# Evaluation of the genetic association between adult obesity and neuropsychiatric disease

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**Abstract**

Extreme obesity (EO, BMI>50) is frequently associated with neuropsychiatric disease (NPD). As both EO and NPD are heritable central nervous system disorders, we assessed the prevalence of protein truncating (PTV) and copy number variants (CNV) in genes/regions previously implicated in NPD, in adults with EO (n=149) referred for weight loss/bariatric surgery. We also assessed the prevalence of CNVs in patients referred to University College London Hospital (UCLH) with EO (n=218) and obesity (O, BMI 35-50, n=374) and a Swedish cohort of participants from the community with predominantly O (n=161). The prevalence of variants was compared to controls in ExAC/gnomAd database.

In the discovery cohort (high NPD prevalence: 77%), the cumulative PTV/CNV allele frequency (AF) was 7.7 % vs 2.6% in controls (Odds Ratio (OR) 3.1, (95% CI 2-4.1, p<0.0001). In the UCLH EO cohort (intermediate NPD prevalence: 47%), CNV AF (1.8% vs 0.9% in controls, OR 1.95, 95% CI 0.96-3.93, p=0.06) was lower than the discovery cohort. CNV AF was not increased in the UCLH O cohort (0.8%). No CNVs were identified in the Swedish cohort with no NPD.

These findings suggest PTV/CNVs, in genes/regions previously associated with NPD, may contribute to NPD in patients with EO.

## INTRODUCTION

Obesity is a growing health challenge (1). In addition to its well established association with cardiometabolic disease, it is also associated with neuropsychiatric disease(2; 3) (NPD) including intellectual disability (ID), eating disorders, depression and bipolar disease, autism, attention deficit hyperactivity disorder, anxiety disorders and schizophrenia which can adversely affect patients' health outcomes (2). The etiology of the association between obesity and NPD is complex and incompletely understood. It has been proposed that NPD may predispose to obesity and similarly obesity has been posited to increase risk of NPD (2; 4; 5).

A shared etiology could also potentially contribute to the association between obesity and NPD. Both obesity and NPD are heritable polygenic conditions of the central nervous system (CNS), influenced by several hundred common genetic variants with individually small effect sizes (6; 7). Several of common genetic variants are associated with multiple NPDs hinting at shared genetic origins (6). In addition to common genetic variants, rare pathogenic genetic variants with large effect sizes, have also been associated with NPD. These have been identified predominantly in patients with early onset and/or severe NPD, who are enriched in rare variants in a single gene and/or large genetic deletions/duplications i.e. copy number variants (CNV). These rare variants frequently have pleiotropic effects and consequently there is substantial genetic overlap between NPDs such as autism, ID, schizophrenia and bipolar disease (8; 9). Rare genetic syndromes manifesting both obesity and NPD (10-12), suggest these CNS disorders may have a shared genetic etiology. The extent of the genetic association between obesity and NPD beyond these rare genetic syndromes is not fully established.

Studying extreme phenotypes can provide important biological insights of relevance to more common disease. We have been studying a cohort of adults with extreme obesity (EO, BMI>50) in the Extreme Obesity Study (EOS), a growing patient demographic that comprises ~30% of referrals to the bariatric medical/surgical program (13). We have previously reported that the majority of these individuals do not manifest severe early childhood onset obesity and known monogenic causes previously associated with severe childhood obesity are not prevalent in this group (13). This cohort has a high burden of NPD and therefore, presents an opportunity to investigate potential genetic associations between obesity and NPD. Here we assessed the prevalence of protein truncating variants (PTV: stop gain, frameshift and splice variants) in genes previously associated with NPD as well as CNVs in regions previously implicated in NPD. We undertook further studies to assess the prevalence of CNVs in two other cohorts with microarray data: a cohort of patients referred for obesity management to University College London Hospital, London UK (UCLH cohort) comprising patients with EO and less extreme obesity (O, BMI 35-50) and a Swedish cohort of participants with predominantly O recruited from the community. Notably the UCLH cohort had a lower prevalence of NPD than EOS while participants with NPD were excluded in the Swedish cohort.

## Materials and methods

### Discovery cohort (Extreme Obesity Study, EOS):

<u>Patient recruitment and phenotypic analysis</u>

The Extreme Obesity Study (EOS) has been approved by the University Health Network (Toronto) Institutional Research Ethics Board and has been conducted in compliance with the Declaration

of Helsinki. All patients gave informed consent. Patients were referred for weight loss to the endocrine clinic and/or bariatric program at University Health Network, Toronto (13). We approached all patients referred to the program, including those who did not undergo treatment and/or did not attend their initial appointment. For participants who did not attend their appointment, we had approval to undertake home visits to facilitate recruitment. Here we have reported the phenotypic and genetic analysis for 149 patients analyzed to date. For participants post bariatric surgery, pre-operative peak BMI, psychiatric co-morbidities and eating disorders (based on objective clinic assessments) were considered. Phenotypic parameters were compared with age and gender matched patients with less extreme obesity (O) from the same bariatric program (13). Family members were contacted where possible and recruited for assessment.

Psychiatric diagnoses were made based on MINI (Mini-International Neuropsychiatric Interview) and/or prior diagnosis and treatment for mental health conditions. We analyzed the prevalence of generalized anxiety disorder, panic disorder, social phobia, agoraphobia, post-traumatic stress disorder and obsessive-compulsive disorder under the category of anxiety related disorders. A diagnosis of an eating disorder (binge eating/emotional eating/loss of control eating) was made based on prior diagnosis and/or with the use of Binge Eating Scale (BES) and Emotional Eating Scale (EES) (14; 15). A diagnosis of ID was based on Wechsler Abbreviated Scale of Intelligence (16) and/or a prior clinical diagnosis. Education was ascertained by direct questioning as a routine part of their clinical assessment.

