**Supplementary material**

**Medical consequences of pathogenic CNVs in adults: Analysis of the UK Biobank, by Crawford et al.**

**Supplementary Table 1.** **List of CNVs analysed in the study.** “Genomic disorders (Cooper et al, 2011)” shows the list of CNVs proposed by Cooper et al,[8]; “Significant (Coe et al, 2014)” shows the CNVs that were significantly associated with neurodevelopmental disorders in Coe et al,[3]; “Genomic disorder (Dittwald et al, 2013)” shows the CNV list proposed by Dittwald et al.[6] “B-H FDR 0.1” indicates the number of phenotypes that were significantly associated with the CNV at a Benjamini-Hochberg FDR=0.1. The last two columns present known medical phenotypes associated with the CNVs analysed in the current study, and the literature sources they were derived from. We only considered large studies and do not include data on developmental delay, autism spectrum disorders, other neurodevelopmental disorders, behavioural problems or dysmorphisms. An “na“ denotes an absence of medical phenotypes reported in the key papers, although other phenotypes were reported. The Numbers of carriers include first-degree relatives. The number of genes in the CNV are the numbers in the typical regions, indicated by the “Location” according to hg19.

|  |  |  |  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
|  **CNV locus** |  **Location (hg19)** |  **N genes in CNV** |  **N carriers** |  **"Genomic disorders"**  **(Cooper, 2011)** |  **Significant (Coe, 2014)** |  **"Genomic disorder"**  **(Dittwald et al, 2013)** |  **Unreliable** |  **Rare** |  **Include in analysis** |  **B-H FDR <0.1** |  **Medical Phenotypes**  **(excluding**  **developmental delay**  **and neuropsychiatric**  **phenotypes)** |  **Source / reference** |
| 1p36del | chr1:0-2,500,000 | 76 | 1 | X | X |   |   | X |   |   |   |   |
| TAR\_del | chr1:145,39-145,81 | 17 | 75 | X | X | X |   |   | X | 0 | Limb anomalies, renal, cardiac, "Thombocytopenia absent radius" | OMIM, Klopocki et al, 2007 (PMID:17236129); Rosenfeld et al, 2012 (PMC3376272)  |
| TAR\_dup | chr1:145,39-145,81 | 17 | 436 | X | X | X |   |   | X | 1 | Skeletal/facial dysmorphia, ophthalmological | Rosenfeld et al, 2012 (PMC3376272)  |
| 1q21.1del | chr1:146,53-147,39 | 9 | 113 | X | X | X |   |   | X | 2 | Short stature, cardiac, cataracts, microcephaly | OMIM; Brunetti-Pieri et al, 2008 (PMID:19029900) |
| 1q21.1dup | chr1:146,53-147,39 | 9 | 177 | X | X | X |   |   | X | 1 | Short stature, scoliosis, gastric uclers, macrocephaly | OMIM; Brunetti-Pieri et al, 2008 (PMID:19029900) |
| NRXN1del | chr2:50,14-51,26 | 1 | 163 |   | X |   |   |   | X | 1 | Skeletal, cardiac, asthma/allergies | Dabel et al, 2013 (PMID:23495017) |
| 2q11.2del | chr2:96,74-97,68 | 22 | 31 | X | X | X |   |   | X | 0 | na | Riley et al, 2015 (PMID:26227573) |
| 2q11.2dup | chr2:96,74-97,68 | 22 | 29 | X |   | X |   |   | X | 0 | Short stature, gastrointestinal reflux | Riley et al, 2015 (PMID:26227573) |
| 2q13del(*NPHP1*) | chr2:110,86-110,98 | 3 | 2448 | X |   | X |   |   | X(common) | 0 | Nephronophthisis 1 | OMIM |
| 2q13dup(*NPHP1*) | chr2:110,86-110,98 | 3 | 1976 | X |   | X |   |   | X(common) | 0 |   | - |
| 2q13del | chr2:111,39-112,01 | 3 | 53 |   | X | X |   |   | X | 0 | Cardiac, hypogonadism, hypospadias | Riley et al, 2015 (PMID:26227573) |
| 2q13dup | chr2:111,39-112,01 | 3 | 71 |   | X | X |   |   | X | 1 | na | Riley et al, 2015 (PMID:26227573) |
| 2q21.1del | chr2:131,48-131,93 | 5 | 41 |   |   | X |   |   | X | 0 | na | Dharmadhikari et al, 2012 (PMID:22543972) |
| 2q21.1dup | chr2:131,48-131,93 | 5 | 59 |   |   | X |   |   | X | 0 | na | Dharmadhikari et al, 2012 (PMID:22543972) |
| 2q37del | chr2:239,72-243,2 | 51 | 1 | X | X |   |   | X |   |   |   |   |
| 2q37dup | chr2:239,72-243,2 | 51 | 1 | X |   |   |   | X |   |   |   |   |
| 3q29del | chr3:195,72-197,35 | 28 | 9 | X | X | X |   |   | X | 0 | gastrointestinal, ear, dental, cardiac | Glassford et al, 2016 (PMID:26738761) |
| 3q29dup | chr3:195,72-197,35 | 28 | 5 | X |   | X |   |   | X | 6 | Cardiac | Tassano et al, 2018 (PMID:29501613) |
| W-Hdel | chr4:1,55-2,09 | 13 | 0 | X | X |   |   | X |   |   |   |   |
| W-Hdup | chr4:1,55-2,09 | 13 | 3 | X | X |   |   | X |   |   |   |   |
| Sotos\_del | chr5:175,72-177,05 | 39 | 0 | X | X | X |   | X |   |   |   |   |
| 5q35dup | chr5:175,72-177,05 | 39 | 0 | X |   | X |   | X |   |   |   |   |
| 6q16del(*SIM1*) | chr6:100,84-100,91 | 1 | 5 | X |   |   | X |   |   |   |   |   |
| 6q16dup(*SIM1*) | chr6:100,84-100,91 | 1 | 2 | X |   |   | X | X |   |   |   |   |
| WBS\_del | chr7:72,74-74,14 | 26 | 1 | X | X | X |   | X |   |   |   |   |
| WBS\_dup | chr7:72,74-74,14 | 26 | 14 | X | X | X |   |   | X | 0 | Constipation, cardiac, | Morris et al, 2015 (PMID:26333794) |
| 7q11.23del\_distal | chr7:75,14-76,06 | 16 | 1 | X |   | X |   | X |   |   |   |   |
| 7q11.23dup\_distal | chr7:75,14-76,06 | 16 | 24 | X |   | X |   |   | X | 0 | na | Foudes et al, 2016 (PMID:27867344) |
| 8p23.1del | chr8:8,10-11,87 | 35 | 4 | X | X | X |   | X |   |   |   |   |
| 8p23.1dup | chr8:8,10-11,87 | 35 | 6 | X | X | X |   |   | X | 0 | Cardiac | Barber et al, 2013 (PMID:23345203) |
| EHMT1del | chr9:140,51-140,73 | 2 | 0 |   |   |   |   | X |   |   |   |   |
| EHMT1dup | chr9:140,51-140,73 | 2 | 1 |   | X |   |   | X |   |   |   |   |
| 10q11.21q11.23del | chr10:49,39-51,06 | 19 | 57 |   |   | X |   |   | X | 0 | consipation, GI reflux, epilepsy, sleep apnoea | Stankiewicz et al, 2012 (PMID:21948486) |
| 10q11.21q11.23dup | chr10:49,39-51,06 | 19 | 43 |   |   | X |   |   | X | 0 | na | Stankiewicz et al, 2012 (PMID:21948486) |
| 10q23del | chr10:82,05-88,93 | 29 | 3 | X | X | X |   | X |   |   |   |   |
| 10q23dup | chr10:82,05-88,93 | 29 | 7 | X |   | X |   |   | X | 0 | na | van Bon et al, 2010 (PMID:21248748) |
| Potocki-Shaffer\_del | chr11:43,94-46,02 | 22 | 0 | X | X |   |   | X |   |   |   |   |
| 11p11.2dup | chr11:43,94-46,02 | 22 | 1 | X |   |   |   | X |   |   |   |   |
| 13q12del(*CRYL1*) | chr13:20,98-21,10 | 2 | 379 | X |   |   |   |   | X | 0 | na | DECIPHER |
| 13q12dup(*CRYL1*) | chr13:20,98-21,10 | 2 | 10 | X |   |   |   |   | X | 0 | na | DECIPHER |
| 13q12.12del | chr13:23,56-24,88 | 10 | 85 |   |   | X |   |   | X | 0 | Spastic ataxia, Charlevoix-Saguenay | OMIM |
| 13q12.12dup | chr13:23,56-24,88 | 10 | 236 |   |   | X |   |   | X | 0 | na | DECIPHER |
| 15q11.2del | chr15:22,81-23,09 | 5 | 1664 | X | X | X |   |   | X(common) | 0 | Neurological | OMIM, Cox & Butler, 2015 (PMC4346944) |
| 15q11.2dup | chr15:22,81-23,09 | 5 | 2041 | X | X | X |   |   | X(common) | 0 | na | OMIM |
| PWS/AS\_del | chr15:23,68-28,39 | 116 | 1 | X | X | X |   | X |   |   |   |   |
| PWS/AS\_dup | chr15:23,68-28,39 | 116 | 19 | X | X | X |   |   | X | 0 | Dysmorphic, hypotonia, neurological | Piard et al, 2010 (PMID:20635369) |
| 15q11q13del\_BP3-BP4 (*APBA2, TJP*) | chr15:29,16-30,38 | 4 | 16 |   |   | X |   |   | X | 1 | seizures, hypotonia | Rosenfeld et al, 2011 (PMID:21248749) |
| 15q11q13dup\_BP3-BP4(*APBA2, TJP*) | chr15:29,16-30,38 | 4 | 53 |   |   | X |   |   | X | 0 | na | DECIPHER |
| 15q11q13del\_BP3 BP5 | chr15:29,16-32,46 | 17 | 1 |   |   | X |   | X |   |   |   |   |
| 15q11q13dup\_BP3 BP5 | chr15:29,16-32,46 | 17 | 9 |   |   | X |   |   | X | 0 | na | van Bon et al, 2009 (PMID:19372089) |
| 15q13.3del | chr15:31,08-32,46 | 8 | 42 | X | X | X |   |   | X | 2 | Seizures | Deutsch et al 2016 (PMID:26257138) |
| 15q13.3dup | chr15:31,08-32,46 | 8 | 240 | X |   | X |   |   | X | 0 | na | Hassfurther et al, 2016 (PMID:26997942) |
| 15q13.3del(*CHRNA7*) | chr15:32,02-32,45 | 1 | 10 |   |   | X |   |   | X | 0 | Seizures | Gillentine & Schaaf, 2015 (PMID:26095975) |
| 15q13.3dup(*CHRNA7*) | chr15:32,02-32,45 | 1 | 3031 |   |   | X |   |   | X(common) | 0 | na | Gillentine & Schaaf, 2015 (PMID:26095975) |
| 15q24del | chr15:72,90-78,15 | 77 | 1 | X | X | X |   | X |   |   |   |   |
| 15q24dup | chr15:72,90-78,15 | 77 | 9 | X | X | X |   |   | X | 0 | Hearing loss, hernias | Nevado et al, 2014 (PMID:24764755) |
| 15q25del | chr15:83,22-85,72 | 34 | 0 | X | X | X |   | X |   |   |   |   |
| 15q25dup | chr15:83,22-85,72 | 34 | 3 | X |   | X |   | X |   |   |   |   |
| Rubinstein-Taybi\_del | chr16:3,77-3,93 | 1 | 2 | X |   |   |   | X |   |   |   |   |
| Rubinstein-Taybi\_dup | chr16:3,77-3,93 | 1 | 1 | X |   |   |   | X |   |   |   |   |
| 16p13.11del | chr16:15,51-16,29 | 7 | 131 | X | X | X |   |   | X | 1 | na | Watson et al, 2014 (PMID:24773319 ) |
| 16p13.11dup | chr16:15,51-16,29 | 7 | 828 | X | X | X |   |   | X | 2 | na | Watson et al, 2014 (PMID:24773319 ) |
| 16p12.2-p11.2 del7.1-8.7-Mb | chr16:21,59-28,35 | 55 | 0 | X |   | X |   | X |   |   |   |   |
| 16p12.2-p11.2 dup7.1-8.7-Mb | chr16:21,59-28,35 | 55 | 1 | X |   | X |   | X |   |   |   |   |
| 16p12.1del | chr16:21,95-22,43 | 8 | 246 | X | X | X |   |   | X | 7 | Skeletal, congenital cardiac, seizures, hypotonia, microcephaly | Girirajan et al, 2010 (PMID:20154674) |
| 16p12.1dup | chr16:21,95-22,43 | 8 | 202 | X |   | X |   |   | X | 0 | - | - |
| 16p11.2distal\_del | chr16:28,82-29,05 | 11 | 58 | X | X | X |   |   | X | 3 | Obesity | Bachmann-Gagescu et al, 2010 (PMID:20808231) |
| 16p11.2distal\_dup | chr16:28,82-29,05 | 11 | 137 | X | X | X |   |   | X | 0 | - | - |
| 16p11.2del | chr16:29,65-30,20 | 30 | 110 | X | X | X |   |   | X | 7 | Congenital abnormalities, seizures, eye accommodation, obesity | Shinawi et al, 2009 (PMID19914906); Jacquemont et al, 2011 (PMC3637175) |
| 16p11.2dup | chr16:29,65-30,20 | 30 | 138 | X | X | X |   |   | X | 2 | Congenital abnormalities, seizures, eye accommodation, obesity | Shinawi et al, 2009 (PMID19914906), Jacquemont et al, 2011 (PMC3637175) |
| 17p13.3(*YWHAE*)del | chr17:1,25-1,30 | 1 | 26 | X | X |   | X |   |   |   |   |   |
| 17p13.3(*YWHAE*)dup | chr17:1,25-1,30 | 1 | 8 | X | X |   | X |   |   |   |   |   |
| 17p13.3(*PAFAH1B1*)del | chr17:2,49-2,59 | 1 | 1 | X | X |   | X | X |   |   |   |   |
| 17p13.3(*PAFAH1B1*)dup | chr17:2,49-2,59 | 1 | 2 | X | X |   | X | X |   |   |   |   |
| 17p12del(HNPP) | chr17:14,14-15,43 | 8 | 237 | X |   | X |   |   | X | 1 | HNPP | Lupski et al, 1992 (PMID:1301995) |
| 17p12dup(CMT1A) | chr17:14,14-15,43 | 8 | 124 | X |   | X |   |   | X | 3 | CMT1A | Lupski et al, 1992 (PMID:1301995) |
| Smith Magenis Syndrome | chr17:16,81-20,21 | 59 | 2 | X | X | X |   | X |   |   |   |   |
| Potocki-Lupski Syndrome | chr17:16,81-20,21 | 59 | 5 | X | X | X |   |   | X | 0 | Potoki-Lupski Syndrome | Potoki et al, 2007 (PMID:17357070) |
| 17q11.2del(*NF1*) | chr17:29,12-30,27 | 19 | 9 | X | X | X |   |   | X | 0 | Neurofibromatosis 1 (may have more tumours, cardiac and skeletal problems) | Kehrer-Sawatzki et al, 2017 (PMID:28213670) |
| 17q11.2dup(*NF1*) | chr17:29,12-30,27 | 19 | 2 | X | X | X |   | X |   |   |   |   |
| 17q12del | chr17:34,81-36,22 | 17 | 9 | X | X | X |   |   | X | 2 | Kidney, liver, diabetes, ophthalmological, "Renal cysts and diabetes syndrome" | Rasmussen et al, 2016 (PMID:27409573) |
| 17q12dup | chr17:34,81-36,22 | 17 | 101 | X | X | X |   |   | X | 1 | Ophthalmological | Rasmussen et al, 2016 (PMID:27409573) |
| 17q21.31del | chr17:43,70-44,29 | 10 | 0 | X | X | X |   | X |   |   |   |   |
| 17q21.31dup | chr17:43,70-44,29 | 10 | 4 | X |   | X |   | X |   |   |   |   |
| 17q23.1q23.2del | chr17:58,30-60,29 | 13 | 0 |   |   | X |   | X |   |   |   |   |
| 17q23.1q23.2dup | chr17:58,30-60,29 | 13 | 2 |   |   | X |   | X |   |   |   |   |
| 22q11.2del | chr22:19,04-21,47 | 61 | 10 | X | X | X |   |   | X | 0 | VCFS/DGS, multiple phenotypes | OMIM; McDonald-McGinn et al, (PMID:27189754 ) |
| 22q11.2dup | chr22:19,04-21,47 | 61 | 280 | X | X | X |   |   | X | 2 | Hypotonia, seizures, vision, hearing, heart defects | Wentzl et al, 2008 (PMID18707033) |
| 22q11.2distal\_del | chr22:21,92-23,65 | 26 | 5 | X | X | X |   |   | X | 1 | Congenital, cardiac | Garavelli et al, 2011 (PMID:22582037); D'Angelo et al, 2018 (PMID:29441128) |
| 22q11.2distal\_dup | chr22:21,92-23,65 | 26 | 13 | X | X | X |   |   | X | 0 | Seizures, facial dysmorphism, urogenital, hypotonia | Pinchefsky et al, 2017 (PMID:29147671) |
| SHANK3\_del | chr22:51,11-51,17 | 1 | 0 | X | X |   |   | X |   |   |   |   |
| SHANK3\_dup | chr22:51,11-51,17 | 1 | 0 | X | X |   |   | X |   |   |   |   |

