important factors that may have influenced the findings from these studies. A much better test of a genetic relationship between ADHD and GTS can be accomplished with a larger sample of small families that have been consecutively ascertained without regard to familial loading.

1.3. EPIDEMIOLOGY

Most epidemiological studies in GTS have been compromised by methodological problems such as sample selection bias and variability in case and syndrome definition (Tanner 1993). The reported prevalence figures vary widely, the most commonly accepted being 0.5 / 1000 (Bruun 1984). Most studies have been based on targeted populations (for example clinics, schools) and only a few studies have attempted to circumvent this selection bias. In addition, many of these rates were based on data obtained from historical information without direct clinical examination. The only population based study that has systematically screened for the presence of GTS is that by Apter et al (1992) where all 16 and 17 year olds were examined for the presence of tics and GTS whilst being evaluated for fitness to

join the army in Israel. This study gave a prevalence of 4.28 / 10,000.

While studies based on specifically targeted populations are important in understanding the disorder, the bias introduced by such ascertainment cannot be easily incorporated into the analysis of such data. In addition, it may well be that there are differences between clinic populations and the cases in the community (most of them being undiagnosed and having a mild form of GTS), both in the nature and expression of the disorder. From family studies it is clear that the prevalence of GTS is underestimated, partly due to the fact that many relatives with mild form of the disorder do not seek medical help, further compounded by the lack of awareness and recognition of the condition by medical practitioners (Kurlan et al 1987). Thus, community based epidemiological studies are needed to avoid selection bias and to study the full range and frequency of the manifestations of GTS.

Furthermore, sample selection bias affects other parameter estimates such as the sex ratio and sex dependent differences in the expression of GTS. For example, earlier studies reported a male to female ratio of 3:1, while more recent studies using direct clinical examination have suggested a ratio of 1.6:1 (Apter et al 1992). This is particularly relevant as population

parameters including age and sex specific prevalences are incorporated into the analyses while calculating the risk in relatives and determining the genetic model factors. It is therefore crucial to have accurate estimates of these parameters in clarifying the role of environmental and genetic, as well as protective and risk factors, as they affect the expression of the syndrome.

1.4. NEUROIMAGING

Structural imaging studies using computerised tomography (CT) scans have not revealed any specific abnormalities in GTS (Lees et al 1984; Robertson et al 1988), except for one study (Caparulo et al 1981), which suggested ventricular enlargement. Magnetic Resonance (MR) studies have also failed to show any gross abnormalities (Chase et al 1986, Robertson and Trimble 1991). However, these studies are limited because of the small numbers involved and the lack of quantitative analysis. A few abnormalities reported with magnetic resonance imaging have included a reduction in the volume of the left putamen and globus pallidus in GTS compared to controls (Peterson et al 1993; Singer et al 1993), as well as asymetric cerebral peduncles (Sandyk 1988), a high signal lesion in the right globus pallidus (Robertson et al 1990) and focal abnormalities involving the basal ganglia (Demeter 1992). Positron Emission

Tomography (PET) in GTS has shown an inverse relationship between the severity of tics and cortical metabolism in frontal and temporal areas (Chase et al 1984), and a reduction in frontal, cingulate, insular cortices and in the inferior corpus striatum (Chase et al 1986). In another PET study examining the presynaptic functional integrity of dopaminergic terminals, the density of striatal D2 receptors was found to be normal in GTS patients, and there was no difference in the striatal metabolism of exogenous levodopa between the treated and the untreated groups (Turjanski et al 1994).

The measurement of regional Cerebral Blood Flow (rCBF) reflects dynamic alterations in neuronal activity. In GTS, SPET studies have shown hypoperfusion involving basal ganglia structures and prefrontal areas (Riddle et al 1992; Dimitsopulos et al 1993). In addition, SPET studies with the D2 dopamine neuroreceptor marker 123I IBZM indicate that medicated GTS patients have significantly lower availability of D2 receptors than controls in both the right and left basal ganglia (George et al 1994). However, unmedicated GTS patients showed no difference from normal controls. In another study, Malison et al (1995) reported findings that are consistent with a dysregulation in presynaptic dopamine function in GTS.

Under resting conditions, rCBF and regional glucose or oxygen metabolism are closely correlated across brain regions. The underlying mechanism that couples neuronal activity and rCBF may include potassium release during neuronal depolarisation or the effect of adenosine, nitric oxide or other neuronal factors. Technetium-99m-hexamethylpropylene amine oxime (HMPAO) uptake has been shown to reflect rCBF as HMPAO crosses the blood brain barrier with a high first pass extraction. HMPAO distribution has also been reported to show detectable changes in pathological conditions where an rCBF change is expected. Lassen et al (1987) have developed an algorithm to correct any non linearity due to back perfusion and it has been established that this `linearization' correction is accurate (Inugami et al 1988) and, when applied, distribution of HMPAO in the brain as measured by SPET gave a linear correlation ($r=0.93$) with rCBF.

In GTS, the neuroimaging technique using HMPAO has some unique advantages. Given the rapid brain uptake and very slow redistribution of HMPAO, it helps to overcome difficulties encountered due to head movement caused by tics and the waxing and waning course of the symptoms. Rapid brain uptake allows observation of tic severity over the 1-2 minutes after the injection, during which time HMPAO is being taken up in the brain and slow redistribution permits scanning to be done at a

later time, when the subject is feeling more relaxed. Furthermore, sedative medication can be administered during scanning without changing the previous pattern of HMPAO uptake, which is most helpful in children, who may have difficulty keeping still.

The multiplicity of symptoms and associated features seen in GTS underlines the complexity of the disorder. Given the fact that it is not possible to make a valid clinical distinction between the physical expressions that are related to the genotype (i.e. the phenotype) and those that are not (i.e. phenocopies), the next step towards a better understanding of these distinctions will be to identify an "endophenotype" (a finding that co-segregates with the phenotype, thus indicating a link to the genotype). In this endeavour, functional neuroimaging using HMPAO is a promising technique with unique advantages.

Available data suggest that rCBF changes in GTS have been remarkably consistent with brain regions that are already implicated to be affected in GTS. If this is indeed true, one would expect these findings to hold true in all cases sharing the same pathophysiology of GTS (clinical phenotypes) and thus indicating the link with the primary abnormality, which is now generally agreed to be genetic. Thus the clinical phenotypes (GTS, Tics, OCB) can be better classified based on the clinical

features that co-segregate with the identified endophenotype. If, on the other hand, the clinical manifestation resembles the phenotype but does not share the same underlying pathophysiologic and genetic mechanism (phenocopy), the relevant findings will not be expected to co-segregate. However, there is always a possibility that, if the selected endophenotype is a shared final common pathway for the phenotype as well as the phenocopy, the findings will not be specific and hence a link with the genotype cannot be established. Absolute certainty regarding phenotypes can only be achieved by identifying the gene(s) involved.

1.5. GENETICS

Results from previous family history studies suggest that there is a single major gene that confers susceptibility for GTS (Baron et al 1981; Comings et al 1984; Curtis et al 1992; Devor 1984; Kidd & Pauls 1982; Pauls et al 1990; Pauls & Leckman 1986; Price et al 1984; 1988). However findings from these studies have not always been consistent as to the precise mode of inheritance; whilst several studies have reported an autosomal dominant pattern of transmission (Pauls and Leckman 1986; Curtis et al 1992), others have suggested alternative patterns (Comings et al 1989, Comings and Comings 1990). An alternative hypothesis of homozygosity and a semi-dominant semi-recessive pattern of

inheritance have been postulated (Comings et al 1989; Comings 1990, Comings and Comings 1992), but this hypothesis was derived by assuming that the GTS spectrum of behaviours (phenotypes) incorporate about twelve different psychiatric conditions including alcohol and drug abuse, schizoid behaviours, eating disorders, as well as panic and phobic disorders in both the maternal and paternal sides of the family. Other investigators have questioned the inclusion of these behaviours as part of the GTS spectrum, especially given the relatively high prevalence of these psychiatric conditions when both sides of the family are taken into account. Other investigators have refuted this hypothesis about a genetic relationship between these psychiatric conditions and GTS (Pauls et al 1988a; 1988b, Pauls et al 1993, Carter et al 1994). In addition to the differences in the phenotypic definition, there are also other possible reasons for these disparate findings, and this include the use of family history data, differences in sampling strategies, as well as the use of multigenerational pedigrees with high genetic loading.

First of all, let us examine the issue of phenotypic definitions. If it is assumed that there are different clinical phenotypic expressions of the putative GTS gene, including clinical manifestations that are unrelated to the gene, or, excluding clinical presentations that are due to the same

genetic diathesis, are both likely to result in spurious results. Another common source of error is the use of family history data, (i.e. data collected through one or two informants per family, by enquiring from them about the occurrence of tics and related behaviours in other family members) as opposed to direct clinical examination. Previous studies in psychiatry have shown that family history data significantly underestimate the true rate of illnesses in the relatives and consequently the pattern of illness within families can be affected by this reporting bias (Orvaschel et al 1982; Pauls et al 1986a). This reporting bias is of particular concern when studying OCB, as many of these subjects are secretive about their obsessions and compulsions. Thirdly, different studies have used different methods for sampling the families. In this regard, most studies have used large GTS multigenerational kindreds and results from these studies need to be interpreted with the knowledge that the bias introduced by the ascertainment of such multiplex families cannot be easily incorporated into the analysis. In these instances, there is a danger that the findings may represent the genetic mode of transmission and other characteristics that are unique to the family studied, and something that may not necessarily be true for all GTS families.

Future studies on the mechanism of inheritance in GTS may well be assisted by more precise definition of the phenotype.

Furthermore, genetic linkage studies are under way in several centres. Although reports have tentatively assigned the gene to different chromosomes, none have so far been conclusive, and no specific chromosomal abnormalities have been found in GTS (Robertson and Trimble 1993).

Yet another modifying factor in this context may be the effect of genomic imprinting. It has recently been recognised that the specific expression of a number of heritable human disorders depends on whether the defective gene is of paternal or maternal origin. Genomic imprinting has been used to refer to the differential expression of genetic material at either a chromosomal or allelic level, depending on whether the genetic material has come from the male or the female parent (Surani 1988). Modification of DNA through methylation may give a means of determining whether a particular allele of a gene is inactivated at a particular time. In this context, the stage during which germ-line cells are formed may represent one critical period during which genetic information is `tagged' or marked, and methylation may be the molecular mechanism involved in temporarily changing the genetic information to permit differential expression (Hall 1990). This is quite contrary to the basic Mendelian tenet that the parental source of genetic information does not influence the gene expression. Genomic imprinting, however, appears to be a form of regulation allowing

another level of flexibility in the control of expression of the human genome, and seems to be in operation in several genetic disorders as illustrated below.

In the case of both Prader-Willi and Angelman syndromes, there is deletion of chromosome 15. The available evidence suggests that the difference in the phenotype of these two syndromes is due to the differential function of the q11-13 regions of maternally versus paternally derived chromosome 15 (Knoll et al 1989). In another example, the bilateral retinoblastoma, family studies have suggested an autosomal dominant trait with a high degree of penetrance. Molecular work has demonstrated that at least two steps are needed for the tumour to develop; first the inheritance/mutation of the abnormal gene, and second, the loss of the complementary normal gene by one of the molecular mechanisms, thus uncovering the abnormal gene. In non-familial retinoblastoma, the sporadic cases may first have a mutation in the gene from either parentally derived chromosome 13, while new germ-line mutations (i.e. those resulting in bilateral tumours and capable of being transmitted to the offspring) appear to be primarily of the paternally derived chromosome 13 (Dryja et al 1989).

There are a number of other human disorders where differences in phenotypes, age at onset and severity seem to be related to the

sex of the parent transmitting the gene. In myotonic dystrophy, when the gene is transmitted through the mother, this results in a severe form of the disorder (Harper 1975), and in Huntington's disease, when the gene is transmitted through the father, a severe rigid and juvenile form of the disorder occurs (Ridley et al 1988). Other examples where the sex of the transmitting parent has been shown to influence the severity or nature of the clinical expression include neurofibromatosis 1 and 11 (Miller and Hall 1978; Eldridge 1981), cerebellar ataxia (Harding 1981), seizures (Ottman et al 1988), spinocerebellar ataxia (Zoghbi et al 1988) and Fragile X syndrome (Laird 1987). Furthermore, if there are two loci for a disorder, then there may be two different types of imprinting, as may be the case for tuberous sclerosis and adult polycystic kidney (Hall 1990). The expression of specific genes when inherited from father versus mother has not yet been evaluated for most of the genetic disorders, and it seems essential to ask the question of parent of origin effect in all genetically determined disorders. This is particularly relevant in the case of GTS, because there are known sex effects observed in this disorder; for example, there are more affected males than females; and the possible sex differences in the nature of expression of the disorder, with females more often having obsessive compulsive symptoms and males having Tics and GTS (Pauls and Leckman 1986).

CHAPTER 2

OBSESSIVE COMPULSIVE DISORDER

CHAPTER 2

OBSESSIVE COMPULSIVE DISORDER

2.1. DEFINITION AND CLINICAL PHENOMENOLOGY

Obsessive Compulsive Disorder (OCD) is characterised by recurrent obsessions or compulsions that 1) cause marked distress, 2) are time consuming (take more than an hour a day); or 3) significantly interfere with the person's normal routine functioning, social activities or relationships (American Psychiatric Association 1987). Obsessions are recurrent, intrusive and unwelcome ideas, thoughts, images or impulses, which are recognised by the individual as absurd. Compulsions are repetitive purposeful behaviours performed in response to an obsession. The diagnosis of OCD as per DSM-1V (American Psychiatric Association 1994) incorporates an additional criteria that, "at some point during the course of the disorder, the person has recognised that the obsessions or compulsions are excessive or unreasonable; however, this does not apply to children."

Several investigators have tried to identify obsessive compulsive (OC) symptom subtypes in an attempt to find

homogenous subgroups within OCD patients. Hodgson and Rachman (1977), using the Maudsley Obsessive Compulsive Inventory (MOCI) described four factors; checking, cleaning, slowness and doubting in descending order of variance. However, the use of MOCI has an inherent problem of item selection bias, in that, whilst checking (9 items) and cleaning (10 items) symptoms are well represented, others, such as aggressive obsessions (2 items), symmetry, ordering and hoarding compulsions (no items), are underrepresented (Goodman et al 1989a, Rasmussen & Eisen 1988). Khanna et al (1990) in a cluster analysis of 410 OCD patients assessed using a checklist (developed by the authors but with similar symptom selection bias as the MOCI) reported five symptom subgroups; checking, washing, the past, death and sex.

The Yale Brown Obsessive Compulsive Scale (YBOCS) symptom checklist overcomes the symptom selection bias of the MOCI and provides a comprehensive list of more than 50 obsessions and compulsions, comprising 15 general symptom categories (Goodman et al 1989b). Using this checklist, Rasmussen and Eisen (1988) found that, in a series of 250 OCD patients, 60% had multiple obsessions while 48% had multiple compulsions. Rettew et al (1992) using the same instrument assessed 79 children and adolescents with OCD and found that 47% had both washing and checking compulsions at some time and that none maintained the

same symptom constellation at follow up 2 to 7 years later. This questions the validity of categorising patients into mutually exclusive subgroups such as cleaners or checkers based on symptoms at a given point.

2.2. EPIDEMIOLOGY

OCD was once thought of as an uncommon psychiatric disorder, but is now recognised to be a rather more common psychiatric illness affecting some 2% to 3% of population (Fineberg and Montgomery 1990). To date, a total of nine Epidemiological Catchment Area (ECA) studies have been conducted and the life time risk of OCD is estimated to be 1.9% to 3.2% (Bebbington 1990). Other community based studies have noted that the prevalence estimates are similar for males and females, whites and blacks, and across different socio-economic status (Valleni-Basile et al 1994). However, the central issue in epidemiological research in OCD is that of case definition. Even if there were a reasonable consensus over case definition, difficulties would remain because of their frequent coexistence with other disorders such as Generalised Anxiety Disorder, Depressive Disorder and GTS. This is further compounded by the lack of consensus as to when, in these situations, a separate diagnosis of OCD is justified. Solutions to this particular issue have been inadequate, and

none has gained sufficient acceptance to dispel ambiguity from epidemiological studies.

2.3. GENETICS

Aetiologic theories of OCD have changed fundamentally in the past decade. Viewed as a manifestation of psychodynamic conflict throughout most of this century, OCD is now widely accepted as a model of neuropsychiatric illness. Treatment advances, brain imaging studies and results of pharmacological challenges have redefined aetiologic theories and generated new research paradigms. While response to pharmacological agents and findings that specific regions of the brain may be involved with the observed symptomatology suggest a biologic aetiology, little work has been done to examine the possible role of genetic factors. A genetic element for a disorder is assumed if an enzyme or structural protein is abnormal or absent. Biochemical aberrations are presumptive evidence of genetic influences even in the absence of family data. In general, evidence that suggests a genetic aetiology includes 1) twin studies in which there is a higher concordance rate among Monozygotic (MZ) twins than Dizygotic (DZ) twins; 2) adoption studies in which a higher incidence among the biological offsprings of affected individuals is observed even when they have been adopted away and reared in adoptive homes by unaffected parents; and 3)

family studies showing a significant aggregation of the illness within families when compared to the population prevalence.

Thus, Rasmussen and Tsuang (1986) in a review reported that, of the 51 MZ twin pairs where at least one twin had OCD, 32 (63%) pairs were concordant for OCD. However, these studies are limited because of the small sample size and methodological problems. Most of these studies were carried out in clinic population and given this ascertainment bias, they are not representative of the general population. Carey and Gottesman (1981) documented a sample of 30 twins; 15 DZ and 15 MZ, where at least one twin had received a diagnosis of OCD, and found higher concordance rates for MZ than for DZ twins. Four hundred and nineteen pairs of normal twins were studied by Clifford and colleagues (1984) using the Leyton Obsessional Inventory (LOI). The results from this study suggested that genetic and specific environmental factors were both important for the manifestation of OCD. Heritabilities of 44% for OC traits and 47% for OC symptoms were reported. In another study, McGuffin and Mawson (1990) reported on identical twin pairs who were separated prior to the onset of symptoms and neither were aware of the other's problems. Despite this, the OC symptoms started at similar ages and followed a similar course in both pairs. In addition it was noted that the fathers in both sets of twins had obsessional traits. It is interesting to note that one of these twins had

childhood tics and two of the four sets of identical twins with OCD described by Inouye (1965) had GTS. However, it should be noted that in all twin data reported, the concordance for MZ twins was less than 1.0 and heritability estimates were consistently less than 1.0. In addition, an analysis of OC traits in twins (Cox et al 1975) showed a strong interaction between genetic and environmental factors. Thus, while genetic factors are important in the expression of OC symptomatology it is clear that these behaviours are also influenced by environmental factors.

More recently, two twin studies have suggested that, whilst genetic factors are important for anxiety disorders in general, this contribution is obscured by the grouping of anxiety symptoms into specific disorders (Andrews et al 1990; Torgerson 1983). Black et al (1992) studied first degree relatives (FDRs) of 32 adult OCD probands and 33 psychiatrically normal controls. They found that the morbid risk for anxiety disorders was increased among the relatives of OCD subjects when compared to the relatives of controls, but the risk for OCD was not. Risk for a more broadly defined OCD was increased among the parents of OCD probands but not among the parents of controls (16% Vs 3%). These findings suggest that an anxiety disorder diathesis is transmitted in families with OCD but that it's expression within these families is variable.

Several family studies have reported significantly higher rates of OCD in parents and siblings of OCD probands, with rates among parents being 5 to 10 times higher, when compared to population prevalence estimates (Pauls 1992). Two recent studies have found remarkably similar risk rates in FDRs of young OCD probands. Lenane et al (1990) studied 145 FDRs of 46 children and adolescents with OCD and reported an age corrected morbid risk of 35% in FDRs, when subclinical OCD was included. Riddle et al (1990) examined families of 21 children and adolescents with OCD and found that 35.7% of parents received a diagnosis of clinical or subclinical OCD. Bellodi et al (1992) in a study of 92 adult OCD probands found that the rate of OCD among FDRs was only 3.4%. However, when probands were separated into two groups based on whether the age of onset was before or after 14 years, it was noted that the morbid risk for OCD among relatives of the early onset probands was 8.8% compared to 3.4% among the relatives of probands with a later age of onset.

Additional evidence that at least some forms of OCD are genetically determined comes from the work on GTS. Pauls et al (1986a) reported that 23% of FDRs of GTS probands had OCD. Approximately 40% of them had OCD without GTS or tics, hence about 10% of all relatives had OCD without tics. Further support for an association comes from others who found the occurrence of

OC thoughts and actions without tics or vocalisations in relatives of GTS patients (Kurlan et al 1986; Comings and Comings 1987; Robertson and Gourdie 1990; Robertson and Trimble 1991).

CHAPTER 3

GILLES DE LA TOURETTE SYNDROME

AND

OBSESSIVE COMPULSIVE DISORDER

CHAPTER 3

GILLES DE LA TOURETTE SYNDROME AND OBSESSIVE COMPULSIVE DISORDER

3.1. PHENOMENOLOGY

The occurrence of OC symptoms in the context of GTS was recognised by Gilles de la Tourette himself (Gilles de la Tourette 1885). In his description of the case of Marquise de Dampierre, he reported that obsessive thoughts tormented her in addition to the tics and vocalisations. Charcot was the first, however, to identify involuntary "impulsive" ideas such as arithmomania (counting obsessions), doubting, checking and touching (Gilles de la Tourette 1889). Grasset (1890) referred to the obsessions, which were to him an accompaniment of the tic disorder, representing psychical tics. Robertson and Reinstein (1991) translating and drawing from the writings of Gilles de la Tourette, Guinon and Grasset, illustrated how these early clinicians documented the psychopathology of people of "convulsive tic disorder" with particular reference to OCB, including checking, arithmomania, folie du doute, delire de toucher (forced touching) and folie du pourqoui (the irresistible habit of seeking explanations for the most commonplace insignificant facts by asking perpetual questions).

Meige and Feindel (1907) in the "confessions of a victim to tic" described a patient with impulsions and OCB, and stated that "the frequency with which obsessions, or at least a proclivity for them, and tics are associated, cannot be a simple coincidence". Wilson (1927) also acknowledged a relationship between tics and OCD: "no feature is more prominent in tics than its irresistibility.....The element of compulsion links the condition intimately to the vast group of obsessions and fixed ideas". Ascher (1948) noted obsessive personalities in all of the five GTS patients he reported, while Bockner (1959) commented that the majority of GTS cases described in literature had OC symptoms.

Patients with GTS were reported to have high rates of OCB by several investigators (Morphew and Sim 1965; Fernando 1967; Fernando 1976; Nee et al 1980; Montgomery et al 1982; Frankel et al 1986; Pauls et al 1986; Comings and Comings 1987; Grad et al 1987; Pitman et al 1987; Yayura - Tobias et al 1981; Robertson et al 1988). However the prevalence of these symptoms has varied considerably, with the rates ranging from 11% to 90% (Robertson 1989). Robertson et al (1988) reported significant associations between OCB and core GTS symptoms such as coprolalia and echophenomena. It has been shown that these symptoms vary based on the severity of GTS, in that the frequency of echolalia has been reported to be 9.3% in grade 1 (mild) GTS and 48.3% in

grade 111 (severe) GTS (Comings 1990). Montgomery et al (1982) suggested that OC symptoms were more pronounced and severe in older GTS patients; of 30 patients with GTS over 21 years of age, 27 patients (90%) had OCD. Robertson et al (1988), however, failed to find any relationship between age and OC symptomatology. Thus, the variations in the reported frequencies of OC symptoms in GTS may well be due to a bias in sample selection.

Empirical studies based on clinic samples reported that 12 to 35% of patients with GTS also had OCB (Fernando 1967; Kelman 1965; Morphew and Sim 1965). However, these estimates could be an underestimate, as the absence of a report of symptoms could not be equated with the absence of the symptoms (Fernando 1967). Much higher rates of 55% to 80% were reported in more recent studies (Nee et al 1980; Jagger et al 1982; Stefl 1984; Yayura-Tobias et al 1981). Robertson et al (1988) documented that 37% of 90 GTS patients not only reported OC behaviour but obtained higher scores on standardised rating scales than normals. Robertson and Gourdie (1990) interviewed 85 members of a multiply affected GTS family. 50 were diagnosed as GTS cases, with four members having only OCB. Cases and non-cases could be distinguished on the basis of OC features and the trait score of the LOI.

Few studies in this context have included control groups. In one study, 52% of GTS patients were found to have OCB as compared to 12.2% of the controls (Frankel et al 1986); and, in another study, 45% of GTS patients compared to 8.5% of controls (Comings and Comings 1987). Given that the population prevalence of OCD is between 0.9% and 3.2% (Bebbington 1990), it seems that the prevalence of OCD in GTS patients is much greater than that expected by chance. In a controlled study, Robertson et al (1993) found GTS patients to be disproportionately obsessional, which was not accounted for by depression.

Although several studies have attempted to define the precise phenomenology of OC symptoms in GTS, few have attempted to compare them to the symptomatology that occurs in OCD patients without a tic disorder. Despite considerable overlap in symptoms, the two conditions are not phenomenologically identical. Pitman et al (1987) reported that certain kinds of compulsions such as touching and symmetry behaviours occurred more often in GTS patients than in the OCD group. Frankel et al (1986) reported that GTS patients had more counting compulsions and impulses to hurt themselves, while OCD patients had compulsions to do things in a specified order and to arrange things; other symptoms, however, showed an overlap between the two disorders. They also noted that the symptoms changed with age, with the younger patients exhibiting compulsive behaviours

related to impulse control. Montgomery et al (1982) suggested that the frequency of OC symptoms increases with the duration of GTS.