Diabetes was defined by an HbA1c of >6.5% (48mmol/mol) or the use of glucose lowering medications. Hypertension was defined by a persistent blood pressure reading of >140/90 mm Hg or use of anti-hypertensive medication. Dyslipidemia was defined by the use of lipid lowering

medication or as a fasting triglyceride of >150mg/dl (1.7 mmol/l), HDL < 40mg/dl (<1mmol/l) and/or LDL of >135mg/dl (3.5 mmol/l). Coronary artery disease was defined by prior percutaneous intervention, coronary artery bypass graft, use of anti-anginal medications and/or evidence of myocardial ischemia during angiography or stress testing.

Psychotropic and anticonvulsant medication usage was documented in both groups. Antipsychotic medications, mood stabilisers (lithium, valproate), anticonvulsant pain medications (pregabalin, gabapentin) and some antidepressants have been reported to be associated with weight gain (17).

Genetic analyses

Whole exome sequencing

149 patients underwent whole exome sequencing (WES) using Agilent SureSelect Human Exome Library Preparation V5 kit with paired end sequencing on a HiSeq2500 platform as described previously (13). Trimmed reads were aligned to the GRCh37 build human reference genome using BWA-MEM 0.7.8. Variants (SNV, indel) were called using GATK haplotype caller 3.2.2. An Annovar based pipeline was used for adding gene-based, feature-based and frequency-based annotations for variant filtering and prioritization. We further filtered out variants with less than 10X coverage and QD (quality by depth) <2.

Microarray:

Genome-wide microarray analysis was undertaken with the Illumina Infinium Global Screening Array-24 V2.0 as per manufacturer's instructions.

Panel of genes/CNVs:

We compiled a list of autosomal genes and CNV regions associated with various NPD based on a literature search: we conducted a PubMed search with the terms 'genetics' along with 'neuropsychiatric disease', 'autism', 'ID', 'mental retardation', 'schizophrenia', 'bipolar disease' and 'Tourette syndrome'. Genes/loci with rare variants identified in patients with NPD were selected if they had functional data or were identified in multiple studies. A list of reference genes/CNVs is included in Table 1 with further details in Tables 4 &5 and Supplementary Table 3.

WES for PTVs:

We assessed the prevalence of rare PTVs (minor allele frequency <0.5% in gnomAD) from our panel in the multi-ethnic EOS cohort. All PTVs were confirmed with Sanger sequencing. Novel PTVs have been submitted to the ClinVar portal (https://www.ncbi.nlm.nih.gov/clinvar/): Accession codes SCV000914238-SCV000914245.

We also assessed the prevalence of all PTVs in this gene panel in the gnomAD databases (http://gnomAd.broadinstitute.org/ last accessed October 9, 2018) (18), which includes whole exome and whole genome sequencing data from 141,000 participants of mixed ethnicities (55% Non-Finnish European, 11% South Asian, 8 % African/African American, 12% Latino, 8% Finnish European) and free of severe pediatric disease. We assessed PTVs in the entire gnomAD cohort as well as subsets of the cohort: those without neurological disease (non-neuro cohort, n=114,704) and healthy controls (n=60,146). As the overwhelming majority of patients in this study of mixed ethnicity were Caucasian of European descent and all PTVs were identified in this

ethnic group, we also assessed the prevalence of PTVs amongst non-Finnish Europeans in gnomAD.

The prevalence of PTVs from this gene panel was also investigated in the publicly available open access data set from the DECIPHER (DatabasE of genomiC varIation and Phenotype in Humans using Ensembl Resources) community(19) (www.decipher.sanger.ac.uk). We analyzed SNV and CNV data from 6057 patients enriched for NPD, predominantly ID and autism. The data is compiled from >250 genetic centers using a variety of methods including whole exome/genome sequencing and microarray analysis.

CNV analysis from WES and microarray:

CNV analysis was undertaken on both microarray and WES samples. CNVs confirmed by both methods were included in the final analysis. The prevalence of CNVs was compared to that in ExAC (http://exac.broadinstitute.org/) (20), a subset of gnomAD, which utilized similar methods (see below) to assess CNVs from WES. As the majority of CNVs in the cohorts with mixed ethnicity (EOS and UCLH) were identified in Caucasian subjects of European descent, we also compared the prevalence of CNVs amongst Caucasian patients vs non-Finnish participants from ExAC. We also assessed the prevalence of CNVs from this panel from open access data in DECIPHER (www.decipher.sanger.ac.uk) (19).

Microarray and WES CNV analysis: The Genome studio CNV partition plugin v2-1-1 was used to detect CNVs using a CNV confidence cut-off of 75. CNVs were called using the Log R ratio and B allele frequency. The Log R ratio and B allele frequency were jointly modelled as a bivariate Gaussian distribution, based on 14 possible genotypes, to calculate the likelihood for a given Log

R ratio and B allele frequency. The 14 genotypes are: DD (homozygous deletion), A, B, AA, AB, BB, AAA, AAB, ABB, BBB, AAAA, AAAB, ABBB, AABB. A sliding window strategy is used to define breakpoints.

The presence of these CNVs was also confirmed using XHMM C++ (21) from WES data. We have only presented the CNVs that were confirmed with both WES and microarray in this report. Read-depths across exome targets were normalized by principle-component analysis, then CNVs were identified and genotyped using a hidden Markov model. Regions with extreme GC-content, low complexity, or low coverage were excluded from analysis. We selected CNVs from our panel in Table 1 as well as deletions in genes associated with NPD from our gene panel for further assessment.

