**Effects of pathogenic CNVs on biochemical markers: a study on the UK Biobank**

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**ABSTRACT**

**Background**. Pathogenic copy number variants (CNVs) increase risk for medical disorders, even among carriers free from neurodevelopmental disorders. The UK Biobank recruited half a million adults who provided samples for biochemical and haematology tests which have recently been released. We wanted to assess how the presence of pathogenic CNVs affects these biochemical test results.

**Methods**. We called all CNVs from the Affymetrix microarrays and selected a set of 54 CNVs implicated as pathogenic (including their reciprocal deletions/duplications) and were present in five or more persons. We used linear regression analysis to establish their association with 28 biochemical and 23 haematology tests.

**Results**. We analysed 421k participants of white British or Irish descent who passed our CNV quality control filters. There were 268 associations between CNVs and biomarkers that were significant at a false discovery rate of 0.05. Deletions at 16p11.2 had the highest number of significant associations, but several rarer CNVs showed higher average effect sizes indicating that the lack of significance was likely due to the reduced statistical power for rarer events.

**Conclusions**. Carriers of many pathogenic CNVs have changes in biochemical and haematology tests, and many of those are associated with adverse health consequences. These changes did not always correlate with increases in diagnosed medical disorders in this population. Carriers should have regular blood tests in order to early identify and treat medical consequences. Levels of cholesterol and other lipids were lower in carriers of CNVs associated with weight gain, presumably due to increased use of statins among such people.

**INTRODUCTION**

Large copy number variants (CNVs) have been shown to have significant effects on common medical disorders even among the relatively healthy individuals with no early-onset neurodevelopmental disorders, taking part in the UK Biobank (Crawford et al, 2018). Such carriers also tended to have changes in physical traits, such as weight, height, body fat content, pulse rate and blood pressure (Owen et al, 2018).

Participants in the UK Biobank agreed to donate blood, saliva and urine samples for biochemical tests at the point of their recruitment. Biochemical and haematology tests were performed on the full set of Biobank participants and the data was recently released. We expected that there will be significant changes in the levels of many of these tests among carriers of pathogenic CNVs, in line with the increased morbidity and mortality and changes in the physical traits in this population.

**METHODS**

Approval for the study was obtained from the UK Biobank under project 14421: “Identifying the spectrum of biomedical traits in adults with pathogenic copy number variants (CNVs)”.

**Participants**: The UK Biobank recruited just over half a million people from the UK general population. We restricted analysis to individuals of White British or Irish descent whose samples passed our standard CNV QC filters (genotyping call rate < 0.96, > 30 CNVs per person, a waviness factor of < -0.03 & > 0.03 & LRR standard deviation of > 0.35).

**Choice of CNVs**: We tested 54 CNVs that have been proposed to be pathogenic and were carried by at least five participants (the choice of the CNVs, their chromosomal positions and details of analysis are given in our previous publications (Crawford et al, 2018, Owen et al, 2018). Briefly, the CNVs follow the lists of Coe et al (2013) and Dittwald et al (2014).

**Tests**: We analysed these CNVs for association with a set of 28 biomarkers and 23 haematology tests that were available for the whole dataset (Table 1). Details on the tests and methods used for their measurements are presented on the Biobank website: biobank.ctsu.ox.ac.uk/showcase/showcase/docs/serum\_biochemistry.pdf, and biobank.ctsu.ox.ac.uk/showcase/showcase/docs/haematology.pdf. Between 401k and 319k people who passed our QC filters had valid results for the tests (**Table 1**). Two of the available tests, Oestradiol and Rheumatoid Factor, were only performed on around 76k and 41k individuals, too rare for analysis on most rare CNVs, and were therefore excluded.