George et al (1992) compared 10 OCD patients to 15 GTS patients with comorbid OCD. It was found that more violent, sexual and symmetrical obsessions, as well as forced touching, counting and self-damaging compulsions were more common in co-morbid OCD/GTS subjects. On the other hand, obsessions concerning dirt or germs and cleaning compulsions were more commonly encountered in OCD subjects. Miguel et al (1995) reported that intentional repetitive behaviours in OCD differ from those in GTS in that the former is preceded by cognitive phenomena and autonomic anxiety, and the latter by sensory phenomena. In addition, Holzer et al (1994) reported that patients with a history of tic disorder had significantly more touching, repeating, self damaging, counting and ordering compulsions. However, a problem inherent in this approach of comparing OCD patients with or without tic disorder is that, there is disagreement as to whether certain symptoms should be classified as compulsions or complex motor tics (Shapiro & Shapiro 1992). Furthermore, Leckman et al (1993) found considerable overlap between GTS and OCD symptoms in that 93% of their 135 subjects with a tic disorder reported experiencing premonitory urges before performing tics. Thus, it seems that the common distinction

based on the involuntary nature of tics as compared to OC symptoms is not entirely valid. Others including Nee et al (1980) and Cummings and Frankel (1985) have also observed that GTS and OCD share clinical features such as the waxing and waning of symptoms, an early age of onset, a life long course, egodystonic behaviour, worsening with anxiety, and their occurrence in the same families. It may well be that OCD is a heterogeneous entity, a subtype of which is related to GTS.

An alternate approach to distinguish GTS+OCB subjects from pure OCD individuals will be to search for a symptom profile rather than individual symptoms. By identifying such phenomenological similarities and differences, it may be possible to have a better understanding of the underlying aetiology and pathogenesis of both GTS and OCD.

3.2. NEUROCHEMISTRY AND NEUROPATHOLOGY

The strongest body of evidence favouring the serotoninergic basis of OCD comes from studies indicating the effectiveness of Specific Serotonin Reuptake Inhibitors (SSRIs) in OCD (Fineberg and Montgomery 1990). Available neurobiological and pharmacological data in OCD implicate the serotonin system in its neurochemical dysfunction, and the basal ganglia and frontal cortex as the prime anatomic loci of its neuropathology. Interestingly, these same brain regions have been implicated in

the pathophysiology of GTS. There is growing evidence to suggest the existence of anatomic and functional interactions between 5-Hydroxytryptamine (5HT) and dopaminergic systems (Graybiel 1990). 5HT neurones are believed to maintain a tonic inhibitory influence on dopaminergic function in some regions of the brain, especially the midbrain and brainstem projections to the forebrain (George 1991). The neuroanatomic hypothesis that the basal ganglia and its orbitofrontal connections may form the neuronal circuit which subserves GTS and OCB, and the available evidence about the interaction between 5HT and dopamine, is compatible with the role of the above structures and neurotransmitters in the pathophysiology of GTS spectrum OCB.

3.3. NEUROIMAGING

Functional imaging studies have thrown some light on the brain substrates of GTS and related behaviours. Although no definitive abnormalities have been found, there is a tentative consensus as to the brain areas involved. Particularly implicated are the striatal and frontal areas in both GTS and OCD. OCD has been associated with hyperperfusion; increased metabolic changes in the orbitofrontal cortices and basal ganglia (Baxter et al 1987; 1989; Baxter and Guze 1993; Nordahl et al 1989; Swedo et al 1989). It has also been postulated that the `frontal hyperperfusion' seen in OCD may be linked to increased arousal and anxiety in these cases (Cath et al 1992). Although limited,

available literature on perfusion patterns in GTS suggest hypoperfusion rather than increased blood flow. For example, Chase et al (1986) found increased relative metabolic activity and rCBF in certain frontal cortical areas in OCD, when compared to GTS. Preliminary studies in GTS as reported by Riddle et al (1992), Dimitsopulos et al (1993) and Moriarty et al (1995) suggest involvement of caudate, anterior cingulate, medial temporal and dorsolateral prefrontal areas in the form of hypoperfusion. OCD and GTS thus have apparent genetic and biological associations, but conflicting cerebral blood flow findings.

3.4. GENETICS

In addition to the clinical relationship between GTS and OCB, studies have also suggested that OCB may be aetiologically related to the GTS both biochemically and genetically (Eapen & Robertson 1994; Robertson 1994). Pauls et al (1986a) in a family study reported GTS and OCB to be genetically related. The frequency of OCD in the absence of tics among FDRs was significantly elevated in families of both GTS+OCD and GTS-OCD probands. The rate of OCD among FDRs was significantly increased over estimates of the general population and a control sample of adoptive relatives. The rates of GTS, tics and OCD were the same among relatives of GTS probands with OCD (GTS+OCD) when compared with families of probands without OCD (GTS-OCD).

Whilst there is a familial relationship between OCD and GTS, not all cases of OCD are aetiologically related to GTS (Pauls 1990). An implication of this observation is that, there may be a subtype of OCD that is genetically related to GTS, while others are not.

Segregation analysis of 24 families of OCD, CMT and GTS subjects was performed by Nicolini and colleagues (1991). Hypotheses of single-locus Mendelian inheritance were tested by segregation analysis performed with the computer programme SEGRAN. In SEGRAN, the segregation ratio is calculated from the number of affected and unaffected siblings of the proband, taking into account the size of the sibship. The affected status of the relatives was assigned as OCD, GTS and CMT. These investigators obtained a segregation ratio in the normal by normal parental mating type (both parents unaffected) 0.33+/- 0.16, and in the normal by affected parental mating type 0.39+/- 0.14. Since the ratio in the normal by affected parental mating type was around 0.4; i.e. very close to the expected 0.5, (0.5% = 100%; 0.45 = 90%; 0.4 = 80%), the best likelihood was for the dominant model assuming a penetrance of 80%. These investigators were not able to reject either the autosomal dominant or the recessive model (restricted model) when compared with the unrestricted model by means of a chi-square. Thus, there is increasing evidence to

support the hypothesis that OCD is familial and that genetic factors are important in the expression of the disorder. However, most studies to date have relied on family history data and it is known that in psychiatric disorders such methodology usually underestimates the true prevalence of the disorder in question. This is particularly relevant in the case of OCD, since individuals may be secretive about their symptoms and is therefore subject to reporting bias. Therefore it will only be possible to examine hypothesis about the genetic transmission of OCD by using data where all family members have been directly interviewed.

The results from these investigations do not, however, suggest that all subjects with OCD have a disorder that is aetiologically related to GTS. It may well be that there are at least two sub groups within OCD: those with a family history of GTS and those without such a history (Green and Pitman 1986). It is debatable whether the OC symptoms observed in members of families with GTS is somewhat a milder form, although the range and character of symptoms may or may not be different from those observed in clinical patients with OCD in the absence of GTS. Yet another question to be addressed therefore is, whether or not the OCD that is unrelated to GTS is also familial, and if so, whether the patterns within families are consistent with genetic transmission.

SECTION 111

THE INVESTIGATION

CHAPTER 4

SUBJECTS AND METHODS

4.1. GENETIC TRANSMISSION IN GTS AND OCD

4.1.i. GTS subjects

Segregation analysis was performed using data obtained from direct clinical examination of families ascertained through 40 consecutive new cases of GTS (DSM 111 R) registered at the National Hospital for Neurology and Neurosurgery (NHNN) Queen Square, London, over an eight month period. Two additional patients were seen in this time period but their families were not included in this study as information was not available on the biological relatives.

The diagnostic criteria for GTS as defined by DSM 111R (APA 1987) are as follows:

A. Both multiple motor and one or more vocal tics must have been present at some time during the illness, although not necessarily concurrently.

B. The tics occur many times a day (usually in bouts), nearly every day or intermittently throughout a period of more than one year.

C. The anatomical location, number and frequency, complexity and severity of the tics change over time.

D. The onset is before the age of 21.

E. Symptoms do not occur exclusively during psychoactive substance intoxication or known Central Nervous System disease.

The diagnosis of TTD and CMT were made as per DSM 111R criteria, where TTD refers to single or multiple motor or vocal tics with a duration of less than one year, and CMT refers to multiple tics (motor or vocal but not both) that have been present for more than a year.

In all the families, direct clinical interviews were conducted with the index case and with all FDRs. Since the unit of analysis in POINTER (the computer programme for complex segregation analysis) is the nuclear family (Lalouel and Morton 1981), families were decomposed into smaller units. Under this scheme, the nuclear family of any FDR of a proband is included

provided that relative is affected; for example if Mr. X is the proband, his/her spouse and children will form one family unit, while his/her parents and siblings will form another nuclear family unit (Fig 1.1). Pointers to nuclear families indicate how each family is related to the proband's nuclear family (Lalouel & Morton 1981). The pointer is taken as the primary proband and the "pointee" is the closest eligible relative. Relationship in the thus extended nuclear unit are conditioned on the degree of relationship to the pointer.

Partitioning families into nuclear units using pointers has several practical advantages. The primary advantage is accurate likelihood estimation that is economical of computer time. However, such a scheme must have a consistent set of inclusion and stopping rules for ascertainment. The rules used in this study are based upon those followed by the Edinburgh Cytogenetics registry.

1) All FDRs of probands are included.
2) Any additional nuclear unit containing a FDR of a proband is included if and only if that relative is also affected regardless of whether or not anyone else in that family is affected.
3) the nuclear unit of any unaffected FDR of a proband is not included even if it does contain other affected individuals.
4) Any spouse and children of the proband and of any affected

sib are always included.

As an example, in Figure 1.1, the inclusion scheme would allow the mother's nuclear family to be included but not the father's. For those probands in the study where such extensions were possible, further nuclear units were included if all the members of that nuclear unit were available for personal interview. Thus, for the GTS group, the 40 ascertained families resulted in 49 nuclear units.

Included in this 49 nuclear family units were a total of 168 FDRs, consisting of 48 fathers, 49 mothers, 10 sons, three daughters, 32 brothers and 26 sisters. The age (range 3 to 53) and sex distribution of the 40 probands and that of the 168 FDRs is given in Table 1 & 11. Table 111 gives the diagnostic status of the 168 FDRs.

Direct clinical examination were carried out in all the subjects by the author, using the National Hospital Interview Schedule (NHIS) for the assessment of GTS and related behaviours (Robertson and Eapen 1996). This is a semi-structured interview schedule designed for use by specially trained clinicians (Appendix 1.1). It takes about an hour to complete by an individual who is trained and experienced. It provides an overall evaluation of the core symptoms of GTS such as the motor and vocal tics, as well as other characteristic features

including coprolalia (the inappropriate uttering of obscenities), copropraxia (the inappropriate making of obscene gestures), echolalia (repeating what other people say), echopraxia (copying of what others do eg. tics or movements), palilalia (repeition of one's own last words or sentences) and palipraxia (repetition of one's own last action or movement). It also covers information about OCB, self-injurious behaviour (SIB) and ADHD. Information is obtained about the specific themes and content of the OCB and some examples include forced touching, concern for symmetry ("evening up"), violent thoughts, and arithmomania (an obsession with counting). The Yale Global Tic Severity Scale (YGTSS) (Leckman et al, 1989) has also been incorporated as an appendix for the assessment of tic severity, which is a clinician rated scale covering aspects such as the number, frequency, intensity, complexity and interference of motor and vocal tics on day to day life.

The NHIS also covers information on the family and, in particular, the presence of GTS and related behaviours in family members. Using the NHIS, the family history is initially sought by asking the subject "does anyone in your family have ....", since this way of questioning has the advantage of eliciting a spontaneous response from the individual about all his/her family members (including those other than FDRs). Depending on the purpose (clinical, research etc) of the interview, the

interviewer can then make a decision as to whether he/she need to seek further information about the family members. For genetic research (as in this study), this is then followed up by the Family Psychiatric Hisotry Interview where the subject is asked specifically about each and every FDR by name. The inclusion of family data makes this an ideal instrument for the initial evaluation of probands for use in family genetic studies. In addition, sociodemographic details and information on personal history, including birth and early development are included. The inclusion of items concerning the overall adjustment of the individual, his/her family life and adjustment with peers, as well as interference of symptoms in personal, social and occupational functioning, makes it a valuable tool for use in the clinical setting as well.

Special training is particularly important since some of the questions are used as a guide by the interviewer rather than asked exactly the way it is presented in the schedule. This is particularly the case for questions relating to behaviours such as coprolalia and arithmomania, as there is a need to explain the phenomenon in a way that the subject would understand (based on the age, level of intelligence and educational status), get examples from the subject if the behaviour is present, and follow it up with explanatory questions. In addition to asking the individual to elaborate on a given example, the interviewer

also need to exercise his/her clinical judgement based on the answers, in deciding whether the phenomenon in question is present or not (for example differentiate voluntary swearing from coprolalia). The author received special training at the Tourette clinic of the NHNN for one year before the start of the present study. There are no other instruments available to date, for the overall evaluation of GTS and related behaviours, where the reliability and validity has been established. Although widely used by the Yale group in similar studies, there are no published reports of reliability and validity for the Yale Schedule for Tourette and Other Behavioural Syndromes (Pauls and Hirst 1987). NHIS was therefore devised, and the reliability and validity established (Robertson and Eapen 1996) [see Appendix 1.2 & 1.3].

One of the advantages of the NHIS over the Yale Schedule include the use of the same instrument for adults and children alike. NHIS has been so designed for use by both clinicians and researchers, and it was felt by the authors that the use of separate adult and children's version will only add to the practical difficulty in collating the information. Another distinct advantage of NHIS is a better method of enquiring about tics where a wide variety of individual motor and vocal tics are enquired about (e.g. eye blinking, eyebrow raising, nasal twitch) and the presence noted, during the interview, those

occurring in the week prior to examination, and tics ever experienced by the individual since the onset of the disorder (unlike in the Yale schedule where this is done as tics ever occurred on the basis of the body part involved [e.g. head and neck] which could result in missing valuable information). Videotape recordings were not used as part of this assessment since it has been shown that this is of limited value due to the highly fluctuating (waxing and waning) nature of tics, and given the fact that the act of videotaping itself may exacerbate tics (van de Wetering 1992).

In this study subjects were interviewed in the company of other informants (typically parents or spouses). For those subjects under age 16, a parent interview was always obtained, and this was combined with the clinical observation at the time of the interview. For those subjects above age 16 whose parents were not part of the study population, information about childhood was obtained by a telephone interview. All the 168 FDRs included in the study were personally interviewed by the author (VE) using the NHIS (132 FDRs were seen at the NHNN and the remaining 36 were seen at home). For those seen at the clinic, independent diagnostic estimates for GTS, TICS and OCB were performed by two clinicians (the author (VE) and Mary M Robertson [MMR]), and disagreements were resolved by a joint interview. Following completion of the direct interview, family description data were

collected from each informant about all his/her FDRs using a semi-structured interview (Family Psychiatric History). This instrument was originally devised by the Yale group (Pauls and Hirst 1987), and as used in the present study, incorporates questions from YBOCS, as well as the relevant sections of the Diagnostic Interview Schedule and the Schedule for Affective Disorders and Schizophrenia for school age children (Appendix 2). Here, information is collected about specific individuals; i.e. each and every FDR included in the study. These family description data were included in the final diagnostic estimates of each of the relatives. Thus after completion of all interviews within a given family, all the available information (personal interview and family history descriptions) for each individual were collated, and consensus was obtained using a `best estimate' method of diagnosis (Leckman et al 1982). When symptoms were present both on history and on examination, a "definite" diagnosis was assigned. If symptoms were present on examination but there was lack of supporting information from personal history and family reports, a "probable" diagnosis was given. Finally, if some symptoms were present on history but not enough to satisfy either a probable or definite diagnosis, a "possible" diagnosis was given. Only definite and probable diagnoses were used in the analyses reported here.

4.1.ii. **OCD subjects**

Twenty families were ascertained through new cases of OCD registered at two clinics; the Harlow Child Guidance Clinic (part of the Academic Department of Psychiatry, University College London Medical School) and the Obsessive Compulsive Disorder clinic at St.Mary's Hospital, London.

The diagnostic criteria for OCD as defined by DSM 111R (APA 1987) are as follows:

A. Presence of either obsessions or compulsions
B. The obsessions or compulsions cause marked distress to the individual; are time consuming (take more than an hour a day); or significantly interfere with the person's normal routine functioning, social activities or relationships
C. Symptoms are not due to another mental disorder or organic mental disorder

The term OCB is used in this study to denote subjects who fulfil the symptoms criteria of the DSM111-R diagnosis as described in criterion A but do not necessarily meet the criterion B.

Included in this 20 families were 66 FDRs; 29 females and 37 males. The mean age was 41 (range 6 to 69 years). The

relationships of the FDRs to the proband were as follows; 20 fathers, 19 mothers, 16 brothers, 8 sisters, 1 son and 2 daughters. In all the 20 families, direct clinical interviews were conducted with the index case and with all the 66 living FDRs using the Yale Schedule for Tourette and other behavioural disorders (Pauls and Hirst 1987). For this part of the study, the Yale schedule was used as detailed phenomenological data needed to be collected, and this instrument had the advantage of incorporating selected parts from the Diagnostic Interview Schedule to yield a lifetime diagnosis of any psychiatric disorder. Family history data was obtained from each study subject by asking about each and every FDR (using the Family Psychiatric History) during the initial interview at the clinic. These family description data were included in the final diagnostic estimates of each of the relatives.

4.1.iii. **SEGREGATION ANALYSIS**

Complex segregation analyses were completed using the unified model as implemented in the computer programme POINTER (Lalouel et al 1983). This programme, in the mixed model of transmission, allows for possible contributions of both a major autosomal locus and polygenic variation in the background of each major locus genotype. The liability for affection in a dichotomous trait determined by a mixed model is shown in Figure 1.2. The

unified model as incorporated in POINTER has five major parameters: q is the frequency of a putative major gene; d is the degree of dominance; h is the heritability which measures background polygenic inheritance; t measures the major gene effect as the distance between two homozygotes; and `tau' the transmission probability of the risk allele from heterozygous genotype. Since it has been found that the transmission probabilities were incorrectly incorporated into POINTER, those analyses were not undertaken in this study.

For the GTS family data, segregation analyses were carried out for five different diagnostic schemes (Table 1V) : GTS only; GTS or CMT; GTS, CMT or TTD; GTS or OCB; and GTS, CMT, TTD or OCB. OCB was included in the diagnostic scheme as previous studies have suggested an association between it and GTS (Fernando 1967; Yaryura - Tobias et al 1981; Montgomery et al 1982; Nee et al 1982; Frankel et al 1986; Pauls et al 1986; Robertson et al 1988; Robertson and Gourdie 1990; Robertson et al 1993). As discussed in section 4.1.ii, the term OCB is used in this context because, the obsessive compulsive symptoms did not necessarily cause distress, or were time consuming, nor did these interfere with the social or occupational functioning in these individuals.

For disorders that represent a dichotomous trait, the relationship between liability and affection status must be specified by estimates of the probability of affection; i.e. the life time risk of the disease in the general population (Kp). It is already known that GTS and OCD have a variable age at onset and GTS, CMT and OCB all show different rates for males and females across age. To incorporate such age and sex differences into analyses, separate estimates of prevalence were incorporated into the analyses. For the GTS family data, for the first three diagnostic schemes, four age classes (0 - 5, 6 - 10, 11 - 15 and over 15) were defined for males and females separately. For the analysis that included OCB, four age classes (0 -15, 16 - 25, 26 - 35 and over 35) were used (Table V). Population prevalences must be specified for all classes of individuals for whom penetrances are expected to vary systematically. The prevalences are used to define threshold positions on an underlying liability continuum from which penetrances are estimated. Analyses were carried out using a wide range of population prevalences (Price et al 1988). A variety of male-to-female prevalence ratios were examined ranging from a ratio of 5 affected males to 1 affected female to a ratio of 1:1 for both affected males and females. For GTS only scheme, prevalences ranged from 0.00032 to 0.001; for GTS or CMT, prevalences ranged from 0.005 to 0.030; while for GTS or CMT/TTD, prevalence rates ranging from 0.008 to 0.05 were used.

When OCB was included in the analyses, prevalences ranged 0.003 to 0.05.

For the OCD family data, four age classes (0 - 10, 11 - 20, 21 - 35 and over 35) were defined (Table V1). In the first set of analyses, prevalences ranging from 0.002 to 0.02 were used and in the second set of analyses, prevalences ranging from 0.001 to 0.01 were used.

Since all families were identified through an affected individual, an ascertainment correction for nonrandom sampling need to be included. Thus, an ascertainment probability (likelihood of an individual with GTS or OCD to be included in the study) of "pi" =0.01 was also incorporated into the analyses for both sets of data. Previous studies have shown that the exact value of "pi" did not affect the results, provided a low value was specified (Comings et al 1984).

Segregation analysis was carried out under the general mixed model of transmission. The different competing genetic models were compared using Likelihood Ratio Test (LRT), by estimating the difference in values of (-2ln (L) + k) where L= likelihood ratio and k= a constant, for a specific hypothesised model. Special cases of the general mixed model were examined by fixing one or more of the model parameters and then obtaining estimates

one or more of the model parameters and then obtaining estimates of the others that maximise the likelihood. Specific alternatives such as the absence of a major locus effect (q=t=d=0) or the absence of a multifactorial component (H=0), were tested against the general model by LRTs. The likelihood ratio is twice the natural logarithm of the ratio of the likelihood of the general model to the likelihood of a restricted case of the general model. The difference in log likelihoods is distributed as a chi-square with degrees of freedom equal to the difference in the numbers of free parameters between the two models. The best fitting model arbitrarily has been assigned a value of (-2ln (L)+k) equal to 0.0; (-2ln (L)k) for all other models are expressed as positive deviations from the best model to make them interpretable as chi-squares. Evidence for a major locus component in transmission is assessed by comparing the likelihood for the given model to that of mixed model (including both major locus and polygenic components) in which the major locus has been removed; i.e. determining whether the hypothesis of "no major locus component to transmission" can be rejected. Evidence for a polygenic component is determined by comparing the likelihood for the full model with the major locus model in which polygenic inheritance is excluded; i.e. determining whether the hypothesis of "no polygenic component to transmission" can be rejected.

4.1.iv. **GENOMIC IMPRINTING**

The families for this study were identified through the GTS clinic at the NHNN, Queen Square. In addition to the 168 FDRs ascertained through 40 consecutive GTS probands, all of whom were interviewed by the author (see chapter 4.1.i), the study also included family members from 17 multigenerational GTS pedigrees (Figure 2.01 to 2.17) chosen for the purpose of linkage analyses, where there were more than five affected family members. Among the family members from these 17 pedigrees, 229 members were available for direct clinical examination, and these subjects were included in the analyses after obtaining the best estimate diagnosis (as outlined in chapter 4.1.i). One pedigree of 42 members (Figure 2.02) was interviewed solely by the author (33 members were available for the interview), and the other pedigrees were interviewed by the author along with five other investigators. These interviews were carried out at home and all these investigators had received prior training from MMR at the NHNN. Data on all subjects for this aspect of the study was collated by the author. Age at onset was sought in terms of the onset of first symptom (motor tic, vocal tic or OCB) and for individuals below 16 years of age, this was corroborated by the parent whenever possible. The phenotypic definitions used in the analyses were similar to that in segregation analyses; GTS, CMT and OCB. The age at onset, age at diagnosis and phenotypic expressions in the

offsprings of affected males were compared with that in the offsprings of affected females. Data was verified after entry into a database and t test and chi-square analyses were done using SPSS/PC (Nie et al 1978).

4.2. CLINICAL PHENOTYPES IN GTS: TICS, OCB AND ADHD

4.2.i. SUBJECTS AND METHOD

A total of 168 family members ascertained through 40 GTS probands were studied. Direct clinical examination of all subjects were made as described in section 4.1.i, as it was felt that this is crucial, given that many of the family members may not be aware of others in the family having GTS or related behaviours. This is particularly so when the tics are mild or have been present during childhood (transiently), where others may not recall them as much as they themselves would do. In the case of OCB, individuals may be secretive about their symptoms and therefore may not be known to others in the family. With regard to ADHD, given that these symptoms occur before seven years of age, the subject himself/herself may not be aware of this, and hence the need to seek information from parents or other older members of the family.

All subjects included in the study were personally evaluated using the NHIS and diagnostic estimates were made as described

in section 4.1.i. Of the 40 probands, 21 were below the age of 16 years, and of the 168 FDR's, 34 were below the age of 16 years.

For a diagnosis of ADHD, information was gathered from the parent on problems relating to inattention, hyperactivity and impulsivity as per the DSM 111R criteria. The criteria items as given in the NHIS were used as a guide, and in addition, the data from Family Psychiatric History (questions adapted from the Schedule for Affective Disorders and Schizophrenia for school age children [see Appendix 2]) were used to make a diagnosis of ADHD. Thus questions regarding inattention included information about whether the child had difficulty finishing chores, listening and paying attention, and whether the child was distractible in a number of different settings. For impulsivity, information was collected about the ability of the child to complete tasks, to wait his/her turn in group activities or to think about the consequences of something before acting on it. For hyperactivity, questions were asked about whether the child "often" had trouble sitting still, and whether the child could be considered "always on the go". The term "often" was interpreted to the parent as behaviours occurring in more than 50% of the situations, and this was taken as an indication of the "pervasive" nature of the problem. The age of onset was specified as before seven, and duration as more than six months.

A problem inherent in the methodology used here is the fact that the diagnosis was made retrospectively. However, parental report was obtained whenever possible by direct interview. While interviewing adult subjects whose parents were not part of the study population, information was obtained by a telephone interview with the parent using the Family Psychiatric History. These family description data were included in the final diagnostic estimates of the FDR's. Thus after completion of all interviews within a given family, all the available information (personal interview and family history descriptions) were collated and diagnostic ratings were completed as per DSM111-R criteria using the `best estimate' method (Leckman et al 1982). Only those cases with a `definite' and `probable' diagnosis were included in the analysis. Although it would have been desirable to obtain school or teacher reports, this was not done in this study.

4.2.ii. GOODNESS OF FIT TEST

One approach that has been found to be useful in determining which of the behaviours form part of the phenotypic expression of a given disorder is by performing goodness of fit test. The strategy used here is to show how, the inclusion or exclusion of relatives with specific diagnoses in genetic analyses results in different goodness of fit patterns.

FDRs are grouped according to sex of the proband, sex of the relative, and the relationship to the proband (e.g. fathers of male probands, brothers of female probands etc.). With the computer program POINTER, using the parameter estimates of the best fitting model for the data from the segregation analysis, it is possible to calculate the risk of being affected with GTS, Tics or OCB. This is followed by genetic analyses designed to determine how well the expected values agreed with the observed rates of illnesses in the families.