**Supplementary Table 2**. **CNV Calling Criteria.** Criteria used for calling CNVs (following our previous report, Kendall et al, 2016). CNVs at *EHMT1* and *SHANK3* were required to intersect at least 1Mbp distance, as small deletions and duplications were found to be common in samples with poor QC criteria, indicating that small CNVs in these telomeric regions were likely to be false-positives.

|  |  |
| --- | --- |
| **CNV** | **Criteria** |
| 1p36 del/dup | Size >50% of critical region, affecting *GABRD* |
| TAR del/dup | Size >50% of critical region |
| 1q21.1 del/dup | Size >50% of critical region |
| *NRXN1* del | Exonic deletions |
| 2q11.2 del/dup | Size >50% of critical region, affecting both *LMAN2L* and *ARID5A*  |
| 2q13 del/dup | Size >50% of critical region |
| 2q13 del/dup (*NPHP1*) | Size >50% of critical region, affecting *NPHP1* |
| 2q21.1 del/dup | Size >50% of critical region |
| 2q37 del/dup (*HDAC4*) | Size >50% of critical region, affecting *HDAC4* |
| 3q29 del/dup | Size >50% of critical region |
| Wolf-Hirschhorn del/dup | Size >50% of critical region |
| Sotos Syn/5q35 dup | Size >50% of critical region |
| 6q16 del/dup (*SIM1*) | Exonic deletions; whole gene duplications |
| Williams Beuren Syn del/dup | Size >50% of critical region |
| 7q11.23 distal del/distal dup | Size >50% of critical region |
| 8p23.1 del/dup | At least 1Mbp of critical region |
| 9q34 del/dup (*EHMT1*) | At least 1Mbp CNVs, including *EHMT1* |
| 10q11.21q11.23 del/dup | Size >50% of critical region |
| 10q23 del/dup | At least 1Mbp, including *NRG3* and *GRID1*  |
| Potocki-Shaffer Syn del/11p11.2 dup (*EXT2*) | Size >50% of critical region, including *EXT2* |
| 13q12 del/dup (*CRYL1*) | Exonic deletions; whole gene duplications |
| 13q12.12 del/dup | Size >50% of critical region |
| 15q11.2 del/dup | Size >50% of critical region |
| PWS del/dup | Full critical region, ~4Mbp |
| 15q11q13 del/dup BP3-BP4  | Size >50% of critical region |
| 15q11q13 del/dup BP3-BP5 | Size >50% of critical region |
| 15q13.3 del/dup | Size >50% of critical region |
| 15q13.3 del/dup (*CHRNA7*) | Size >50% of critical region, affecting *CHRNA7*  |
| 15q24 del/dup | At least 1Mbp between the A-E intervals |
| 15q25 del/dup | At least 1Mbp between the A-D intervals |
| Rubinstein-Taybi del/dup (*CREBBP*) | Exonic deletions; whole gene duplications |
| 16p13.11 del/dup | Size >50% of critical region |
| 16p12.1 del/dup | Size >50% of critical region |
| 16p12.2-p11.2 del/dup (7.1-8.7 Mb) | Size >50% of critical region |
| 16p11.2 distal del/distal dup | Size >50% of critical region |
| 16p11.2 del/dup | Size >50% of critical region |
| 17p13.3 del/dup (*YWHAE*) | Exonic deletions; whole gene duplications |
| 17p13.3 del/dup (*PAFAH1B1*) | Exonic deletions; whole gene duplications |
| 17p12 del (HNPP)/dup (CMT1A) | Size >50% of critical region, affecting *PMP22* |
| Smith-Magenis/Potocki-Lupski Syn | Size >50% of critical region |
| 17q11.2 del/dup (*NF1*) | Size >50% of critical region, affecting *NF1* |
| 17q12 del/dup | Size >50% of critical region |
| 17q21.31 del/dup | Size >50% of critical region |
| 17q23.1q23.2 del/dup | Size >50% of critical region |
| 22q11.2 del/dup | Size >50% of critical region |
| 22q11.2 distal del/dup | Size >50% of critical region |
| *SHANK3* del/dup | At least 1Mbp CNVs, including *SHANK3* |
| “Large” CNVs | Size > 20Mbp + >50 genes |