|  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- |
| **Test** | **Function** | **N people** | **Mean** | **Min** | **Max** | **Std. Dev.** | **Unit** |
| Alanine aminotransferase (ALT) | Liver | 401476 | 23.56 | 3.01 | 495.19 | 14.15 | U/L |
| Albumin | Liver | 367822 | 45.22 | 18.87 | 59.80 | 2.61 | g/L |
| Aspartate aminotransferase (AST) | Liver | 400150 | 26.22 | 3.30 | 947.20 | 10.54 | U/L |
| Direct bilirubin | Liver | 341413 | 1.83 | 1.00 | 70.06 | 0.85 | mcmol/L |
| Gamma glutamyltransferase (GGT) | Liver | 401418 | 37.45 | 5.00 | 1184.90 | 42.18 | U/L |
| Total bilirubin | Liver | 399948 | 9.13 | 1.08 | 144.52 | 4.42 | mcmol/L |
| Alkaline phosphatase (ALP) | Bone and joint | 401640 | 83.73 | 8.00 | 1416.7 | 26.53 | U/L |
| Vitamin D | Bone and joint | 383994 | 49.67 | 10.00 | 340.00 | 20.98 | nmol/L |
| Calcium | Bone and joint | 367686 | 2.38 | 1.05 | 3.57 | 0.09 | mmol/L |
| Apolipoprotein A1 (APOA1) | Cardiovascular | 365618 | 1.54 | 0.42 | 2.50 | 0.27 | g/L |
| Apolipoprotein B (APOB) | Cardiovascular | 399665 | 1.03 | 0.40 | 2.00 | 0.24 | g/L |
| Cholesterol | Cardiovascular | 401615 | 5.71 | 0.60 | 15.46 | 1.14 | mmol/L |
| C-reactive protein (CRP) | Cardiovascular | 400753 | 2.60 | 0.08 | 79.96 | 4.38 | mg/L |
| HDL cholesterol | Cardiovascular | 367652 | 1.45 | 0.22 | 4.40 | 0.38 | mmol/L |
| LDL cholesterol | Cardiovascular | 400878 | 3.57 | 0.27 | 9.80 | 0.87 | mmol/L |
| Lipoprotein (a) | Cardiovascular | 319638 | 44.11 | 3.80 | 189.00 | 49.38 | nmol/L |
| Triglycerides | Cardiovascular | 401301 | 1.76 | 0.23 | 11.28 | 1.03 | mmol/L |
| HbA1c | Diabetes | 401566 | 35.97 | 15.00 | 515.2 | 6.52 | mmol/mol |
| Glucose | Diabetes | 367387 | 5.12 | 1.01 | 36.81 | 1.21 | mmol/L |
| Creatinine | Renal | 401421 | 72.29 | 10.80 | 1499.3 | 17.95 | mcmol/L |
| Cystatin C | Renal | 401577 | 0.91 | 0.30 | 7.49 | 0.17 | mg/L |
| Phosphate | Renal | 367125 | 1.16 | 0.37 | 4.70 | 0.16 | mmol/L |
| Total protein | Renal | 367406 | 72.36 | 36.27 | 117.36 | 4.04 | g/L |
| Urea | Renal | 401346 | 5.43 | 0.81 | 41.83 | 1.39 | mmol/L |
| Uric acid (UA) | Renal | 401135 | 309.39 | 89.10 | 884.30 | 80.41 | mcmol/L |
| Insulin-like Growth Factor-1 (IGF-1) | Cancer | 399465 | 21.37 | 1.45 | 126.77 | 5.66 | nmol/L |
| Sex Hormone Binding Globulin (SHBG) | Cancer | 364235 | 51.90 | 0.39 | 241.92 | 27.72 | nmol/L |
| Testosterone | Cancer | 363579 | 6.57 | 0.35 | 54.34 | 6.05 | nmol/L |
| Basophill number | haematology | 407888 | 0.00 | 2.60 | 0.03 | 0.05 | x 109 cells/L |
| Basophill percent | haematology | 407894 | 0.00 | 33.80 | 0.57 | 0.61 | percent |
| Eosinophill number | haematology | 407888 | 0.00 | 9.60 | 0.17 | 0.14 | x 109 cells/L |
| Eosinophill percent | haematology | 407894 | 0.00 | 100.00 | 2.56 | 1.85 | percent |
| Haematocrit | haematology | 408607 | 0.05 | 72.48 | 41.12 | 3.52 | percent |
| Haemoglobin concentration (HGB) | haematology | 408607 | 0.11 | 22.27 | 14.20 | 1.23 | g/dl |
| Lymphocyte number | haematology | 407888 | 0.00 | 177.00 | 1.95 | 1.16 | x 109 cells/L |
| Lymphocyte percent | haematology | 407894 | 0.00 | 98.70 | 28.65 | 7.36 | percent |
| Mean corpuscular volume (MCV) | haematology | 408605 | 53.52 | 160.30 | 91.33 | 4.39 | fL |
| Mean corpuscular haemoglobin (MCH) | haematology | 408604 | 0.00 | 95.67 | 31.55 | 1.83 | g/dL |
| Mean corpuscular haemoglobin concentration (MCHC) | haematology | 408600 | 16.10 | 97.30 | 34.54 | 1.06 | fL |
| Mean reticulocyte volume (MRV) | haematology | 402048 | 46.00 | 249.45 | 105.84 | 7.77 | fL |
| Monocyte number | haematology | 407888 | 0.00 | 34.26 | 0.48 | 0.22 | x 109 cells/L |
| Monocyte percent | haematology | 407894 | 0.00 | 96.90 | 7.09 | 2.70 | percent |
| Neutrophill number | haematology | 407888 | 0.00 | 52.02 | 4.25 | 1.41 | x 109 cells/L |
| Neutrophill percent | haematology | 407894 | 0.00 | 97.70 | 61.13 | 8.40 | percent |
| Nucleated red blood cell number | haematology | 407878 | 0.00 | 6.90 | 0.00 | 0.03 | x 109 cells/L |
| Nucleated red blood cell percent | haematology | 407874 | 0.00 | 48.86 | 0.03 | 0.40 | percent |
| Platelet count | haematology | 408605 | 0.30 | 1821.0 | 253.44 | 59.89 | x 109 cells/L |
| Red blood cell count | haematology | 408607 | 0.01 | 7.91 | 4.51 | 0.41 | x 1012 cells/L |
| Reticulocyte number | haematology | 402047 | 0.00 | 2.39 | 0.06 | 0.04 | x 1012 cells/L |
| Reticulocyte percent | haematology | 402047 | 0.00 | 90.91 | 1.35 | 0.89 | percent |
| White blood cell count (WBC) | haematology | 408602 | 0.00 | 189.50 | 6.90 | 2.06 | x 109 cells/L |