Using different diagnostic hierarchies, comparisons can then be made between the segregation patterns observed within families when members with OCB, CMT and TTD are considered to be "unaffected" by the syndrome, with the patterns observed when these members are considered to be "affected". If there is a statistically significant difference between the predicted and observed rates, this could be regarded as an indication to suggest poor fit for the data. If, on the other hand, for any particular clinical behaviour in question, the expected and observed rates are not statistically different, this would indicate that it is an integral part of the expression of the syndrome and hence a clinical phenotype.

Similarly, to examine the association between GTS and ADHD, analyses were repeated, this time focusing on probands and FDRs who fulfilled the diagnostic criteria for ADHD as per DSM 111R

criteria. The data was analysed in two groups; the relatives of probands with both GTS and ADHD, and relatives of probands with GTS only. If there is indeed a genetic relationship between GTS and ADHD, it would be expected that significantly greater number of relatives of GTS patients will have ADHD. In addition, the morbid risk in relatives of GTS + ADHD probands will be higher than in relatives of GTS - ADHD probands. However, if those with GTS and ADHD represent a distinct genetic subentity of the syndrome, it will be noted that the two conditions co-segregate within families and that both GTS and ADHD would coexist in a given individual much more than expected by chance alone. Goodness of fit chi-square analysis was performed and segregation patterns observed in these families were compared, using expected and observed rates for the FDRs as detailed above.

4.3. SINGLE PHOTON EMISSION TOMOGRAPHY (SPET)

4.3.i. SUBJECTS

Five families with at least one child affected by GTS were identified. Each nuclear family unit consisted of four members including the identified proband; two parents and two children. A total of 20 subjects thus ascertained from these five GTS families registered at the GTS clinic at the NHNN Queen Square, London, were studied. The families were selected, where all

members of the nuclear family were available for inclusion in the study, and to include individuals with a spectrum of behaviours considered to be possible phenotypes of the putative GTS gene(s); GTS, CMT and OCB, as well as unaffected family members. All subjects were personally interviewed by the author (VE) using NHIS for the assessment of GTS and related behaviours, in order to ascertain `caseness'. In addition, each family member was asked about every other member of his/her family. Only those subjects where symptoms were present both on history and on examination were considered as `cases'. Details of age, gender and diagnostic status of these individuals are given in Table XX1.

4.3.ii. **THE PROCEDURE**

SPET neuroimaging was performed in a total of twenty subjects from five nuclear GTS families, to explore the patterns of cerebral blood flow seen in families containing subjects with GTS, OCB and Tics, and specifically, to test the hypothesis that patients with the phenotypic expression OCB could be distinguished from patients with GTS by SPET.

All subjects were scanned using the GE Neurocam triple-headed brain dedicated camera (Kouris et al 1992). Subjects were injected with 550 MBq Tc 99m HMPAO at rest with eyes closed. All subjects were rated for anxiety at the time of the injection

using a visual analogue scale. Ambient light conditions were artificial and the same for all scans. All scans were reconstructed and analysed on the Star 4000 computer (Costa et al 1988). Reconstructions used a filtered back-projection technique with Hanning pre-filter and attenuation corrections. These were in three orientation planes with a final slice thickness of 2 pixels. All scans were reported by an independent rater (Dr DC Costa, Institute of Nuclear Medicine, University College London Medical School), who was blind to the subject's clinical status.

The brain regions analysed were as follows: a) in transverse images: right and left anterior striatum at the level of the thalamus, cingulum and visual cortex at the same level, and three cerebellar regions (right, left and midline) at the level where the inferior poles of the temporal lobes are first seen. In coronal images: the cingulum measured in the slice immediately posterior to that containing the cingulum in its caudal direction, orbital frontal cortex bilaterally, dorsolateral prefrontal region bilaterally in the same slice at the same level lateral to the cingulum, and anterior and posterior medial temporal regions bilaterally; the former immediately anterior to the slice containing the temporal lobes in their greatest width and the latter at the slice containing the brainstem, and two slices posterior to this. The measure for

the cingulum was taken as the average of the coronal and the horizontal readings. The scans were reported qualitatively and quantitative radioactivity ratios (cortical/cerebellum) were calculated. Normality was defined relative to a control database (Costa et al 1993).

4.4 PHENOMENOLOGY OF OCB IN GTS AND OCD

4.4.i. SUBJECTS

Sixteen GTS subjects for this study were recruited from the GTS clinic at the NHNN, Queen Square, London. Subjects fulfilled DSM 111R criteria for GTS and had associated OCB. The term OCB is used in this context because, although they had obsessions and compulsions as detailed in criterion A of the DSM 111R (1987) diagnosis, these symptoms did not necessarily cause distress, were time consuming, nor interfere with social or occupational functioning in these individuals.

Sixteen OCD probands, comparable in age and sex, were identified from two separate clinics, the Child Guidance clinic at Harlow (part of the Academic Department of Psychiatry, University College London Medical School) and the Obsessive Compulsive Disorder clinic at the St Mary's Hospital, London. All subjects fulfilled the DSM 111R criteria for OCD, and none had a tic spectrum disorder nor a family history of tics.

Of the 16 GTS probands studied, seven were females and nine were males. The mean age was 20; range 6 to 35 years. For the OCD group, the mean age was 22, with range 6 to 47 years. There were eight females and eight males. There were six probands below the age of 15 years in both the groups.

4.4.ii. **PSYCHOLOGICAL DATA**

All the OCD probands were evaluated as described earlier (section 4.1ii). Furthermore, all subjects were asked to complete the self report versions of the Leyton Obsessional Inventory (LOI); adult version (Snowdon 1980) [Appendix 3], or LOI - child version for those aged 16 years or less (Berg et al 1986; 1988), [Appendix 4]. Adult subjects were also asked to complete The State Trait Anxiety Inventory [STAI], (Spielberger et al 1970), [Appendix 5], all of which have been shown to be reliable and valid, and used in a previous family/genetic study of GTS (Robertson and Gourdie 1990). All subjects were interviewed using the Yale Schedule as detailed in section 4.1.ii, and the OC section of the Family Psychiatric History (see appendix 2) both of which incorporates questions as in the Diagnostic Interview Schedule. After completion of the Yale Schedule and the self report questionnaires, and based on the information thus obtained, an OC symptom profile (Appendix 6) was compiled for each subject that consisted of 10 obsession

items and 10 compulsion items. The scoring was done based on the presence or absence (yes/no) of each of the item in question. This method ensured that all the 20 symptom categories had equal representation, regardless of how many specific symptom examples were provided under each item.

The rating scales employed and a detailed description of them are given in Appendices 3 to 6.

4.4.iii. **STATISTICAL ANALYSIS**

Fisher's Exact tests were computed to compare the frequencies of specific symptoms in the two proband samples. In addition, t-tests were used to examine the mean differences on continuous measures of anxiety and obsessionality. Cluster analyses were performed using SPSS-PC.

CHAPTER 5

RESULTS

CHAPTER 5

RESULTS

5.1. GENETIC TRANSMISSION IN GTS

5.1.i. SEGREGATION ANALYSIS

Of the total 168 relatives studied, thirty (17.9%) relatives were diagnosed as having GTS. Twenty one (12.5%) of the relatives had CMT and ten (6%) had OCB (Table V11). A wide range of genetic models were examined for all the diagnostic schemes (Table 1V). The programme POINTER allows the use of different diagnostic schemes (a narrow definition of the phenotype as in diagnostic scheme 1 where only FDRs with GTS are considered as cases, to a broader definition as in scheme V) in a hierarchical fashion in different sets of analysis; thus each phenotype can be tested at a time, and the pattern that is most consistent with the data can be selected.

Table V11 gives the recurrence rate among the FDR's for each of the diagnostic scheme. For example, among the 90 male FDR's there were 19 subjects who received a diagnosis of GTS; a further 13 subjects and 2 subjects had a diagnosis of CMT and TTD respectively thus making a total of 32 subjects (19 GTS + 13 CMT) in the diagnostic scheme GTS or CMT; and 34 subjects (19 GTS

+ 13 CMT + 2 TTD) in the GTS, CMT or TTD group. Three male subjects received a diagnosis of OCB only and hence there were 22 subjects (19 GTS only + 3 OCB only) in the GTS or OCB diagnostic scheme; and 37 subjects in the Tics or OCB scheme (19 GTS+ 13 CMT + 2 TTD + 3 OCB).

Segregation analyses were undertaken to evaluate the mode of inheritance. The results are given in Tables V111 and 1X. All hypotheses were tested using likelihood ratios. All tests were done in a hierarchical fashion. First, the null hypothesis was tested - that is, no transmission against an alternative hypothesis of transmission due to a single major genetic locus with polygenic background (the mixed model hypothesis). There was evidence for vertical transmission in these families (i.e., the null hypothesis could be rejected), and hence additional analyses were performed to test specific genetic hypotheses. For example, the likelihood of the mixed model was compared with the likelihood of polygenic inheritance (i.e., no major locus; q = t = d = 0) as well as with the likelihood of single gene inheritance (no polygenic background). Since the polygenic inheritance hypothesis could be rejected, specific mendelian hypotheses were examined. It was noted that the generalised single locus model converged to the dominant model for all the diagnostic hierarchies. Results are presented in detail only for the first diagnostic scheme (i.e. GTS only). For this scheme the

mixed model solution gave parameter estimates almost identical to the best fitting Mendelian major locus model (d=1; t=5.36; q=0.0002; h=0; and 0% phenocopies for males and females). The mixed model moved to a boundary with the polygenic heritability (h) being zero, suggesting the absence of a multifactorial component. There was no evidence to suggest non-Mendelian transmission probabilities. For the GTS only scheme, the penetrance for males was 0.966 and females 0.452. When the definition of `affected' status included those with GTS or OCB (diagnostic scheme 1V), the results were still consistent with an autosomal dominant model. The penetrance estimated for this analysis was 0.882 for males and females. In the next set of analyses where subjects with GTS, Tics (CMT/TTD) or OCB were included (diagnostic scheme V), the penetrance rate was 0.980 for both sexes. Details of the genetic model estimates for male and female subjects, for all the diagnostic schemes are given in Table X. As a consequence of hypothesis testing procedures under the unified model of segregation analysis, the probability of ascertainment bias due to the pedigree extension rule (figure 1.1) was considered, and different values were ascribed for `pi'. Initially, a low value of .01 was set for the analyses. However, since it was not possible to determine the precise probability of a proband being ascertained, the analyses were repeated incorporating three different values. It was noted that changing the value of `pi' from .01 to 0.50 and 0.99 had only

negligible effect on the parameter estimates and changed none of the statistical inferences.

5.1.ii. GENOMIC IMPRINTING

Of the total 437 subjects, 73 of the affected family members (16.7%) demonstrated evidence of maternal transmission, and 61 cases (13.9%) that of paternal transmission. The age at onset, the age at diagnosis, and phenotypic expressions were compared in these two groups. The maternally transmitted offsprings showed a significantly earlier age at onset ($t = -2.48$, $df = 132$, $p < 0.014$) [Table X1]. In order to check whether this finding was due to a bias through sampling younger or older people in either of the two groups, Mann Whitney U test was performed on the age at interview. The age distribution was found to be not significantly different (two tailed $p = .3379$) between the two groups. Chi-square analyses (chi-square for heterogeneity) of the different phenotypic definitions and sex of the transmitting parent failed to provide evidence of significant group differences (Table X11). In addition, there were no significant differences between the two groups when age at diagnosis was compared.

5.2. GENETIC TRANSMISSION IN OCD

The details of the affection status of the 20 nuclear families included in the study are detailed in Table X111. Of the 20 probands (male=12; female=8), four (20%) subjects also had tics. A total of 66 FDRs were studied and 13.6% (9/66) relatives were diagnosed as having OCD. One of these individuals also had tics. Segregation analyses were undertaken to evaluate the mode of inheritance. Results are given only for the diagnostic scheme assuming the broad definition of OCD or Tics. The first three schemes did not give any definitive results as the sample was too small. The results are given in Table X1V. All hypotheses were tested using likelihood ratios. A wide range of genetic models were examined. When the maximum population prevalence was set at 0.02, there was no statistical evidence for genetic transmission. However, in the second set of analyses using a population prevalence of 0.01 for OCD, the chi-square for the comparison of the likelihoods between the mixed model and the no transmission model was 8.93 (4 df, $p = 0.063$). Thus, there was suggestive evidence of genetic transmission when the prevalence was set at 0.01. The best likelihood was that of a single gene model, although none of the genetic models were significantly different from one another. The mixed model solution gave parameter estimates almost identical to the mendelian major locus model (d=1; t=2.25; q=0.003; h=0). The mixed model moved

to a boundary with the polygenic heritability (h) being zero, suggesting that for this particular model, the background variance is most likely not genetic.

5.3. CLINICAL PHENOTYPES IN GTS

5.3.i. TICS AND OCB IN GTS

The observed and expected frequency of occurrence of GTS, Tics and OCB in the FDR's of GTS probands calculated using the computer program POINTER is given in Table XV. The results of the goodness of fit test analyses are given in Table XV1. For the GTS diagnosis, the predicted and observed frequencies were not significantly different (chi sq = 12.4; 6 df; $0.05<p<0.10$), suggesting that, when the values are estimated adequately, they predict the observed frequencies correctly. However, when relatives with CMT were also included as affected, the observed rates were significantly different from the expected (chi sq = 20.33; 6 df; $p<0.005$), indicating a poor fit for the data. Similar findings were obtained when family members with TTD were also considered as cases (chi sq = 21.60; 6 df; $p<0.005$). The difference was most marked in the rates for mothers of male probands, where the observed rate was much higher than expected. The rates for fathers showed a slight but similar trend. The estimated values did not correspond with the observed rates in the relatives, when CMT and TTD were considered as part of the GTS diagnosis thus suggesting that, whilst most cases of tic

disorders may form part of the GTS diathesis, not all relatives with tics have a disorder that is genetically related to GTS.

It was interesting to note that the estimated values compared best with the observed values for the GTS/OCB scheme. For this scheme, the chi-square for goodness of fit was not statistically significant (chi -sq = 3.7934; 6 df; $0.990<p<0.9995$); i.e. the expected risk (calculated using the best fitting genetic model parameters) and the observed rates were almost identical, suggesting that OCB is an integral part of the spectrum of expression of GTS. Goodness of fit test for GTS, TICS or OCB again gave statistically significant values (chi sq = 119.465; 6df; $p<0.0005$) indicating that the expected and the observed rates were different. The most likely reason for this is that, some of the cases of tics included in the observed rate were not part of the expression of the underlying genetic diathesis.

5.3.ii. **ADHD AND GTS**

Of the 40 GTS probands, 16 subjects (40%) fulfilled the diagnostic criteria for ADHD (DSM 111R). The male to female ratio of the probands was 3:1. A total of 168 relatives (male= 90; female= 78) were studied and 30 (17.9%) had GTS, 21 (12.5%) CMT and 11 (6.5%) ADHD. When the data was divided into two groups; relatives of GTS+ADHD probands and relatives of GTS-ADHD probands, it was noted that, the occurrence of ADHD was 10.3% in

the former group, as compared to 4.5% in the latter [this did not reach statistical significance], while the occurrence of tics was 32.8% Vs 29.1% between the two groups (Table XV11). Eighty one percent of the GTS+ADHD probands and 70% of the GTS-ADHD probands were males.

Table XV111 gives the frequency of occurrence of individual and combined diagnosis of GTS, CMT and ADHD among all the 168 FDRs and Table X1X gives the frequency separately for GTS+ADHD probands and GTS-ADHD probands. Only three individuals had ADHD without some tic disorder. The probability of ascertainment bias due to the pedigree extension rule was considered as in section 5.1.i, but changing the value of "pi" did not change any of the findings with regard to the frequency estimates.

Furthermore, while the majority of probands diagnosed as having GTS+ADHD, were rated as moderate to severe (mild=12.5%, moderate=56%, severe=31.5%) on the NHIS (based on the impairment of functioning and need for medication) and the Yale Global Tic Severity Scale (Leckman et al 1989; appendix to NHIS), those with GTS-ADHD more often received mild to moderate rating (mild=40%, moderate=31%, severe=29%).

To test whether or not GTS and ADHD were co-segregating within families, the association of GTS and ADHD in the affected

relatives of GTS+ADHD probands was studied. If there is co-segregation, there should be a nonrandom association, different from that predicted. The observed and expected risks of being affected with individual (GTS, CMT, ADHD) and the combined diagnoses (GTS+ADHD and CMT+ADHD) as calculated using the programme POINTER (assuming autosomal dominant transmission as the best fitting genetic model) are given in Table XX. Goodness of fit chi-square test showed that the expected and observed rates were not significantly different (chi-square = 4.28; df = 5) suggesting that the association is not in any way different from that expected by chance alone. Since this is a non-significant finding, the power of the analysis was estimated to be 0.78 (df =5; alpha = 0.38; beta = 0.22).

5.4. SINGLE PHOTON EMISSION TOMOGRAPHY

None of the seven family members who were entirely symptom free (non cases) had abnormalities of their SPET scans. Detailed results are presented in Table XX1, grouped according to the family (A to E). Of the 13 symptomatic subjects, only three had normal SPET scans and nine were abnormal (Chi-square $p<.05$). It was found that the affected family members of GTS probands, irrespective of whether they had GTS, OCD or Tics, showed `hypoperfusion' in different brain areas. One scan in an 8 year old boy with GTS (A4) was obscured by movement artefact. Of the

seven subjects with GTS who had good quality scans, hypoperfusion of the caudate nucleus (on either side or bilaterally) was seen in five, parietal or temporal in five, frontal in one, thalamus in two and brainstem in one. In the three subjects with OCB, several brain areas showed `hypoperfusion' including caudate, frontal, parietal and temporal areas. None of the affected subjects, including those with only OC symptoms, showed `hyperperfusion'. Measurement of state anxiety at the time of injection using the visual analogue scale showed that, although not statistically significant, the `affected' family members scored lower (mean=1.6; sd=1.4) than the `unaffected' family members (mean=3.1; sd=2.2).

5.5. THE PHENOMENOLOGY OF OCB IN GTS AND OCD

There were statistically significant differences between GTS and OCD probands on the OC symptom profile. The details are given in Table XX11 and XX111. Four types of obsessions were significantly different between the two groups. Sexual (Fisher's exact test, P =0.029) and violent (Fisher's exact test, P=0.004) themes were more common in the GTS group and a concern for dirt/germ/ contamination (Fisher's exact test, P =0.009) and fear of something going wrong/becoming ill/or bad happening (Fisher's exact test P =0.001) were more prevalent in the OCD group. A chi-square was calculated to simultaneously compare obsessions where at least 10 individuals had endorsed them over

their lifetime. The result was highly significant (chi-square = 23.53, df = 6; p< 0.00064) suggesting a different profile of symptoms between the two groups. Of the compulsions, five items reached statistical significance. Symmetry/evening up behaviours (Fisher's exact test, P =0.0000009), saying or doing things `just right' (Fisher's exact test, P =0.0002) and forced touching (Fisher's exact test P = 0.0002) were more prevalent in the GTS group, and washing (Fisher's exact test P =0.001) and cleaning (Fisher's exact test P =0.001) predominated in the OCD group. The composite chi-square statistic comparing all compulsive categories endorsed by at least 10 individuals over their lifetime was highly significant (chi-square = 47.00; df = 9; p< 0.000001).

Since GTS is more common in males, and given the possibility that sexual and violent obsessions are more likely to be present in males, the analysis was repeated controlling for gender. Sex of the proband did not account for any of these differences. There was a trend within the GTS group, for females to more often endorse that they had a fear of saying certain things or doing something embarrassing. Likewise, males were more likely to endorse having ordering and arranging compulsions, but neither of the items reached statistical significance.

Next, anxiety and overall obsessional scores were compared between the two groups. The GTS group had significantly lower scores on the Spielberger state anxiety scale (t= -2.97, df=22, p=0.007); and on the LOI trait scale (t= -2.74, df=12, p =0.018), when compared to the OCD sample (Table XX1V). There were no statistically significant differences on the Spielberger trait or the LOI state scales.

Since there was considerable overlap between the two samples for some symptoms, cluster analyses were undertaken to determine whether or not there were different constellations of symptoms that would differentiate between individuals. Cluster analyses were performed using SPSS/PC+. A solution with two clusters gave the best fit to the data. Cluster 1 contained 15 of the 16 GTS probands, and 7 of the 16 OCD probands. The GTS proband who was not in cluster 1 was a 17 year old male with other psychopathology including psychosis. In addition to this GTS proband, nine of the 16 OCD probands formed the second cluster. The symptom profile (note numbering of items as in Appendix 6) of these two clusters is presented in Figure 3. It must be noted that aggressive obsessions (either to self or others) were more prevalent in cluster 1, and obsessions dealing with contamination and the need to know characterised the second cluster. In fact, all the ten members in cluster 2 had obsession about contamination. Compulsions that were more

prevalent in the first cluster included symmetry, doing things `just right' and forced touching, while the second cluster was characterised by washing and cleaning compulsions.

Further analyses were done to determine which of the symptoms were contributing to the inclusion of individual probands into the two separate clusters (Table XXV). The following symptoms were found to be contributing significantly to the GTS cluster; fear of harming self/others, fear of saying certain things or doing something embarrassing, violent/aggressive themes, symmetry/evening up, doing things `just right', forced touching and arranging. Six items were found to be contributing significantly to the OCD cluster. They were: contamination; the need to tell/ask/know; fear of something going wrong; the obsession to be neat and clean; washing and cleaning. The remaining items were not significantly different between the two clusters.

Finally, it was examined whether membership in a cluster was related to familiality of OCD in FDRs of these 16 OCD probands. There were 55 FDRs; 30 males and 25 females. The mean age of the FDRs was 38 (range 6 to 69 years, and there were five members who were below the age of 16 years). The results are presented in Table XXV1. All of the OCD probands in the "GTS" cluster had at least one FDR with OCD, while none of the probands in the

"OCD" cluster had a positive family history of OCD. The rate of OCD among relatives of OCD probands in the "GTS" cluster was 0.42 compared to 0 among the relatives of OCD probands in the "OCD" cluster (Fisher's Exact Test, $p = 0.00009$). Of interest is that there appears to be a gender difference, with female relatives being more likely to be affected than male relatives (Fishers Exact Test, $p = 0.015$).

SECTION 4

DISCUSSION, SUMMARY AND CONCLUSIONS

CHAPTER 6

DISCUSSION

CHAPTER 6

DISCUSSION

6.1. GENETIC TRANSMISSION IN GTS

6.1.i. SEGREGATION ANALYSIS

The study identified 17.9% FDRs with GTS and 12.5% with CMT. Although this is higher than some of the earlier studies (Pauls and Leckman 1986), this is less than more recently reported figures by Devor 1992 (GTS + CMT = 37%) and MacMohan et al 1992 (GTS = 26%). Thus this may be a reflection of the change in trend in the diagnosis of GTS over time. Incorrect diagnosis and the inclusion of false positive cases is another possible reason for this finding. However, this is unlikely since the genetic parameter estimates for the present family data set revealed 0% phenocopies. Yet another point to be remembered is that this may at least be partly contributed by the referral bias in that NHNN, Queen Square is a tertiary centre, and families with more than one affected member are possibly more likely to be referred.

The results of the present study show that GTS is inherited as an autosomal dominant trait with high penetrance. Presence of

sex dependent differences in the underlying liability was also demonstrated. In order to allow comparison with previous studies, data were reanalysed using higher prevalence rates as assumed by Comings et al (1984) and Devor (1984). However, this did not alter the inferences, suggesting that the findings are robust. Even when only relatives identified to have GTS were included in the analysis, the findings were consistent with autosomal dominant transmission.

The sex ratio distribution of affected relatives in this data is different from other published studies (Pauls and Leckman 1986), with more number of females being affected than expected. However, a more recent epidemiological study (Apter et al 1992) has shown a male to female ratio of 1.5 to 1, similar to the present findings. This may be the effect of the inclusion of relatives with OCB as "affected". It is interesting to note that more of the male relatives had Tics or GTS, while OCB was more commonly noted in the female relatives. This suggests that there may be sex dependent differences in the expression of specific symptoms. It may also be that the use of the direct clinical examination method allowed detection of mild cases, and that the difference in the sex ratio noted in this study is accounted for by the inclusion of these mild cases. Thus it emerges that phenomenological studies using personal interview technique addressing different possible expressions in members of families

with GTS are indicated. Sound epidemiological studies are also of crucial importance at this juncture to address some of the issues raised here, particularly that of true estimates of the prevalence of GTS in the general population, sex ratio and sex dependent differences in the expression of the disorder.

The age effect and the low fertility rate noted in this family data set also need consideration. Included in the 49 nuclear units, there were only 168 FDRs, suggesting a low fertility rate. Although not reported before, this issue need to be addressed in future studies, especially since there is evidence for incomplete penetrance. Given the variable age at onset, there is also a need for periodical updating of the pedigree data in order to verify whether the younger subjects remain well or develop symptoms as they grow older. In this regard it should be noted that in the present family data set, there were 34 subjects who were below the age of 16 years.

As evident from Table X, the results from this study predict lower rates for phenocopies than reported in some earlier work (Kidd & Pauls 1982, Comings et al 1984, Price et al 1984). This may be due to the fact that all family members were interviewed personally, thus allowing a more accurate estimate of the underlying genetic model. The data was of such high quality that the findings were consistent over many combinations of pi and

Kp. Furthermore, this study is unique in the use of consecutive probands and families, unlike previous studies that have used multiply affected multigenerational pedigrees. As discussed earlier (chapter 1.5), the ascertainment bias introduced by the use of such families with high genetic loading cannot easily be incorporated into the analysis, and hence the findings may be misleading. More accurate estimates of recurrence risks will result in more accurate estimates of the genetic parameters of the underlying model. In order to fully understand the genetic mechanisms, it is important to use the best available data on genetic parameter estimates in future linkage studies.

6.1.ii. GENOMIC IMPRINTING

The finding that there was an earlier age at onset in maternally transmitted GTS cases when compared to paternally transmitted cases needs further exploration. The age at onset of symptoms in a genetic disorder may reflect changes in gene expression over time. Changes in the degree of methylation of DNA can control gene activation and inactivation, and age dependent changes in gene expression can occur as part of the ageing process (Holliday 1985). It is possible that heritable states such as methylation may also contribute to the variable expression and incomplete penetrance.

