Genetic testing in children and adolescents with intellectual disability

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Purpose of review
Investigation for genetic causes of intellectual disability has advanced rapidly in recent years. We review the assessment of copy number variants (CNVs) and the use of next-generation sequencing based assays to identify single nucleotide variation in intellectual disability. We discuss the diagnostic yields that can be expected with the different assays. There is high co-morbidity of intellectual disability and psychiatric disorders. We review the relationship between variants which are pathogenic for intellectual disability and the risk of child and adolescent onset psychiatric disorders.

Recent findings
The diagnostic yields from genome wide CNV analysis and whole exome sequence analysis are high – in the region of 15 and 40%, respectively – but vary according to exact referral criteria. Many variants pathogenic for intellectual disability, notably certain recurrent CNVs, have emerged as strong risk factors for other neurodevelopmental disorders such as autism spectrum disorders, attention deficit hyperactivity disorder, and schizophrenia.

Summary
It is now conceivable that etiological variants could be identified in the majority of children presenting with intellectual disability using next-generation sequencing based assays. However, challenges remain in assessment of the pathogenicity of variants, reporting of incidental findings in children and determination of prognosis, particularly in relation to psychiatric disorders.

Keywords
chromosomal microarray analysis, developmental disorders, intellectual disability, whole exome sequencing, whole genome sequencing

INTRODUCTION

Half of all mental health problems encountered in adulthood have already been established by the age of 14, and up to 75% by age 24 [1]. Ten percent of children aged 5–16 years have a diagnosable problem such as conduct disorder, anxiety disorder, attention deficit hyperactivity disorder (ADHD), or depression [2]. These figures are substantially higher in children with intellectual disability [3]. DSM-5 [4] defines intellectual disability as a disorder with onset during the developmental period that adversely affects both intellectual and adaptive functioning, causing deficits in conceptual, social, and practical domains. Mild, moderate, severe, and profound degrees of disability are defined on the basis of adaptive functioning nowadays, rather than in terms of IQ test results. This is because every day reasoning and judgment-making by people with intellectual disability is often poorer than formal cognitive assessments imply. In the United Kingdom, the management of people with intellectual disability is led by local specialist learning disability services, if these are available.

In most cases, the cause of intellectual disability is unknown, especially in people who have a non-syndromic condition that lacks physical signs. Genomic variation is probably the leading cause of mild intellectual impairment in the general population. We each possess around 3 million polymorphic nucleotide variants in our genomes, the great majority of which are 'common' in the sense that we

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KEY POINTS

- CMA detects pathogenic variants in approximately 15% of children with developmental delay.
- WES may detect pathogenic variants in more 50% of children with developmental delay if used as a first tier diagnostic test and where parents are available for genotyping.
- Some variants pathogenic for intellectual disability, particularly CNVs, are strong risk factors for other neurodevelopmental disorders such as schizophrenia, ADHD and ASD.
- There is a paucity of information about specific associations of childhood onset psychiatric disorders with more recently identified variants pathogenic for intellectual disability.
- Systematic psychiatric phenotyping in genomic intellectual disability disorders is important to inform prognosis and facilitate early intervention.

share those variants with a substantial minority of other healthy individuals. These are often called single nucleotide polymorphisms (SNPs), defined as genomic differences in a single nucleotide, at a particular position in the genome where such variation is not rare. The cumulative impact of such variants, which occur in over 90% of all human genes, accounts for individual differences in complex physical and cognitive characteristics such as height and general intelligence. Most mild intellectual disability is probably attributable to common variation. Polygenic variation is also thought to contribute most genetic risk to the development of autism spectrum disorders (ASDs) [5].

A small proportion of such variants are unique, or almost unique to us as individuals (although they may also be found in our blood relatives). These are often known as private mutations, or as single nucleotide variants (SNVs). If they occur in a protein coding or regulatory part of a gene, they may alter genetic function if they are nonsynonymous with the typical nucleotide at that position. SNVs that arise in the germline of egg or sperm are termed 'de novo'. Disruptive SNVs are often associated with rare syndromes, and in a substantial proportion of such syndromes there is associated intellectual disability [6,7]. De-novo SNVs are thought to be responsible for most severe and profound intellectual disability [8], because affected individuals are unlikely to reproduce (and therefore do not pass on the mutation to future generations). SNVs in over 700 genes have been identified as contributing to autosomal dominant, autosomal recessive, and X-linked intellectual disability [9]. Whole exome sequencing (WES) can detect de-novo coding mutations if they occur within genes, but many SNVs are in intergenic regions, hence are not picked up by this technique. Whole genome sequencing (WGS) has the capacity to identify rare variants in the regions between genes too and is reported to find coding mutations and potentially pathogenic structural changes in up to 60% of severe/profound intellectual disability cases. However, the interpretation of WGS-identified noncoding (intergenic) variants is problematic because we know relatively little about their impact on gene regulation [7].