**Replication studies**

(UCLH) cohort:

Adult patients referred for management of their obesity were recruited as described previously (22). Genotyping was undertaken with the Illumina Human Core Exome array V1. CNVs were called for UCLH dataset (N=977) using PennCNV software (23). The results were filtered by: minimum number of SNPs in CNV>=10; CNV length>=30kb, confidence score>=10. After filtering and removal of patients without phenotyping data, we included data for 592 patients of whom 218 had EO and 374 had O. Cardiometabolic disease and NPD were diagnosed as per the criteria outlined above.

Karolinska cohort

Genotype array data for CNV analyses was available on 161 participants aged 18 with BMI >40 kg/m$^2$ and as reference 163 lean participants >45 years old who never had been overweight (BMI always < 25.0 kg/m$^2$). They were recruited by local advertisements or amongst participants in population-based surveys (EO n=24, O n=137). Inclusion criteria were BMI >40 at any age. This cohort has been described before (24). All subjects were at least third generation Scandinavian and lived in Sweden. Patients with a medical history of chronic inflammatory diseases other than cardiovascular disease, type 1 diabetes mellitus, renal insufficiency (serum creatinine > 200 µmol/L), drug addiction or psychiatric disease were excluded. They were genotyped using Affymetrix Human Mapping 500K SNP arrays. Genotype calling and quality controls has been described previously (24). Copy number variation was analyzed using one set of Affmetrix Human Mapping 500K SNP arrays, i.e. Mapping 250K Sty Array. The CNV analyses were carried using CNAG software, version 3.5.1 (http://www.genome.umin.jp/CNAG_DLpage/files/CNAGdownload_list.html).

**Statistical Analysis:**

Genetic analysis: We have reported the number of patients with a PTV/CNV as well as allele frequency (AF). AF=number of variants detected/ (2X number of patients). Analysis of phenotypes was undertaken using Proc Freq of SAS (version 9.4, Cary, NC). Contingency tables were generated using the CHISQ option with the Cochran-Mantel-Haenszel option to compute odds ratios. For dichotomous data, chi-squared tests and odd ratios were calculated. Fisher's Exact test was undertaken if cell count was less than 5. The Cochran-Armitage trend test was undertaken for ordinal variables. A p-value of <0.05 was considered significant. For all PTVs and CNVs in gnomAD/ExAC and DECIPHER, we corrected for the number of genomes/exomes

analyzed in the database to calculate AF. For PTV data from gnomAD, we also assessed the depth of coverage for each exon and nucleotide using a cut-off of 10.

**Results**

**EOS**

Phenotypic data in EOS:

Patient phenotypes are presented in Table 2. Phenotypic parameters were compared to patients with less extreme obesity (O, BMI 35-50) from the same programme. Patients with EO had a higher burden of NPD (EO 77.2% vs O 56.5%, p=0.002) including ID (EO 15.4% vs O none, p<0.0001), depression (EO 57.1% vs O 30.5%), Odds Ratio (OR) 6.84 (95% CI 3.54-13.19, p<0.0001) and anxiety related disorders (EO 43% vs O 9.9%), OR 2.61 (95% CI 1.56-4.36, p<0.0001). A greater proportion of patients with EO were on antidepressant medication (EO 57.7% vs O 40.4%) (OR 2, 95% CI 1.2-3.4, p=0.01) with no difference in antipsychotic medication use.

Genetic Analysis

Variants in known monogenic obesity genes/CNV regions: We did not detect any PTVs/CNVs variants in known monogenic obesity genes/CNVs including distal 16p11.2 deletions and *MC4R* (25; 26).

Variants in NPD-associated genes/loci (Tables 4&5, Figure 1, Supplementary Table 1):

We detected 23 genetic variants (combined AF 7.7%) in 23 patients (15.4%), including 8 stop gain variants (AF 2.7%) (Table 4) in our gene panel and 15 CNVs (8 deletions and 7 duplications, AF

5%) (Table 5) partially/completely overlapping our selected regions. The combined AF of PTV (stop gain, frameshift and splice variants) and CNVs from the panel of genes/loci in Table 1 was higher in EOS vs gnomAD/ExAC (AF 2.7% (PTV 1.7%, CNV 0.94%), (Odds Ratio 3.1, 95% CI 2-4.7, p<0.0001). The prevalence of PTVs/CNVs was similarly increased in EOS vs gnomAD participants without neurological disease (7.7% vs 2.5% OR 3.3, 95% CI 2.1-5, p<0.0001) and control participants (7.7% vs 2.8%, OR 2.9, 95% CI 1.9-4.4, p<0.0001) in gnomAD. The prevalence of PTV and CNV variants from our panel in the DECIPHER cohort was higher with a combined AF of 41.5 % (Supplementary Table 5). (Odds ratio vs EO 4.9, 95% Confidence Interval 3.4 to 6.8, p<0.0001)

PTV/CNV prevalence in Caucasian patients

20 of the 23 patients with PTVs/CNVs were Caucasian. The cumulative AF of PTV/CNVs amongst Caucasian patients in the cohort was significantly higher than non-Finnish Europeans in gnomAD/ExAC (8.5% vs 2.8%, OR 3.2 95% CI 2-5.1, p<0.0001).