If the age at onset of symptoms in GTS is determined by an age dependent methylation of the putative GTS gene(s) or some other chronogenetic mechanism (Holliday 1985), then the effect must stem from early embryogenesis. In the case of adult polycystic kidney, there are families with both paternal and maternal transmission (Gal et al 1989). However, in any one family, the early onset phenotype seems to be consistently transmitted only by a parent of one or the other sex. Since there are some linkage data to suggest that there are two or more linkage groups for dominant polycystic kidney one might predict the association of early onset of disease with maternal imprinting for one group and with paternal imprinting for the other (Gal et al 1989). If a similar mechanism is in operation in GTS, it could be argued that there are more than one linkage groups and more than one locus involved in causing distinct subtypes. This could be considered as one of the reasons, among other explanations, for a failure as yet to establish linkage in GTS. Another plausible explanation of the finding may be that an intrauterine environmental influence may act to produce the early onset of GTS symptoms in those individuals carrying the putative gene(s). It has been shown that such a mechanism is in operation in myotonic dystrophy (Harper and Dyken 1972). Possible candidates for such an influence in GTS include perinatal events, exposure to chronic intermittent psychosocial stress, exposure to thermal stress, exposure to androgenic

steroids and exposure to cocaine or other stimulants (Leckman et al 1992).

In this study there were no between group differences with regard to age at diagnosis or phenotypic expressions. The latter finding is in keeping with the results of a recent study by Furtado and Suchowersky (1994), who failed to find any significant differences in the age at onset or the frequency of occurrence of various GTS related symptoms between maternally and paternally transmitted cases. However, that study was limited because of the small sample size, and the use of retrospective medical chart review method given that the information in the medical charts would be particularly unreliable for the age at onset. In the present study reported here, a more accurate estimate of the age at interview and diagnostic status of the relatives has been achieved by using the direct interview method coupled with the family history data. Although the clinical rater was not blind as to the family history this is unlikely to have influenced the information about the age at onset, which is the main finding in this study.

In a more recent study by Lichter and colleagues (Lichter et al 1995) using family history methodology, it was found that maternal transmission was associated with greater motor tic

complexity and more frequent non-interfering rituals, while paternal transmission was associated with increased vocal tic frequency and more prominent attention deficit hyperactivity behaviours.

It has already been reported that the pedigree of a gene that is imprintable can look like autosomal dominant, autosomal recessive or multifactorial inheritance, depending on which part of the family is being observed (Reik et al 1987). Thus, the findings from this study indicate that there is a need to re-examine family data separately for maternally versus paternally transmitted cases, in order to address the question as to the effect of parental inheritance on differential phenotypic expressions.

6.2. GENETIC TRANSMISSION IN OCD

The results of the present study suggest a major locus mode of transmission in OCD. 13.6% FDRs with OCD were identified. It was interesting to note that in 12 of the 20 families (60%), the proband was the only affected individual, suggesting that, these are probably non familial cases. This is similar to the finding from an independent US sample, where it was noted that about 50% of cases were familial, as indicated by more than one family member being affected (Pauls et al 1995). Because of the small

sample size, it was not possible to analyse the data separately, for those probands with positive family history and those without. Instead, the analyses were repeated using several different population prevalences. In this family data set, a genetic aetiology as evidenced by a positive family history was present in only about 40% of OCD cases, and hence the prevalence rate used in segregation analysis was adjusted accordingly. In this regard it is interesting to note that, in the present analyses when the prevalence rate was cut by half (0.01), in order to account for the fact that only about half of the cases had evidence of familial OCD, there was evidence to suggest genetic transmission. Whilst these results give some estimate of the most likely model of inheritance in this family data set, the results are not necessarily definitive. There is a need to repeat similar analyses in different sets of family data using several population prevalences to determine whether these patterns are robust. Understanding the underlying genetic mechanism of complex disorders such as OCD is an iterative process and this is one of the first steps in the iteration.

Yet another dimension in understanding the genetics of OCD is its relationship to GTS and Tics. Segregation analysis in GTS families has suggested that OCB form an alternative expression of the putative GTS gene(s) (chapter 5.3.i). Earlier studies have also suggested that OCD is probably heterogeneous in

aetiology, with at least two subgroups; those with tics or family history of tics and those without (Green and Pitman 1986). It remains to be seen whether the inheritance pattern of these two groups are similar or different. In addition, phenomenological studies have indicated that the OC symptom profile in GTS subjects is somewhat different to that seen in primary OCD subjects, with violent and sexual themes for obsessions, and concern for symmetry, forced touching and counting compulsions being predominant in GTS subjects (George et al 1992). A similar pattern emerged with regard to obsessions, in an Israeli sample ascertained through primary OCD subjects, when comparisons were made between those who also had tics and those without tics (Zohar et al personal communication). In addition, previous studies have suggested that there may be a sex difference, not only in the frequency of occurrence of GTS but also in the frequency of expression of specific behaviours associated with GTS, in that OC symptoms are more common in the female members of the family, while Tics and GTS are more common in the male relatives (Pauls and Leckman 1986). If this is the case, it could be predicted that the OCD probands with a symptom profile similar to that in GTS, and where there is a family history of tics, will be more often females than males. Thus it emerges that studies using personal interview techniques addressing the phenomenology, and detailing

the symptom profile, are indicated before conclusive inference can be made about the genetic mechanisms in OCD.

Although the number of families in this study was small, direct clinical evaluation of all the family members has allowed a more accurate diagnostic estimate, with less number of phenocopies. However, the findings need to be replicated in a larger sample.

6.3. CLINICAL PHENOTYPES IN GTS

6.3.i. TICS AND OCB IN GTS

Results from this study indicate that, OCB is part of the spectrum of expression of GTS, given that the best fit for the data was obtained when OCB was included as a phenotype. However, within these GTS families, at least some individuals with tics do not seem to have a disorder that is genetically related to GTS and in these circumstances, motor tics (chronic and transient) may be phenocopies. It is well known that, when individuals with a particular diagnosis are being subjected to a closer degree of surveillance, it is a common error to tap a broad range of behaviours with a high probability of the disorder, but whose psychopathology include symptoms of many different types. This has been described as detection/ surveillance bias (Caron and Rutter 1991). However, in order to make this distinction, it is extremely crucial that in genetic studies, direct clinical examination is performed by experienced

and trained personnel. While interviewing subjects for this thesis, and for another study of tic disorders in special education population (Eapen et al 1993), the author has noted some important clinical features that would help clinicians and researchers make this distinction. GTS tics typically vary in anatomical distribution over time, with old tics being replaced by new ones involving different body parts. Thus the pronounced variability in both the presence and nature of the movements and phonations are characteristic of GTS. Their intermittency also distinguishes them from other movement disorders. While non-GTS tics, for example habits, occur at more or less regular frequency, tics in GTS tend to show variable frequency often occurring in bouts intermixed with periods of quiescence. It has also been noted that, in some cases, particularly in children with learning disability, tic like movements were observed which were less frequent in occurrence, they were lower in amplitude and intensity, and hence lacked the distinct `Tourette like' quality. Perhaps these tic like movements represent habits, mannerisms or other physiologic tics. Tics related to GTS on the other hand are voluntarily suppressible, they are suggestible and are exacerbated by stress and anxiety. Furthermore, most GTS subjects experience a premonitory sensation (that the tic is about to occur) which is relieved by the tic. A waxing and waning course with fluctuations in frequency, intensity and distribution are other characteristic features (Jankovic 1992).

A Diagnostic Confidence Index (DCI) is now being developed (Robertson, Pauls, van de Wetering et al in preparation) to help identify with confidence (0 to 100%) GTS cases for use in genetic studies. In the DCI, the tics of GTS are characterised by suppressibility, rebound after suppression, premonitory sensations and a waxing and waning course. In future genetic studies, it is suggested that an instrument such as the DCI be used for a more tight definition of GTS cases.

Several groups of researchers have undertaken a search for the genome in a systematic way using highly polymorphic markers that have been mapped, and as much as 66% of the genome has been excluded (Pakstis et al 1991). At the present time, over 600 autosomal markers have been tested in an attempt to map the gene, and no definite linkage has been obtained (Pauls and van de Wetering 1995). However, the failure to obtain linkage may be a reflection of incorrect definition of the phenotypes. It has been shown that a slight change in the genetic model factors can cause large fluctuations in the linkage studies. Thus, in order to facilitate linkage studies, it is crucial to use the most accurate genetic parameter estimates and population prevalences. Future research should attempt to refine the diagnosis of cases, and the findings from this study suggest that it is extremely crucial to differentiate between relatives with tics that form

6.3.ii. ADHD and GTS

The results of this study indicate that the rate of occurrence of ADHD is increased in GTS probands (40%), which is in keeping with the earlier studies (Comings and Comings 1990; Bornstein et al 1990). However, only 6.5% of the FDRs qualified for a diagnosis of ADHD. Since there were no control subjects in this study, it is difficult to compare this rate with the available general population prevalence, estimated to be between 3% and 10% (Shaywitz et al 1983).

Although the male to female ratio of the total sample of probands was 3:1, there were proportionately more males in the GTS+ADHD group, as expected. Between group comparisons showed a much higher occurrence of ADHD among relatives of GTS+ADHD probands. There are different ways of explaining this finding. 1) the two disorders are not genetically related 2) GTS+ADHD represent a distinct genetic subtype and that they co-segregate within families. However, the findings from the goodness of fit test suggest that the two disorders appear to segregate independently. 3) It is possible that GTS+ADHD is a clinically separate group representing a more severe form of the disorder with more extensive involvement of neurochemicals and neuroanatomical structures and thus perhaps more at risk of

exhibiting ADHD symptoms. The finding that the GTS+ADHD subjects had a more severe form of the disorder tends to support this view. Age and sex may be other modifying factors. Very few of the probands in the GTS+ADHD group were females, to allow any meaningful comparison between groups, based on the sex of the proband. If there is indeed an association between age of onset, sex and severity, this may further compound to the referral bias in clinic samples.

The finding that only three relatives had ADHD in the absence of tics, is interesting. If ADHD was an alternative expression of the same gene, one would expect more relatives to have ADHD, in the absence of any tics. However, it may well be that ADHD is one aspect of the GTS phenotype, mediated by an overlap in the intermediate or final pathways of expression, rather than an alternative phenotypic expression. The overlap could be at a biochemical (common neurotransmitter involvement, such as dopamine and norepinephrine) or neuroanatomical level with basal ganglia and frontal lobe being implicated in both the disorders. It is interesting to note that in PET studies, reduced cerebral glucose metabolic rates have been found in these regions in both GTS and ADHD. GTS appears to involve metabolic changes in the orbito frontal cortices and basal ganglia (Stoetter et al 1992), and in ADHD, changes in the superior sensorimotor structures centred in the premotor cortices and basal ganglia have been

reported (Zametkin et al 1990). Furthermore, in a study of the event related auditory evoked potential in GTS subjects, it was found that, although there were no abnormalities in the early and late components, the components in the range 90-280 ms were affected, probably reflecting attention deficits in these subjects (van de Wetering et al 1985).

The overlap may also be at a symptom level, with ADHD symptoms forming part of GTS, or a secondary manifestation. Thus, ADHD may predate the onset of GTS and represent a precursor phenomenon in a developmental context, or indeed be secondary to GTS symptoms. For example, children with GTS, because of their involuntary movements, may appear fidgety and overactive. In addition, if they try to suppress their tics, they may experience mounting inner tension and this in turn may affect their ability to attend to and concentrate in tasks. Thus, it seems that ADHD occurring in the context of GTS may be the result of different mechanisms, varying from being a clinical aspect of GTS itself; secondary to the GTS symptoms; a behaviour that form a final common pathway for a variety of conditions where frontal lobe and basal ganglia are involved, of which GTS is one; or a co-morbid condition exaggerated by referral and ascertainment bias. This may also be the result of Berkson (1946) effect by which, for statistical reasons separate from referral biases, the co-morbidity rate in clinic samples will

always be greater than that in the general population whenever only a small proportion of the conditions making up the co-morbidity pattern are referred to the clinics. Other explanations include shared and overlapping risk factors and diagnostic considerations.

Previous studies have suggested that the two disorders may share the same underlying genetic mechanism and that ADHD may represent a different manifestation of the GTS diathesis (Comings and Comings 1984; Knell and Comings 1993). However, others have refuted such an association (Pauls et al 1986; 1988; 1993) using data obtained from direct clinical examination of family members. Family data can be useful in delineating which behaviours appear to be part of the broad spectrum of a given disorder, and this can be done by showing how the inclusion or exclusion of relatives with specific diagnoses yields different goodness of fit patterns consistent with a genetic hypothesis (Egeland et al 1990). To do this requires a careful detailed recording of all possible clinical manifestations of illness within the family members using direct interview method, and following this up with goodness of fit test to study the co-segregation patterns. Although this strategy was followed in the present study, one major limitation is the fact that the information was collected retrospectively for the adult cases, and no corroborative account has been obtained; for example a

school report. However, attempts have been made to achieve as accurate a diagnosis as possible by direct interview with the parent (face to face in majority of the cases, and for the minority where this was not feasible, this was done by a telephone interview). In addition, the family psychiatric interview method allows gathering of information about each subject, independently from all the FDRs. All these information together with the findings from clinical examination were taken into consideration for the best estimate method of diagnosis.

The failure to detect co-segregation in the present study will have to be interpreted cautiously given the small sample size. However, since the findings were not significant, the power of the analysis was estimated to be high at 0.78 (DF =5; Alpha=0.33; Beta=0.22). Other limitations of the study include not having a control group to allow calculation of the base rates of ADHD, and to compare the rate of GTS in the FDRs. Furthermore, the interviewer was not blind as to the GTS diagnosis of the proband. However, this is unlikely to have biased the findings of this study as the main focus was the difference in the rates between relatives of GTS+ADHD and GTS-ADHD probands, and although not blind as to the GTS status of the proband, the author was not aware at the time of interviewing the family members, whether or not the proband also

had a diagnosis of ADHD (diagnostic estimates and consensus diagnoses were made after the completion of all the interviews).

Further studies are indicated with a larger sample size using normal controls and ADHD probands as controls, and taking into account some of the relevant patient characteristics such as the age at onset of Tics and ADHD, sex of the proband, and severity of the disorder.

6.4. SINGLE PHOTON EMISSION PHOTOGRAPHY

The SPET findings of a variable pattern of 'hypoperfusion' involving frontal, striatal, and temporal areas in patients with GTS which has been reported by other investigators (Hall et al 1990; 1991, Riddle et al 1992; Dimitsopulos et al 1993) is confirmed by this study. It was interesting to note that unaffected family members had normal scans. Normal scans in clinically symptomatic subjects were seen in both patients with tics alone and in one subject with OCB and tics. The scan of the subject with tics and OCB was suboptimal and it cannot be unequivocally described as normal. Thus it seems that, whatever the perfusion abnormalities seen in patients with GTS, they are not a reflection of the tics per se. On the other hand, they may be related to severity (this was not formally rated as part of this study), or reflect the complexity of the affective,

cognitive, and motor abnormalities which may be present in patients with GTS. In the affected family members, whenever there was a perfusion abnormality, this was in the form of `hypoperfusion'. None of the affected subjects, including those with only OC symptoms, showed `hyperperfusion', which is in contrast to the available perfusion findings indicating `hyperperfusion' in primary OCD subjects (Baxter et al 1987; Swedo et al 1989; Rubin et al 1992). It is possible that these subjects with OCB had clinically less severe symptomatology than those reported elsewhere in the literature. While this would possibly account for the failure to find frontal hyperperfusion described in patients with OCD, it cannot account for the finding of abnormal 'hypoperfusion'. Further studies of patients with OCB matched for severity, with and without family histories of tic disorders would clarify this issue.

In the efforts to control for anxiety, it was observed that the GTS patients, including those with OC symptoms, scored lower than normal controls on the visual analogue anxiety scale. Although the difference was not statistically significant, it may point to an important clinical difference between patients with GTS (including GTS spectrum OCB) and primary OCD patients which can be ignored in a literature bent on emphasising similarity. This is that patients with GTS, unlike those with OCD, are not distressed by many of their ruminations. Nor are

they plagued with obsessional's fear of acting out their ritualistic ideas. Indeed, it is arguable that in some ways patients with GTS are at the opposite pole to those with OCD in that, for example, their scatological ideas are not resisted and are not associated with marked anxiety, but are vented, any resultant anxiety being associated with the embarrassment caused rather than the dislike of the thoughts themselves.

There is some research evidence to support the above notion. Various imaging studies have implicated three areas in the pathophysiologic origin of OCD symptoms; the orbitofrontal cortex, cingulate cortex and head of the caudate nucleus. It has been postulated that these regions form a circuit that is `hyperactive' in OCD, and that the increased orbitofrontal metabolic activity in patients with OCD might be a measure of the resistance or effort expended to control intrusive thoughts (Insel 1992). Consistent with this hypothesis are the findings of Laplane et al (1989) who described cases of necrosis of globus pallidus associated with obsessional symptoms but with low levels of anxiety and resistance, and the findings from the present study that GTS subjects including those with GTS+OCB have low levels of anxiety. This reflects a fundamental difference between GTS and OCD subjects and it may be that the OC symptoms associated with low levels of anxiety and resistance as occurs in GTS, are linked to `hypoperfusion'. In a similar

vein, it could be postulated that primary OCD will be associated with `hyperperfusion,' where obsessions and compulsions are associated with considerable levels of underlying anxiety, such as the fear of contamination/germ/dirt and fear of something going wrong, and the compulsions to counteract these fears, for example washing and cleaning. Further evidence for the validity of this distinction comes from the study of OCD by Swedo et al (1992), who found a trend towards a positive correlation between improvement in global anxiety in response to treatment with SSRI, and a reduction in right orbitofrontal metabolism in OCD subjects. Thus, it may be that the differences in the perfusion findings are linked to the differences in the anxiety levels of these individuals, which, in turn, may be related to the differences between GTS and primary OCD subjects in the OC symptom profile and the content of the obsessions and compulsions.

Furthermore, it has been shown that individuals likely to develop Huntington's disease, who have low cerebral metabolic rate in the caudate nucleus/ipsilateral hemisphere (Cd/hem), had increased expressions of `anger and hostility' when compared to siblings with normal Cd/hem values who were less likely to develop the disorder (Baxter et al 1992). It has been postulated (Baxter et al 1990) that this may be the result of abnormalities in the basal ganglia function `gating', by which certain motor,

sensory and cognitive impulses are either allowed to proceed through to perception and behaviour, or are held back (`filtered') and dissipated. It is possible that such a mechanism is defective in GTS with the consequent disruption of gating functions resulting in a "leaking through" of sensations, thoughts, impulses and fixed action patterns. Thus, any given patient can have combinations of cognitive and motor symptoms in varying degrees, depending on which region of the striatum are defective and the severity of the pathology. Swedo et al (1989) reported an association between OCD and Sydenham's chorea, which affects the striatum in a variable and patchy fashion, thus supporting the above theory. This also suggests that, although patients with dysfunction in only one area could give the appearance of mutually exclusive subgroups of clinical symptoms, most can have varying combinations of tics, obsessions or compulsions. Thus it is possible that a certain pattern of neuroanatomical involvement is more likely to result in a specific symptom profile rather than any particular symptom types.

McDougle et al (1994) performed a double blind placebo controlled trial of haloperidol as add-on therapy for patients with OCD refractory to treatment with fluvoxamine. Treatment was of benefit in patients who had a co-morbid tic disorder. However, this study did not distinguish patients without a

comorbid diagnosis of tic disorder but with a family history of a tic disorder from those without a family history. If the relevant distinction were between those with a genetic predisposition towards tic disorders (including GTS spectrum OCB), and those with no family history of tic disorders, this would be consistent with the present finding of regional cerebral 'hypoperfusion' in the OCB subjects with a family history of tic disorders (GTS spectrum OCB) in contrast to the usual finding of 'hyperperfusion' in patients with OCD described in the literature.

6.5. The phenomenology of OCB in GTS and OCD

The phenomenological differences seen between OCD probands with and without a positive family history supports the hypothesis that genetic heterogeneity is associated with clinical heterogeneity, and deserve further exploration. It was found that the OCD probands with a family history shared a similar symptom profile to that of GTS probands. The rate of OCD among the relatives of these OCD probands in the "GTS" cluster was noted to be significantly more than that in the "OCD" cluster. These findings tend to suggest a common aetiology and pathogenesis for GTS and familial OCD, while suggesting that alternative mechanisms may be in operation for non-familial OCD. Furthermore, there was a gender difference, with female

relatives being more commonly affected with OC symptoms than male relatives. It will be important to replicate this finding in another independent sample of OCD families.

In the present study, GTS subjects were found to be having less levels of anxiety on the Speilberger state anxiety score and low scores on the Leyton obsessional trait score. It could be postulated that OC symptoms associated with low levels of anxiety are seen in GTS, while in OCD, specific types of obsessions associated with considerable levels of underlying anxiety, (e.g.: fear of germ/dirt/contamination or fear of something going wrong) and the compulsions to counter these fears (e.g.: washing and cleaning) are more commonly seen.

Thus, it seems that there are some qualitative differences in the OC symptom profile in the two disorders, perhaps pointing to a differential biochemical involvement; i.e. dopamine in GTS spectrum OC symptoms, and serotonin in OCD. For example, in GTS, where the primary abnormality is believed to be in the dopamine pathways, the OC symptoms are less goal directed and more stereotypic (e.g. evening up and forced touching), unlike the more goal directed and purposeful activities seen in OCD (e.g. washing and cleaning). Shapiro and Shapiro (1992) have described the former behaviours as `impulsions' and `self- echokinesis'. This is in keeping with the observation of stereotypic

behaviours seen in response to dopamine agonists, such as amphetamine.

Further support for the hypothesis that the differences in the OC symptom profile seen in GTS and OCD may be determined by a differential biochemical involvement comes from treatment studies. Mc Dougle et al (1990) in a study of treatment resistant OCD patients, found that comorbid tic spectrum disorders were associated with a positive response to the addition of neuroleptic to an SSRI drug. George et al (1993) also reported synergistic effect with a combination of neuroleptic and an SSRI in the treatment of GTS patients with OC symptoms, while the SSRI by itself caused worsening of GTS symptoms and the neuroleptic alone was not effective in controlling the OC symptoms.

The combination of somatosensory urges and fragmentary motor behaviours seen in GTS is consistent with the involvement of the cortico-striato-thalamo-cortical circuits that channel and subchannel information involved in the anticipation and performance of OCB in GTS (Leckman et al 1992). The neuroanatomical hypothesis that the basal ganglia and related orbitofrontal connections are involved in GTS (Chappel et al 1990) and that these circuits subserve the OC symptoms seen in GTS is compatible with the hypothesis that the dopaminergic

system may play a role in the pathophysiology of at least the GTS spectrum OCB. The site and extent of involvement of these structures and its connections, as well as other modifying factors such as age, sex and the developmental stage of the individual concerned, may determine the clinical presentation and the symptom profile.

Thus the available pharmacological data from the literature, together with the phenomenological and neuroimaging data from the present study, suggest that there may be aetiologically distinct subgroups within the OCD population. However, these findings need to be replicated in a larger sample. Further research is needed to establish whether such symptom clusters `breed true' in families, that is whether or not, other affected family members will have a similar symptom profile to that of the proband. Such differentiation, if present, will help to categorise OCD subjects into more homogeneous subgroups (e.g. familial and non familial). This will undoubtedly further the understanding of the aetiology, genetics and pathogenesis of OCD. In addition, this will also help to clarify the clinical phenotypes of the putative GTS gene(s).

CHAPTER 7

SUMMARY OF MAIN FINDINGS AND IMPLICATIONS FOR FUTURE RESEARCH

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7.1. SUMMARY OF MAIN FINDINGS

Based on the findings from this study, the following answers, to the questions addressed (as outlined in the introduction), are felt justified.

1. Whether or not GTS and primary OCD have a genetic aetiology and whether the patterns within families of subjects with primary GTS and primary OCD are consistent with any specific models of genetic transmission?

a) The results from this study are consistent with a hypothesis that posits the existence of an autosomal dominant gene with high penetrance in GTS.

b) There is tentative evidence to suggest a major locus mode of transmission in OCD.

2. Whether there are differences in the phenotypic expression, age at onset and age at diagnosis of GTS based on the sex of the transmitting parent?

a) The maternally transmitted cases had a significantly earlier age at onset when compared to paternally transmitted cases.

b) There were no differences between maternally versus paternally transmitted cases for age at diagnosis or phenotypic expressions.

3. Whether Tics, OCB and ADHD are genetically related to GTS, thereby forming alternative phenotypic expressions of the GTS diathesis?

a) The findings from this study suggest that Tics are aetiologically heterogeneous and that all cases of motor tics are not necessarily due to the same genetic mechanism and that at least some cases are phenocopies.

b) The findings provide strong support for the hypothesis that in these GTS families, OCB is genetically related and form an integral part of the spectrum of expression.

c) The frequency of occurrence of ADHD was increased in GTS probands and it appears that ADHD is an important clinical aspect of GTS in some cases. However, there was no evidence to suggest that ADHD is an alternative phenotypic expression of GTS, as the two disorders were found to segregate independently.

4. Whether there are perfusion patterns specific to GTS and whether there are distinctions based on the clinical expressions such as GTS, Tics and OCB?

a) The affected family members of GTS probands showed `hypoperfusion' in different brain areas.

b) The present SPET methodology cannot distinguish between different symptomatic subgroups such as GTS, Tics and OCB. However, OCB patients from families affected by tic disorders (GTS spectrum OCB) seem to differ from primary OCD patients in that the former is characterised by reduced cerebral perfusion.

5. Whether the phenomenology of OCB occurring in the context of GTS are similar or different to that in primary OCD?

a) Significant differences were noted in the OC symptom profile between GTS and OCD subjects.

b) The familial OCD subjects shared a similar OC symptom profile to that of GTS subjects. In these families, female relatives were more commonly affected with OC symptoms than male relatives

7.2. CONCLUSIONS AND IMPLICATIONS FOR FUTURE RESEARCH

Review of the literature suggests that the aetiology and pathogenesis of GTS remain unclear, more than a century after its original description. During this time, the aetiological gamut has shifted from an hereditary disorder to a psychological malady and back again. Today, even though details of the exact genetic mechanism are being debated, the hypothesis that the disorder is hereditary, is unquestioned.