**Supplementary Table 3. List of UK Biobank disease codes used to construct each phenotype group**.

(This table is available as a stand-alone file)

**Supplementary Table 4.** **Comparison of CNV frequencies with previous control populations**. The frequencies of the 54 CNV in the UK Biobank (including first-degree relatives, but excluding people who are not white British or Irish) are compared with 26,626 population controls from previous studies reported by us. These other controls originated from various datasets where we had access to the raw data, or had completed all the analysis ourselves, applying the same criteria. Details on these control datasets are presented in our previous publication [10].

|  |  |  |  |
| --- | --- | --- | --- |
| **CNV** | **Number of carriers in UK Biobank** | **UK Biobank frequency** **(%)** | **Control frequency (Kendall et al, 2016) (%)** |
| TAR\_del | 75 | 0.018 | 0.026 |
| TAR\_dup | 436 | 0.103 | 0.060 |
| 1q21.1del | 113 | 0.027 | 0.026 |
| 1q21.1dup | 177 | 0.042 | 0.049 |
| NRXN1del | 163 | 0.039 | 0.034 |
| 2q11.2del | 31 | 0.007 | 0.004 |
| 2q11.2dup | 29 | 0.007 | 0.008 |
| 2q13del | 53 | 0.013 | 0.004 |
| 2q13dup | 71 | 0.017 | 0.015 |
| 2q13del\_NPHP1 | 2448 | 0.581 | 0.571 |
| 2q13dup\_NPHP1 | 1976 | 0.469 | 0.593 |
| 2q21.1del | 41 | 0.010 | 0.004 |
| 2q21.1dup | 59 | 0.014 | 0.015 |
| 3q29del | 9 | 0.002 | 0.004 |
| 3q29dup | 5 | 0.001 | 0.008 |
| WBS\_dup | 14 | 0.003 | 0.008 |
| 7q11.23dup\_distal | 24 | 0.006 | 0.011 |
| 8p23.1dup | 6 | 0.001 | 0.000 |
| 10q11.21q11.23del | 57 | 0.014 | 0.019 |
| 10q11.21q11.23dup | 41 | 0.010 | 0.000 |
| 10q23dup | 7 | 0.002 | 0.000 |
| 13q12.12del | 85 | 0.020 | 0.019 |
| 13q12.12dup | 236 | 0.056 | 0.045 |
| 13q12del\_CRYL1 | 379 | 0.090 | 0.101 |
| 13q12dup\_CRYL1 | 10 | 0.002 | 0.008 |
| 15q11.2del | 1664 | 0.395 | 0.368 |
| 15q11.2dup | 2041 | 0.484 | 0.571 |
| PWS\_dup | 19 | 0.005 | 0.000 |
| 15q11q13del\_BP3\_BP4 | 16 | 0.004 | 0.004 |
| 15q11q13dup\_BP3\_BP4 | 53 | 0.013 | 0.015 |
| 15q11q13dup\_BP3\_BP5 | 9 | 0.002 | 0.000 |
| 15q13.3del | 42 | 0.010 | 0.019 |
| 15q13.3dup | 240 | 0.057 | 0.038 |
| 15q13.3del\_CHRNA7 | 10 | 0.002 | 0.011 |
| 15q13.3dup\_CHRNA7 | 3031 | 0.719 | 0.687 |
| 15q24dup | 9 | 0.002 | 0.000 |
| 16p11.2del | 110 | 0.026 | 0.019 |
| 16p11.2dup | 138 | 0.033 | 0.045 |
| 16p11.2distal\_del | 58 | 0.014 | 0.049 |
| 16p11.2distal\_dup | 137 | 0.033 | 0.030 |
| 16p12.1del | 246 | 0.058 | 0.045 |
| 16p12.1dup | 202 | 0.048 | 0.049 |
| 16p13.11del | 131 | 0.031 | 0.045 |
| 16p13.11dup | 828 | 0.197 | 0.222 |
| 17p12del\_HNPP | 237 | 0.056 | 0.030 |
| 17p12dup\_CMT1A | 124 | 0.029 | 0.030 |
| Potocki\_Lupski | 5 | 0.001 | 0.000 |
| 17q11.2del\_NF1 | 9 | 0.002 | 0.004 |
| 17q12del | 9 | 0.002 | 0.000 |
| 17q12dup | 101 | 0.024 | 0.026 |
| 22q11.2del | 10 | 0.002 | 0.000 |
| 22q11.2dup | 280 | 0.066 | 0.079 |
| 22q11.2distal\_del | 5 | 0.001 | 0.004 |
| 22q11.2distal\_dup | 13 | 0.003 | 0.000 |

**Supplementary Figure 1. Comparison of CNV frequencies with previous control populations**: The figure is based on Supplementary Table 4, above.

**Supplementary Table 5. CNV calls in each batch.** The UK Biobank genotyped the samples in 106 batches. This table presents the numbers of each CNV in each of these batches, for white British or Irish subjects, including first-degree relatives, and after array QC. There are no outliers from the expected Poisson distribution, after multiple testing correction, indicating a lack of batch effects on the calling of these 54 CNVs.

(This table is available as a stand-alone file)

**Supplementary Table 6. All CNV/phenotype associations, grouped by CNV**. The nomenclature follows that for Table 1 in the main text.

(This table is available as a stand-alone file)

**Supplementary Table 7. All CNV/phenotype associations, grouped by phenotype.** Significant results at FDR=0.1 are shown in bold.

(This table is available as a stand-alone file)

**Supplementary Table 8. Causes of death during follow-up among CNV carriers**. The list is sorted by CNV.

(This table is available as a stand-alone file)

**Supplementary Table 9**. **Effect of 16p11.2 deletions on phenotypes before and after correction with BMI**. Obesity is a known consequence of deletions at 16p11.2. We tested whether obesity is the factor leading to other (“novel”) associations. The table shows the changes to p-values and ORs after BMI was added as a co-variate to Firth’s logistic regression analysis. Other co-variates were kept the same. Significant results at FDR=0.1 are shown in red. Excluding obesity, four of six originally significant associations are still significant.