10q11.22 duplications and 10q21.2q21.3 deletion:

We detected a 5.2 MB duplication in 10q11.22. 5MB CNVs have been reported in this region in patients with schizophrenia (27) and intellectual disability (28). Although it was not the focus of this project, we also detected a number of smaller duplications (624Kb-1.7MB) in this region (Supplementary Table 6). Smaller CNVs (both deletions and duplications) in this region have been associated with obesity (29-31). Increased copy number of *PPYR1* (NPY4R), a gene within this region, have been associated with increased BMI, especially in women (32).

We detected a 4MB deletion in chromosome 10q21.2q21.3 in a patient, who was also a participant in a prior pediatric obesity research study (33). Here we have confirmed that this is a

*de novo* variant (Supplementary Figure 1). We have presented additional previously unreported phenotypic details including a low average IQ (88, 23rd centile) with reduced perceptual reasoning (T score 95, 19th centile) in comparison to verbal comprehension (T score 95, 37th centile). This CNV region includes the gene *JMJD1C* which has been implicated in ID and Rett syndrome (34) and *ARID5B* which has been implicated in beiging of white adipocytes and energy expenditure (35).

**Phenotypes of patients with PTVs/CNVs**

There were no significant differences in age, gender or BMI, ethnicity, psychotropic medication usage or cardiometabolic parameters between those with and without PTVs and CNVs (Supplementary Table 2). Carriers of rare PTV/CNVs were likely to have a greater number of NPDs (2.5 ± 0.3 vs 1.7 ± 0.1, p=0.01) with greater prevalence of ID (n=10, 43.5% vs n=13, 10.3%, OR 6.7, 95% CI 2.4-18.3, p<0.0001) and lower education attainment (p=0.03).

Further details of the phenotypes of CNV carriers are included in Supplementary Table 1.

**UCLH cohort**

Phenotypic data for patients with EO and O are included in Table 3 and Figure 1. In total, there were 218 patients with EO. Compared to patients with EO in EOS, patients with EO in this cohort had lower BMI (EOS: 62.3 +/- 0.74, UCLH: 57.2 +/- 0.46; p <0.0001) and lower prevalence of NPD (EOS 77.2% vs 47%, p<0.0001) (Figure 1). None of the patients had ID.

NPD- associated CNV prevalence tended to be higher in patients with EO in this cohort vs ExAC. 8 CNVs were identified in total (Table 5, Figure 1, Supplementary Table 1) (AF 1.83% vs 0.94% ExAC, OR 1.95, 95% CI 0.97-3.93, p=0.06).

CNV prevalence amongst Caucasian patients

7 of the 8 CNVs were identified in Caucasian patients with EO. The cumulative AF of CNVs amongst Caucasian patients was 1.94% compared to 0.88% in non-Finnish Europeans in ExAC (OR 2.2, 95% CI 1.05-4.7, p=0.035).

CNV prevalence in patients with O

6 CNVs were identified in patients with 0 (AF 0.8% vs 0.94% ExAC, OR 0.8, 95% CI 0.4-1.8, p=0.7). 4 CNVs were seen in Caucasian patients (AF 0.68%) vs 0.88% in non-Finnish Europeans in ExAC (OR 0.7, 95% CI 0.3-2, p=0.6).

In the UCLH cohort a total of 13 small duplications (EO 7 duplications, AF 1.6%, O 6 duplications AF 0.8%) and 3 small deletions (EO 3 deletions, AF 0.7%, O no deletions) were seen in 10q11.22 involving *GPRIN2/NPY4R* (Supplementary Table 6).

**Karolinska cohort**

This cohort comprised 137 participants with O and 24 patients with EO recruited from the community. Presence of NPD was an exclusion criteria. No NPD- associated CNVs were detected. Smaller CNVs involving *GPRIN2/NPY4R* in 10q11.22 were seen with a total of 17 duplications (AF 6.2%) and 3 deletions (1.1%) amongst patients with O. 1 duplication was seen in a patient with EO (AF 2.1%) (Supplementary Table 6).

**Combined Data**

The cumulative CNV AF in participants with EO across 3 cohorts was 2.94 % vs 0.94% in ExAC (OR 3.1, 95% CI 2.1-4.8, p<0.0001). The AF amongst Caucasians with EO was 3.1% vs 0.88% in ExAC (OR 3.4, 95% CI 2.2-5.1, p<0.0001).

**Discussion**

Obesity and NPD are both heritable disorders of the CNS. The association between these disorders is complex and causal links in both directions have been proposed (2; 4; 5). More recent GWAS have highlighted that common variants can influence risk of NPD and obesity with Mendelian randomization studies indicating that BMI raising alleles causally increase the risk of various NPD i.e. obesity *per se* increases the risk of some NPD (6). Rare genetic syndromes characterized by both obesity and NPD indicate they may also have shared genetic origins (25). Studies of extreme phenotypes are powerful approaches to identify underlying biological pathways. Here we report a significantly higher cumulative prevalence of both PTVs/CNVs in genes/loci previously implicated in NPD, in a cohort of EO with high burden of NPD. The prevalence of CNVs was lower in patients from the UCLH cohort, which had a significantly lower burden of NPD. No pertinent CNVs were found in the Karolinska cohort in which participants with NPD were excluded. These studies suggest that genetic factors may contribute to the burden of NPD in patients with EO.

There was variability in NPD phenotypes amongst carriers of NPD- associated CNVs with some patients not manifesting any NPD. This is consistent with the published literature reporting pleiotropic effects and variable penetrance of these variants (36; 37).