**Table 1**. List of biochemical and haematological tests, their ranges and the number of people with valid results. The “Function” that the tests measure is listed according to the UK Biobank website.

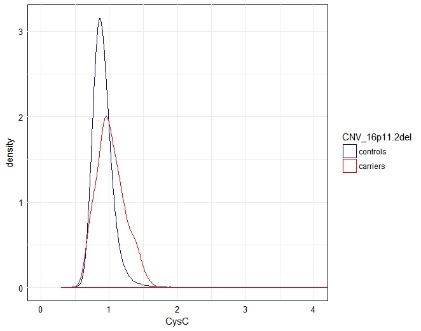
**Statistical analysis**: The tested variables followed normal distributions, therefore we did not further transform the data prior to analysis and show the results in non-normalised (original) units, to allow clinicians to relate them more easily to known tests (e.g. mmol/L, U/L). We used linear regression analysis with sex and age as co-variates. Other potential confounders were not included, as it is not known which confounding factors lead to the abnormalities, or are a consequence of the presence of a CNVs. For example, we previously showed that carrying a CNV from this list has strong adverse effects on measures of social deprivation, occupation and education (Kendall et al, 2019), all factors that could be also perceived as contributing to some biochemical tests results abnormalities. In our previous work (Crawford et al, 2018) we also observed practically no effect from controlling for principal components, as should be expected for genetic variants whose frequencies are determined by selection pressure and mutation rates, rather than genetic drift (Rees et al, 2011). We used the Benjamini-Hochberg false-discovery rate (FDR) method to estimate the project-wide statistical significance (Benjamini and Hochberg 1995). We accepted a conservative false discovery rate (FDR) of 0.05 as our significance threshold (Supplementary Tables 1 and2).

**RESULTS**

The comparisons of 54 CNVs and 51 tests produced 2751 associations, of which 268 were significant at FDR=0.05 (marked in bold in Supplementary Tables 1 and 2). All results are also displayed on our institutional website (<http://kirov.psycm.cf.ac.uk/>).