Findings from this study support an autosomal dominant mode of transmission, with high but incomplete penetrance. The earlier age at onset found in maternally transmitted cases offers a new dimension for further investigations, as it suggests a new level of control in the nature and expression of the putative GTS gene(s). At present however, only a small percentage of families seem to manifest this differential effect suggesting that, if these are imprinting effects, they do not occur in all families or between all chromosome parts. Nevertheless, the trend towards differential expression of a phenotype when inherited primarily from the parent of one sex or the other, poses a new challenge and raises the possibility of imprinting as one of the modifying factors in the genesis and expression of GTS.

With regard to the phenotypic expressions of the putative GTS gene(s), there is evidence to suggest that OCB is indeed an integral part. However, it seems that, not all cases of Tics in these families of GTS probands are related to GTS. Thus it appears that whilst OCB is indeed a clinical phenotype, at least some cases of tics are phenocopies. Determining the range of expression of GTS is critical for linkage studies. If there are individuals with tics that are not genetically related to GTS in these families, including them in the linkage analysis will result in reduced power and the possibility of missing a linkage relationship. The finding from the present study that not all tics are genetically related to GTS, and the author's observation about some of the characteristic features of GTS tics as opposed to non-GTS tics, emphasise the need for direct clinical examination by experienced and trained personnel. Researchers should be aware of the difficulties in the diagnostic process, and exercise rigor in procedural methods that would take into account these issues. For example, the uncertainty about which illnesses belong to the genetic diathesis emphasises the need to obtain full diagnostic histories on all relatives, and the use of different diagnostic hierarchies in the analyses. Furthermore, attempts should be made to identify an independent finding that co-segregates with the relevant phenotypic expressions.

Findings from the SPET study are promising and need replication. The observation of `hypoperfusion' in the different brain areas despite the varying clinical manifestations of GTS (eg.Tics, GTS and OCB) does not yield readily to simplistic explanations as to their pathogenesis. Based on the SPET findings from this thesis and that from the available literature, it could be hypothesised that the 'hyperperfusion' noted in OCD probands is perhaps linked to the anxiety and resistance component, and that OCB patients from families affected by tic disorders differ from the former group in being less anxious, and being characterised by reduced cerebral perfusion. Present SPET methodology however cannot distinguish between different phenotypes within GTS (i.e.: GTS, Tics, OCB).

It is possible that tics occur as a result of disturbances in the basal ganglia and this may include causes other than GTS, thus accounting for some phenocopies. It could be argued that the same is true for OCB; that is, not all individuals with OC symptoms in these families have a disorder that is genetically related to GTS. It would therefore be prudent to assume that all cases of tics, or indeed OCB, are phenotypes of GTS. The phenomenological differences noted in this study between GTS and OCD probands tend to indicate clinical as well as genetic heterogeneity.

Questions also remain, as to whether the OC symptoms seen in GTS probands and OCD probands `breed true' in families, and whether the apparent sex differences seen in GTS families are also present in OCD families. For a better understanding of the relationship between GTS and OCD, thorough epidemiological studies are needed, particularly addressing issues such as the true estimate of GTS and OCD in the general population, sex ratio and sex dependent differences in the expression of the disorders. Furthermore, the evidence found in this study for single major gene transmission in OCD needs replication using a larger sample.

An abnormality in the function of dopamine in the substantia nigra or receptors in the striatum, even if limited to a small region, is likely to affect wide areas of the cortico striatal loops. In this way, specific areas of the basal ganglia can modulate and integrate both limbic and frontal motor circuits. As already noted, there are genetic and environmental factors that exert an influence on this neurodevelopmental process, of which age and sex, as well as imprinting effects are most crucial. Thus, the site and extent of involvement of these structures and its connections, as well as the developmental stage of the individual concerned, will in turn, determine the age at onset and clinical presentation. Other aspects of the

circuitry of the basal ganglia may be responsible for the variation in the anatomic distribution of motor tics and the choice of themes/content of GTS symptoms including that of involuntary vocalisations, coprolalia and OCB. Available evidence has highlighted the role of basal ganglia and multiple parallel fronto-striato-pallido-thalamo-frontal circuits that concurrently subserve a wide variety of motor, sensory, cognitive or emotive processes. It may well be that, in mild cases, there is a limited involvement of some of these circuits, and, as the disorder develops into its fullest form, more and more areas in the frontal lobe, basal ganglia and its connections become involved, resulting in several associated symptoms and behaviours. This notion is supported by the finding that majority of the GTS+ADHD probands had a moderate to severe form of the disorder when compared with GTS-ADHD probands who more often received a mild to moderate rating on severity. It is also possible that, in some cases, there is more involvement of the basal ganglia regions, resulting in a clinical presentation where tics are predominant while in some others, the fronto limbic regions are more affected leading to a predominance of other symptoms such as impulsivity, aggressivity, attentional impairment, coprophenomena etc. In some severe cases, all these regions may be affected, resulting in a multiplicity of symptoms, all of which are of severe degree.

The finding that familial OCD probands shared a similar OC symptom profile to that of GTS probands suggest that, within OCD cases, there are aetiologically distinct subgroups. If this finding is replicated in a larger sample, this would urge the inclusion of those relatives with such a symptom profile in the linkage analysis. Thus, in family studies and linkage analysis, those family members with OCB (with or without tics), and having the symptom profile noted in this study as characteristic of GTS could be considered as phenotypes, and the others as phenocopies. The findings from this thesis also suggest that the diagnostic confidence of these subjects being phenotypes would be further increased if they also show cerebral 'hypoperfusion' on SPET. Furthermore, the differences in the OC symptom profile between GTS and primary OCD probands emphasise genetic heterogeneity of OC symptoms. The answer to questions such as how many genes are involved and what percentage of them are related to GTS, will have to await the development of a genetic marker for the putative GTS gene(s).

Future research should therefore focus on establishing a linkage relationship between a genetic marker and the hypothetical gene for the disorder. Given that even slight changes in the genetic model factors can cause large fluctuations in the results, it is crucial to have highly accurate estimates of the genetic model factors to be incorporated into analysis of linkage. At the

start of the linkage study, rules for deriving consensus diagnoses should be established at two levels; using the research diagnostic criteria, and at a clinical level. Rules should also be derived for the different diagnostic hierarchies to be used in the analyses. It is hoped that the use of various levels of diagnostic certainty and a variety of diagnostic hierarchies, will ultimately lead to an improved definition of what constitutes the genetic spectrum for GTS. In addition, variable age at onset of the illness and incomplete penetrance of the gene requires a rigorous effort to follow subjects longitudinally. Methods for continuous updating of the pedigrees should be developed before investing in the DNA phase of the study, because of the need to establish whether or not unaffected persons included in the DNA study remain well or become ill later.

Whilst molecular genetics offers a promising method for exploring the underlying aetiologic heterogeneity of GTS and related behaviours, the findings from the present study emphasise the need to make further progress in refinements at the diagnostic level. The debate about clinical phenotypes will continue, until such time a genetic marker is found and the gene is identified.

Table 1: Age & Sex distribution of the GTS probands

GTS PROBANDS	*0 to 5 years*	*6 to 10 years*	*11 to 15 years*	*≥16 years*
Male (N=29)	0	5	11	13
Female (N=11)	1	2	2	6
Total (N=40)	1	7	13	19

Table 11: Age & Sex distribution of the GTS family members

FDR'S	*0 to 5 years*	*6 to 10 years*	*11 to 15 years*	*≥16 years*
Male (N=90)	1	13	10	66
Female (N=78)	0	4	6	68
Total (N=168)	1	17	16	134

Table 111: Diagnostic status of GTS family members

FDRs	GTS only	GTS/CMT	GTS/TICS	GTS/OCB	TICS/OCB
Affected fathers	10/48	14/48	14/48	11/48	15/48
Affected mothers	9/49	15/49	15/49	11/49	17/49
Affected brothers and sons	9/42	18/42	20/42	11/42	22/42
Affected sisters and daughters	2/29	4/29	5/29	7/29	10/29
TOTAL	30/168	51/168	54/168	40/168	64/168

Table 1V: Diagnostic schemes as used in the segregation analyses of GTS family data

Scheme	Diagnosis
1	Gilles de la Tourette syndrome only (GTS)
11	GTS or Chronic multiple tics (CMT)
111	GTS, CMT or Transient tic disorder (TTD)
1V	GTS or Obsessive Compulsive behaviours (OCB)
V	GTS, CMT, TTD or OCB

Table V: Age liability classes as defined for POINTER (GTS family data)

Age range (years) for diagnostic schemes 1 to 111	Age range (years) for diagnostic schemes 1V & V
0 - 5	0 - 15
6 - 10	16 - 25
11 - 15	26 - 35
15 +	35 +

Table V1: Age liability classes as defined for POINTER (OCD family data)

		Age range (years)	Population prevalence Wide	Narrow
Class	1	0 - 10	0.006	0.003
	11	11 - 20	0.008	0.004
	111	21 - 35	0.01	0.005
	1V	35 +	0.02	0.01

Table V11: Recurrence rate of GTS, CMT and/or OCB among FDRs of GTS probands

Sex of Relative	Diagnosis									
	GTS		GTS/CMT		GTS/TICS		GTS/OCB		GTS/TICS/OCB	
	N	%	N	%	N	%	N	%	N	%
Male N=90	19	21.1	32	35.6	34	37.8	22	24.4	37	41.1
Female N=78	11	14.1	19	24.4	20	25.6	18	23.1	27	35.9
Total N=168	30	17.9	51	30.4	54	32.1	40	23.8	64	38.1

Table V111: Genetic model estimates on segregation analyses of GTS families (GTS only scheme)

Model	d	t	q	h	-2ln(L)
Polygenic	0	0	0	0.995	-197.213
Aut.Recessive	0	6.987	0.0229	0	-178.214
Additive model	0.5	10.732	0.0002	0	-221.208
Aut.Dominant	1.0	5.365	0.0002	0	-221.308
No transmission	0	0	0	0	-8.363
Mendelian	0.9	5.294	0.0002	0	-221.203
Mixed model	1.0	5.364	0.0002	0.000	-221.724

Table 1X: Summary of Complex segregation analyses on 49 nuclear GTS families

Model	Diagnostic scheme			
	GTS	GTS/TICS	GTS/OCB	GTS/TICS/OCB
No transmission	Rejected***	Rejected***	Rejected***	Rejected***
Polygenic	Rejected**	Rejected*	Rejected***	Rejected**
Mendelian	Consistent$	Consistent$	Consistent$	Consistent$
Aut.Dominant	Consistent$	Consistent$	Consistent$	consistent$
Additive	Consistent$	Rejected*	Consistent$	Consistent$
Aut.Recessive	Rejected**	Rejected*	Rejected***	Rejected**

*Rejected at $p<0.05$, **Rejected at $p<0.010$

***Rejected at $p<0.001$, $ Cannot be rejected at $p<0.05$

Table X: Genetic model estimates for male and female subjects according to the diagnostic schemes

Sex	Prevalence (Kpm/Kpf)	p2	p1	p0	q
GTS only					
Male	0.0005	0.9658	0.9658	0.0000	
					0.0002
Female	0.00015	0.4518	0.4518	0.0000	
GTS/CMT					
Male	0.0029	0.9996	0.9996	0.0001	
					0.0009
Female	0.0010	0.5540	0.5540	0.0000	
GTS/TICS					
Male	0.0030	1.0000	1.0000	0.0001	
					0.0009
Female	0.0010	0.5816	0.5816	0.0000	
GTS/OCB					
Male	0.0030	0.8818	0.8818	0.0020	
					0.0009
Female	0.0010	0.8818	0.8818	0.0020	
GTS/TICS/OCB					
Male	0.0250	0.9806	0.9806	0.0210	
					0.0021
Female	0.0250	0.9806	0.9806	0.0210	

p2, p1 and p0 denote the penetrance for genotype with two susceptibility alleles (aa), one susceptibility allele (Aa) and no susceptibility allele (AA) respectively and q the frequency of the susceptibility allele `a'.

Table X1: Comparison of age at onset in offsprings of affected males and offsprings of affected females

	Offsprings of affected males	offsprings of affected females	t	df	p
	N = 61	N = 73			
age at onset:	mean = 8.50	mean =7.04	-2.48	132	0.014
	s.d = 3.79	s.d = 3.05			

Table X11: Rate of occurrence of GTS, CMT and OCB in offsprings of transmitting males and females

	GTS		CMT		OCB	
	N	(%)	N	(%)	N	(%)
Paternal transmission	50/77	(50%)	70/77	(90.9%)	26/77	(33.6%)
Maternal transmission	60/80	(75%)	77/80	(96.2%)	29/80	(36.2%)
p with 1 df	0.168		0.172		0.744	

Table X111: Recurrence rate of OCD and or tics among FDRs of OCD probands

	N	%
Fathers affected	2/20	10
Mothers affected	5/19	26.3
Siblings affected	2/24	8.3
Children affected	0/3	0
Total affected	9/66	14.3

Table X1V: Genetic model estimates on segregation analyses of OCD families

Model	d	t	q	h	likelihood ratio [-2LN(L)]
No transmission	0.000	0.000	0.000	0.000	124.488
Polygenic model	0.000	0.000	0.000	8.254	132.895
Mendelian model	1.000	2.203	0.003	0.050	133.386
Mixed model	1.000	2.250	0.003	0.000	133.419

Table XV: Observed (O) and expected (E) rates of GTS, Tics and OCB in the first degree relatives of GTS probands*

	GTS		GTS/CMT		GTS/TICS		GTS/OCB		GTS/TICS/OCB	
	O	E	O	E	O	E	O	E	O	E
Affected fathers										
Male proband	6	9	10	8	10	10				
							11	12	15	4
Female proband	4	5	4	5	4	5				
Affected mothers										
Male proband	8	4	13	4	13	4				
							11	6	17	4
Female proband	1	2	2	3	2	3				
Affected brothers										
Male proband	7	8	11	8	12	8				
							8	9	13	3
Female proband	0	1	1	1	1	1				
Affected sisters										
Male proband	0	2	2	3	3	3				
							4	4	6	2
Female proband	1	1	1	1	1	1				

* Rates were calculated separately for relatives of male and female probands for the first three diagnostic schemes while same sex ratio was assumed and combined rates were calculated for the latter two diagnostic schemes.

Table XV1: Results of goodness of fit test analyses in GTS families

Diagnostic scheme	chi square with 6df	p
GTS only	12.40	0.05<p<0.10
GTS/CMT	20.33	p<0.005
GTS/CMT/TTD	21.00	p<0.005
GTS/OCB	3.79	0.990<p<0.9995
GTS/TICS/OCB	119.469	p<0.0005

Table XV11: Rates of Tics and ADHD among FDRs of GTS probands

	Tics		ADHD	
	N	(%)	N	(%)
Relatives of GTS+ADHD probands (n=58)	19	(32.8)	6	(10.3)
Relatives of GTS-ADHD probands (n=110)	32	(29.1)	5	(4.5)
Total (n=168)	51	(30.6)	11	(6.5)

Table XV111: Frequency of GTS, CMT and ADHD among FDRs of GTS probands

Diagnosis	No:	Frequency (Observed)
GTS ONLY	23	23/168 (0.137)
CMT ONLY	20	20/168 (0.119)
ADHD ONLY	3	3/168 (0.012)
GTS + ADHD	7	7/168 (0.041)
CMT + ADHD	1	1/168 (0.006)

Table X1X: Frequency of GTS, CMT and ADHD among relatives of GTS+ADHD and GTS-ADHD probands

Diagnosis	Relatives of GTS+ADHD probands	Relatives of GTS-ADHD probands
GTS	13/58 (0.224)	17/110 (0.154)
CMT	6/58 (0.103)	15/110 (0.136)
ADHD	6/58 (0.103)	5/110 (0.045)

Table XX: Expected and observed rates of GTS, CMT and ADHD in FDRs of GTS+ADHD probands

Diagnosis	Expected risk	Observed rate
GTS only	6.02	9
CMT only	4.20	6
ADHD only	2.18	2
GTS+ADHD	2.38	4
CMT+ADHD	0.32	0
None	42.89	37

(chi-square = 4.28; df=5)

Table XX1: Perfusion findings in GTS probands and their FDRs

(Families are numbered A to E)

SUBJECT	AGE & SEX	DIAGNOSIS	ANXIETY RATING	SCAN FINDINGS:
A1	43 M	OCD	1	↓B PAR, ↓L FR, ↓R TMP
A2.	39 F	TICS	1	NORMAL
A3	6 F	NIL	2	NORMAL
A4	8 M	GTS	5	OBSCURED BY ARTEFACT
B1	11 M	OCD	1	↓B PAR
B2	15 M	GTS	3	↓B PAR ↓R CN
B3	47 F	NIL	2	NORMAL
B4	57 M	GTS	1	↓B PAR ↓B FR ↓B THA ↓L TMP ↓BS
C1	49 F	NIL	2	NORMAL
C2	15 M	GTS	3	NORMAL
C3	13 F	NIL	5	NORMAL
C4	55 M	GTS	2	↓B PAR ↓B TMP ↓B CN
D1	10 M	GTS	2	↓B CN
D2	43 F	OCD	0	↓B CN
D3	43 M	NIL	0	NORMAL
D4	20 F	NIL	6	NORMAL
E1	45 F	OCD & TICS	2	NORMAL~
E2	12 M	GTS	0	↓B CN ↓R TMP
E3	46 M	GTS	0	↓L PAR ↓R TMP ↓B CN ↓R THA
E4	9 M	NIL	5	NORMAL

Key:

↓ hypoperfusion (compared to control population).

~ due to a degree of claustrophobia in this subject, this scan excluded some of the inferior and anterior parts of the temporal lobes bilaterally.

BS	Brainstem	CN	Caudate
FR	Frontal	PAR	Parietal
THA	Thalamus	TMP	Temporal

B	Bilateral
R	Right

Table XX11: Number of GTS and OCD probands with specific obsessions.

	GTS probands (n=16)	OCD probands (n=16)	Fisher's Exact Test p
Sexual theme	10	3	0.029*
Dirt/germ/ contamination	2	10	0.009*
Need to tell/ask/ know/remember	4	7	0.458*
Fear of something going wrong/becoming ill/bad happening	2	12	0.001*
Neat and clean	3	6	0.433
Fear of harming self/ others	11	8	0.473*
Fear of saying certain things/doing something embarassing	9	6	0.479*
Violent/aggressive theme	12	3	0.004*
Miscellaneous/ superstitious	3	6	0.433
Somatic obsessions	0	2	0.484

Table XX111:Number of GTS and OCD probands with specific compulsions

	GTS probands (n=16)	OCD probands (n=16)	Fishers' Exact Test p
Symmetry/evening up	15	1	0.0000009*
Saying/doing things `just right'	13	2	0.0002*
Checking	10	12	0.704*
Washing	2	12	0.001*
Cleaning/measures to remove contaminant	2	12	0.001*
Forced touching	12	1	0.0002*
Hoarding	1	4	0.333
Arranging	7	3	0.252*
Counting	8	10	0.722*
Repeating rituals	5	10	0.156*

Table XX1V: Anxiety and obsessional scores in GTS and OCD probands

	Mean	SD	t	df	p
Spielberger State Score					
GTS	41.90	8.56	-2.9709	22	0.007
OCD	53.00	9.54	Equal Variances		
Spielberger Trait Score					
GTS	51.54	10.34	-0.4290	22	0.672
OCD	53.30	9.76	Equal Variances		
Leyton State Score					
GTS	20.00	8.52	-0.7824	22	0.442
OCD	22.76	8.74	Equal Varaiances		
Leyton Trait Score					
GTS	9.54	4.41	-2.7357	12.2	0.018
OCD	13.38	1.60	Unequal Variances		

Table XXV: Obsessive compulsive symptom profile significantly contributing to the "GTS" and "OCD" clusters.

obsession/compulsion	fisher's exact test
OCD DIAGNOSIS	
dirt/germ/contamination	.000001
need to tell/ask/know	.01
fear of something going wrong/ bad happening	.05
neat and clean	.001
washing	.0005
cleaning	.0005
GTS DIAGNOSIS	
fear of harming self/others	.04
violent/aggressive theme	.04
symmetry/evening up	.05
saying/doing things `just right'	.007
forced touching	.02

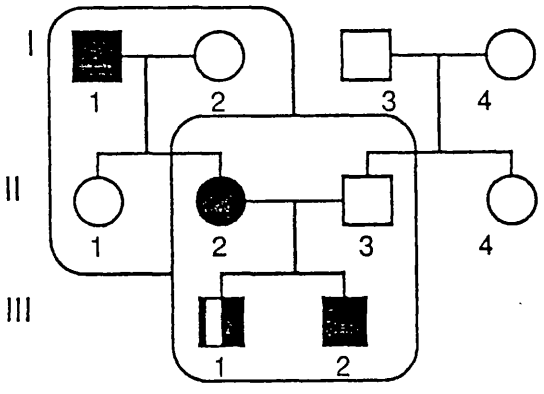
Table XXV1: Rates of OCD among relatives of OCD probands in "GTS" and "OCD" clusters

	Gender		
Cluster	Male	Female	Total
"GTS"	1/9(.11)	7/10(.70)	8/19(.42)
"OCD"	0/18	0/16	0/34
Total	1/27(.04)	7/26(.27)	8/53(.15)

Fisher's Exact Test ("GTS" vs "OCD") P = 0.00009

Fisher's Exact Test(Male vs Female within "GTS" cluster) p = 0.015

Figure 1.1: Pedigree showing decomposition into nuclear family units



A representative pedigree from the present study showing partitioning via the pointer method. The pointer is taken as the primary proband (II-2). The spouse and children are regarded as one nuclear family unit, while the sibling and parents are considered as another nuclear family unit.

Figure1.2: The mixed model for liability to affection in a dichotomous trait determined by a major locus with a polygenic background

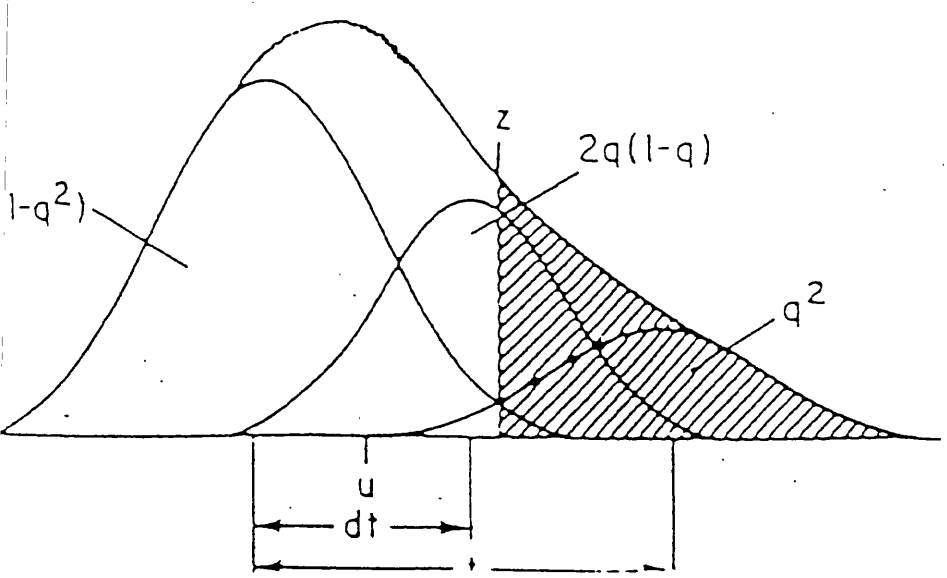


Figure 2.01 to 2.17: Multigenerational GTS pedigrees used for the section on genomic imprinting