The differing prevalence of CNVs amongst cohorts is likely multi-factorial. Differences in recruitment between studies influenced patient demographics. The discovery cohort included all patients with BMI >50 referred to the bariatric surgical/medical program. A significant proportion of patients did not undergo bariatric surgery in part due to the high prevalence of NPD: uncontrolled NPD and inability to comply with clinical recommendations, are contra-indications to surgery (38). Several patients did not attend their clinic appointments and were recruited outside of regular clinic hours and in some cases home visits were undertaken by the research team. Therefore, this cohort may be more representative of patients with EO in general but not a cohort of EO undergoing assessment for bariatric surgery. Notably, the prevalence of ID is concordant with detailed assessments in patients with severe obesity (3). The UCLH cohort was comprised entirely of patients who had been referred for assessment for bariatric surgery, for which ID and uncontrolled NPD is a contra-indication. This likely explains the lower overall prevalence of NPD and absence of ID. The EOS cohort also had a higher BMI compared to patients with EO in the UCLH cohort. In the Karolinska cohort, participants were recruited from the community and those with addiction and mental health concerns were excluded. Differences in microarray platforms and analysis may also explain the differences in CNV prevalence. This is less likely to be the major contributor based on coverage of the regions in which we detected CNVs across the 3 microarray platforms (Supplementary Figure 2-13).

The cumulative prevalence of CNVs was increased in EO (particularly in Caucasians) but not O, with highest prevalence in the EOS cohort which had the highest mean BMI. This is perhaps suggestive of a causal role in obesity. However, as these variants were individually rare, no definitive conclusions can be drawn. Familial studies for variants in *POGZ*, *NRXN1, DNM1L* and

10q21.2q21.3 deletion (Supplementary Figure 1) suggest these variants may influence body weight. Prior studies in children with *FBX011* (39) and *POGZ* (11) have reported increased body weight in some cases, although reports on adult BMI are lacking. More recent data from the UK Biobank study population indicate that CNVs in some genes/regions reported here are associated with increased body weight and BMI (40) in the general population, even in the absence of overt NPD. These include CNVs in *NRXN1,* 15q13.3 and 2q13 (all deletions) and 22q11.2 (distal) and 15q11.2 (deletions and duplications) (40). The CNVs/PTVs reported in this study are predicted to dysregulate synaptic formation, neurogenesis and neurotransmission, which have previously been shown to influence body weight and NPD (8; 12). Based on our findings and prior studies, we hypothesize that these PTVs/CNVs might predispose to obesity. Larger studies, with familial data and functional data are needed to confirm this hypothesis. If confirmed this may have clinical implications as increasingly CNV analysis is undertaken as part of the routine clinical work up of children with severe NPD. Children with CNVs reported here may be at risk of EO.

These variants may also potentially influence obesity risk indirectly by increasing risk for NPD, which *per se* has been associated with an increased risk of obesity (41-44). This may in part be due to the presence of eating disorders/reduced impulse control and the use of psychotropic medications. Antipsychotic medications (17), in particular, have been associated with body weight increases of ~5-10% (17). However, as the majority of patients do not have a history of antipsychotic medication use it is unlikely to be the major driver of obesity in these patients.

As alluded to above, familial data was available for 4 variants, of which 3 were *do novo.* The contribution of *de novo* vs inherited variants to NPD in patients with EO remains to be established.

Although not the major focus of the study, we detected a number of small duplications in 10q11.22 with variable sizes and start points. Smaller CNVs of similar size in this region including deletions and duplications have been reported in obesity (29-31). This region includes genes *GPRIN2* and *PPYR1* (*NPY4R*). *GPRIN2* is a regulator of neurite outgrowth (45) and expressed in the hypothalamus (27; 46). *PPYR1* encodes a receptor for neuropeptide Y (NPY) and pancreatic polypeptide (PP) a potential regulator of food intake (32). This gene region has a number of segmental duplications with variable coverage across microarrays making definitive conclusions about this region difficult and CNVs across this region are not rare in the general population (http://dgv.tcag.ca/dgv/app/home). Recent studies have suggested that individuals can carry up to 8 copies of *PPYR1* which are not detected with standard CNV detection methods (32; 47). In the Swedish Obesity Study (SOS) copy numbers of *PPYR1*, assessed by droplet PCR, have been positively correlated to BMI (32). Our findings appear to be consistent with the SOS with greater overall prevalence of 10q11.2 duplications in EO vs O. However, due to the limitations in interpreting CNV data with methods used in this study as outlined above, the findings need to be confirmed with more definitive methods with the inclusion of a control group assessed by the same method.

This study has several limitations. We do not have functional data to assess the impact of the identified genetic variants and familial data was not available in most cases. The participants in the current study were mainly Caucasian and therefore the prevalence of NPD- associated variants could not be reliably assessed in other ethnic groups. Whole exome sequencing data was unavailable for the UCLH and Karolinska cohorts and thus the presence of PTVs in these cohorts could not be determined. Due to the rarity of most individual CNVs and PTVs, we were

underpowered to ascertain the phenotypic effects of individual variants. Using publicly available datasets such as gnomAD and DECIPHER as a comparator can introduce bias due to differences in ethnicity, sequencing platforms and analysis methods across studies (48; 49). CNV analysis with WES, as taken in ExAC, is impacted by areas with low read depth (50). The depth of coverage at sites of single nucleotide changes in gnomAD are similar to EOS which may have attenuated the bias in comparing PTV between EOS and gnomAd. Individuals in gnomAd and ExAC were free of severe pediatric disease, but we do not have further data on their weight/BMI, medication use and current mental health status. Patients in DECIPHER were referred from various different populations with differing methods of genetic analysis and anthropometric data was not available. Many of the genes/CNVs identified have been associated with ID, but we were not able to undertake formal cognitive tests on all participants. Population studies have shown that control participants with CNVs associated with NPD are more likely to have impaired cognitive abilities when formally assessed (51; 52).