Another class of genetic anomaly is responsible for many cases of intellectual disability. Copy-number variants (CNVs) are structural changes in the genome that may duplicate or delete a segment of DNA. Such CNVs may be inherited or they may arise de novo, and they are usually between 15 kb and 1 Mb in length. They contribute to a range of neurodevelopmental disorders in both childhood [10] and adulthood [11▪▪]. Not all CNVs are pathogenic [12], but pathogenic CNV are found in up to 15% of children referred for genetic investigation of developmental delay [13]. Some CNVs are particularly strongly associated with intellectual disability [14], especially the milder forms, and these are often familial. Recent research has shown, in both European and North American general population cohorts, that deletions of medium size and large duplications of DNA have a small but measurable detrimental impact on the IQ, and educational achievement, of people who possess them. The explanation is thought to be that large CNVs disrupt the action of many genes within the affected region, and the detriment to cognition is therefore polygenic in origin [15,16▪,17▪].

GENETIC TESTING IN INTELLECTUAL DISABILITY

Chromosomal microarray analysis (CMA) encompass all types of array-based genomic analyses, including array-based comparative genomic hybridization (aCGH) and SNP arrays. To identify potentially pathogenic CNVs, DNA testing with aCGH is often the first-line diagnostic test for children with intellectual disability, in both Europe and North America [18,19▪,20]. The introduction of array-based copy-number analysis has led to the identification of both inherited and de-novo microdeletions and duplications in up to 15% of cases [21]. It is important to be aware that the attribution of pathogenicity to a CNV identified by a microarray is by no means straightforward, and there is no universally agreed standard in the United Kingdom. Many CNVs are excessively rare events, and conclusions regarding

the apparent strength of their association with cognition and psychiatric risk are therefore critically dependent on the interpretation of genomic data from unaffected comparison populations. In that regard, some variants previously considered to be pathogenic are being re-evaluated in light of increasing knowledge regarding their lack of association with disease in the general population.

WES is not routinely available in the UK's National Health Service, but some Regional Genetics Centres are using specialist panel arrays to detect small nucleotide variants that are known to be associated with intellectual disability and other disorders of neurodevelopment. The proportion of sporadic cases of intellectual disability caused by point mutations (SNV) is unknown. Exome sequencing has led to an increasing identification of de-novo variants [22], but in clinical practice, because of high locus heterogeneity, we often cannot with confidence attribute pathogenicity to individual mutations [8]. Evidence to guide such decision-making is slowly emerging from two recent UK national research studies that have recruited children with intellectual disability, of probable genetic etiology. The Deciphering Developmental Disorders (DDD) project employed genome-wide microarray and WES in a nationwide survey of children with complex developmental disorders of probable genetic origin [23▪▪]. Damaging de-novo coding mutations were found in 42% of these previously investigated, yet undiagnosed, children, the vast majority (~90%) of whom had associated intellectual disability. The more recent 100 000 Genomes project has used WGS to investigate a similar cohort, but the results are as yet unpublished [24].

WHO GETS TESTED?

A recent review, summarizing the outcome of several years of genetic testing for intellectual disability by a London community paediatric clinic [25▪], stated referrals had been made by a wide range of paediatric specialists, general practitioners, therapists, and schools. Practitioners called for genetic testing when they predicted it was likely to be of diagnostic value, based on criteria that included significant developmental delay, an unusual physical phenotype, epilepsy and parental consanguinity. Rarely, if ever, was the reason for genetic testing in intellectual disability prompted by a neurodevelopmental disorder that manifested in terms of behavior. If a genetic diagnosis is made following CMA investigation, this may lead to counseling about the likely prognosis or potential complications associated with the disorder [26▪]. A positive genetic finding in association with intellectual disability can provide information about recurrence risk in any future children, following cascade testing of biological relatives. It is important to be aware that CMA testing is not without drawbacks. In addition to the challenges of determining the pathogenicity of many variants that could have contributed to the neurodevelopmental disability, there is the ethical dilemma of reporting incidental findings to the family of the affected child. Such incidental findings could include the discovery of risk variants for serious adult-onset diseases, such as breast cancer. Genetic testing of children with intellectual disability is nowadays focused on the preschool population, whereas most child psychiatry services do not routinely assess children under 6 years of age. However, a recent survey of child and intellectual disability psychiatrists in the United Kingdom found that just over half had directly ordered genetic investigations at some time. Although the majority of psychiatrists thought genetic diagnosis was helpful for the family, the responses suggested that the diagnosis did not often result in management changes [27▪].

GENETIC CAUSES OF ID AND RISK OF PSYCHIATRIC DISORDERS

A broad range of childhood-onset psychiatric disorders is found in association with intellectual disability [28,29], but there is rarely any evidence of a specific genetic cause, with the exception of some cases of ASD. In adults with intellectual disability, there is a better understanding of the risks of psychiatric comorbidity in those bearing some rare genetic anomalies [30▪], such as a few well studied pathogenic CNVs, including schizophrenia's association with 22q11.2 or 1q21.1 microdeletions [31]. The reason for this paucity of knowledge is partly because the focus of previous research in children with intellectual disability has been on individuals with a small range of conditions, especially ASD [32▪] and ADHD [33▪], who are then subject to genetic screening. If damaging variants are found that are excessively rare in controls, there is a tendency to assume specificity. But because of high locus heterogeneity, it is hard to draw firm conclusions about the specific psychiatric pathogenicity of individual mutations [8]; mutations in genes associated with intellectual disability cause a wide range of phenotypes [34]. The alternative approach, undertaking broad psychiatric phenotyping of a representative sample of children with intellectual disability who have pathogenic genetic anomalies, is essential in order to set existing findings in context.