**Table 2** summarises the significant findings. Deletions at 16p11.2 (110 carriers) produced the largest number of significant associations, followed by carriers of 15q11.2 deletions, 16p11.2 distal deletions, 15q13.3 deletions and duplications and 17q12 deletions, with 15 or 16 significant associations each. **Figure 1** is as an example of the spread of test values for the top three results for 16p11.2 deletions.

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**Figure 1**. Spread of the values of the top three findings for 16p11.2 deletions and controls: a) HbA1c. b) Cystatin-C, c) Alkaline phosphatase.

All possible distributions can be visualised interactively on our web repository (<https://kirov.psycm.cf.ac.uk/>) hopefully will be done in time (Matt), if not, will be dropped. Several rarer CNVs had even larger average differences compared to controls (in terms of standard deviations), which did not always reach significance, very likely due to the small sample size. The most pathogenic ones appear to be very rare CNVs, with 5-10 observations each: 17q12 deletions (Renal Cysts and Diabetes syndrome), 17p11.2 duplications (Potocki-Lupski syndrome), 3q29 deletions and duplications, 22q11.2 classic and distal deletions, 15q24 duplications and 10q23 duplications.

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
| **CNV** | **SD of mean difference** | **N CNV carriers** | **N sign. results** | **Sign. associated tests** | **Sign. associated medical phenotypes** |
| 10q11.21q11.23del | 0.1323 | 57 |  |  |  |
| 10q11.21q11.23dup | 0.0998 | 41 |  |  |  |
| 10q23dup | 0.4658 | 7 |  |  |  |
| 13q12.12del | 0.0786 | 85 | 4 | WBC and lymphocyte number, reticulocyte number and % |  |
| 13q12.12dup | 0.0628 | 236 | 2 | reticulocyte number and % |  |
| 13q12del\_CRYL1 | 0.0348 | 379 | 1 | RBC |  |
| 13q12dup\_CRYL1 | 0.2401 | 10 | 1 | Monocyte number and % |  |
| 15q11.2del | 0.0533 | 1664 | 15 | APOA1\*, Creatinine, Cys-C, Direct bilirubin, HDL\*, IGF-1, Phosphate, Total bilirubin, Urea, Vit-D, MCV, MCH, RBC, monocyte % |  |
| 15q11.2dup | 0.0174 | 2041 | 1 | SHBG |  |
| 15q11q13del\_BP3\_BP4 | 0.2224 | 16 | 2 | Albumin, CRP | gastric\_reflux |
| 15q11q13dup\_BP3\_BP4 | 0.1330 | 53 |  |  |  |
| 15q11q13dup\_BP3\_BP5 | 0.1495 | 9 | 5 | MRV, MCV, neutrophil %, RBC, lymphocyte % |  |
| 15q13.3del | 0.2451 | 42 | 13 | APOA1\*, Glucose, HbA1c, HDL\*, Triglyceride, Vit-D, RBC, MCV, MCH, neutrophil number, WBC, MRV, haematocrit | Asthma, diabetes type2 |
| 15q13.3del\_CHRNA7 | 0.1717 | 10 |  |  |  |
| 15q13.3dup | 0.1058 | 240 | 15 | ALP, CRP, Cys-C, GGT, Vit-D, MCV, MCH, lymphocyte %, RBC, MRV, neutrophil number and %, basophil number and %, monocyte number | death |
| 15q13.3dup\_CHRNA7 | 0.0157 | 3031 |  |  |  |
| 15q24dup | 0.4853 | 9 | 3 | ALT, AST, GGT |  |
| 16p11.2del | 0.4237 | 110 | 28 | ALT, Albumin, ALP, APOA1\*, AST, Calcium, Cholesterol\*, CRP, Creatinine, Cys-C, GGT, Glucose, HbA1c, HDL\*, IGF-1, SHBG, Total bilirubin, Triglyceride, Uric acid, Vit-D, platelet count, neutrophil %, MRV, WBC, monocyte %, eosinophil % | diabetes type2, obesity, anaemia, hypertension, asthma, renal failure, ostheoarthritis, respiratory, death, high cholesterol, heart failure, hernia |