In conclusion, we demonstrate that rare PTVs and CNVs in genes/loci previously associated with NPD are prevalent in adults with EO and may contribute to the increased burden of NPD in these patients. The genes identified likely affect processes previously implicated in both NPD and body weight regulation. We therefore hypothesize that these variants may manifest pleiotropic CNS effects and contribute to NPD and possibly EO. Further studies are needed to confirm these findings and delineate underlying mechanisms.

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SD is the guarantor of this work and, as such, had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis

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Table 1. Panel of genes & CNVs (Further details in Supplementary Table 3)

| **Gene** | **Gene** | **Gene** | **Gene** |
|---|---|---|---|
| *ADNP* | *DEAF1* | *GRIN2A* | *NRXN2* |
| *ANK2* | *DIP2B* | *GRIN2B* | *RELN* |
| *ARID1A* | *DISC1* | *HIVEP2* | *SCN1A* |
| *ARID1B* | *DIXDC1* | *INPP5E* | *SCN2A* |
| *ASH1L* | *DNM1L* | *KAT6A* | *SETD5* |
| *ASXL3* | *DOCK8* | *KIF1A* | *SLC1A1* |
| *AUTS2* | *DSCAM* | *KIRREL3* | *SYN2* |
| *CDH15* | *EMC1** | *KMT2A* | *TBR1* |
| *CHD8* | *EPB41L1* | *KMT5B/SUV420H1* | *TRIP12* |
| *CNTNAP2* | *FBXO11* | *MBD5* | *ULK4* |
| *POGZ* | *GATAD2B* | *MYT1L* | *YAP1* |
| *COL4A3BP* | *GMPPB* | *NAA15* | |
| *CUL3* | *JMJD1C* | *NRG1* | |
| *SYNGAP1* | *GRIA4* | *NRXN1* | |

| **CNV** | **CNV CATEGORY** | **CANDIDATE GENES** |
|---|---|---|
| 2q13 | Deletion | *ANAPC1, BCL2L11, ZC3H8, FBLN7* |
| 10q11.2 | Duplication | *CHAT, MAPK8, SLC18A3* |
| 2p25.3 | Duplication & Deletion | *MYT1L* |
| 1q21.1 | Deletion & Duplication | *BCL9, GJA5, GJA8, PDZK1, PRKAB2* |
| 2q13 | Duplication | *ANAPC1, BCL2L11, MERTK* |
| 3q13.31 | Deletion | *DRD3, GAP43, LSAMP, ZBTB20* |
| 5p15.33-p15.32 | Deletion | *IRX1, IRX2, IRX4, NDUFS6* |
| 15q11.2 | Deletion & Duplication | *GABRB3, GABRA5, GABRG3, MAGEL2, NDN, UBE3A, TUBGCP5, NIPA1, NIPA2* |
| 15q13.3 | Deletion & Duplication | *CHRNA7, TRPM1* |
| 16p11.2 | Distal Deletion & Duplication | *DOC2A, MAPK3, PRRT2, QPRT, SEZ6L2, TBX6* |
| 22q11.2 | Distal Deletion and duplication | *TOP3B, MED15, DGCR6L, PIK4A* |

Inheritance is autosomal dominant for all genes except *: autosomal dominant and recessive

Table 2.

| | EOS Cohort | | | |
|---|---|---|---|---|
| | **BMI < 50** | **BMI ≥ 50** | ***P-Value*** | **Odds ratio** |
| N | 131 | 149 | | |
| Age (years) | 45.9 ± 0.9 | 46.4 ± 0.9 | 0.71 | |
| Male/female | 27/104 | 35/114 | 0.56 | |
| BMI | 43.3 ± 0.3 | 62.3 ± 0.7 | <0.0001 | |
| **Ethnicity** | | | 0.52 | |
| Caucasian | 98 (74.8%) | 118 (79.2%) | | |
| African-American | 8 (6.1%) | 11 (7.4%) | | |
| South Asian | 9 (6.8%) | 2 (1.3%) | | |
| Other | 16 (12.2%) | 21 (12.1%) | | |
| **Education** | | | 0.002 | |
| Some High School | 7 (5.3%) | 19 (12.8%) | | |
| High School Graduate | 21 (16%) | 36 (24.2%) | | |
| Post-secondary | 103 (78.7%) | 92 (61.7%) | | |
| Unknown | | 2 (1.3%) | | |
| **Neuropsychiatric Disease** | | | | |
| Number of conditions | 0.49 ± 0.05 | 1.33 ± 0.10 | <0.0001 | 2.61 (1.56-4.36) |
| Overall presence of NPD | 74 (56.5%) | 115 (77.2%) | 0.0002 | 48.9 (2.94-812.9) |
| Intellectual Disability | 0 | 23 (15.4%) | <0.0001 | 6.55 (0.79-54.05) |
| OCD | 1 (0.8%) | 7 (4.7%) | 0.04 | 3.66 (0.40-33.22) |
| ADHD | 1 (0.8%) | 4 (2.7%) | 0.18 | 1.46 (0.47-4.58) |
| Bipolar | 5 (3.8%) | 8 (5.4%) | 0.51 | 6.42 (0.33-125.4) |
| Schizophrenia | 0 | 3 (2%) | 0.15 | 0.89 (0.22-3.62) |
| Alcohol abuse | 4 (3.1%) | 4 (2.7%) | 0.87 | 3.02 (1.84-4.95) |
| Depression | 40 (30.5%) | 85 (57.1%) | <0.0001 | 6.84 (3.54-13.19) |
| Anxiety related disorders | 13 (9.9%) | 64 (43%) | <0.0001 | 2.61 (1.56-4.36) |
| **Use of antipsychotic Medications** | 6 (6.1%) | 16 (10.7%) | 0.20 | 1.86 (0.70-4.94) |
| **Use of antidepressant Medications** | 40 (40.4%) | 86 (57.7%) | 0.01 | 2.01 (1.20-3.37) |
| **Eating disorders** | | | | |
| Binge and/or emotional eating | 28 (21.4%) | 70 (47.6%) | <0.0001 | 3.34 (1.97-5.67) |
| **Cardiometabolic disease** | | | | |
| Type 2 Diabetes Mellitus | 54 (41.2%) | 47 (31.6%) | 0.10 | 0.66 (0.41-1.08) |
| Coronary Artery Disease | 20 (15.3%) | 16 (10.7%) | 0.28 | 0.68 (0.34-1.37) |
| Hypertension | 68 (51.9%) | 77 (51.6%) | 0.98 | 1.00 (0.63-1.61) |
| Dyslipidemia | 47 (35.9%) | 55 (36.9%) | 0.79 | 1.07 (0.66-1.74) |
| Sleep Apnea | 61 (46.6%) | 97 (65.1%) | 0.001 | 2.18 (1.35-3.54) |