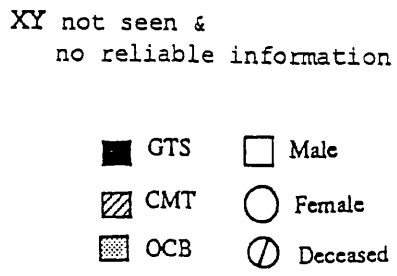


Figure 2.01

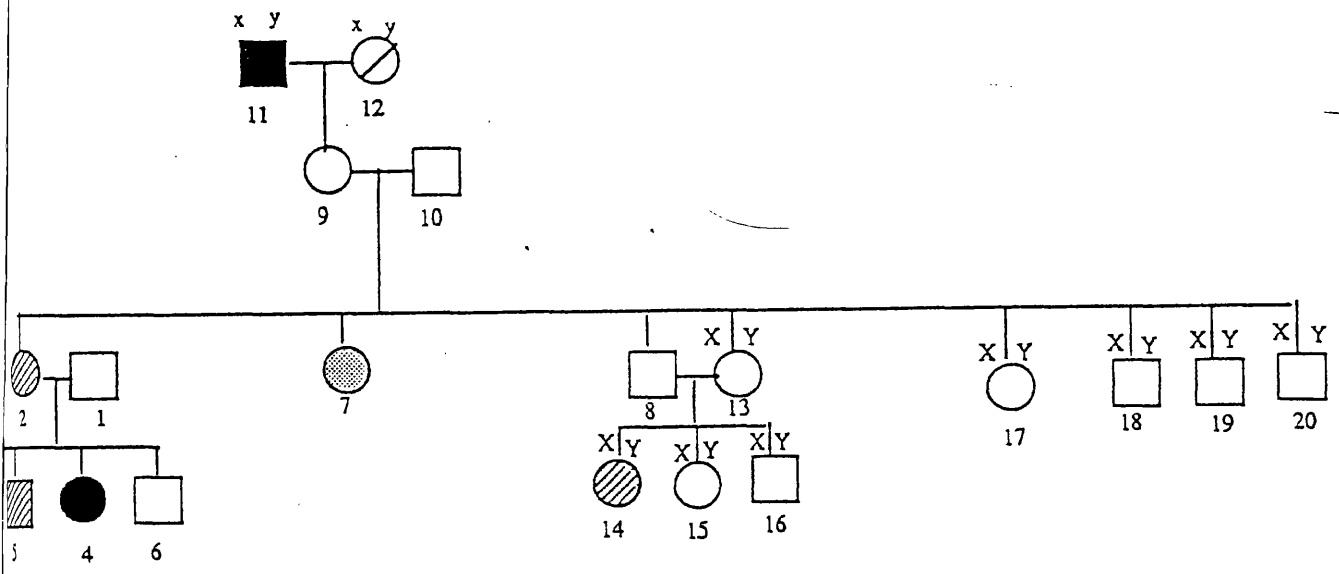
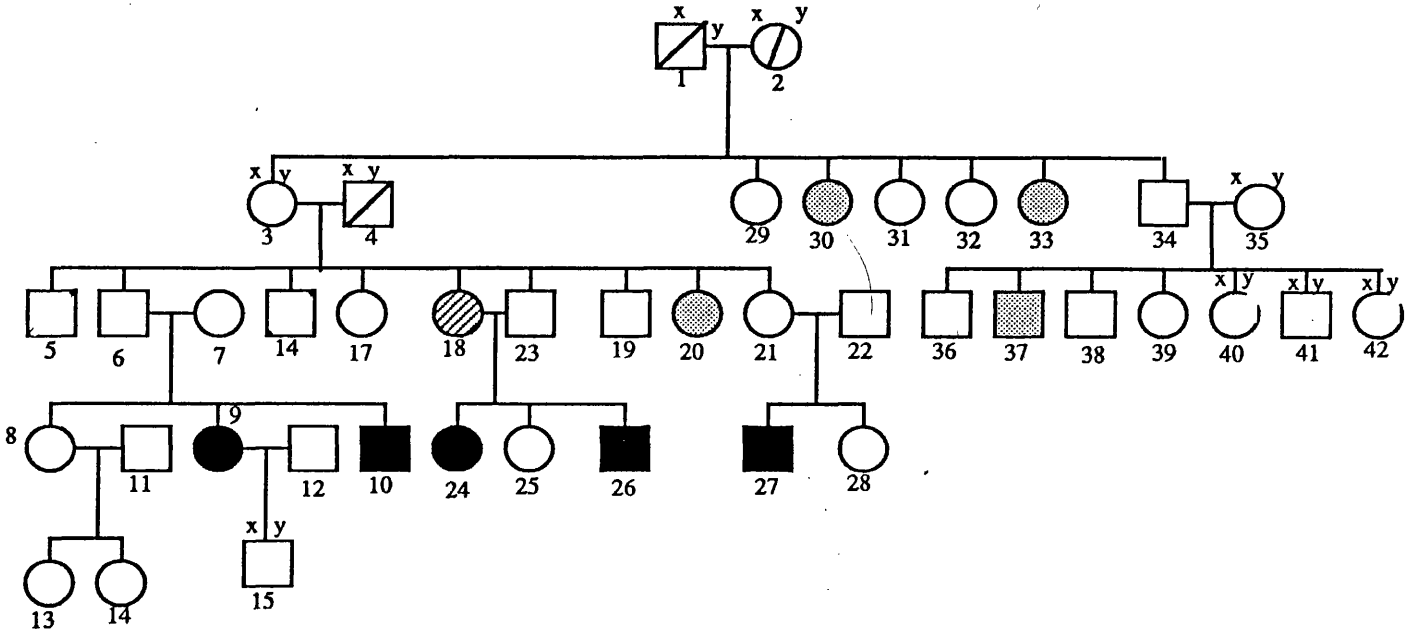


Fig. 2.02


x y
1
x y
2
x y
3
x y
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x y
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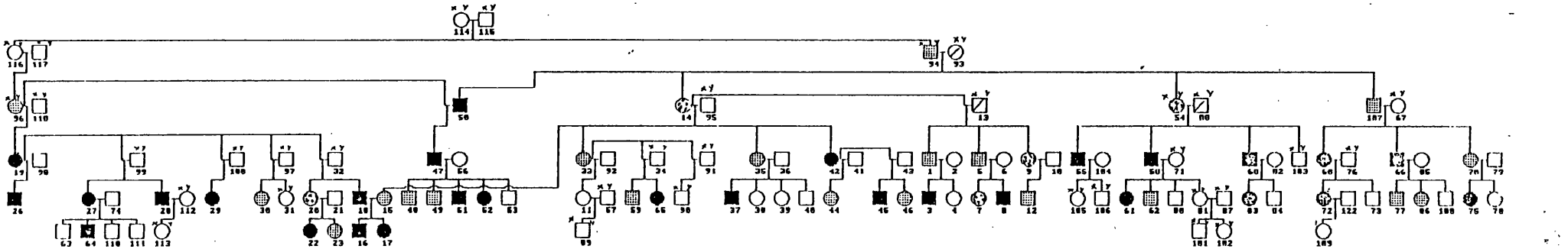
Fig.2.03



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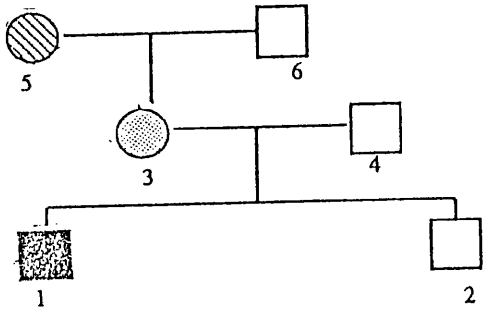


Fig. 2.05

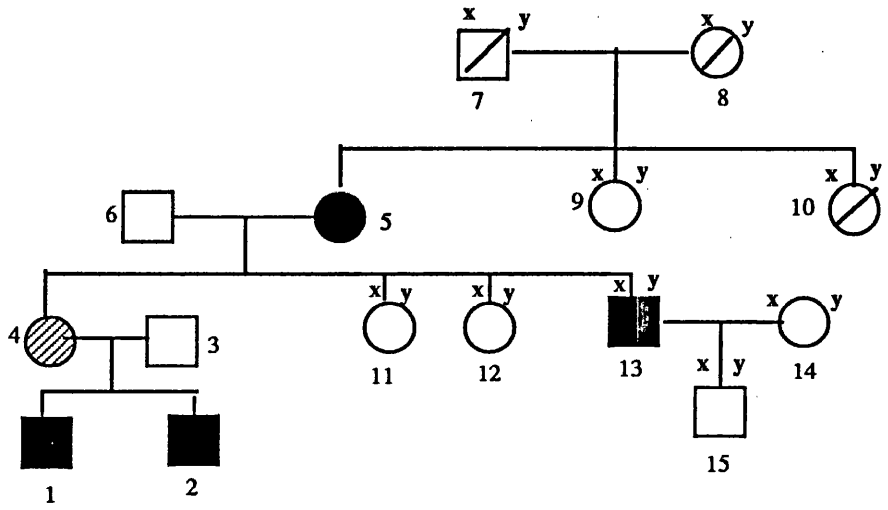


Fig 2.06

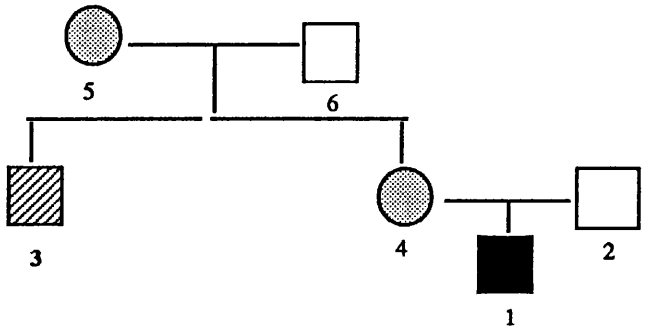


Fig 2.07

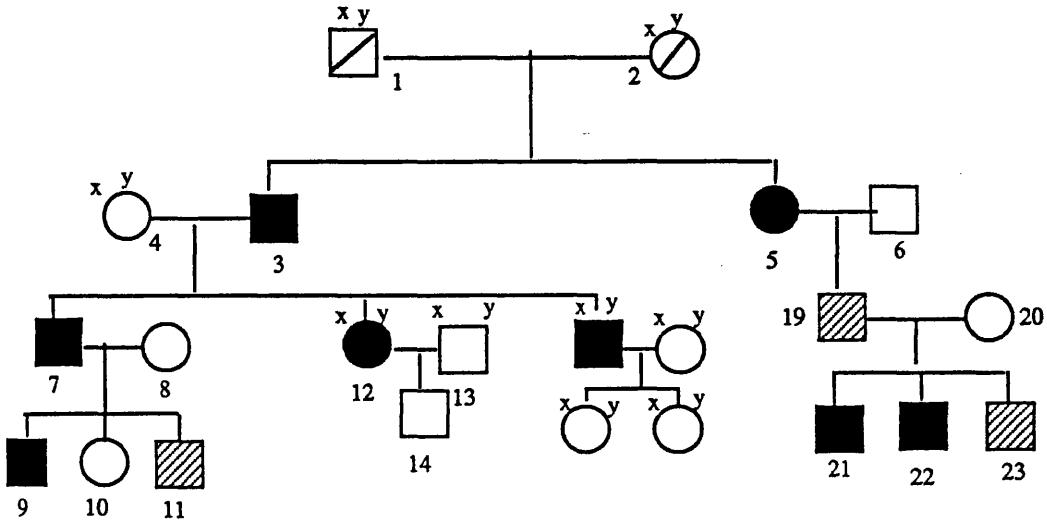


Fig. 2.08

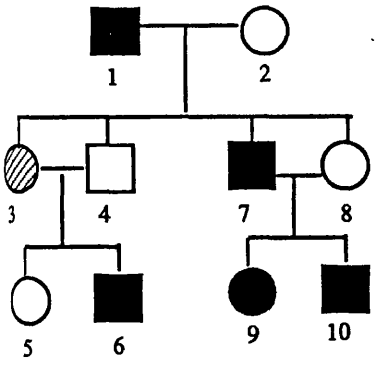


Fig. 2.09

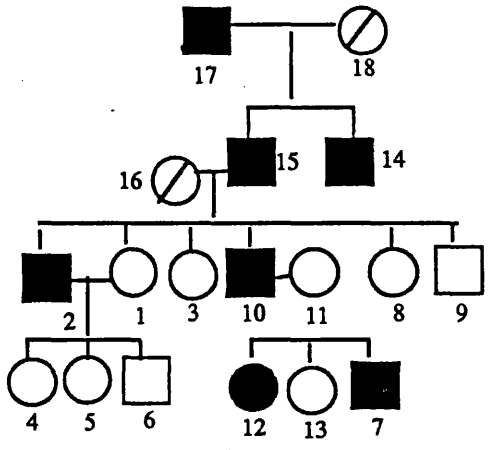
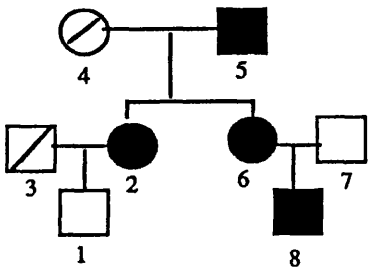


Fig 2.10



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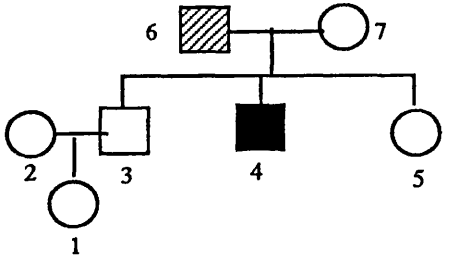
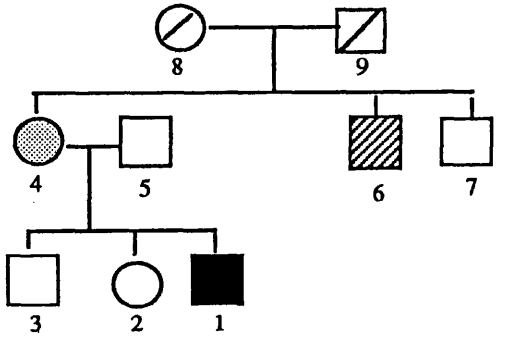


Fig 2.14



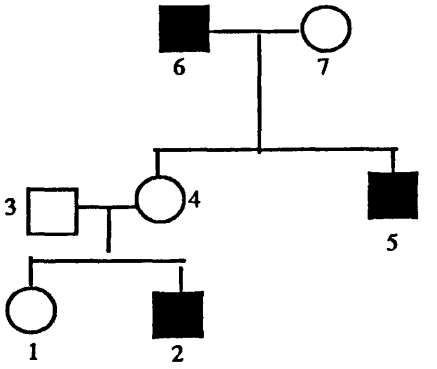


Fig. 2.13

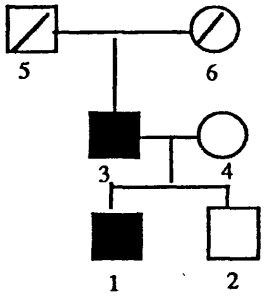


Fig 2.15

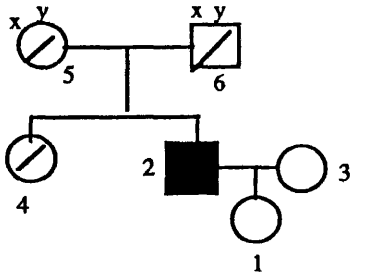


Fig 2.16

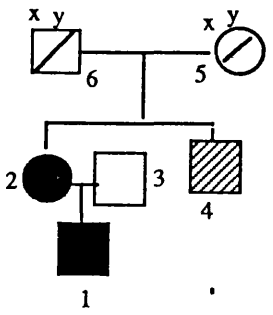


Fig 2.17

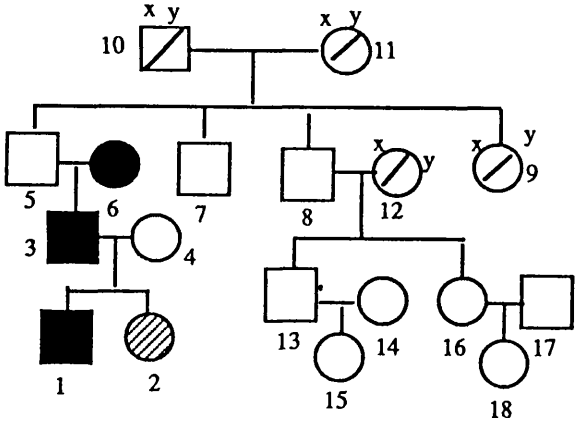
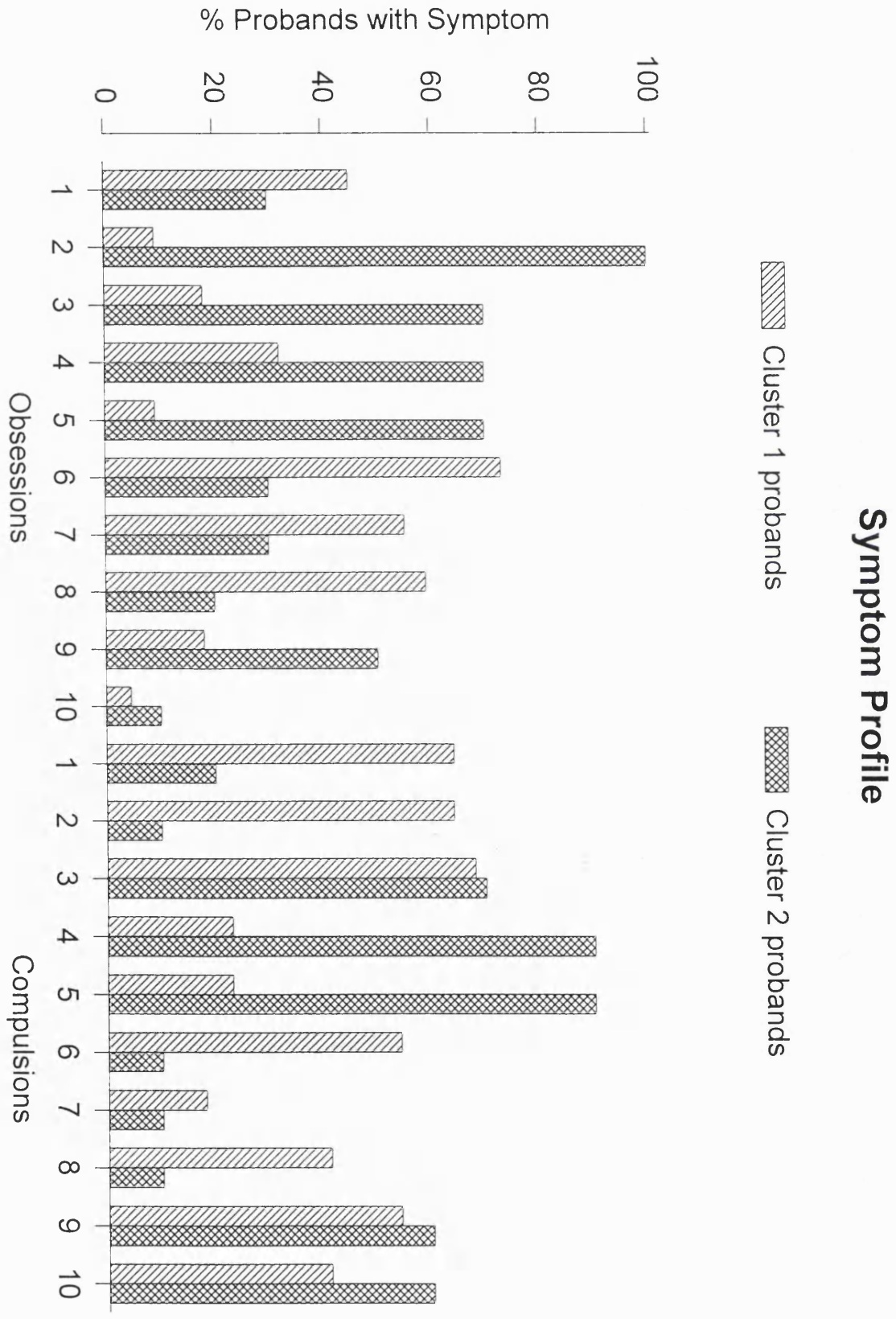


Figure 3: Obsessive Compulsive symptom profile in GTS and OCD clusters



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Appendix 1: The National Hospital Interview Schedule for the assessment of GTS and related behaviours

This is a semi-structured interview schedule for the assessment of GTS, Tics, OCB, ADHD and other related behaviours. Evidence for the validity of the schedule comes from high correlations with the Yale Schedule for Tourette and other behavioural syndromes (Pauls and Hurst 1987). Inter rater reliability of the instrument has also been established (Robertson and Eapen 1996).

1. Interviewer 2. Date

Initials Day Month Year

3. Name of the person being interviewed.....

Address:.....

.....

.....Tel. No:.....

4. Sex 5. Age 6. Date of Birth

[ ] [ ] [ ] [ ] [ ]

(1=M 2=F) Day Month Year

7. Interview Status [ ]

1 = Face to Face Interview
2 = Phone Interview
3 = Mailed

8. If the person being interviewed is a relative, please give the name of the proband (patient).....
and the relationship.....

To Interviewer:
please code the degree of relatedness [ ]

1 = first degree - sib - sib; parent-child
2 = second degree - aunt/uncle or nephew/niece etc.
3 = third degree - first cousins
4 = fourth degree - second cousins
5 = other (e.g. spouse)

9. How old were you when the first tics or habits (symptoms) began?

[ ][ ]

10. What was the first tic, habit or mannerism you developed?

..... [ ][ ]

To interviewer. Please use the following list to code the answer.

1 = Eye blinking
2 = Other facial tics
3 = Tics involving upper or lower limb
4 = Other motor tic
5 = Vocal tic
6 = Echophenomenon
7 = OCB (obsessive compulsive behaviour)
8 = Coprophenomenon
9 = ADD/Hyperactivity
10 = Others

11. Has the diagnosis of GTS been made? ☐ 1=Yes; 2=No

12. If yes,
how old were you when the diagnosis was made ☐☐

and by whom? ☐

13. Have you every consulted anyone for your ☐ 1=Yes
for your tics/movements/noises 2=No
and have you been given any other diagnosis?

14. If yes, what were they?

Diagnosis		Diagnostician	
a).....	☐☐	.....	☐
b).....	☐☐	.....	☐
c).....	☐☐	.....	☐
d).....	☐☐	.....	☐
e).....	☐☐	.....	☐

To interviewer use the following list to code answers to question 12 and 14.

Diagnosis:
1 = Multiple tic
2 = Simple (transient tic)
3 = Nervous twitch
4 = Psychological problem (attention seeking etc.)

5 = Epilepsy
6 = Any other neurological disorder
7 = Habit
8 = No diagnosis given
9 = Other (specify).....

Diagnostician
1 = Physician
2 = Psychiatrist
3 = Neurologist
4 = Paediatrician
5 = Psychologist
6 = Other health professional (specify).....
7 = Other (e.g. relatives, teachers etc.).....

15. What is your level of education? [ ]

1 = Left school before 16
2 = Attended school till 16 but no exams
3 = GCSE/O levels
4 = A levels
5 = Technical/vocational training
6 = Partial university (degree) training
7 = University graduate
8 = Higher professional training after university
9 = Others (e.g. at school)

16. What is your job if you have one..... [ ]

17. What is/was your father's job ..... [ ]

To Interviewer - use the following list to code items 16 & 17
1 = Professionals
2 = Managerial and technical occupations
3 = Skilled occupations (manual and non-manual)
4 = Partly skilled
5 = Unskilled

18. Are you an adopted child [ ] 1=Yes; 2=No

19. If yes, do you have any information about biological parents

[ ] 1=Yes; 2=No

(If the answer is no, proceed to question 31)

20. Do you have any brothers or sisters and if so give details.

Name	Sex	Age now
a).....	[ ] 1=M 2=F	[ ][ ]
b).....	[ ] 1=M 2=F	[ ][ ]

c)..... ☐ 1=M 2=F ☐☐

d)..... ☐ 1=M 2=F ☐☐

e)..... ☐ 1=M 2=F ☐☐

f)..... ☐ 1=M 2=F ☐☐

21. Do you live: ☐

1 = At home with parents. If yes, give name and age

..... ☐ 1=M 2=F ☐☐

..... ☐ 1=M 2=F ☐☐

2 = With wife/husband/children
3 = With someone of oppostive sex
4 = With relatives not your parents
5 = With adopted/foster family
6 = Alone
7 = Other/s (specify).....

22. Any twins? ☐ 1=Yes; 2=No

23. If yes ☐ 1=identical; 2=non identical

24. Any half siblings ☐ 1=Yes; 2=No

25. If yes ☐ 1=paternal; 2=maternal; 3=both

26. Did your mother have any miscarriages or abortions?

☐ 1=Yes; 2=No

27. If yes, when? ☐ 1=before you were born
2=after you were born

28. Do any members of your family have GTS tics or habits?

(To Interviewer: please code degree of relatedness as in question 8 and tics as in question 10 on page 1 and 2)

	Person	Relationship	Age Now	Tics	Duration
(1)	.....	.....	☐	☐☐	☐ .....
(2)	.....	.....	☐	☐☐	☐ .....
(3)	.....	.....	☐	☐☐	☐ .....
(4)	.....	.....	☐	☐☐	☐ .....
(5)	.....	.....	☐	☐☐	☐ .....
(6)	.....	.....	☐	☐☐	☐ .....

29. Do any members of your family have intrusive thoughts (obsessions), compulsive rituals or are excessively houseproud? ☐ 1=Yes 2=No

If yes:

	Person	Relationship	Age Now	Describe	Duration
(1)	.....	.....	☐	☐☐	.....
(2)	.....	.....	☐	☐☐	.....
(3)	.....	.....	☐	☐☐	.....

30. Do any members of your family stammer/stutter? ☐ 1=Yes 2=No

If yes:

	Person	Relationship	Age Now	Age of S	Duration
(1)	.....	.....	☐	☐☐	☐☐ .....
(2)	.....	.....	☐	☐☐	☐☐ .....
(3)	.....	.....	☐	☐☐	☐☐ .....

31. Was anyone in your family thought to have attention deficit/hyperactivity? ☐ 1=Yes 2=No

If yes:

	Person	Relationship		Age Now	Age of **ADD/H**
(1)	.....	.....	☐	☐☐	☐☐
(2)	.....	.....	☐	☐☐	☐☐
(3)	.....	.....	☐	☐☐	☐☐

32. Was anyone in your family thought to have learning disability? ☐ 1=Yes 2=No

	Person	Relationship		Age Now	Age Diagnosed
(1)	.....	.....	☐	☐☐	☐☐
(2)	.....	.....	☐	☐☐	☐☐
(3)	.....	.....	☐	☐☐	☐☐

33a. Do you have any of the following motor tics? ☐ 1=Yes 2=No

b. How old were you when the first tics began? ☐☐

	If yes:	At Interview	Ever	During the Past Week
(1)	Scalp	.....	....	.....
(2)	Brow/frown	.....	....	.....
(3)	Raise eyebrow(s)	.....	....	.....
(4)	Blink	.....	....	.....
(5)	Wink	.....	....	.....
(6)	Roll eyes up	.....	....	.....
(7)	Eyes looking down	.....	....	.....
(8)	Eyes looking sideways	.....	....	.....
(9)	Eyes staring	.....	....	.....
(10)	Nasal twitch	.....	....	.....
(11)	Nasal flare	.....	....	.....
(12)	Other nasal	.....	....	.....
(13)	Upper lip	.....	....	.....
(14)	Lower lip	.....	....	.....
(15)	Kissing self	.....	....	.....
(16)	Kissing others	.....	....	.....

(17)	Swallowing			
(18)	Mouth pout			
(19)	Mouth open			
(20)	Mouth to side			
(21)	Smile			
(22)	Grip on lips (lipstick)			
(23)	Moving dentures			
(24)	Tongue protrusion			
(25)	Tongue other			
(26)	Rubbing tongue on back of teeth.			
(27)	Bruxism (grinding of teeth)			
(28)	Gnashing of teeth			
(29)	Facial grimace			
(30)	Puffing cheeks out			
(31)	Spit			
(32)	Smell			
(33)	Lick (things)			
(34)	Lick (lips)			
(35)	Blowing			
(36)	Jaw protrusion)			
(37)	Platysma tightening			
(38)	Drooping of head			
(39)	Ear movements			
(40)	Head nod forward			
(41)	Head nod backward			
(42)	Head turning sideways			
(43)	Hair out of eyes flick			
(44)	Neck stretch			
(45)	Shoulder shrug			
(46)	Arms flex			
(47)	Arms extend			
(48)	Arms other (describe)			
(49)	Fingers - drumming or flexing...			
(50)	Fingers through hair			
(51)	Abdominal contractions			
(52)	Torso/thorax twist or movement..			
(53)	Hip/pelvis(backfront/copulatory)			
(54)	Wiggle bottom			
(55)	Leg flex			
(56)	Leg extend			
(57)	Leg other (describe)			
(58)	Kicks			
(59)	Toe (eg scratch shoes inside)...			
(60)	Feet (describe)			
(61)	Abnormal gait			
(62)	Whole body movement/jump			
(63)	Looking at watch as a habit			
(64)	Looking over shoulder			
(65)	Adjusting clothing			
(66)	Looking in mirror			
(67)	Putting fingers or hand in mouth			
(68)	Touching parts of own body & what?			
	(a)			
	(b)			
	(c)			
	(d)			
(69)	Describe complex tics- stamp...			
	- hop...			
	- squat...			
	- skip...			
	- turn...			