| 16p11.2distal\_del | 0.3724 | 58 | 16 | ALT, ALP, APOA1\*, AST, Cholesterol\*, CRP, Cys-C, GGT, Glucose, HbA1c, HDL\*, LDL\*, Reticulocyte number, HGB, reticulocyte %, haematocrit | diabetes type2, obesity, gout |
| 16p11.2distal\_dup | 0.1011 | 137 | 5 | Total protein, lymphocyte number, WBC, platelet count, HGB |  |
| 16p11.2dup | 0.1192 | 138 | 7 | Creatinine, SHBG, Vit-D, platelet count, HBG, haematocrit, RBC | Irritable bowel syndrome, sciatica |
| 16p12.1del | 0.1097 | 246 | 9 | Albumin, ALP, Creatinine, Cys-C, HDL\*, monocyte number, RVC, MCH, MCV, | Hypertension, obesity, renal failure, diabetes type2, heart disease (not ishaemic), ureter/bladder |
| 16p12.1dup | 0.0544 | 202 |  |  |  |
| 16p13.11del | 0.0792 | 131 | 1 | Lymphocyte % |  |
| 16p13.11dup | 0.0709 | 828 | 12 | ALP, APOA1\*, APOB\*, Cholesterol\*, HDL\*, LDL\*, SHBG, Uric acid, Vit-D, HGB, MCH, basophil number | Hypertension |
| 17p12del\_HNPP | 0.0653 | 237 |  |  | neuropathies |
| 17p12dup\_CMT1A | 0.1375 | 124 | 4 | Albumin, Calcium, Creatinine, Cys-C | Neuropathies, anaemia |
| 17q11.2del\_NF1 | 0.2958 | 9 | 5 | WBC, Monocyte, basophil and neutrophil number, basophil % |  |
| 17q12del | 1.0214 | 9 | 15 | ALT, ALP, AST, Creatinine, Cys-C, GGT, Glucose, HbA1c, Urea, Vit-D, WBC, lymphocyte, monocyte, neutrophil and basophil number | Diabetes type1, digestive system |
| 17q12dup | 0.2307 | 101 | 9 | APOB, Cholesterol, Creatinine, Cys-C, Lopo(a), SHBG, Total protein, Urea, Uric acid | Renal failure |
| 1q21.1del | 0.0827 | 113 | 3 | ALP, platelet count, lymphocyte % | Cataracts |
| 1q21.1dup | 0.1313 | 177 | 8 | APOA1, Cholesterol\*, Cys-C, Glucose, HbA1c, HDL\*, monocyte number and % | Diabetes type2 |
| 22q11.2del | 0.4129 | 10 | 5 | Calcium, Cys-C, platelet count, MRV, lymphocyte % |  |
| 22q11.2distal\_del | 0.7607 | 5 | 8 | Cholesterol, Cys-C, Testosterone, Urea, monocyte and basophile number and % |  |
| 22q11.2distal\_dup | 0.2419 | 13 | 0 |  |  |
| 22q11.2dup | 0.0967 | 280 | 11 | Albumin, Cys-C, Total protein, Triglyceride, Vit-D, RBC, HGB, haematocrit, platelet count, eosinophil % | Gastric reflux, hernia |
| 2q11.2del | 0.2376 | 31 | 3 | Cys-C, Phosphate, MRV |  |
| 2q11.2dup | 0.1375 | 29 | 2 | Calcium, eosinophil number |  |
| 2q13del | 0.2135 | 53 | 4 | CRP, Cys-C, IGF-1, SHBG |  |
| 2q13del\_NPHP1 | 0.0296 | 2448 | 4 | Cholesterol, Direct bilirubin, LDL, Total protein |  |
| 2q13dup | 0.1492 | 71 | 4 | ALT, AST, HbA1c, neutrophil number |  |
| 2q13dup\_NPHP1 | 0.0185 | 1976 |  |  |  |
| 2q21.1del | 0.1150 | 41 |  |  |  |
| 2q21.1dup | 0.0893 | 59 |  |  |  |
| 3q29del | 0.6042 | 9 | 8 | ALT, APOB, GGT, Glucose, HbA1c, Glucose, MCH, MCV, RBC, |  |
| 3q29dup | 0.5964 | 5 | 4 | Glucose, WBC, lymphocyte number and % | Cancer, diverticular disease of intestine, inflammatory bowel disease, renal failure |
| 7q11.23dup\_distal | 0.1688 | 24 | 3 | RBC, HBG, haematocrit |  |
| 8p23.1dup | 0.2359 | 6 |  |  |  |
| NRXN1del | 0.1254 | 163 | 5 | Albumin, HDL\*, Phosphate, Total bilirubin, Triglyceride\* | Aneurisms |
| Potocki\_Lupski | 0.4313 | 5 | 2 | Albumin, Total protein |  |
| PWS\_dup | 0.2946 | 19 | 1 | Calcium |  |
| TAR\_del | 0.1469 | 75 | 8 | Albumin, Uric acid, MCV, MRV, reticulocyte number, RBC, MCR, reticulocyte % |  |
| TAR\_dup | 0.0833 | 436 | 6 | ALP, APOA1\*, Cholesterol\*, HbA1c, HDL\*, Uric acid | obesity |
| WBS\_dup | 0.3730 | 14 | 5 | Albumin, ALP, CRP, Uric acid, MCV |  |