|  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| **Phenotype** | **p-value original** | **p-value BMI** | **B-H FDR** | **OR original** | **OR BMI** | **OR Lower 95% original** | **OR Upper 95%\_original** | **OR Lower 95%\_BMI** | **OR Upper 95%\_BMI** |
| diabetes\_other | 2.54E-11 | 0.0064 | 0.088 | 6.07 | 2.11 | 3.77 | 9.50 | 1.24 | 3.48 |
| obesity | 7.39E-10 | 0.43 | 0.76 | 6.81 | 1.31 | 4.01 | 11.01 | 0.66 | 2.48 |
| anaemia | 2.15E-06 | 5.40E-05 | 0.0050 | 4.03 | 3.30 | 2.38 | 6.48 | 1.92 | 5.36 |
| hypertension | 9.44E-06 | 0.66 | 0.90 | 2.55 | 1.11 | 1.69 | 3.83 | 0.71 | 1.72 |
| asthma | 1.33E-05 | 0.0030 | 0.052 | 2.71 | 1.97 | 1.77 | 4.08 | 1.27 | 3.00 |
| renal\_failure | 6.04E-05 | 0.0051 | 0.078 | 5.11 | 2.93 | 2.49 | 9.45 | 1.42 | 5.47 |
| osteoarthritis | 0.00031 | 0.36 | 0.70 | 2.36 | 1.24 | 1.50 | 3.63 | 0.78 | 1.95 |
| respiratory | 0.0023 | 0.026 | 0.19 | 2.59 | 1.97 | 1.44 | 4.37 | 1.09 | 3.33 |
| heartfailure | 0.0045 | 0.074 | 0.36 | 4.16 | 2.31 | 1.64 | 8.84 | 0.91 | 4.93 |
| died\_to\_2016 | 0.0050 | 0.012 | 0.11 | 2.88 | 2.54 | 1.42 | 5.27 | 1.25 | 4.66 |
| high\_cholesterol | 0.0058 | 0.80 | 0.96 | 2.00 | 1.06 | 1.23 | 3.15 | 0.65 | 1.70 |
| hernia | 0.0084 | 0.072 | 0.36 | 1.99 | 1.58 | 1.20 | 3.16 | 0.96 | 2.52 |
| atherosclerotic\_vascular\_disease | 0.010 | 0.016 | 0.13 | 3.50 | 3.19 | 1.40 | 7.33 | 1.27 | 6.67 |
| renal | 0.015 | 0.083 | 0.38 | 3.16 | 2.20 | 1.28 | 6.49 | 0.89 | 4.54 |
| gout | 0.017 | 0.92 | 1 | 3.15 | 1.05 | 1.26 | 6.64 | 0.37 | 2.42 |
| migraine | 0.020 | 0.019 | 0.15 | 2.59 | 2.63 | 1.18 | 4.98 | 1.20 | 5.06 |
| low\_WBC\_count | 0.021 | 0.11 | 0.39 | 4.74 | 3.41 | 1.32 | 11.90 | 0.71 | 9.78 |
| coagulation\_defects | 0.024 | 0.048 | 0.29 | 4.60 | 3.67 | 1.28 | 11.58 | 1.01 | 9.26 |
| connective\_tissue\_disorder | 0.029 | 0.091 | 0.39 | 2.79 | 2.16 | 1.13 | 5.76 | 0.87 | 4.47 |
| ureter\_bladder | 0.034 | 0.18 | 0.50 | 1.76 | 1.41 | 1.05 | 2.81 | 0.84 | 2.27 |
| psoriasis | 0.039 | 0.13 | 0.43 | 2.86 | 2.11 | 1.06 | 6.16 | 0.78 | 4.58 |
| arrhythmia | 0.040 | 0.20 | 0.51 | 2.05 | 1.54 | 1.04 | 3.68 | 0.78 | 2.78 |
| diabetes\_insulin\_dependent | 0.045 | 0.33 | 0.67 | 3.75 | 1.81 | 1.04 | 9.48 | 0.49 | 4.70 |
| cataract | 0.064 | 0.23 | 0.54 | 2.14 | 1.66 | 0.95 | 4.23 | 0.70 | 3.38 |
| ischaemic\_heart\_disease\_not\_MI | 0.071 | 0.47 | 0.11 | 2.08 | 1.32 | 0.93 | 4.06 | 0.59 | 2.58 |
| diverticular\_disease\_intestine | 0.071 | 0.010 | 0.79 | 0.37 | 0.26 | 0.08 | 1.08 | 0.05 | 0.77 |
| hepatic | 0.077 | 0.28 | 0.62 | 2.24 | 1.60 | 0.91 | 4.61 | 0.65 | 3.32 |
| allergy | 0.081 | 0.21 | 0.53 | 1.56 | 1.37 | 0.94 | 2.46 | 0.83 | 2.18 |
| digestive | 0.099 | 0.36 | 0.70 | 1.45 | 1.23 | 0.93 | 2.20 | 0.79 | 1.87 |
| COPD | 0.12 | 0.24 | 0.55 | 1.83 | 1.55 | 0.85 | 3.52 | 0.72 | 2.99 |
| uterine\_problem | 0.14 | 0.57 | 0.87 | 1.62 | 1.20 | 0.84 | 2.95 | 0.63 | 2.21 |
| ocular | 0.16 | 0.23 | 0.54 | 1.73 | 1.58 | 0.79 | 3.31 | 0.72 | 3.03 |
| irritable\_bowel\_syndrome | 0.20 | 0.17 | 0.49 | 0.41 | 0.38 | 0.05 | 1.47 | 0.04 | 1.39 |
| ear | 0.21 | 0.33 | 0.67 | 1.74 | 1.52 | 0.70 | 3.56 | 0.62 | 3.12 |
| prostate\_hyperplasia | 0.22 | 0.23 | 0.56 | 0.41 | 0.42 | 0.05 | 1.55 | 0.05 | 1.57 |
| any\_Ca | 0.26 | 0.22 | 0.55 | 1.41 | 1.45 | 0.77 | 2.40 | 0.79 | 2.47 |
| heart\_other | 0.26 | 0.65 | 0.89 | 1.72 | 1.23 | 0.63 | 3.75 | 0.45 | 2.69 |
| congenital | 0.31 | 0.27 | 0.61 | 0.31 | 0.29 | 0.00 | 2.15 | 0.00 | 1.97 |
| gastric\_reflux | 0.32 | 0.81 | 0.83 | 1.37 | 0.93 | 0.72 | 2.39 | 0.49 | 1.64 |
| ovarian\_cysts | 0.32 | 0.51 | 0.96 | 1.82 | 1.47 | 0.50 | 4.71 | 0.40 | 3.83 |
| gastrointestinal\_ulcer | 0.34 | 0.57 | 0.88 | 1.57 | 1.30 | 0.58 | 3.44 | 0.48 | 2.84 |
| stroke\_derived2017 | 0.37 | 0.67 | 0.91 | 1.61 | 1.24 | 0.52 | 3.76 | 0.41 | 2.90 |
| venous\_thromboembolic\_disease | 0.39 | 0.79 | 0.96 | 1.49 | 0.89 | 0.55 | 3.22 | 0.33 | 1.94 |
| glaucoma | 0.41 | 0.40 | 0.74 | 0.37 | 0.37 | 0.00 | 2.59 | 0.00 | 2.56 |
| nasal | 0.44 | 0.43 | 0.78 | 2.05 | 2.08 | 0.23 | 7.42 | 0.24 | 7.55 |
| thyroid | 0.47 | 0.093 | 0.38 | 0.71 | 0.48 | 0.23 | 1.66 | 0.16 | 1.12 |
| cerebrovascular\_disease\_not\_stroke | 0.56 | 0.48 | 0.80 | 0.48 | 0.42 | 0.00 | 3.32 | 0.00 | 2.93 |
| osteoporosis | 0.58 | 0.91 | 0.47 | 0.65 | 1.10 | 0.07 | 2.42 | 0.12 | 4.14 |
| MI\_derived2017 | 0.58 | 0.15 | 0.99 | 0.74 | 0.48 | 0.20 | 1.93 | 0.13 | 1.25 |
| neuropathies | 0.67 | 0.11 | 0.41 | 0.80 | 0.46 | 0.22 | 2.00 | 0.13 | 1.17 |
| sciatica | 0.74 | 0.51 | 0.84 | 1.10 | 0.83 | 0.59 | 1.89 | 0.44 | 1.42 |
| paralytic\_syndromes | 0.75 | 0.65 | 0.91 | 0.66 | 0.56 | 0.01 | 4.52 | 0.00 | 3.85 |
| heart\_valve | 0.76 | 0.95 | 1 | 1.23 | 1.04 | 0.25 | 3.53 | 0.22 | 3.01 |
| varicose\_veins | 0.84 | 0.96 | 0.92 | 1.12 | 1.03 | 0.31 | 2.81 | 0.29 | 2.58 |
| endocrine\_other | 0.84 | 0.63 | 0.98 | 0.77 | 0.54 | 0.01 | 5.26 | 0.00 | 3.74 |
| biliary | 0.94 | 0.087 | 0.39 | 1.03 | 0.50 | 0.38 | 2.24 | 0.18 | 1.10 |
| inflammatory\_bowel\_disease | 0.95 | 0.71 | 0.93 | 0.97 | 0.85 | 0.36 | 2.09 | 0.32 | 1.83 |
| aneurism | 0.96 | 0.90 | 0.99 | 0.94 | 0.84 | 0.01 | 6.52 | 0.01 | 5.83 |

**Supplementary Figure 2.** **Effect of 16p11.2del on phenotypes before and after correction for BMI, based on the above table**. It shows the changes in ORs after correction for BMI. The CNVs are ordered according to the strength of the original p-value (strongest on the left). The first 23 CNVs were nominally significant (p<0.05) in the original analysis. The correction with BMI removes most of the effect on diabetes type 2, hypertension, heart and renal failure, while those on anaemia, atherosclerotic valve disease and mortality remain largely unchanged.

**Supplementary Table 10. Effect of “distal” 16p11.2 deletions on phenotypes before and after correction with BMI**. Obesity is a known consequence of this deletion. We tested whether obesity is the factor leading to other (“novel”) associations. The table shows the changes to p-values and ORs after BMI was added as a co-variate to Firth’s logistic regression analysis. Other co-variates were kept the same. Significant results at FDR=0.1 are shown in red. Excluding obesity, four observations are significant after correction for BMI.