Table 3. UCLH cohort

| | **UCLH cohort** | | |
|---|---|---|---|
| | **BMI < 50** | **BMI ≥ 50** | ***P-Value***** |
| N | 374 | 218 | |
| Age (years) | 44.7 ± 0.6 | 43.4 ± 0.8 | 0.15 |
| Male/female | 75/299 | 66/152 | 0.005 |
| BMI | 44.0 ± 0.20 | 57.2 ± 0.46 | <0.001 |
| **Ethnicity** | | | 0.08 |
| Caucasian | 294 (78.6%) | 180 (82.6%) | |
| African-American | 21 (5.6%) | 13 (6 %) | |
| South Asian | 16 (4.3%) | 9 (4.1%) | |
| Other | 43 (11.5%) | 16 (7.3%) | |
| **Neuropsychiatric Disease** | | | |
| Number of conditions | 0.57 ± 0.04 | 0.58 ± 0.05 | 0.93 |
| Overall presence of NPD | 167 (45.9%) | 100 (46.7%) | 0.84 |
| Intellectual Disability | 0 | 0 | |
| OCD | 3 (0.8%) | 1 (0.5%) | 0.37 |
| ADHD | 0 | 0 | |
| Bipolar | 2 (0.55%) | 0 | 0.39 |
| Schizophrenia | 2 (0.55%) | 0 | 0.39 |
| Alcohol abuse | 8 (2.2%) | 2 (0.9%) | 0.15 |
| Depression | 97 (26.8%) | 61 (28.5%) | 0.66 |
| Anxiety related disorders | 5 (1.4%) | 0 | 0.10 |
| Binge and/or emotional eating | 90 (25.1%) | 60 (27.5%) | 0.45 |
| **Cardiometabolic disease** | | | |
| Type 2 Diabetes Mellitus | 124 (33.2%) | 73 (33.5%) | 0.95 |
| Coronary Artery Disease | 12 (3.3%) | 2 (0.9%) | 0.07 |
| Hypertension | 132 (36.4%) | 88 (41.1%) | 0.26 |
| Dyslipidemia | 102 (28.2%) | 57 (26.6%) | 0.69 |
| Sleep Apnea | 59 (16.3%) | 57 (26.6%) | 0.003 |

Table 4. Protein truncating variants detected in EOS. All variants are heterozygous.

| Subject ID | Ethnicity | Gene | Protein | Function | Variant | Variant classification | CADD-Phred | Frequency of variant in gnomAD | Variant previously reported | Frequency of PTV variants in this gene in gnomAD | Patient phenotypes | Known phenotypes associated with gene | References |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| S003 | Caucasian | *NRXN1* | Neurexin1 | Presynaptic membrane | NM_001135659, c.C3619T, pR1207X | Stop gain | 44 | 0 | No | 0.0005 | BMI 66, ID, GAD, MDD, OCD, BED, PCOS, OSA, IR | Autism, schizophrenia, ID, Tourette's, OCD | PMID: 27195815, 21424692, 28641109, |
| s030 | Caucasian | *GRIA4* | Glutamate Ionotropic Receptor AMPA Type Subunit 4 | Glutamate neurotransmission | NM_000829, c.C2209T, pR737X | Stop gain | 38 | 0 | No | 0.0001 | BMI 86, ID, MDD, GAD, IHD, PCOS | ID, epilepsy | PMID: 29220673, 19623214 |
| S041 | Caucasian | *EMC1* | ER Membrane Protein Complex Subunit 1 | ER membrane protein | NM_001271427, c.C313T, p.R105X | Stop gain | 38 | 0.00001 | No | 0.0009 | BMI 57, ID, MDD, GAD, OCD, BED, T2DM, OSA, dyslipidemia | ID, cerebellar hypoplasia, hypotonia | PMID: 26942288 |
| S045 | Caucasian | *FBXO11* | Fbox protein 11 | Ubiquitination | NM_025133, c.C188G, p.S63X | Stop gain | 38 | 0 | No | 0.0001 | BMI 54, ID, facial dysmorphism, MDD with psychosis, GAD, BED, T2DM, CKD | Facial dysmorphism, ID, developmental delay, increased weight, neurobehavioural phenotypes | PMID:30057029 |
| S046 | Caucasian | *POGZ* | Pogo Transposable Element Derived With ZNF Domain | Zinc finger protein, mitosis | NM_001194938,c.G3452A,p.W1151X | Stop gain | 43 | 0 | No | 0.0001 | BMI 78, ID, cleft palate, neurobehavioural issues, T2DM, OSA, hypopituitarism | ID, schizophrenia, autism | PMID: 26942287 |
| S061 | Caucasian | *ULK4* | Unc-51 Like Kinase | Serine/threonine kinase, neuronal growth | NM_001322500, c.C2584T,p.R862X (rs199884004) | Stop gain | 48 | 0.00281 | No | 0.0047 | BMI 52, Schizo-affective disorder with bipolar features, emotional eating, PTSD, gambling, OSA | Schizophrenia, biplolar disorder, GAD | PMID: 24284070, 29391390, 30086552 |
| S072 | Caucasian | *DIXDC1* | DIX Domain Containing 1 | Actin binding, cell growth | NM_033425, cC160T, pR54X | Stop gain | 36 | 0 | No | 0.00045 | BMI 72.3, MDD, BED | Autism, bipolar disorder, schizophrenia | PMID: 27752079, 27829159 |
| S073 | Caucasian | *DNM1LL* | Dynamin 1 like | GTPase, mitochondrial and peroxisomal division | NM_005690, c.A28T, p.K10X | Stop gain | 41 | 0.00002 | No | 0.0002 | BMI 74, ID, MDD, GAD, borderline personality | ID, epileptic encepaholapthy | PMID:27145208, 30109270 |