**Table 2**. CNVs analysed and the associated biochemical tests and medical conditions (as presented in Crawford et al, 2018). An \* denotes cholesterol and related lipid levels that are unexpectedly reduced in carriers of CNVs associated with increased BMI.

Some of the well-established medical consequences of CNVs were associated with corresponding abnormalities in biochemical tests. For example 17q12 deletions (Renal Cysts and Diabetes syndrome) were associated with increased levels of creatinine, urea, Cystatin-C and glucose; 22q11.2 deletion carriers exhibited reduced calcium levels; 16p11.2 deletion carriers had the expected multiple abnormalities associated with cardiometabolic disorders shown for this condition; and 16p12.1 deletion carriers, who have high rates of renal failure and heart disease, have abnormalities in creatinine and Cystatin-C (**Table 2**). Other abnormalities were more subtle and would have escaped detection, if they not been analysed in this large dataset. Most notable are the many changes detected among carriers of 15q11.2 deletions, a CNV with neurodevelopmental phenotypes, but no confirmed medical co-morbidities. The changes were subtle (around 0.1 SD for the significant results and 0.05 SD overall) and therefore unlikely to result in significant increases of overt medical disorders. However, they might cause problems in later life and reduce life expectancy if left untreated.

Most but not all significant changes suggest deterioration of function:

**Liver**: Nearly all significant changes affecting liver function test (except bilirubin levels) were in the direction of higher levels, indicating liver abnormalities. **Bone**: All significant results for the three tests connected with bone function were adversely changed: reduced Vitamin D and Calcium, raised ALP. **Diabetes**: All significant changes were in the direction of raised glucose and HbA1c. **Cardiovascular**: As explained below, these tests are not informative in this population, most likely due to statins intake. **Renal**: All significant Cystatin-C results (in 14 CNVs) were increased, as were nearly all significant urea and uric acid levels, suggesting reduced renal function in several CNVs, but there were exceptions: 17p12 duplications (causing Charcot-Marie-Tooth disease type 1A) and 16p11.2 deletion carriers had reduced creatinine levels. **Cancer markers**: There were only a few significant results, with mixed effects. It is difficult to interpret these as a group, as they are relevant for specific cancers. **Haematology**: Apart from trends for increases in neutrophil and lymphocyte counts, there were no clear patterns. Several CNVs showed predominant changes in haematological test results: 13q12.12 and 15q13.3 deletions and duplications, 15q11q13\_BP3\_BP5 duplications, 16p11.2 distal duplications, 17q11.2 (NF1) deletions, 7q11.23 distal duplications and TAR deletions.

Homozygous deletions at 2q13del locus affect the gene NPHP1 and are known to cause the kidney disorder *juvenile nephronophthisis*. Previously we reported that all three homozygous individuals in the cohort had renal failure (Crawford et al, 2018). Therefore we excluded these three people from analysis. It appears that heterozygous individuals have subtle phenotypes, with changes in cholesterol and total protein (reductions) and increases in direct bilirubin. Creatinine was also increased but the difference was only significant prior to multiple testing correction, with a change of less than 1 mcmol/L.

Mirror-image phenotypes, as reported for physical traits in our previous work (Owen et al, 2018) were rare, almost entirely confined to 16p11.2 (creatinine, platelet count and SHBG) and for 15q13.3 (MCH, MCV and MRV).