|  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| **Phenotype** | **p-value original** | **p-value BMI** | **B-H FDR** | **OR original** | **OR BMI** | **OR Lower 95% original** | **OR Upper 95%\_original** | **OR Lower 95%\_BMI** | **OR Upper 95%\_BMI** |
| diabetes\_other | 8.86E-08 | 1.39E-05 | 0.0038 | 6.95 | 4.79 | 3.67 | 12.57 | 2.47 | 8.89 |
| obesity | 1.14E-05 | 0.0015 | 0.038 | 7.06 | 4.25 | 3.27 | 13.73 | 1.81 | 9.11 |
| gout | 0.00046 | 0.0017 | 0.036 | 6.50 | 5.19 | 2.52 | 14.40 | 2.00 | 11.54 |
| uterine\_problem | 0.0020 | 0.0067 | 0.084 | 3.60 | 3.06 | 1.63 | 7.97 | 1.38 | 6.82 |
| diabetes\_insulin\_dependent | 0.0033 | 0.0076 | 0.091 | 8.60 | 6.69 | 2.35 | 22.23 | 1.82 | 17.38 |
| biliary | 0.014 | 0.068 | 0.35 | 3.06 | 2.25 | 1.29 | 6.27 | 0.94 | 4.69 |
| ovarian\_cysts | 0.050 | 0.071 | 0.36 | 3.77 | 3.34 | 1.00 | 10.35 | 0.89 | 9.21 |
| heart\_other | 0.070 | 0.11 | 0.39 | 2.81 | 2.44 | 0.91 | 6.72 | 0.79 | 5.84 |
| renal\_failure | 0.071 | 0.13 | 0.44 | 3.26 | 2.60 | 0.89 | 8.48 | 0.71 | 6.81 |
| ureter\_bladder | 0.077 | 0.14 | 0.44 | 1.88 | 1.69 | 0.93 | 3.50 | 0.84 | 3.15 |
| stroke\_derived2017 | 0.10 | 0.14 | 0.45 | 2.86 | 2.54 | 0.78 | 7.41 | 0.69 | 6.61 |
| hypertension | 0.11 | 0.90 | 0.99 | 1.59 | 1.04 | 0.90 | 2.78 | 0.58 | 1.84 |
| hepatic | 0.13 | 0.19 | 0.50 | 2.63 | 2.26 | 0.72 | 6.77 | 0.62 | 5.82 |
| paralytic\_syndromes | 0.14 | 0.14 | 0.45 | 4.66 | 4.54 | 0.53 | 17.22 | 0.51 | 16.79 |
| high\_cholesterol | 0.15 | 0.47 | 0.80 | 1.64 | 1.28 | 0.83 | 3.05 | 0.64 | 2.38 |
| COPD | 0.16 | 0.13 | 0.45 | 0.22 | 0.20 | 0.00 | 1.54 | 0.00 | 1.42 |
| coagulation\_defects | 0.17 | 0.20 | 0.52 | 3.96 | 3.55 | 0.45 | 14.57 | 0.40 | 13.11 |
| ischaemic\_heart\_disease\_not\_MI | 0.18 | 0.30 | 0.49 | 2.11 | 1.74 | 0.68 | 5.06 | 0.56 | 4.18 |
| ear | 0.18 | 0.16 | 0.64 | 0.23 | 0.22 | 0.00 | 1.62 | 0.00 | 1.51 |
| cataract | 0.20 | 0.23 | 0.55 | 2.03 | 1.92 | 0.65 | 4.92 | 0.62 | 4.64 |
| varicose\_veins | 0.20 | 0.23 | 0.55 | 2.19 | 2.09 | 0.60 | 5.64 | 0.57 | 5.38 |
| migraine | 0.22 | 0.22 | 0.54 | 0.25 | 0.26 | 0.00 | 1.78 | 0.00 | 1.79 |
| arrhythmia | 0.24 | 0.17 | 0.50 | 0.42 | 0.37 | 0.05 | 1.57 | 0.04 | 1.39 |
| died\_to\_2016 | 0.24 | 0.27 | 0.61 | 2.06 | 1.95 | 0.57 | 5.32 | 0.53 | 5.03 |
| heart\_valve | 0.26 | 0.31 | 0.65 | 2.26 | 2.10 | 0.47 | 6.66 | 0.43 | 6.16 |
| diverticular\_disease\_intestine | 0.28 | 0.44 | 0.76 | 1.70 | 1.44 | 0.62 | 3.80 | 0.52 | 3.24 |
| gastrointestinal\_ulcer | 0.32 | 0.27 | 0.62 | 0.31 | 0.29 | 0.00 | 2.19 | 0.00 | 2.00 |
| anaemia | 0.36 | 0.43 | 0.77 | 1.63 | 1.51 | 0.53 | 3.85 | 0.49 | 3.59 |
| inflammatory\_bowel\_disease | 0.39 | 0.34 | 0.68 | 0.53 | 0.49 | 0.06 | 1.94 | 0.06 | 1.82 |
| connective\_tissue\_disorder | 0.45 | 0.37 | 0.71 | 0.40 | 0.35 | 0.00 | 2.77 | 0.00 | 2.43 |
| congenital | 0.46 | 0.48 | 0.80 | 1.98 | 1.89 | 0.22 | 7.27 | 0.21 | 6.97 |
| gastric\_reflux | 0.48 | 0.28 | 0.62 | 0.69 | 0.57 | 0.19 | 1.78 | 0.16 | 1.48 |
| osteoporosis | 0.50 | 0.70 | 0.92 | 0.44 | 0.61 | 0.00 | 3.10 | 0.00 | 4.32 |
| neuropathies | 0.58 | 0.36 | 0.71 | 0.65 | 0.51 | 0.07 | 2.41 | 0.06 | 1.89 |
| osteoarthritis | 0.59 | 0.18 | 0.52 | 0.81 | 0.60 | 0.34 | 1.67 | 0.25 | 1.25 |
| psoriasis | 0.61 | 0.52 | 0.84 | 0.52 | 0.45 | 0.00 | 3.63 | 0.00 | 3.16 |
| atherosclerotic\_vascular\_disease | 0.67 | 0.64 | 0.91 | 0.58 | 0.55 | 0.00 | 4.03 | 0.00 | 3.86 |
| renal | 0.69 | 0.84 | 0.96 | 1.41 | 1.19 | 0.16 | 5.19 | 0.14 | 4.41 |
| glaucoma | 0.70 | 0.69 | 0.92 | 0.60 | 0.60 | 0.00 | 4.24 | 0.00 | 4.19 |
| venous\_thromboembolic\_disease | 0.71 | 0.97 | 0.79 | 1.28 | 1.02 | 0.26 | 3.76 | 0.21 | 3.01 |
| asthma | 0.71 | 0.46 | 0.95 | 0.86 | 0.74 | 0.34 | 1.82 | 0.29 | 1.57 |
| aneurism | 0.71 | 0.73 | 0.99 | 1.77 | 1.69 | 0.01 | 12.50 | 0.01 | 11.92 |
| ocular | 0.72 | 0.78 | 0.95 | 1.23 | 1.17 | 0.34 | 3.16 | 0.32 | 3.02 |
| any\_Ca | 0.74 | 0.75 | 0.95 | 0.86 | 0.87 | 0.31 | 1.92 | 0.32 | 1.94 |
| heartfailure | 0.76 | 0.62 | 0.91 | 0.66 | 0.53 | 0.01 | 4.67 | 0.00 | 3.76 |
| allergy | 0.76 | 0.62 | 0.92 | 0.89 | 0.83 | 0.38 | 1.81 | 0.35 | 1.69 |
| irritable\_bowel\_syndrome | 0.78 | 0.75 | 0.96 | 0.80 | 0.77 | 0.09 | 2.97 | 0.09 | 2.87 |
| endocrine\_other | 0.79 | 0.87 | 0.98 | 1.51 | 1.28 | 0.01 | 10.52 | 0.01 | 8.94 |
| MI\_derived2017 | 0.80 | 0.99 | 0.91 | 1.19 | 1.01 | 0.24 | 3.57 | 0.21 | 3.02 |
| hernia | 0.80 | 0.61 | 0.99 | 0.90 | 0.81 | 0.36 | 1.93 | 0.32 | 1.73 |
| digestive | 0.84 | 0.95 | 1 | 1.07 | 0.98 | 0.54 | 1.95 | 0.50 | 1.80 |
| respiratory | 0.85 | 0.97 | 0.99 | 1.11 | 0.98 | 0.30 | 2.86 | 0.27 | 2.52 |
| low\_WBC\_count | 0.88 | 0.88 | 0.99 | 1.25 | 1.26 | 0.01 | 8.67 | 0.01 | 8.72 |
| thyroid | 0.90 | 0.80 | 0.96 | 1.07 | 0.87 | 0.29 | 2.81 | 0.23 | 2.30 |
| cerebrovascular\_disease\_not\_stroke | 0.93 | 0.89 | 0.99 | 0.88 | 0.83 | 0.01 | 6.17 | 0.01 | 5.78 |
| prostate\_hyperplasia | 0.94 | 0.94 | 1 | 1.05 | 1.05 | 0.21 | 3.28 | 0.21 | 3.28 |
| nasal | 0.96 | 0.96 | 0.99 | 1.07 | 1.07 | 0.01 | 7.48 | 0.01 | 7.45 |
| sciatica | 0.97 | 0.76 | 0.95 | 1.02 | 0.88 | 0.40 | 2.15 | 0.35 | 1.87 |

**Supplementary Figure 3.** **Effect of “distal” 16p11.2 deletions on phenotypes before and after correction for BMI, based on the above table**. The CNVs are ordered according to the strength of the original p-value (strongest on the left). The first six phenotypes on the left were nominally significant in the original analysis. A partial effect of BMI on the ORs can be seen on diabetes type 1 and 2, and gout.

**Supplementary Table 11. Effect of 16p12.1 deletions on phenotypes before and after correction for BMI.** Obesity is not an established consequence of this deletion, but was a prominent finding in our analysis. We tested whether obesity is the factor leading to other (“novel”) associations. The table shows the changes to p-values and ORs after BMI was added as a co-variate to Firth’s logistic regression analysis. Other co-variates were kept the same. Significant results at FDR=0.1 are shown in red. Five of the original six associations (obesity excluded) remain significant and risk of death has also become significant.