An excess of males is ascertained with neurodevelopmental disorders, including intellectual disability. The reasons for this bias is not known, but it is apparently not attributable to X-linked variants

because 'monogenic' X-linked intellectual disability accounts for no more than 8% or so of male cases [35], and a wide range of epidemiological studies has shown that the excess of males over females is up to 50%. This observation has been linked to the theory that for females, at genetic risk, to manifest the phenotype of neurodevelopmental dysfunction they need to possess higher mutational burden than males [36]. The phenomenon has been termed the female protective effect [37]. We know that males with normal-range IQ are more likely to be referred for genetic testing than females carrying the same autosomal variant, in populations with ASD. In the Simons Simplex Collection (SSC) of individuals with ASD, rare truncating SNVs show a slight female excess [38], but there are significantly more females than males with large (more than 400 kb) CNVs. Where the CNV was familial, maternal transmission was significantly higher than paternal transmission for these large deleterious CNVs. This contrasts with evidence that the rate of de-novo point mutations is generally increased among older fathers [39].

GENETIC TESTING IN INTELLECTUAL DISABILITY AND AUTISM SPECTRUM DISORDERS

NICE guidelines in the United Kingdom [40] do not recommend routine genetic tests for children with an autistic disorder, but states these will be done 'as recommended by your regional genetics center, if there are specific dysmorphic features, congenital anomalies and/or evidence of a learning (intellectual) disability'. It used to be thought that children with autistic disorders were usually developmentally delayed. In a sense that is true, insofar as there is a substantially increased risk of ASD in children with intellectual disability [3], and consequently the apparent population prevalence of ASD is influenced by the prevalence of intellectual disability. In the United States, the 2014 National Health Interview Survey of Autism [41] used a revised question ordering and a new approach that asked about autistic characteristics before developmental disabilities. This change resulted in substantial increases in the apparent prevalence of autistic disorders because children formerly assigned as developmental disabilities were designated as having a primary diagnosis of ASD instead.

At a population level, most newly diagnosed autism is not nowadays associated with generalized learning disabilities, probably because the clinical ascertainment of autistic features in children of normal range intelligence has improved in recent years [42▪]. The heritability of autism is very high [43▪] implying shared, familial genetic risk factors increase the likelihood of the diagnosis. Most risk at a population level is because of common variation, but this acts additively with rare variation to enhance risk in those ASD cases who carry a strongly acting de-novo variant [44▪]. A recent review of genetic risk in autism [45▪] emphasized that CNVs that are associated with a high risk of autism overlap with those known to cause intellectual disability. Not only are they expressed in the brain but are especially likely to involve genes that are structurally or functionally engaged in chromatin remodeling and transcription regulation. CNVs that are particularly strongly associated with ASD include duplications of 16p11.2, deletions of 15q13.3, 2p16.3, and 15q11.2 [46]. The yield of genetic testing of non-syndromal cases of autism in simplex families (which are less likely than multiplex families to carry heritable private mutations) can be estimated from internationally curated samples. Large structural abnormalities (CNVs), which are detectable by microarray, can be found in up to 10% of cases [32▪]. These CNVs are usually associated with relatively mild learning disabilities, and they comprise both inherited and de-novo anomalies. The wider use of exome sequencing is likely to increase the proportion of cases with an identifiable point mutation or indels that are the cause of loss of function or otherwise disrupting, the great majority of which are *de novo* (and likely to be paternal in origin [47]).

CONCLUSION AND FUTURE DIRECTIONS

In summary, when applied as a first-tier test for broadly defined developmental delay, current widely-available arrays (aCGH) detect pathogenic variants in approximately 15% of children. We know that, in a research context, WES gives a greater diagnostic yield of around 40% in children with severe developmental delay and it is estimated that yield could exceed 50% if used as a first tier diagnostic test [48▪▪]. We anticipate that WGS may provide even better identification of pathogenic variants, although there is still debate about the interpretation of intergenic SNV. However, accurate assignment of pathogenicity to SNV is getting better, prompting some to advocate re-analyzing existing data sets [48▪▪,49▪]. Economic analysis suggests that current use of WES reduces healthcare costs when applied to the investigation of intellectual disability [50▪].

The falling cost of WGS, and the associated improvement in our ability to detect very small CNVs, makes it likely that the first-tier investigation of childhood intellectual disability will be WGS-based in the future. However, our understanding of the relationship between genotype and phenotype in intellectual disability and related

neurodevelopmental disorders is at an early stage for the majority of variants. Epigenetic changes are also likely to have important modifying effect on these neurodevelopmental trajectories, but measurement of epigenetic changes and integration of this information and polygenic risk for prognostic predication represents a significant research challenge.

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Conflicts of interest

There are no conflicts of interest.

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