**DISCUSSION**

Most pathogenic CNVs tested in this study are known to increase risk for neurodevelopmental disorders and common medical phenotypes. Therefore it is not surprising that they are also associated with abnormal biochemical tests. About 10% of all possible CNV/test associations were significant at a conservative FDR = 0.05, suggesting multiple effects. While most are expected, e.g. high creatinine and Cystatin-C for CNVs associated with renal failure, others suggest more subtle effects that could affect medical outcomes and all-cause mortality, some of which have so far not been demonstrated. Indeed, we previously showed that carriers of 11 of these CNVs have statistically increased mortality, which was not fully explained by the statistically associated medical conditions (Crawford et al, 2018).

One set of associations runs against the expected directions and deserves a special discussion: Cholesterol and associated biochemical tests (LDL, HDL, ApoA1 and ApoB) were *reduced* (rather than increased) among carriers of CNVs that are associated with obesity or ischaemic heart disease, such as 16p12.1 deletions, 16p11.2 deletions and 16p11.2 distal deletions (Bochukova et al, 2010, Crawford et al, 2018). We suspect that this is due to a large proportion of such patients taking statins, precisely because they are overweight or have cardiovascular problems. This possibility is confirmed by an extreme example: people diagnosed with “high cholesterol” in the sample as a whole also showed significantly reduced levels of these tests, a seemingly completely counter-intuitive finding. For example, levels of cholesterol were, on average, 0.66 mmol/L lower among the 70,052 people who had this diagnosis, which can only make sense if they had taken statins after being diagnosed (**Table 3**). This class of medicines is highly effective in lowering cholesterol and lipid concentrations (Cholesterol treatment trialists, 2019). At the point of recruitment the participants listed the medications they were taking, so we tested whether reductions in cholesterol were present only among those on statins. This could not fully explain the observations. Even CNV carriers who had not declared statins intake had lower cholesterol levels than non-carriers who were not taking statins. In a linear regression analysis, being on statins was associated with a 1.61 mmol/L lower cholesterol for the population as a whole, while a diagnosis of “high cholesterol” was associated with only 0.4 mmol/L higher cholesterol. Similar analysis on 16p11.2 deletion carriers showed that being on statins was associated with a 1.34 mmol/L lower cholesterol, while carrying the deletion was associated with 0.19 mmol/L lower cholesterol. We suggest that the only way to reconcile these findings is that a proportion of people (CNV carriers and non-carriers) had either taken statins at an earlier time, or had not declared them. Obviously, people who are obese or have cardiovascular incidents are more likely to have been prescribed statins. We present all biochemical results separately with statins intake as a co-variate to enable readers to draw their own conclusions (**Supplementary Table 2**). Researchers need to be aware of this potential bias in the UK Biobank when interpreting findings on cholesterol and other lipids. This potential problem could be resolved once the primary care (GP) data become available.

|  |  |  |  |
| --- | --- | --- | --- |
| Group | On statins | Cholesterol mean (SD) | N participants |
| People with no diagnosis of “High cholesterol” | No | 5.89 (1.05) | 316856 |
| Yes | 4.39 (0.89) | 14707 |
| People with a diagnosis of “High cholesterol” | No | 6.38 (1.23) | 19153 |
| Yes | 4.74 (0.93) | 50899 |
| CNV non-carriers | No | 5.92 (1.07) | 323170 |
| Yes | 4.66 (0.94) | 63000 |
| 16p11.2del carriers | No | 5.58 (1.31) | 78 |
| Yes | 4.45 (1.14) | 25 |

**Table 3**. Cholesterol levels in cases and controls, according to statins intake, being diagnosed with “high cholesterol” and having a 16p11.2 deletion (an example of a CNV highly associated with obesity and cardiometabolic disorders).

**CONCLUSIONS**

Our findings of changes in biochemical tests confirm our previous reports on this population, where we found adverse changes in basic physical characteristics in CNV carriers (Owen et al, 2018) and higher rates of common medical disorders (Crawford et al, 2018). This strengthens the case for general monitoring of such carriers and treatment and prevention of biochemical abnormalities, e.g. with statins, antidiabetic drugs etc. These findings cannot be yet be used for analysis of cholesterol and related lipids, due to high rates of statins intake in this population.

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