ID=Intellectual disability, IR: insulin resistance, OCD: obsessive compulsive disorder, GAD: generalized anxiety disorder, MDD: major depression, OSA: obstructive sleep apnea, BED: Binge eating disorder

Table 5. Summary of CNVs identified in all 3 cohorts

| CNV ctoband | Type | Number of variants EOS cohort | Number of variants UCLH cohort | Number of variants Karolinska cohort | Range of estimated CNV size | Frequency in ExAC | Candidate genes | Phenotypes reported with CNVs at loci | References |
|---|---|---|---|---|---|---|---|---|---|
| 10q11.22 | Duplication | 1 | 0 | 0 | 5185 Kb | 8.30E-05 | *CHAT, MAPK8, SLC18A3* | Schizophrenia, ID | PMID: 23813976, 21948486, 27244233, 29621259 |
| 1q21.1 | Deletion | 2 | 0 | 0 | 1495 Kb-4206Kb | 4.84E-04 | *BCL9, GJA5, GJA8, PDZK1, PRKAB2* | Schizophrenia, ID, autism | PMID: 23813976, 26066539 |
| 22q11.21 | Deletion | 2 | 2 | 0 | 130 Kb-1150 Kb | 0.00E+00 | *TOP3B* | ID, schizophrenia, autism, congenital heart defects, obesity. Phenotypes have been reported with both large deletions and microdeletions | PMID: 21792059, 27537705, 28114601 |
| 22q11.21 | Duplication | 2 | 3 | 0 | 130 Kb-1150 Kb | 0.00E+00 | *TOP3B, DGCR6, PRODH, DGCR2, DGCR9, DGCR10, MED15, DGCR6L, PIK4A* | ID, autism. Phenotypes have been reported with both large and small CNVs | PMID: 21792059, 30614210, 28114601 |
| 15q13.3 | Duplication | 2 | 6 | 0 | 392 Kb-906 Kb | 2.00E-03 | *CHRNA* | ID, autism, MDD | PMID:21792059, 27853923, 26095975 |
| 15q11.2 | Deletion | 1 | 0 | 0 | 314 Kb | | *TUBGCP5, NIPA1, NIPA2* | Schizophrenia, ID, autism, seizures | PMID:21792059 |
| 15q11.2 | Duplication | 1 | 0 | 0 | 196 Kb | | *TUBGCP5, NIPA1, NIPA2* | Schizophrenia, ID, autism, seizures | PMID:21792059 |
| 10q21.2-21.3 | Deletion | 1 | 0 | 0 | 4400 Kb | 0.00030294 | *JMJD1C, ARID5B* | ID, cardiac defects | PMID:28378413, 26181491. This patients CNV has been reported previously in PMID: 29976977 |
| 3p22.1 | Deletion | 1 | 0 | 0 | 462 Kb | 0.00039672 | *ULK4* | Schizophrenia, biplolar disorder, anxiety | PMID: 24284070, 27670918, 29391390 |
| 2q13 | Deletion | 1 | 0 | 0 | 1704Kb | 0.00039672 | *ANAPC1, BCL2L11* | Schizophrenia, ID, ADHD | PMID:23813976, 29603867 |
| 2p25.3 | Duplication | 1 | 0 | 0 | 429 Kb | 0.0008 | *MYT1L* | Schizophrenia, ID, obesity | PMID: 22547139 , 25232846 |
| 9p24.3 | Deletion | 0 | 1 | 0 | 63 Kb | 0 | *DOCK8* | Autism | PMID:27824329 |
| 7q35 | Deletion | 0 | 2 | 0 | 563 Kb-891 Kb | 6.5022E-05 | *CNTNAP2* | Autism | PMID: 18179895 |

Further details on individual CNVs are in Supplementary Table 1. ID=Intellectual disability, IR: insulin resistance, OCD: obsessive compulsive disorder, GAD: generalized anxiety disorder, MDD: major depression, OSA: obstructive sleep apnea, BED: Binge eating disorder