|  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| **Phenotype** | **p-value original** | **p-value BMI** | **B-H FDR** | **OR original** | **OR BMI** | **OR Lower 95% original** | **OR Upper 95%\_original** | **OR Lower 95%\_BMI** | **OR Upper 95%\_BMI** |
| hypertension | 8.64E-08 | 4.02E-05 | 0.0055 | 2.11 | 1.83 | 1.61 | 2.76 | 1.37 | 2.43 |
| obesity | 1.11E-07 | 0.00027 | 0.011 | 3.99 | 2.85 | 2.53 | 5.99 | 1.66 | 4.66 |
| renal\_failure | 7.23E-06 | 6.99E-05 | 0.0039 | 3.85 | 3.26 | 2.26 | 6.13 | 1.90 | 5.25 |
| diabetes\_other | 0.00021 | 0.023 | 0.17 | 2.34 | 1.72 | 1.53 | 3.46 | 1.08 | 2.64 |
| heart\_other | 0.00029 | 0.00090 | 0.031 | 2.77 | 2.52 | 1.65 | 4.36 | 1.50 | 3.98 |
| ureter\_bladder | 0.00033 | 0.0010 | 0.031 | 1.85 | 1.76 | 1.34 | 2.52 | 1.26 | 2.40 |
| respiratory | 0.00069 | 0.0019 | 0.037 | 2.18 | 2.03 | 1.42 | 3.21 | 1.32 | 3.00 |
| ischaemic\_heart\_disease\_not\_MI | 0.0023 | 0.011 | 0.10 | 2.22 | 1.94 | 1.35 | 3.45 | 1.18 | 3.03 |
| died\_to\_2016 | 0.0052 | 0.0066 |  0.087 | 2.29 | 2.23 | 1.31 | 3.72 | 1.27 | 3.62 |
| arrhythmia | 0.0069 | 0.017 | 0.14 | 1.86 | 1.72 | 1.20 | 2.78 | 1.11 | 2.57 |
| ovarian\_cysts | 0.0070 | 0.010 | 0.11 | 2.58 | 2.44 | 1.33 | 4.52 | 1.26 | 4.29 |
| gastric\_reflux | 0.0098 | 0.037 | 0.24 | 1.67 | 1.51 | 1.14 | 2.38 | 1.03 | 2.16 |
| COPD | 0.010 | 0.016 | 0.14 | 2.04 | 1.95 | 1.20 | 3.27 | 1.14 | 3.12 |
| uterine\_problem | 0.016 | 0.043 | 0.27 | 1.61 | 1.49 | 1.10 | 2.33 | 1.01 | 2.16 |
| hernia | 0.020 | 0.046 | 0.28 | 1.53 | 1.44 | 1.07 | 2.13 | 1.01 | 2.00 |
| high\_cholesterol | 0.022 | 0.16 | 0.48 | 1.47 | 1.27 | 1.06 | 2.02 | 0.91 | 1.76 |
| MI\_derived2017 | 0.025 | 0.061 | 0.34 | 1.94 | 1.73 | 1.09 | 3.19 | 0.97 | 2.86 |
| anaemia | 0.027 | 0.037 | 0.25 | 1.74 | 1.68 | 1.07 | 2.68 | 1.03 | 2.58 |
| osteoarthritis | 0.066 | 0.39 | 0.73 | 1.35 | 1.16 | 0.98 | 1.84 | 0.83 | 1.59 |
| venous\_thromboembolic\_disease | 0.068 | 0.18 | 0.50 | 1.71 | 1.47 | 0.96 | 2.81 | 0.82 | 2.44 |
| atherosclerotic\_vascular\_disease | 0.070 | 0.079 | 0.37 | 2.13 | 2.08 | 0.93 | 4.13 | 0.91 | 4.03 |
| ear | 0.075 | 0.096 | 0.38 | 1.69 | 1.63 | 0.95 | 2.77 | 0.91 | 2.67 |
| diabetes\_insulin\_dependent | 0.075 | 0.15 | 0.47 | 2.68 | 2.18 | 0.89 | 6.06 | 0.72 | 4.99 |
| inflammatory\_bowel\_disease | 0.081 | 0.064 | 0.35 | 0.53 | 0.52 | 0.22 | 1.07 | 0.21 | 1.03 |
| heartfailure | 0.092 | 0.19 | 0.50 | 2.13 | 1.77 | 0.87 | 4.33 | 0.72 | 3.64 |
| digestive | 0.10 | 0.18 | 0.51 | 1.28 | 1.23 | 0.95 | 1.71 | 0.91 | 1.64 |
| cerebrovascular\_disease\_not\_stroke | 0.11 | 0.13 | 0.40 | 2.16 | 2.07 | 0.81 | 4.59 | 0.78 | 4.40 |
| paralytic\_syndromes | 0.11 | 0.11 | 0.44 | 2.69 | 2.75 | 0.75 | 6.66 | 0.77 | 6.82 |
| gastrointestinal\_ulcer | 0.14 | 0.18 | 0.51 | 1.67 | 1.58 | 0.84 | 2.95 | 0.79 | 2.80 |
| diverticular\_disease\_intestine | 0.14 | 0.30 | 0.64 | 1.42 | 1.28 | 0.89 | 2.16 | 0.80 | 1.95 |
| biliary | 0.14 | 0.50 | 0.83 | 1.46 | 1.19 | 0.88 | 2.29 | 0.70 | 1.89 |
| gout | 0.15 | 0.32 | 0.66 | 1.82 | 1.50 | 0.79 | 3.56 | 0.65 | 2.99 |
| thyroid | 0.17 | 0.38 | 0.72 | 1.38 | 1.23 | 0.86 | 2.10 | 0.76 | 1.88 |
| osteoporosis | 0.22 | 0.097 | 0.38 | 1.52 | 1.79 | 0.76 | 2.72 | 0.89 | 3.22 |
| prostate\_hyperplasia | 0.24 | 0.24 | 0.56 | 1.49 | 1.49 | 0.75 | 2.70 | 0.75 | 2.70 |
| sciatica | 0.37 | 0.61 | 0.91 | 1.19 | 1.11 | 0.80 | 1.71 | 0.74 | 1.59 |
| migraine | 0.43 | 0.44 | 0.77 | 0.74 | 0.74 | 0.30 | 1.49 | 0.30 | 1.50 |
| hepatic | 0.44 | 0.59 | 0.89 | 1.35 | 1.23 | 0.59 | 2.60 | 0.54 | 2.37 |
| any\_Ca | 0.47 | 0.46 | 0.78 | 1.15 | 1.15 | 0.78 | 1.64 | 0.78 | 1.65 |
| psoriasis | 0.48 | 0.39 | 0.73 | 0.66 | 0.61 | 0.14 | 1.85 | 0.13 | 1.72 |
| coagulation\_defects | 0.52 | 0.57 | 0.88 | 1.55 | 1.47 | 0.33 | 4.40 | 0.31 | 4.15 |
| cataract | 0.55 | 0.65 | 0.90 | 1.18 | 1.13 | 0.67 | 1.93 | 0.64 | 1.86 |
| asthma | 0.63 | 0.93 | 0.99 | 1.10 | 1.02 | 0.75 | 1.56 | 0.69 | 1.45 |
| low\_WBC\_count | 0.64 | 0.64 | 0.90 | 1.36 | 1.37 | 0.29 | 3.85 | 0.29 | 3.87 |
| congenital | 0.67 | 0.65 | 0.90 | 0.77 | 0.76 | 0.16 | 2.18 | 0.16 | 2.15 |
| renal | 0.69 | 0.86 | 0.97 | 1.20 | 1.08 | 0.45 | 2.53 | 0.40 | 2.28 |
| stroke\_derived2017 | 0.69 | 0.84 | 0.98 | 1.17 | 1.09 | 0.48 | 2.37 | 0.44 | 2.20 |
| ocular | 0.74 | 0.81 | 0.96 | 1.10 | 1.07 | 0.62 | 1.80 | 0.60 | 1.76 |
| irritable\_bowel\_syndrome | 0.77 | 0.74 | 0.95 | 0.90 | 0.89 | 0.40 | 1.74 | 0.39 | 1.71 |
| nasal | 0.78 | 0.78 | 0.95 | 0.80 | 0.80 | 0.09 | 2.87 | 0.09 | 2.86 |
| aneurism | 0.79 | 0.82 | 0.92 | 1.25 | 1.21 | 0.14 | 4.52 | 0.14 | 4.37 |
| heart\_valve | 0.79 | 0.71 | 0.96 | 0.88 | 0.84 | 0.29 | 2.00 | 0.28 | 1.90 |
| connective\_tissue\_disorder | 0.79 | 0.95 | 1 | 1.11 | 1.03 | 0.46 | 2.24 | 0.42 | 2.07 |
| glaucoma | 0.81 | 0.80 | 0.96 | 0.88 | 0.88 | 0.25 | 2.19 | 0.24 | 2.18 |
| neuropathies | 0.90 | 0.70 | 0.92 | 1.04 | 0.88 | 0.52 | 1.83 | 0.44 | 1.57 |
| allergy | 0.97 | 0.82 | 0.96 | 0.99 | 0.96 | 0.68 | 1.40 | 0.66 | 1.35 |
| varicose\_veins | 0.99 | 0.96 | 0.99 | 1.00 | 0.98 | 0.44 | 1.93 | 0.43 | 1.89 |
| endocrine\_other | 0.99 | 0.90 | 1 | 1.01 | 0.91 | 0.12 | 3.61 | 0.10 | 3.26 |

**Supplementary Figure 4. Effect of 16p12.1 deletions on phenotypes before and after correction for BMI, based on the above table.** BMI correction has little effect on the associated phenotypes.



a b c



 d

**Supplementary Figure 5 (a-d)**. **Distribution of BMI in the CNVs associated with obesity**. The distribution of BMI is different in the three analysed CNVs. It is most strongly shifted towards high values in 16p11.2 deletions (a), where 71.6% of carriers have BMI>30. It is less shirted for 16p11.2 distal deletions (b), where 55.6% have a BMI>30, while in 16p12.1 deletion carriers (c), only 37% of carriers have BMI>30, making the distribution much closer to that in the full sample (d). The vertical red lines indicate the point where obesity could be diagnosed using the BMI>30 criterion. The carriers who had been diagnosed with an ICD10 hospital discharge code for “Obesity” (marked in red) also constitute correspondingly smaller proportions: 18.6%, 16.7% and 9.8% respectively for the three CNVs. Only 2.6% of the whole Biobank population had a diagnosis of Obesity, but 24.3% could be diagnosed with the BMI>30 criterion. i.e. only one in 10 people meeting the criterion received the medical diagnosis. These differences could be one reason why correcting for BMI causes different changes to the associations with obesity for the studied CNVs. From a purely statistical point of view, categorical and continuous traits (even if the category is derived from a threshold imposed on exactly the same measurement representing the continuous trait) are not equivalent, and therefore adjusting an analysis of one for another does not necessarily remove evidence for association (Obesity is a binary state, while BMI is a continuous one). These factors could explain why correcting for BMI does not completely remove the association with Obesity.