	- bend....	.....	....	.....
	- hit.....	.....	....	.....
	- other...	.....	....	.....
(70)	Looking at clock over shoulder..	.....	....	.....
(71)	Patting abdomen (not injuring)..	.....	....	.....
(72)	Tapping parts of own body.....	.....	....	.....
(73)	Pinching bottom.....	.....	....	.....
(74)	Chin on chest or shoulder.....	.....	....	.....
(75)	Twisting hair.....	.....	....	.....
(76)	Pinching or poking self.....	.....	....	.....
(77)	Tics/movements or neck muscles, excluding stretching.....	.....	....	.....
(78)	Stroking (self, material, others) as a tic.....	.....	....	.....
(79)	Others (describe).....	.....	....	.....

33b. Complex motor tics (slower, "purposeful")

(1)	Eye gestures or movements.....	.....	....	.....
(2)	Shoulder gestures.....	.....	....	.....
(3)	Writing tics.....	.....	....	.....

34a. Have you ever found yourself making noises/voices involuntarily?

☐ 1=Yes
2=No

b. How old were you when the first vocal tics began?

☐☐

	If yes:	At Interview	Ever	During the Past Week
(1)	Grunt.....	.....	....	.....
(2)	Throat clearing.....	.....	....	.....
(3)	Bark.....	.....	....	.....
(4)	Snort.....	.....	....	.....
(5)	Ugh.....	.....	....	.....
(6)	Ah/Eh.....	.....	....	.....
(7)	Gulp.....	.....	....	.....
(8)	Hiccup.....	.....	....	.....
(9)	Sniffing.....	.....	....	.....
(10)	Hum.....	.....	....	.....
(11)	Squeak.....) high pitched.	.....	....	.....
(12)	Shriek/scream....) sound.....	.....	....	.....
(13)	Burp.....	.....	....	.....
(14)	Hoot (like a car).....	.....	....	.....
(15)	Ooh.....	.....	....	.....
(16)	Hiss.....	.....	....	.....
(17)	Growl.....	.....	....	.....
(18)	WaWa.....	.....	....	.....
(19)	Sucking noise.....	.....	....	.....
(20)	Sh Sh Sh.....	.....	....	.....
(21)	Pant.....	.....	....	.....
(22)	Wail.....	.....	....	.....
(23)	Gasp.....	.....	....	.....
(24)	Click.....	.....	....	.....
(25)	Yelp.....	.....	....	.....

(26)	t,t,t,t.....	.....	....	.....
(27)	Noisy breathing.....	.....	....	.....
(28)	Whistling.....	.....	....	.....
(29)	Inappropriate fluctuations in pitch		....	.....
(30)	Moan.....	.....	....	.....
(31)	Cough.....	.....	....	.....
(32)	Raspberries.....	.....	....	.....

35. Complex vocalisations? ☐ 1=Yes 2=No

	If yes:	At Interview	Ever	During the Past Week
(1)	Animal sounds - cow.....	.....	....	.....
	- chicken	.....	....	.....
	- rooster.	.....	....	.....
	- quack....	.....	....	.....
	- others....	.....	....	.....
(2)	Barely audible muttering.....	.....	....	.....
(3)	Talking to oneself with multiple characters, assuming different intonations.....	.....	....	.....

36. Coprolalia:(inappropriate swearing) Have you ever sworn inappropriately as a tic habit? ☐ 1=Yes 2=No

	If yes:	At Interview	Ever	During the Past Week
(1)	Fuck.....	.....	....	.....
(2)	Cunt.....	.....	....	.....
(3)	Bastard.....	.....	....	.....
(4)	Piss.....	.....	....	.....
(5)	Sod.....	.....	....	.....
(6)	Cock.....	.....	....	.....
(7)	Shit.....	.....	....	.....
(8)	Bollocks.....	.....	....	.....
(9)	Tits.....	.....	....	.....
(10)	Breast.....	.....	....	.....
(11)	Wanker.....	.....	....	.....
(12)	Bugger.....	.....	....	.....
(13)	Arse.....	.....	....	.....
(14)	Racial (eg. nigger).....	.....	....	.....
(15)	Nazi/Hitler/Zeig Heil.....	.....	....	.....
(16)	National Front.....	.....	....	.....
(17)	Mod, rockers.....	.....	....	.....
(18)	Hell.....	.....	....	.....
(19)	Twat(ing).....	.....	....	.....
(20)	Damn.....	.....	....	.....
(21)	God.....	.....	....	.....
(22)	Blast.....	.....	....	.....
(23)	Git.....	.....	....	.....
(24)	Terd.....	.....	....	.....
(25)	Nerd.....	.....	....	.....
(26)	A string of swear words.....	.....	....	.....
(27)	Others.....	.....	....	.....

37. Do you make obscene or socially inappropriate statements?

☐ 1=Yes
2=No

If yes, describe.....

38. Do dirty thoughts and words come into your head when you are thinking about other things (mental coprolalia)?

☐ 1=Yes
2=No

If yes, describe.....

39. Have you sometimes worried about blurting out an obscenity?

☐ 1=Yes
2=No

If yes, describe.....

40. Have you worried about doing something sexual like exposing yourself in public?

☐ 1=Yes
2=No

If yes, describe.....

41. At what age did this coprophenomenon start?

Age ☐☐

42a. Copropraxia: Do you make obscene gestures inappropriately as a habit?

☐ 1=Yes
2=No

b. How old were you when the copropraxia began?

☐☐

If yes:	At Interview	Ever	During the Past week
(1) V sign.....	.....	....	.....
(2) Elbow sign.....	.....	....	.....
(3) Third finger.....	.....	....	.....
(4) Holding groin.....	.....	....	.....
(5) Other.....	.....	....	.....

43. Echopraxia?

☐ 1=Yes
2=No

If yes:	At Interview	Ever	During the Past Week
(1) Do you imitate things?.....	.....	....	.....

(2)	What age did it start?.....	.....	....	.....
(3)	What do you imitate?.....	.....	....	.....
	- other people's movements?.....	.....	....	.....
(4)	What else?.....	.....	....	.....

44. Echolalia?

☐ 1=Yes 2=No

If yes:	At Interview	Ever	During the Past Week
(1) Do you repeat things other people say? e.g. Accents.	.....	....	.....
(2) What age did it start?.....	.....	....	.....
(3) What do you repeat?.....	.....	....	.....
.....	.....	....	.....

45. Palilalia (repetition of last word)?

☐ 1=Yes 2=No

If yes, describe.....

46. Palipraxia (repetition of last act)?

☐ 1=Yes 2=No

If yes, describe.....

47. Do you feel forced to touch objects, other people or anything else repeatedly?

☐ 1=Yes 2=No

If yes, at what age did it start

and describe..... ☐☐

48. Do you experience any feeling of squeezing, stretching, tightness, tension, itch or other (somatic) sensation prior to and in the area of a motor or phonic tic which is temporarily releived by the tic?

☐ 1=Yes 2=No

If yes, describe.....

49. Do you ever become aggressive or attack people?
If yes, who is usually assaulted and give details..... ☐ 1=Yes 2=No

50. Do you ever attack things or property?

☐ 1=Yes 2=No

51. Do you have impulses to hurt other people?

☐ 1=Yes 2=No

52. Have you ever been fascinated by knives?

☐ 1=Yes
2=No

53. Have you ever been in trouble with the law?

☐ 1=Yes
2=No

54. Have you ever tried to injure yourself?

☐ 1=Yes
2=No

55. If yes:

(a) How? ☐

1 = head banging
2 = overdose
3 = self-injurious behaviour
4 = others (specify).....

(b) Is it an impulse to do so?

☐ 1=Yes
2=No

(c) Is there pain?

☐ 1=Yes
2=No

(d) Do you like or dislike the pain?

☐ 1=Yes
2=No

(e) Has it needed treatment?

☐ 1=Yes
2=No

56. Do you feel you need to do things which you know will cause you bodily harm, such as touching hot objects or hitting yourself? Or, do you get thoughts of doing this.

☐ 1=Yes
2=No

If yes, describe.....

57. Have you ever had images involving bloody or violent scenes that "pop" into your head (for no apparent reason) while you are thinking/engaged in other things?

☐ 1=Yes
2=No

If yes, describe.....

58. Have you ever been bothered by recurring obsessional thoughts, ideas, images or urges that "go round and round" in your mind? For example, concerns about dirt, germ, illness,(These are not natural to you and you do not wish to think about them, but you cannot help it)

☐ 1=Yes
2=No

If yes, state age when it started ☐☐

Duration.....and describe.....

59. Arithmomania: Do you find yourself repeatedly counting things/numbers in your mind?

☐ 1=Yes
2=No

60. Some people will do something over and over (eg: repeated checking, cleaning, washing etc); or have rituals, such as going through certain steps to accomplish a task. Have you ever had such repetitive actions, activities or behaviours (obsessional actions or rituals)?

☐ 1=Yes
2=No

If yes, describe.....

61. Are you excessively tidy (particular about being neat & clean)?

☐ 1=Yes
2=No

(Ask the following to clarify the answer: (a) Are you so clean and tidy that you could eat off the floor? (b) Would you get upset by things being moved?)

62. Do you make obsessional actions in order to "even things up" (concern about symmetry)?

☐ 1=Yes
2=No

If yes, describe.....

63. Do you make any obsessional actions in order to "ward off danger" (doing something in order to avoid some untoward consequence you fear might happen)?

☐ 1=Yes
2=No

If yes, describe.....

64. Have you ever had any thoughts which keep "going round" in your head for no apparent reason but they are pleasant thoughts which doesn't distress/bother you and perhaps you like them and it doesn't make you feel anxious if you try to resist (some people even don't try to resist this)?

☐ 1=Yes
2=No

If yes, describe.....

65. Have any of the above (obsessions/ compulsions) bothered you socially, or interfered with your daily activities?

☐ 1=Yes
2=No

If yes, describe.....

66. Have any of these needed treatment?

☐ 1=Yes
2=No

If yes, describe.....

67. Is there anything that makes your obsessions/impulses/compulsions worse?

☐ 1=Yes
2=No

If yes, specify.....

68. Is there anything that makes them better?

☐ 1=Yes
2=No

If yes, describe.....

69. Is there any situations or factors that make your tics/noises worse?

☐ 1=Yes
2=No

If yes, specify.....

70. Is there anything that makes it better?

☐ 1=Yes
2=No

If yes, describe.....

71. Do your symptoms wax and wane?

☐ 1=Yes
2=No

72. Are you able to suppress your symptoms voluntarily?

☐ 1=Yes
2=No

73. What is the longest period of time since the onset of your illness that you have been free from all tics?

☐

1 = not at all
2 = seconds
3 = minutes
4 = hours
5 = days
6 = weeks
7 = months
8 = years

74. Have they lasted for more than a year?

☐ 1=Yes
2=No

75. Do infections, temperatures or other illnesses have any effect on the severity of your tics?

1 = improve
2 = no change
3 = worsen
4 = don't know
5 = others

☐

76. Have the tics and or noises bothered you socially?

☐ 1=Yes
2=No

77. Have you had any treatment for your tics/habits in the past?

☐ 1=Yes
2=No

If yes, specify

☐

treatment.....effect.....
.....
.....
.....
.....

78. What treatment are you having now?

☐

treatment.....effect.....
.....
.....
.....
.....

To interviewer, please use the following code the answer to questions 77 and 78.

1 = Haloperidol 2 = Pimozide 3 = Sulpiride
4 = Other neuroleptics 5 = Clonidine
6 = Serotenergic drugs
7 = Anticonvulsants (including clonazepam and carbamazepine)
8 = Benzodiazepines (other than clonazepam)
9 = others

79. Do you have any theories about what could have caused your tics/habits/illness?

☐ 1=Yes
2=No

If yes, describe.....

80a. Did you have any illnesses before the onset of your habits/tics?

☐ 1=Yes
2=No

If yes, specify.....

Illness	1=Yes 2=No	Age of Onset
(a) Epilepsy	☐	☐☐
(b) Rheumatic fever	☐	☐☐
(c) Infections of the brain (eg meningitis, encephalitis)	☐	☐☐
(d) Asthma	☐	☐☐
(e) Allergies If yes, specify type of allergen.....	☐	☐☐
(f) Migraine	☐	☐☐
(g) Diabetes	☐	☐☐
(h) Heart disease	☐	☐☐
(i) Childhood infections (eg mumps, measles, chicken pox)	☐	☐☐
(j) Others	☐	☐☐

80b. What is your racial background?

☐

1 = Caucasian 2 = Black 3 = Asian 4 = Oriental

5 = Others 6 = Mixed; If yes specify .....

81. What was your birth weight? lb. ☐☐ oz. ☐☐

82. Were there any complications at your birth?

[ ] 1=Yes
2=No

If yes, [ ][ ]

1 = Toxaemia	2 = Breech
3 = Caesarian	4 = Premature
5 = Cord round neck	6 = Jaundice
7 = Incubator	8 = Twin
9 = Forceps	10 = Accidents
11= Infections in first 3 months	12 = Other

83. Mother's age at your birth? [ ][ ]

84. Father's age at your birth? [ ][ ]

85. Did you cry excessively as a baby?

(ask parents) [ ] 1=Yes
2=No

86. Did you suffer from bed wetting?

[ ] 1=Yes
2=No

If yes, age [ ][ ]

87. Do you or did you, bite your nails?

[ ] 1=Yes
2=No

If yes, age [ ][ ]

88. Have you ever stammered or stuttered?

[ ] 1=Yes
2=No

If yes, age [ ][ ]

89. Were you ever thought to have learning disability?

[ ] 1=Yes
2=No

If yes, age ☐☐

90. Did you have to attend a special school?

☐ 1=Yes 2=No

If yes, age ☐☐

91. Do you have any problems with handwriting?

☐ 1=Yes 2=No

If yes, describe.....

92 a) Were you ever thought to be hyperactive (exceptionally active and full of energy when compared to ther children), or diagnosed as having attention deficit hyperactivity disorder?

☐ 1=Yes 2=No

b) To interviewer, code yes in the box below if 1) at least eight of the following were present (please circle the items present); 2) onset before 7 years of age and 3) duration of more than six months

☐ 1=Yes 2=No

If yes, age of onset ☐☐

c) Hyperactivity (at least 2 items should have persisted and been characteristic of the child)

1 = often fidgets with hands or feet or squirms in seat
2 = has difficulty remaining seated when required to do so
3 = overactive even during sleep
4 = always "on the go" as if driven by a motor

d) Impulsivity (at least 3 items should have persisted and been characteristic of the child)

5 = has difficulty waiting for his/her turn in games or group situations
6 = often blurts out answers to questions before they have been completed (talking out of turn or without being asked)
7 = has difficulty following through on instruction from others (not due to oppositional behaviour or failire of comprehension) eg fails to finish chores

8 = doing one thing and then another and couldn't seem to stay with anything for long, often interrupting or intruding on others eg butts into other children's games

9 = requiring a lot of supervision; someone has to stay with him/her while playing or doing school work

10 = often engages in physically dangerous activities without considering possible consequences (act without thinking about it) eg runs into street without looking

e) Inattention (at least 3 items should have persisted and been characteristic of the child)

11 = has difficulty sustaining attention or keeping his/her mind on tasks

12 = has difficulty sticking to a play activity

13 = is easily distracted by extraneous stimuli (almost anything could get his/her mind off the track)

14 = has trouble finishing things and often shifts from one uncompleted activity to another

15 = often does not seem to listen

16 = often loses things necessary for tasks or activities at school or at home

93. Do you/did you suffer from any sleep related problems such as?

	1 = Yes 2 = No	Age
(a) Frequent nightmares	☐	☐☐
(b) Night terrors	☐	☐☐
(c) Insomnia	☐	☐☐
(d) Walk in your sleep	☐	☐☐
(e) Talk in your sleep	☐	☐☐

94. Some people have phobias, that is a strong and persistent fear of something or some situation that they try to avoid it. Have you ever had such an unreasonable fear and avoidance of any of the following that it interfered with your life and activities

	1=Yes; 2=No
(a) social situations?	☐
(b) heights?	☐
(c) open spaces?	☐
(d) closed spaces?	☐

(e) others? specify..... ☐

95. Have you ever abused (characterized by persistent or episodic use over at least one month period, with at least minimal social or functional impairment) ?

1=Yes; 2=No

(a) drugs? ☐

(b) alcohol? ☐

96. Have you ever been diagnosed as having

1=Yes; 2=No

(a) anxiety disorder? ☐

(b) depression? ☐

(c) manic depressive illness ☐

(d) others? If yes, specify..... ☐

97. Did you or do you have difficulty making friends or close personal relationships?

☐ 1=Yes 2=No

If yes, age ☐☐

98. What is your marital status? ☐

1 = single 2 = married 3 = common-law
4 = separated 5 = divorced 6 = widowed
7 = remarried

99. Total number of years married? ☐☐

100. How many children do you have? ☐

Name	Age	Sex	Health
1.....	☐☐	☐ 1=M 2=F	.....

2..... ☐☐ ☐ 1=M 2=F .....

3..... ☐☐ ☐ 1=M 2=F .....

4..... ☐☐ ☐ 1=M 2=F .....

5..... ☐☐ ☐ 1=M 2=F .....

101 How many jobs have you had since leaving school? ☐

Job description	code	Duration (yrs)
(a).....	☐	☐☐
(b).....	☐	☐☐
(c).....	☐	☐☐
(d).....	☐	☐☐

To interviewer, please use the list as in questions 16 & 17 on page 3 to code the answer.

102 Have you ever seen a psychiatrist before?

☐ 1=Yes 2=No

If yes, give details.....

103 Have you ever been treated for depression?

☐ 1=Yes 2=No

104 Have you ever been treated for MDP?

☐ 1=Yes 2=No

105 Have you ever been treated for schizophrenia?

☐ 1=Yes 2=No

106 Have you ever been treated for OCD?

☐ 1=Yes 2=No

107 Have you ever been treated for any other psychiatric illness?

☐ 1=Yes
2=No

108 Are you being treated for any other illnesses?

☐ 1=Yes
2=No

If yes, give details.....

109 To interviewer - please code the diagnosis as probable if evidence is present only on history and not on examination; definite if evidence present on both history and examination:

1 = probable OCD ☐ 1=Yes 2=No

2 = definite OCD ☐ 1=Yes 2=No

3 = probable transient motor tic ☐ 1=Yes 2=No

4 = definite transient motor tic ☐ 1=Yes 2=No

5 = probable chronic motor tic ☐ 1=Yes 2=No

6 = definite chronic motor tic ☐ 1=Yes 2=No

7 = probable Gilles de la Tourette syndrome ☐ 1=Yes 2=No

8 = mild Gilles de la Tourette Syndrome ☐ 1=Yes 2=No

9 = moderate Gilles de la Tourette Syndrome (requiring treatment, but not socially or functionally disruptive) ☐ 1=Yes 2=No

10= severe Gilles de la Tourette Syndrome (requiring treatment and socially and functionally disruptive) ☐ 1=Yes 2=No

11= others ☐ 1=Yes 2=No

Yale Global Tic Severity Scale

A. Number: a) Motor Score: ☐ b) Phonic Score: ☐

0 None
1 Single tic
2 Multiple discrete tics (2-5)
3 Multiple discrete tics (more than 5)
4 Multiple discrete tics plus at least one orchestrated pattern of multiple simultaneous or sequential tics where it is difficult to distinguish discrete tics
5 Multiple discrete tics plus several (>2) orchestrated pattern of multiple simultaneous or sequential tics where it is difficult to distinguish discrete tics

B. Frequency: a) Motor Score: ☐ b) Phonic Score: ☐

0 None. No evidence of specific tic behaviours.
1 Rarely. Specific tic behaviours have been present during previous week. These behaviours occur infrequently, often not on a daily basis. If bouts of tics occur, they are brief and uncommon.
2 Occasionally. Specific tic behaviours are usually present on a daily basis, but there are long tic-free intervals during the day. Bouts of tics may occur on occasion and are not sustained for more than a few minutes at a time.
3 Frequently. Specific tic behaviours are present on a daily basis. Tic free intervals as long as 3 hours are not uncommon. Bouts of tics occur regularly but may be limited to a single setting.
4 Almost Always. Specific tic behaviours are present virtually every waking hour of every day, and periods of sustained tic behaviours occur regularly. Bouts of tics are common and are not limited to a single setting.
5 Always. Specific tic behaviours are present virtually all the time. Tic-free intervals are difficult to identify and do not last more than 5 to 10 minutes at most.

C. Intensity: a) Motor Score: ☐ b) Phonic Score: ☐

0 Absent
1 Minimal intensity, tics not visible or audible (based solely on patient's private experience) or tics are less foreceful than comparable voluntary actions and are typically not noticed because of their intensity.
2 Mild intensity, tics are not more forceful than comparable voluntary actions or utterances and are typically not noticed because of their intensity.
3 Moderate intensity, tics are more forceful than comparable voluntary actions but are not outside the range of normal expression for comparable voluntary actions or utterances. They may call atention to the indivual because of their forceful character.
4 Marked intensity, tics are more forceful than comparable voluntary actions or utterances and typically have an "exaggerated" character.

Such tics frequently call attention to the individual because of their forceful and exaggerated character.

5 Severe intensity, tics are extremely forceful and exaggerated in expression. These tics call attention to the individual and may result in risk of physical injury (accidental, provoked, or self-inflicted) because of their forceful expression.

D. Complexity: a) Motor Score: ☐ b) Phonic Score: ☐

0 None, if present, all tics are clearly "simple" (sudden, brief, purposeless) in character.

1 Borderline, some tics are not clearly "simple" in character.

2 Mild, some tics are clearly "complex" (purposive in appearance) and mimic brief "automatic" behaviours, that could be readily camouflaged, (e.g. grooming).

3 Moderate, some tics are more "complex" (more purposive and sustained in appearance) and may occur in orchestrated bouts that would be difficult to camouflage but could be rationalized or "explained" as normal behaviour or speech (e.g. picking, tapping).

4 Marked, some tics are very "complex" in character and tend to occur in sustained orchestrated bouts that would be difficult to camouflage and could not be easily rationalized as normal behaviour or speech because of their duration and/or their unusual, inappropriate, bizarre, or obscene character, (e.g. echolalia).

5 Severe, some tics involve lengthy bouts of orchestrated behaviour or speech that would be impossible to camouflage or successfully rationalize as normal because of their duration and/or extremely unusual, inappropriate, bizarre, or obscene character (e.g. copropraxia, or coprolalia).

E. Interference:a)Motor Score: ☐ b) Phonic Score: ☐

0 None

1 Minimal, when tics are present, they do not interrupt the flow of behaviour or speech.

2 Mild, when tics are present, they occasionally interrupt the flow of behaviour or speech

3 Moderate, when tics are present, they frequently interrupt the flow of behaviour or speech.

4 Marked, when tics are present, they frequently interrupt the flow of behaviour or speech, and they occasionally disrupt intended action or communication.

5 Severe, when tics are present, they frequently disrupt intended action or communication.

F. a) Total Motor Tic Score ☐

b) Total Phonic Tic Score ☐

G. Overall Impairment: ☐

0 None.

1 Minimal, tics associated with subtle difficulties in self-esteem, family life, social acceptance, or school or job functioning.

2 Mild, tics associated with minor difficulties in self-esteem family life, social acceptance, or school or job functioning.

3 Moderate, tics associated with some clear problems in self-esteem, family life, social acceptance, or school or job functioning

4 Marked, tics associated with major difficulties in self-esteem, family life, social acceptance, or school or job functioning

5 Severe, tics associated with extreme difficulties in self-esteem, family life, and severely restricted life because of social stigma and social avoidance, removal from school or loss of job.

H. Global Severity Score (overall impairment score + total motor score + total phonic score)

Appendix 1.1: Inter-Rater Reliability for the NHIS

NHIS items	ICC Overall Agreement	ICC Overall Bias
Family History	.64 *	NS
Total tics	.95 **	NS
Echophenomenon	.75 **	NS
Coprophenomenon	1.00 **	NS
SIB (Self Injurious Behaviour)	.81 **	NS
ADHD	.81 **	NS
OCB	.65 *	NS
Severity	.86 **	NS

* Significant at 0.05 level
** Significant at 0.01 level

To establish inter-rater reliability, comparisons were made with the findings from the evaluation interviews carried out by two different raters on eight key areas; family history, total tics (ever), coprophenomena, echophenomena, SIB, ADHD, OCB, and overall severity. Total tics (ever) was chosen rather than the tics at interview to avoid discrepancies that may be caused by the fluctuations in the occurrence of tics at any given point in time. Scoring for the purposes of reliability was done based on the presence or absence of each of the item in question.

The intraclass correlation coefficient (ICC) for each of the eight items on the NHIS indicate good overall agreement between the two raters. Findings on two items (family history and OCB) achieved a lower level of agreement (significant at 0.05 level) when compared to the other six items (significant at 0.01 level). The intraclass correlation coefficient for overall rater bias was non- significant for all the items. The overall rater bias refers to any tendency by the individual raters to consistently over-rate or under-rate a particular item that is being studied (for example a consistent tendency on the part of one rater to over-rate the occurrence of SIB).

Appendix 1.2: Validity for the NHIS

NHIS items	Overall Agreement	Overall Bias
Diagnosis GTS	1.00 **	NS
Motor tics ever	.85 **	NS
Vocal tics ever	.95 **	NS
Coprophenomenon	.82 **	NS
Echophenomenon	.85 **	NS
ADHD	.82 **	NS
OCB	.82 **	NS

** Significant at 0.01 level

In order to establish the concurrent validity of the instrument, the findings from the evaluation interviews using NHIS on seven key areas were compared with those of the Yale Schedule, an instrument expected to provide measures of the same dimensions of GTS. Although there are no published reports of reliability and validity on the Yale Schedule, this instrument was chosen since it has been widely used by the Yale group in several GTS studies and has been demonstrated to have good agreement between clinicians on a 'best estimate' method of diagnosis. Furthermore, there are no other instruments to date, for the overall evaluation of GTS and related behaviours, for which reliability and validity have been established.

The findings from the comparison between the NHIS and Yale Schedule on the seven key areas suggest that these items correlate well with the comparable items on the Yale Schedule. In fact, the findings on the seven key areas on the NHIS and the Yale Schedule were very similar. It was also demonstrated that there was no significant overall rater bias.

APPENDIX - 2

FAMILY PSYCHIATRIC HISTORY

☐☐☐☐☐ Family ☐☐☐☐ Person being interviewed ☐☐☐☐ Person being described

Name of person being described _____ Relationship to person being interviewed _____

First tell me about .....Does he/she work? What kind of job does she/he do? In general, what kind of person is she/he?

Now for some more specific questions:

Has..... ever had or does she/he now have any motor tics?

No ☐
Yes ☐

If YES, please describe these tics:

Has .....ever had or does she/she now have any vocal tics?

No ☐
Yes ☐

If YES, please describe these sounds:

If YES to both the above, has .....ever been diagnosed as having Tourette Syndrome?

No ☐
Yes ☐

If YES, when and by whom?

Has..... ever been a stutterer?

No ☐
Yes ☐

If YES, please describe and give age of onset and recovery if applicable:

Has .....ever had or does she/he now have behaviours that would be considered as obsessive compulsive (e.g. being excessively concerned about dirt, germ, contamination, or have repetitive thoughts that she/he considers as silly and irrational, or do repetitive acts such as cleaning, washing, checking, need for exactness and symmetry; or perform other rituals)

No ☐
Yes ☐

If YES, please describe:

BEHAVIOUR

		Ever ___	Age of onset
1	Fear might harm others	☐	.....
2	Fear might harm self	☐	.....
3	Violent or horrific images	☐	.....
4	Fear of blurting out obscenities or insults	☐	.....
5	Fear of doing something embarrassing	☐	.....
6	Fear will act on other Impulses (i.e. rob bank, shoplift, cheat cashier)	☐	.....
7	Fear will be responsible for things going wrong (i.e. company will go bankrupt because of self)	☐	.....
8	Fear something terrible might happen (burglary, fire, deaths, illnesses, misc. superstitions)	☐	.....
9	Other (aggressive obsessions)	☐	.....

10	Concerns or disgust with bodily waste or secretions (i.e. urine, faces, saliva)	☐	.....
11	Concerns about dirt or germs	☐	.....
12	Excessive concern with environmental contaminants (asbestos, radiation, toxic wastes)	☐	.....
13	Excessive concern with household items (i.e. cleansers, solvents, pets)	☐	.....
14	Concerned (self) will get ill	☐	.....
15	Concerned will get others ill (aggressive)	☐	.....
16	Other (contamination obsessions)	☐	.....
17	Forbidden or perverse sexual thoughts, images, or impulses	☐	.....
	IF EVER:		
18	Content involves children	☐	.....
19	Content involves animals	☐	.....
20	Content involves incest	☐	.....
21	Content involves homosexuality	☐	.....
22	Aggressive sexual behaviour towards others	☐	.....
23	Other (sexual obsessions)	☐	.....
24	Hoarding/Collecting obsessions	☐	.....
25	Religious obsessions	☐	....
26	Need for symmetry, exactness, or order	☐	....
27	Need to know or remember	☐	....
28	Fear of not saying certain things	☐	....
29	Fear of not saying things "just right"	☐	....
30	Intrusive (neutral) images	☐	....
31	Intrusive nonsense sounds, words, music	☐	....
32	Lucky/unlucky numbers	☐	....
33	Colors with special significance	☐	....
34	Other (miscellaneous obsessions)	☐	....

35	Somatic obsessions/compulsions	☐	....
36	Excessive or ritualized handwashing	☐	....
37	Excessive or ritualized showering, bathing, toothbrushing, or grooming	☐	....
38	Excessive cleaning of household items or other inanimated objects	☐	....
39	Other measures to remove contact with contaminants	☐	....
40	Other measures to remove contaminants	☐	....
41	Counting compulsions	☐	....
42	Checking doors, locks, stove, curling iron, coffee pot, emergency brake on car, etc.	☐	....
43	Checking that did not/will not harm others	☐	....
44	Checking that did not/will not harm self	☐	....
45	Checking that nothing terrible will happen	☐	....
46	Checking for contaminants	☐	....
47	Other (checking compulsions)	☐	....
48	Going in/out door, up/down chair, etc	☐	....
49	Other (repeating rituals)	☐	....
50	Ordering/arranging compulsions	☐	. . . .
51	Hoarding/collecting compulsions	☐	. . . .

52	Mental rituals (other than checking/counting)	☐	....
53	Need to tell, ask, confess	☐	....
54	Need to touch	☐	....
55	Measures to prevent: Harm to self (NOT CHECKING)	☐	....
56	Harm to others	☐	....
57	Terrible consequences	☐	....
58	Other (miscellaneous compulsions)	☐	....

Has..... ever had problems in relation to attention, concentration and activity? No ☐ Yes ☐

IF YES, please describe

1 Inattention

At least 3 of the behaviours listed below should have persisted and been characteristic of the child for the duration of the disorder.

		NA/No Info.	NO	YES
1	Did (_____) ever have trouble finishing things she/he was doing? (homework?, class assignments? independent work?) What trouble was that?	x	1	2
2	Did his/her mother (teacher) complain alot that she/he wasn't listening? . . . . . or that she/he was daydreaming alot?	x	1	2
3	Did (_____)find that almost anything could get his/her mind off the track of what she/he was doing? Did she/he get lost in the middle of a conversation?	x	1	2
4	Did (_____)have trouble paying attention or keeping his/her mind on (school work, other tasks)? Did his/her friends have the same trouble? Was (_____)worse than them	x	1	2
5	When (_____)was playing, could she/he usually stay with it for a while or did she/he find she/he wanted to do something else before long? Could she/he go along with the games other kids wanted to play? (score difficulty sticking to a play activity 2)	x	1	2
6	Total number of positive behaviours ☐			

2 Impulsivity

At least 3 of the behaviours listed below should have persisted and been characteristic of the child for the duration of the disorder.

		NA/No Info.	NO	YES
7	Did (_____)get into trouble sometimes because she/he would do things without thinking about them first? Would she/he usually think about something before she/he did it or would she/he just do it? Did she/he take alot of dares?	x	1	2
8	Did (_____)find she/he was doing one thing and then another and couldn't seem to stay with anything for long?	x	1	2
9	Did (_____) have trouble doing things that had to be done in a certain kind of order, or that had a lot of different steps? Like what? Did she/he like to do models? (difficulty not due to cognitive impairment)	x	1	2
10	Did someone (a grown-up) usually have to stay with (_____) when she/he played or did schoolwork; did they help him/her? Did she/he require more supervision than other kids? Were they afraid to leave him/her alone, on his/her own?	x	1	2
11	Did (_____) get into trouble alot for talking out of turn in school or talking without the teacher calling on him/her? What about for bothering people?	x	1	2
12	Did (_____)get into trouble because she/he couldn't always wait his/her turn in games? Was that like his/her friends, or did she/he stand out?	x	1	2
13	Total number of positive behaviours ☐			
14	Evidence of inattention and/or impulsivity	x	1	2

3 Hyperactivity

At least 2 of the behaviours listed below should have persisted and have been characteristic of the child for the duration of the illness.

CODE "2" IF CHILD HAD SYMPTOM:

		NA/No Info.	NO	YES
15	Could she/he NOT sit still? Did she/he fidget?	x	1	2
16	Could she/he NOT stay seated?	x	1	2
17	Was she/he overactive during his/her sleep also Explain	x	1	2
18	Was she/he always on the go? (or did she/he act as if driven by a motor?)	x	1	2
19	Total number of positive behaviours ☐			

4 Impaired Functioning

Sought or was referred for help by someone, took medication or had impaired functioning at home, at school, or with peers.

20	Did she/he or his/her parents look for help?	x	1	2
21	Did she/he take medicine for these problems?	x	1	2
22	Did she/he have trouble at home, at school and with friends? (i.e. in all situations)	x	1	2

5 Onset and duration

23	Age of onset before 7 years	x	1	2
24	Duration of disorder over six months	x	1	2

Has..... ever experienced a period lasting at least two weeks when she/he was depressed, sad, blue, despondent for the entire two weeks?

No ☐
Yes ☐

IF YES, please describe

Has..... ever experienced a period lasting at least two days when she/he was extremely excited, agitated, high for the entire time?

No ☐
Yes ☐

IF YES, please describe

Has..... ever experienced panic attacks in which they were extremely frightened, anxious, and afraid that something bad was going to happen to them? And this occured for no apparent reason?

No ☐
Yes ☐

IF YES, please describe

Has..... ever had any trouble with alcohol?

No ☐
Yes ☐

IF YES, please describe

Has..... ever had any trouble with abusing drugs?

No ☐
Yes ☐

IF YES, please describe

Is there anything else you would like to mention about this person?

Appendix 3: The Leyton Obsessional Inventory (LOI) - Adult version

Cooper's (1970) LOI represent the first rating scale to quantify subjective reports of obsessive feelings and behaviours. The inventory was originally constructed as a card sorting task to study house proud (perfectionist) housewives and validated with obsessionals, hoseproud housewives and normal subjects. The subject is asked to rate yes-no responses to 69 state and trait questions and then weighted responses of resistance (severity of symptoms) and interference (disability of symptoms) to daily activities. Obsessionals subjects were distinguished from normal subjects by not only the number of symptom responses and by the degree of resistance and interference.

A paper and pencil form of the LOI (Snowden 1980) was subsequently developed for administrative convenience using normal subjects. The main criticism of the instrument is the lack of reliability and validity data and the fact that it was not specifically developed for obsessive compulsive patients (Yayura-Tobias and Neziroglu 1983). However, this instrument was used in the present study as it has been shown in a previous GTS family study (Robertson and Gourdie 1990) that the GTS cases and non cases could be differentiated based on the LOI trait score.

TOURETTE LEYTON QUESTIONNAIRE

Name: _____

Age: _____ Sex: _____

Religion: _____

Do you have any Ashkenazi Jewish ancestry? Yes ____ No ____

tructions: Answer "yes" or "no" by placing a tick under either "Yes" or "No" the following questions about how you usually act or feel.

	YES	NO
Are you often inwardly compelled to do certain things even though your reason tells you it is not necessary?	____	____
Do unpleasant or frightening thoughts or words ever keep going over and over in your mind?	____	____
Do you ever have persistent imaginings that someone close to you (e.g. children or parents) might be having an accident or that something might have happened to them?	____	____
Have you ever been troubled by certain thoughts or ideas of harming yourself or persons in your family - thoughts which come and go without any particular reason?	____	____
Do you often have to check things several times?	____	____
Do you ever have to check gas or water taps or light switches after you have already turned them off?	____	____
Do you ever have to go back and check doors, cupboards or windows to make sure that they are really shut?	____	____
Do you hate dirt and dirty things?	____	____
Do you ever feel that if something has been used, touched or knocked by someone else it is in some way spoiled for you?	____	____
Do you dislike brushing against people or being touched in any way?	____	____
Do you feel that even a slight contact with bodily secretions (such as sweat, saliva, urine, etc) is unpleasant or dangerous, or liable to contaminate your clothes of belongings?	____	____

TOURETTE LEXTON QUESTIONNAIRE

Name: _____

Age: _____ Sex: _____

Religion: _____

Do you have any Ashkenazi Jewish ancestry? Yes ____ No ____

structions: Answer "yes" or "no" by placing a tick under either "Yes" or "No" the following questions about how you usually act or feel.

	YES	NO
Are you often inwardly compelled to do certain things even though your reason tells you it is not necessary?	____	____
Do unpleasant or frightening thoughts or words ever keep going over and over in your mind?	____	____
Do you ever have persistent imaginings that someone close to you (e.g. children or parents) might be having an accident or that something might have happened to them?	____	____
Have you ever been troubled by certain thoughts or ideas of harming yourself or persons in your family - thoughts which come and go without any particular reason?	____	____
Do you often have to check things several times?	____	____
Do you ever have to check gas or water taps or light switches after you have already turned them off?	____	____
Do you ever have to go back and check doors, cupboards or windows to make sure that they are really shut?	____	____
Do you hate dirt and dirty things?	____	____
Do you ever feel that if something has been used, touched or knocked by someone else it is in some way spoiled for you?	____	____
Do you dislike brushing against people or being touched in any way?	____	____
Do you feel that even a slight contact with bodily secretions (such as sweat, saliva, urine, etc) is unpleasant or dangerous, or liable to contaminate your clothes of belongings?	____	____

	YES	NO
Do you worry if you go through a day without having your bowels open?	____	____
Are you ever worried by the thought of pins, needles or bits of hair that might have been left lying about?	____	____
Do you worry about household things that might chip or splinter if they were to be knocked or broken?	____	____
Does the sight of knives, hammers, hatchets or other possibly dangerous things in your home ever upset you or make you feel nervous?	____	____
Do you tend to worry a bit about personal cleanliness or tidiness?	____	____
Are you fussy about keeping your hands clear?	____	____
Do you ever wash and iron clothes, or ask for this to be done, when they are not obviously dirty in order to keep them extra clean and fresh?	____	____
Do you take care that the clothes you are wearing are always clean and neat, whatever you are doing?	____	____
Do you like to put your personal belongings in set places or patterns?	____	____
Do you take great care in hanging and folding your clothes at night?	____	____
Are you strict about the house (or flat or room) always being kept very clean?	____	____
Do you dislike having a room untidy or not quite clean for even a short time?	____	____
Do you sometimes get angry that children (or other people) spoil your nice clean and tidy room(s)?	____	____
Do you like furniture or ornaments to be in exactly the same place always?	____	____
Do your easy chairs have cushions which you like to keep exactly in position?	____	____
If you notice any bits or specks on the floor or furniture, do you have to remove them at once (before the next clean-round)?	____	____
Do you ever clean or dust rooms that have not had time to get dirty just to make sure they are really clean?	____	____

	YES	NO
29. Do you ever have to clean, dust or wash things over again several times just to make sure they are really clean?	____	____
30. Do you have to keep to strict timetables or routines for doing ordinary things?	____	____
31. Do you have to keep a certain order for undressing and dressing, or washing and bathing?	____	____
32. Do you get a bit upset if you cannot do your work and/or housework at set times or in a certain order?	____	____
33. Do you ever have to do things over again a certain number of times before they seem quite right?	____	____
34. Do you ever count things without there being any necessity to do so?	____	____
35. Do you ever get behind with the work and/or housework because you have to do something over again several times?	____	____
36. Are you a person who often has a guilty conscience over quite ordinary things?	____	____
37. Are you the sort of person who has to pay a great deal of attention to details?	____	____
38. Are you ever over-conscientious or very strict with yourself?	____	____
39. Do you ever waste time by doing a thing more thoroughly than is really necessary just to see it is really finished?	____	____
40. Even when you have done something carefully, do you often feel that it is somehow not quite right or complete?	____	____
41. Do you feel unsettled or guilty if you haven't been able to do something exactly as you would like?	____	____
42. Do you always fail to explain things properly, in spite of having planned beforehand exactly what to say?	____	____
43. Do you have difficulty in making up your mind?	____	____
44. Do you have to turn things over and over in your mind for a long time before being able to decide about what to do?	____	____
45. Do you ask yourself questions or have doubts about a lot of things you do?	____	____

	YES	NO
46. Are there any particular things that you try to keep away from or that you avoid doing, because you know that you would be upset by them?	____	____
47. Do you find it difficult to throw things away?	____	____
48. Do you keep rather a lot of empty boxes, paper bags, old newspapers, or empty tins in case they come in useful one day?	____	____
49. Do you regard cleanliness as a virtue in itself?	____	____
50. Do you get more pleasure from saving money than from spending it?	____	____
51. Are you more careful with money than most people you know?	____	____
52. Do you keep regular accounts of the money you spend every day?	____	____
53. Do you usually look on the gloomy side of things?	____	____
54. Do people often get on your nerves and make you feel irritable?	____	____
55. When you feel critical of someone do you usually say what you are thinking?	____	____
56. Do you get angry or irritated if people don't do things carefully or correctly?	____	____
57. Do you try to avoid changes in your house or work or in the way you do things?	____	____
58. Do you try to avoid changing your mind once you have made a decision about something?	____	____
59. Are you a person who likes to stick to principles and decisions whatever the opposition or difficulties?	____	____
60. Do you pride yourself on thinking things over very carefully before making decisions?	____	____
61. Do you think that regular daily bowel movements are important for your health?	____	____
62. Do you often get scared that you might be developing some sort of serious illness or cancer?	____	____
63. Are you very systematic and methodical in your daily life?	____	____

	YES	NO
64. Do you like to get things done exactly right, down to the smallest detail?	____	____
65. Do you think it is important to follow rules and regulations exactly?	____	____
66. Do you like to have set times or orders for doing work and/or household jobs?	____	____
67. Are you ever late because you just can't seem to get through everything in time?	____	____
68. If you have to catch a train or keep an important appointment, do you have to plan out how to do it beforehand in great detail?	____	____

Appendix 4: The Leyton Obsessional Inventory (LOI) - Child version

The adult LOI was modified for use in children and termed the LOI- Child version, by Berg and colleagues (Berg et al 1986). This 44 item self report questionnaire has been found to successfully distinguish children and adolescents with OCD from both psychiatric and normal controls (Berg et al 1986). In addition, this instrument showed acceptable test retest reliability (based on patient's score obtained during the placebo phase) and clinical validity as indicated by scores differentiating placebo and active drug treatment.

Subsequently Berg et al (1988) established norms for a 20-item version based on a country-wide population of school students. Four factors accounted for 47% of the total variance in the principal components factor analysis: 1) general obsessive; 2) dirt-contamination; 3) numbers and luck; and 4) obsessional school work habits and indecisiveness. A cut off of 0.40 factor loading was used to associate an item with a factor. The items were internally consistent as demonstrated with Cronbach's alpha, the general obsessive scale showing the highest internal consistency with a Cronbach's alpha of 0.81, followed by dirt-contamination and numbers-luck at 0.65 and obsessional school habits, 0.49. Analyses attempted to determine whether some items were particularly likely to be present in those with the highest score (ie., a possibly high risk group for OCD) showed that eight items scored disproportionately higher in these subjects. These items were: feeling that something touched is spoiled, having to put things away at night in aspecial way, feeling angry if desk is messed up, spending extra time on home work, having trouble finishing home work, having a favourite number, moving in order to avoid bad luck and avoiding special numbers or words (Berg et al 1988).

Age/D.O.B.; Date;

Leyton Questionnaire (C).

Please Circle the appropriate answer either Yes or No.

If the answer is Yes please circle the appropriate number as well;

0 - This habit does not stop me from doing other things I want to do.

1 - This stops me a little or wastes a little of my time.

2 - This stops me from doing other things or wastes some of my time.

3 - This stops me from doing a lot of things and wastes a lot of my time.

1.	Do you often feel like you have to do certain things even though you know you don't really have to?	YES	0	1	2	3	NO
2.	Do thoughts or words ever keep going over and over in your mind?	YES	0	1	2	3	NO
3.	Do you have to check things several times?	YES	0	1	2	3	NO
4.	Do you hate dirt and dirty things?	YES	0	1	2	3	NO
5.	Do you ever feel that if something has been used or touched by someone else it is spoiled for you?	YES	0	1	2	3	NO
6.	Do you ever worry about being clean enough?	YES	0	1	2	3	NO
7.	Are you fussy about keeping your hands clean?	YES	0	1	2	3	NO
8.	When you put things away at night , do they have to be put away just right?	YES	0	1	2	3	NO
9.	Do you get angry if other students mess up your desk?	YES	0	1	2	3	NO

10. Do you spend a lot of extra time checking your homework to make sure that it is just right?	YES	0	1	2	3	NO
11. Do you ever have to do things over and over a certain number of times before they seem quite right?	YES	0	1	2	3	NO
12. Do you ever have to count several times or go through numbers in your mind?	YES	0	1	2	3	NO
13. Do you ever have trouble finishing your schoolwork or chores because you have to do something over and over again?	YES	0	1	2	3	NO
14. Do you have a favorite or special number that you like to count up to a lot or do things just that number of times?	YES	0	1	2	3	NO
15. Do you often have a bad conscience because you've done something even though no one else thinks it is bad?	YES	0	1	2	3	NO
16. Do you worry a lot if you've done something not exactly the way you like?	YES	0	1	2	3	NO
17. Do you have trouble making up your mind?	YES	0	1	2	3	NO
18. Do you ever go over things a lot that you have done because you aren't sure that they were the right things to do?	YES	0	1	2	3	NO
19. Do you move or talk in a special way to avoid bad luck?	YES	0	1	2	3	NO
20. Do you have special numbers or words you say, just because it keeps bad luck or bad things away?	YES	0	1	2	3	NO

Appendix 5: The Spielberger State Trait Anxiety Inventory (STAI)

The STAI (Spielberger et al 1970) is comprised of 2 separate self-report scales for measuring two distinct anxiety concepts: State anxiety and Trait anxiety. State anxiety is conceptualised as a transitory emotional state or condition of a person that varies in intensity and fluctuates in time, in reaction to circumstances that are perceived as threatening. Trait anxiety, on the other hand, is conceived of as a relatively stable personality predisposition that remains the same over time and across situations.

The validity of this concept was investigated by factor analysis (Bartsch and Nesslroade 1973) and obtained results supporting the State-Trait distinction. The STAI-State scale consists of 20 statements, that ask people how they feel at the time of completing the questionnaire. The STAI-Trait scale also consist of 20 statements about how they generally feel. Normative data give ranges of the mean Trait scores from 33 to 38, while the means of State scores range from 35 to 40 (Spielberger et al (1970).

The range of possible scores of the STAI varies from a minimum score of 20 to a maximum score of 80 on both the State and Trait subscales. The four categories of the State scale are 1) not at all; 2) somewhat; 3) moderately so; and 4) very much so. The categories for the Trait scale are 1) almost never; 2) sometimes; 3) often and 4) almost always.

The reliability of the STAI Trait scale is relatively high but low for the State scale, as would be expected for a measure designed to be influenced by situational factors. Evidence for the validity of the Trait scale comes from high correlations found by the authors (.79, .80, .83) with the Taylor Manifest Anxiety Scale (Spielberger et al 1970).

This scale was chosen for the present study as it measures both State and Trait anxiety, the former being sensitive to change, and the latter more stable across time and situations. It was felt that this is particularly relevant in the case of GTS, where situational anxiety is known to influence the symptoms.

NAME _____ DATE _____

DIRECTIONS. Read each statement and then tick to indicate how you feel right now, that is, at this moment. There are no right or wrong answers. Do not spend too much time on any one statement but give the answer which seems to describe your present feelings best.

	NOT AT ALL	SOME-WHAT	MODERATELY SO	VERY MUCH SO
1. I feel calm	☐	☐	☐	☐
2. I feel secure	☐	☐	☐	☐
3. I am tense	☐	☐	☐	☐
4. I am regretful	☐	☐	☐	☐
5. I feel at ease	☐	☐	☐	☐
6. I feel upset	☐	☐	☐	☐
7. I am presently worrying over possible misfortunes	☐	☐	☐	☐
8. I feel rested	☐	☐	☐	☐
9. I feel anxious	☐	☐	☐	☐
10. I feel comfortable	☐	☐	☐	☐
11. I feel self-confident	☐	☐	☐	☐
12. I feel nervous	☐	☐	☐	☐
13. I am jittery	☐	☐	☐	☐
14. I feel "high strung"	☐	☐	☐	☐
15. I am relaxed	☐	☐	☐	☐
16. I feel content	☐	☐	☐	☐
17. I am worried	☐	☐	☐	☐
18. I feel over-excited and "rattled"	☐	☐	☐	☐
19. I feel joyful	☐	☐	☐	☐
20. I feel pleasant	☐	☐	☐	☐

NAME _____ DATE _____

DIRECTIONS: Read each statement and then tick to indicate how you generally feel. There are no right or wrong answers. Do not spend too much time on any one statement but give the answer which seems to describe how you generally feel.

	ALMOST NEVER	SOME-TIMES	OFTEN	ALMOST ALWAYS
21. I feel pleasant	☐	☐	☐	☐
22. I tire quickly	☐	☐	☐	☐
23. I feel like crying	☐	☐	☐	☐
24. I wish I could be as happy as others seem to be	☐	☐	☐	☐
25. I am losing out on things because I can't make up my mind soon enough	☐	☐	☐	☐
26. I feel rested	☐	☐	☐	☐
27. I am "calm, cool, and collected"	☐	☐	☐	☐
28. I feel that difficulties are piling up so that I cannot overcome them	☐	☐	☐	☐
29. I worry too much over something that really doesn't matter	☐	☐	☐	☐
30. I am happy	☐	☐	☐	☐
31. I am inclined to take things hard	☐	☐	☐	☐
32. I lack self-confidence	☐	☐	☐	☐
33. I feel secure	☐	☐	☐	☐
34. I try to avoid facing a crisis or difficulty	☐	☐	☐	☐
35. I feel blue	☐	☐	☐	☐
36. I am content	☐	☐	☐	☐
37. Some unimportant thought runs through my mind and bothers me	☐	☐	☐	☐
38. I take disappointments so keenly that I can't put them out of my mind	☐	☐	☐	☐
39. I am a steady person	☐	☐	☐	☐
40. I get in a state of tension or turmoil as I think over my recent concerns and interests	☐	☐	☐	☐

Appendix 6: Obsessive compulsive symptom profile as used in the phenomenological analysis

OBSESSIONS

1. sexual theme
2. dirt/germ/contamination
3. need to tell/ask/know/remember
4. fear of something going wrong/becoming ill/bad happening
5. neatness and cleanliness
6. fear of harming self/others
7. fear of saying certain things/doing something embarassing
8. violent/aggressive theme
9. miscellaneous/superstitious
10. somatic obsessions

COMPULSIONS

1. symmetry/evening up
2. saying/doing things `just right'
3. checking
4. washing
5. cleaning/measures to remove contaminant
6. forced touching
7. hoarding
8. arranging
9. counting
10. repeating rituals