**Supplementary Table 12. Effect of all CNVs on type 2 diabetes before and after correction with BMI**. The ORs are reduced substantially for 16p11.2del, 16p11.2distal\_del and 3q29dup, suggesting that the diabetes in these CNV carriers is caused mostly via an increased BMI. For 1q21.1dup, 16p12.1del and 3q29del the ORs are unchanged, while for 2q13dup, 22q11.2distal\_del, and 17q12del they increase, suggesting that these CNVs have a more direct effect on the development of diabetes. Significant results at FDR=0.1 are shown in red, with six associations significant after correction for BMI.

|  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| **Phenotype** | **p-value original** | **p-value BMI** | **B-H FDR** | **OR original** | **OR BMI** | **OR Lower 95% original** | **OR Upper 95%\_original** | **OR Lower 95%\_BMI** | **OR Upper 95%\_BMI** |
| 16p11.2del | 2.54E-11 | 0.0064 | 0.088 | 6.07 | 2.11 | 3.77 | 9.50 | 1.24 | 3.48 |
| 16p11.2distal\_del | 8.86E-08 | 1.39E-05 | 0.0038 | 6.95 | 4.79 | 3.67 | 12.57 | 2.47 | 8.89 |
| 1q21.1dup | 0.00017 | 9.67E-05 | 0.0044 | 2.65 | 2.83 | 1.64 | 4.10 | 1.73 | 4.44 |
| 16p12.1del | 0.00021 | 0.023 | 0.17 | 2.34 | 1.72 | 1.53 | 3.46 | 1.08 | 2.64 |
| 15q13.3del | 0.00038 | 0.0059 | 0.086 | 4.87 | 3.69 | 2.15 | 10.15 | 1.50 | 8.30 |
| 2q13dup | 0.0012 | 5.42E-05 | 0.0037 | 3.39 | 5.01 | 1.68 | 6.29 | 2.45 | 9.47 |
| 16p13.11dup | 0.0018 | 0.010 | 0.10 | 1.55 | 1.45 | 1.18 | 1.99 | 1.09 | 1.88 |
| 17p12del\_HNPP | 0.0061 | 0.0016 | 0.037 | 1.97 | 2.25 | 1.23 | 3.00 | 1.38 | 3.50 |
| 10q11.21q11.23dup | 0.0073 | 0.014 | 0.12 | 3.93 | 3.66 | 1.51 | 8.76 | 1.33 | 8.66 |
| 15q11q13del\_BP3\_BP4 | 0.0092 | 0.030 | 0.21 | 6.94 | 5.00 | 1.74 | 21.45 | 1.20 | 16.77 |
| 3q29del | 0.049 | 0.089 | 0.39 | 5.57 | 5.35 | 1.01 | 21.91 | 0.75 | 26.38 |
| 16p11.2distal\_dup | 0.051 | 0.12 | 0.42 | 0.35 | 0.42 | 0.07 | 1.00 | 0.09 | 1.22 |
| 22q11.2del | 0.063 | 0.22 | 0.54 | 5.03 | 3.58 | 0.90 | 19.98 | 0.42 | 18.55 |
| TAR\_dup | 0.068 | 0.095 | 0.38 | 1.44 | 1.41 | 0.97 | 2.04 | 0.94 | 2.05 |
| 3q29dup | 0.069 | 0.52 | 0.82 | 8.24 | 1.99 | 0.81 | 46.69 | 0.18 | 13.21 |
| 22q11.2distal\_del | 0.12 | 0.092 | 0.38 | 5.94 | 7.76 | 0.56 | 35.70 | 0.67 | 56.60 |
| 10q11.21q11.23del | 0.12 | 0.092 | 0.39 | 2.04 | 2.27 | 0.80 | 4.42 | 0.86 | 5.10 |
| NRXN1del | 0.18 | 0.52 | 0.83 | 1.54 | 1.23 | 0.81 | 2.65 | 0.63 | 2.18 |
| 17q12dup | 0.20 | 0.43 | 0.77 | 1.61 | 1.36 | 0.76 | 3.02 | 0.62 | 2.67 |
| 22q11.2dup | 0.21 | 0.98 | 0.99 | 1.35 | 0.99 | 0.83 | 2.09 | 0.59 | 1.59 |
| 15q11.2del | 0.22 | 0.38 | 0.72 | 1.14 | 1.10 | 0.92 | 1.39 | 0.89 | 1.36 |
| 2q21.1dup | 0.25 | 0.19 | 0.65 | 0.43 | 0.37 | 0.05 | 1.60 | 0.04 | 1.50 |
| 15q11q13dup\_BP3\_BP5 | 0.25 | 0.30 | 0.52 | 3.32 | 2.92 | 0.34 | 15.84 | 0.29 | 14.74 |
| 7q11.23dup\_distal | 0.29 | 0.44 | 0.76 | 2.23 | 1.78 | 0.44 | 7.13 | 0.34 | 6.06 |
| 2q11.2dup | 0.32 | 0.30 | 0.46 | 2.09 | 2.22 | 0.42 | 6.56 | 0.42 | 7.55 |
| 17q12del | 0.32 | 0.14 | 0.66 | 2.78 | 5.09 | 0.28 | 14.39 | 0.50 | 28.06 |
| 15q11q13dup\_BP3\_BP4 | 0.38 | 0.52 | 0.83 | 0.52 | 0.59 | 0.06 | 1.94 | 0.06 | 2.39 |
| 15q13.3dup\_CHRNA7 | 0.39 | 0.58 | 0.88 | 1.07 | 1.05 | 0.91 | 1.26 | 0.88 | 1.24 |
| 15q11.2dup | 0.42 | 0.63 | 0.91 | 1.08 | 1.05 | 0.89 | 1.31 | 0.86 | 1.28 |
| 16p13.11del | 0.44 | 0.63 | 0.91 | 1.34 | 1.21 | 0.61 | 2.57 | 0.53 | 2.42 |
| 2q21.1del | 0.46 | 0.40 | 0.74 | 0.57 | 0.52 | 0.06 | 2.16 | 0.06 | 2.07 |
| 17p12dup\_CMT1A | 0.51 | 0.69 | 0.92 | 1.28 | 1.17 | 0.58 | 2.46 | 0.49 | 2.40 |
| 1q21.1del | 0.59 | 0.44 | 0.77 | 0.78 | 0.69 | 0.26 | 1.80 | 0.22 | 1.66 |
| 22q11.2distal\_dup) | 0.63 | 0.69 | 0.92 | 0.53 | 0.58 | 0.00 | 4.16 | 0.00 | 4.84 |
| WBS\_dup | 0.68 | 0.64 | 0.91 | 0.58 | 0.54 | 0.00 | 4.49 | 0.00 | 4.29 |
| 13q12del\_CRYL1 | 0.69 | 0.64 | 0.92 | 0.90 | 0.89 | 0.53 | 1.44 | 0.50 | 1.45 |
| 15q24dup | 0.71 | 0.88 | 0.98 | 1.79 | 1.25 | 0.01 | 14.63 | 0.01 | 10.49 |
| 15q13.3dup | 0.72 | 0.77 | 0.95 | 1.10 | 1.08 | 0.62 | 1.80 | 0.60 | 1.81 |
| 2q13del\_NPHP1 | 0.74 | 0.34 | 0.68 | 0.97 | 0.91 | 0.80 | 1.16 | 0.75 | 1.10 |
| 15q13.3del\_CHRNA7 | 0.75 | 0.60 | 0.90 | 0.65 | 0.50 | 0.00 | 5.29 | 0.00 | 4.41 |
| 2q13del | 0.79 | 0.32 | 0.67 | 0.84 | 0.54 | 0.17 | 2.53 | 0.11 | 1.70 |
| 17q11.2del\_NF1 | 0.80 | 0.98 | 0.50 | 0.70 | 1.03 | 0.01 | 5.75 | 0.01 | 8.30 |
| Potocki\_Lupski | 0.80 | 0.84 | 0.99 | 1.50 | 0.74 | 0.01 | 14.11 | 0.01 | 7.88 |
| 16p11.2dup | 0.80 | 0.17 | 0.97 | 1.10 | 1.72 | 0.50 | 2.09 | 0.78 | 3.33 |
| PWS\_dup | 0.80 | 0.77 | 0.95 | 0.71 | 0.68 | 0.01 | 5.52 | 0.01 | 5.23 |
| 2q13dup\_NPHP1 | 0.82 | 0.76 | 0.92 | 1.02 | 1.03 | 0.83 | 1.24 | 0.83 | 1.26 |
| 13q12.12dup | 0.82 | 0.61 | 0.95 | 0.93 | 1.19 | 0.47 | 1.65 | 0.59 | 2.13 |
| 2q11.2del | 0.83 | 0.21 | 0.53 | 0.84 | 0.34 | 0.09 | 3.28 | 0.03 | 1.69 |
| 8p23.1dup | 0.84 | 0.96 | 0.99 | 1.36 | 1.08 | 0.01 | 12.41 | 0.01 | 11.46 |
| 13q12.12del | 0.89 | 0.99 | 0.99 | 0.93 | 1.01 | 0.31 | 2.18 | 0.33 | 2.38 |
| TAR\_del | 0.89 | 0.83 | 0.97 | 0.93 | 0.88 | 0.25 | 2.40 | 0.24 | 2.36 |
| 16p12.1dup | 0.97 | 0.74 | 0.95 | 1.01 | 1.12 | 0.51 | 1.81 | 0.55 | 2.04 |
| 13q12dup\_CRYL1 | 0.98 | 0.76 | 0.96 | 0.97 | 1.62 | 0.01 | 7.86 | 0.01 | 13.51 |
| 10q23dup | 0.99 | 0.94 | 1 | 0.98 | 1.11 | 0.01 | 8.93 | 0.01 | 9.68 |

**Supplementary Figure 6.** **Effect of CNVs on type 2 diabetes before and after correction for BMI, based on the above table**. It shows the changes in ORs after correction for BMI: some show increased ORs after correction for BMI. The CNVs are ordered according to the strength of the original p-value (strongest on the left).

**Supplementary Table 13. Effect of all CNVs on mortality during the follow-up period, before and after correction with BMI**. The ORs remain almost unchanged. Significant results at FDR=0.1 are shown in red, with two more becoming significant after correction for BMI.

|  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| **Phenotype** | **p-value original** | **p-value BMI** | **B-H FDR** | **OR original** | **OR BMI** | **OR Lower 95% original** | **OR Upper 95%\_original** | **OR Lower 95%\_BMI** | **OR Upper 95%\_BMI** |
| 16p13.11\_dup | 0.00097 | 0.0031 | 0.050 | 1.79 | 1.70 | 1.21 | 2.32 | 1.28 | 2.43 |
| 3q29\_dup | 0.0013 | 0.0020 | 0.037 | 27.81 | 23.62 | 3.82 | 124.78 | 4.54 | 146.05 |
| 15q13.3\_dup | 0.0017 | 0.0015 | 0.041 | 2.42 | 2.46 | 1.45 | 3.90 | 1.43 | 3.85 |
| 16p11.2\_del | 0.0050 | 0.012 | 0.11 | 2.88 | 2.54 | 1.25 | 4.66 | 1.42 | 5.27 |
| 16p12.1\_del | 0.0052 | 0.0066 | 0.087 | 2.29 | 2.23 | 1.27 | 3.62 | 1.31 | 3.72 |
| 13q12.12\_del | 0.0092 | 0.0087 | 0.10 | 3.21 | 3.25 | 1.40 | 6.48 | 1.38 | 6.41 |
| 7q11.23\_dup\_distal | 0.010 | 0.011 | 0.11 | 6.34 | 6.21 | 1.63 | 17.45 | 1.67 | 17.81 |
| 2q21.1\_dup | 0.021 | 0.021 | 0.16 | 3.37 | 3.40 | 1.24 | 7.59 | 1.23 | 7.51 |
| 1q21.1\_del | 0.031 | 0.080 | 0.37 | 2.53 | 2.22 | 0.90 | 4.55 | 1.10 | 5.00 |
| 1q21.1\_dup | 0.038 | 0.037 | 0.26 | 2.09 | 2.10 | 1.05 | 3.75 | 1.05 | 3.73 |
| 17q12\_dup | 0.040 | 0.042 | 0.27 | 2.42 | 2.40 | 1.04 | 4.75 | 1.04 | 4.78 |
| Potocki\_Lupski | 0.048 | 0.050 | 0.29 | 10.52 | 10.17 | 1.00 | 56.33 | 1.02 | 60.19 |
| 13q12.12\_dup | 0.051 | 0.093 | 0.38 | 1.92 | 1.79 | 0.90 | 3.17 | 1.00 | 3.33 |
| 22q11.2distal\_del | 0.052 | 0.050 | 0.29 | 9.90 | 10.21 | 1.00 | 58.15 | 0.97 | 55.97 |
| 22q11.2\_dup | 0.053 | 0.062 | 0.34 | 1.77 | 1.73 | 0.97 | 2.84 | 0.99 | 2.90 |
| 15q24\_dup | 0.061 | 0.066 | 0.35 | 8.45 | 8.00 | 0.83 | 37.33 | 0.88 | 39.62 |
| 17p12\_HNPP\_del | 0.071 | 0.076 | 0.36 | 0.38 | 0.38 | 0.08 | 1.09 | 0.08 | 1.07 |
| 10q11.21q11.23\_dup | 0.075 | 0.075 | 0.36 | 3.21 | 3.22 | 0.87 | 8.50 | 0.87 | 8.49 |
| 17q12\_del | 0.11 | 0.097 | 0.38 | 5.90 | 6.35 | 0.65 | 31.22 | 0.61 | 28.99 |
| 13q12dup\_CRYL1 | 0.11 | 0.100 | 0.40 | 5.68 | 6.00 | 0.64 | 26.27 | 0.61 | 24.93 |
| 15q11q13dup\_BP3\_BP5 | 0.11 | 0.11 | 0.37 | 5.75 | 5.58 | 0.58 | 25.76 | 0.60 | 26.42 |
| 15q13.3\_del | 0.13 | 0.41 | 0.75 | 2.63 | 1.79 | 0.36 | 5.44 | 0.71 | 7.02 |
| 22q11.2\_del | 0.17 | 0.19 | 0.51 | 4.21 | 3.98 | 0.42 | 18.06 | 0.44 | 18.98 |
| 16p11.2distal\_dup | 0.18 | 0.16 | 0.49 | 1.80 | 1.87 | 0.76 | 3.81 | 0.73 | 3.67 |
| PWS\_dup | 0.19 | 0.19 | 0.51 | 3.87 | 3.81 | 0.41 | 15.57 | 0.42 | 15.85 |
| 16p12.1\_dup | 0.22 | 0.20 | 0.52 | 1.59 | 1.62 | 0.75 | 3.04 | 0.73 | 2.98 |
| 16p11.2distal\_del | 0.24 | 0.27 | 0.61 | 2.06 | 1.95 | 0.53 | 5.03 | 0.57 | 5.32 |
| 15q11q13dup\_BP3\_BP4  | 0.30 | 0.32 | 0.66 | 0.31 | 0.31 | 0.00 | 2.19 | 0.00 | 2.14 |
| TAR\_del | 0.31 | 0.30 | 0.65 | 1.84 | 1.88 | 0.52 | 4.80 | 0.51 | 4.71 |
| 15q11.2\_dup | 0.38 | 0.35 | 0.69 | 1.12 | 1.13 | 0.87 | 1.45 | 0.86 | 1.43 |
| 13q12del\_CRYL1 | 0.39 | 0.53 | 0.83 | 1.29 | 1.21 | 0.63 | 2.09 | 0.70 | 2.18 |
| 2q11.2\_dup | 0.43 | 0.42 | 0.76 | 2.10 | 2.12 | 0.24 | 8.23 | 0.23 | 8.14 |
| 15q11.2\_del | 0.47 | 0.53 | 0.83 | 1.11 | 1.10 | 0.82 | 1.44 | 0.83 | 1.45 |
| 2q13dup(NPHP1) | 0.49 | 0.37 | 0.71 | 0.90 | 0.88 | 0.65 | 1.16 | 0.67 | 1.19 |
| 8p23.1\_dup | 0.53 | 0.53 | 0.84 | 2.94 | 2.90 | 0.02 | 26.19 | 0.02 | 26.43 |
| 2q11.2\_del | 0.55 | 0.52 | 0.84 | 0.47 | 0.45 | 0.00 | 3.23 | 0.00 | 3.40 |
| 16p13.11\_del | 0.57 | 0.95 | 0.99 | 1.33 | 1.04 | 0.29 | 2.60 | 0.44 | 3.04 |
| 17p12\_CMT1A\_dup | 0.63 | 0.95 | 0.91 | 1.28 | 1.03 | 0.29 | 2.60 | 0.42 | 2.94 |
| 10q11.21q11.23\_del | 0.63 | 0.62 | 0.99 | 1.40 | 1.41 | 0.29 | 4.15 | 0.29 | 4.11 |
| 10q23\_dup | 0.65 | 0.66 | 0.90 | 2.08 | 2.06 | 0.02 | 17.49 | 0.02 | 17.72 |
| NRXN1\_del | 0.67 | 0.68 | 0.92 | 1.21 | 1.20 | 0.45 | 2.57 | 0.45 | 2.59 |
| 2q13del(NPHP1) | 0.69 | 0.65 | 0.91 | 0.95 | 0.94 | 0.73 | 1.20 | 0.73 | 1.21 |
| 16p11.2\_dup | 0.71 | 0.81 | 0.96 | 0.82 | 0.88 | 0.24 | 2.20 | 0.23 | 2.06 |
| 17q11.2\_del\_NF1 | 0.77 | 0.75 | 0.95 | 1.59 | 1.64 | 0.01 | 13.01 | 0.01 | 12.66 |
| 3q29\_del | 0.78 | 0.78 | 0.96 | 1.53 | 1.55 | 0.01 | 12.40 | 0.01 | 12.28 |
| 2q13\_dup | 0.81 | 0.77 | 0.96 | 1.17 | 1.22 | 0.25 | 3.54 | 0.24 | 3.40 |
| 2q21.1\_del | 0.85 | 0.83 | 0.96 | 1.17 | 1.20 | 0.13 | 4.52 | 0.13 | 4.40 |
| TAR\_dup | 0.86 | 0.88 | 0.98 | 0.95 | 0.95 | 0.50 | 1.64 | 0.50 | 1.63 |
| 15q11q13del\_BP3-BP4  | 0.87 | 0.88 | 0.99 | 1.29 | 1.25 | 0.01 | 9.46 | 0.01 | 9.76 |
| 2q13\_del | 0.89 | 0.85 | 0.97 | 0.89 | 0.85 | 0.10 | 3.18 | 0.10 | 3.32 |
| 15q13.3del(CHRNA7) | 0.92 | 0.93 | 1 | 1.17 | 1.14 | 0.01 | 9.15 | 0.01 | 9.32 |
| WBS\_dup | 0.92 | 0.93 | 0.99 | 1.16 | 1.15 | 0.01 | 8.76 | 0.01 | 8.89 |
| 15q13.3dup(CHRNA7) | 0.92 | 0.98 | 1 | 1.01 | 1.00 | 0.79 | 1.24 | 0.80 | 1.25 |
| 22q11.2distal\_dup | 0.94 | 0.93 | 1 | 1.11 | 1.13 | 0.01 | 8.75 | 0.01 | 8.61 |

**Supplementary Figure 7.** **Effect of CNVs on mortality before and after correction for BMI, based on the above table**. It shows the changes in ORs after correction for BMI: they are essentially unchanged. The CNVs are ordered according to the strength of the original p-value (strongest on the left). The first 12 CNVs were nominally significant in the original analysis.

**Supplementary Table 14. Occurrence of two CNVs in the same person**. The table lists all observed occurrences of two CNVs found in one person. CNVs that were not found in combinations with any other CNV are not shown. Over two thirds of the observations are with one of the five relatively common CNVs: 15q13.3dup(CHRNA7), 15q11.2dup/del and 2q13(NPHP1)dup/del. The observed numbers do not differ from chance expectation.

