Supplementary Online Content

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This supplementary material has been provided by the authors to give readers additional information about their work.
eMethods.

DiscovEHR Cohort

The cohort for this study was identified from Geisinger’s MyCode® Community Health Initiative, a biorepository operating in a CLIA-laboratory environment with >250,000 consented patient-participants, unselected for age or gender, receiving medical care at Geisinger. Exome sequencing (ES) and linked EHR data are currently available for 92,455 MyCode participants - a subset known as the DiscovEHR cohort – on which this study is based. The DiscovEHR cohort is highly homogeneous in terms of European ancestry (97.7%), based on participant report, and primarily includes older adults (mean age: 57 years) recruited from an unselected Geisinger outpatient population with a median follow-up of 14.6 years of EHR-linked data. More than half of the participants are female (60.6%). All DiscovEHR participants provided written consent (IRB #2006-0258) to be contacted through our Genomic Screening and Counseling (GSC) program about clinically relevant genomics results. The list of reportable gene-disease pairs is dynamic and can be updated to add or remove genes or genomic regions as evidence is acquired. It currently is comprised of 61 gene-disease pairs, including those on the American College of Medical Genetics and Genomics (ACMG) secondary findings list.

Exome Sequencing, SNP Genotyping, and CNV Calling

DNA sample preparation and ES for 92,455 DiscovEHR participants were performed in collaboration with the Regeneron Genetics Center, as described previously. In brief, VCRome exome capture probes (Nimblegen, Madison, Wisconsin) were used for the first ~61K samples sequenced and a modified version of xGen probes (Integrated DNA Technologies, Coralville, Iowa) was used for the remaining ~31K samples. Samples were sequenced using 75 basepair paired-end sequencing on a v4 HiSeq 2500 (Illumina, San Diego, CA) to a coverage depth sufficient to provide greater than 20X haploid read depth of over 85% of targeted bases in 96% of samples (approximately 80X mean haploid read depth of targeted bases). Sequence reads were aligned to human reference GRCh38 with BWA (approxim. mem) and the resultant BAM files were processed using Picard (http://broadinstitute.github.io/picard) MarkDuplicates tool to identify and flag duplicate reads for exclusion in downstream analyses. CNV calling was carried out on ES data from 92,387 patient-participants using the Copy number estimation using Lattice-Aligned Mixture ModelS (CLAMMS) algorithm. As part of the CLAMMS QC pipeline, samples with >40 CNV calls or full or partial aneuploidies (n=1,792) were excluded and our analysis was performed on the remaining 90,595 patient-participants.

CNV Selection and Validation

We evaluated the frequency of 31 pathogenic, recurrent, segmental duplication-mediated CNVs in the DiscovEHR cohort. CNVs were selected if there was strong evidence for pathogenicity documented by a Dosage Sensitivity Score of 3, as defined by the Clinical Genome Resource (ClinGen) Dosage Sensitivity Map (https://www.ncbi.nlm.nih.gov/projects/dbvar/clingen/), which uses an evidence-based process to evaluate CNV regions for clinically relevant haploinsufficiency and triplosensitivity. The 31 selected CNVs are all well-established, pathogenic CNVs commonly reported as such by clinical genetic laboratories and known to cause NPD and, often, other medical concerns. Patient-participants were designated as positive for a CNV of interest if breakpoints overlapped at least 50% of the defined region (eTable 1). Most of the calls (n=688, 96%) spanned at least 90% of the defined region. Nearly all sequenced participants (>97%) were also genotyped on either the HumanOmniExpress (HOEE, Illumina; n=59,499) or Global Screening Array (GSA, Illumina; n=31,062) platforms. CNVs called from ES data were confirmed by an array-based call using PennCNV or manual inspection of the signal intensity data (logR and B-allele frequency) within the pathogenic region. ES-called CNVs without array data were included if confirmed by a clinical laboratory as a part of this project or a diagnosis of the genetic disorder was present in the EHR (described below).

Clinical Data Extraction

The frequency of clinically related phenotypes among individuals with NPD-related CNVs was assessed by extracting relevant ICD-9/10 billing codes from the EHR (eTable 2). Our approach broadly captures developmental and psychiatric disorders of varying levels of severity that can be caused by a NPD-related CNV. The neuropsychiatric disorder ICD codes were chosen to capture disorders classified in the DSM-5 as “neurodevelopmental disorders,” “schizophrenia spectrum and other psychotic disorders,” “bipolar and related disorders,” “depressive disorders,” “anxiety disorders,” and “obsessive-compulsive and related disorders” plus epilepsy and cerebral palsy, which are not included in the DSM-5 classification system. Congenital malformation (CM) categories (e.g., cardiac anomalies, cleft lip) were included as relevant phenotypes in our assessment of the
burden of disease that may be caused by NPD CNVs. Five CM categories were selected based on relevance to known CNV-related phenotypes and highest confidence in the accuracy of EHR-derived ICD-9/10 codes (eTable 2). A genetic diagnosis of a NPD-related CNV in the EHR was identified by the presence of an ICD-9/10 billing code indicating a chromosomal/structural abnormality (eTable 2). Tests of association were performed with logistic regression adjusted for age and sex. Thirteen individuals, missing sex information in their EHR were excluded from these analyses. Reported p-values are Bonferroni corrected for the nine tests of association performed in the study. All statistical analyses were performed using R version 3.4.1. Penetrance was calculated using the formula below:

$$\text{CNV penetrance} = \frac{\text{Number of cases with CNV}}{\text{Number of controls with CNV}}$$

### Disclosure Protocol and Assessment of Participant Responses

A subset of nine pathogenic CNVs were prioritized to be returned to participants, based on the frequency in our dataset and the likelihood that the CNV could also cause non-NPD health considerations (e.g., congenital cardiac anomaly) that would be more likely to have implications for medical care. ICD9/10 codes were manually reviewed for individuals with a prioritized CNV to assess for evidence of an NPD phenotype. Individuals with one of these CNVs and a documented NPD, including depression and anxiety, in their EHR were eligible for clinical disclosure of results. DNA from samples maintained in the MyCode® biorepository CLIA environment were sent for orthogonal confirmation in a CAP- and CLIA-certified clinical laboratory and 141 (100%) results were confirmed. The clinical confirmation test report was scanned into the EHR and the disclosure protocol initiated.

We developed a results disclosure process to return prioritized NPD-related CNVs to adult patient-participants (Figure 2), based on the existing MyCode® GSC program. The proposed CNV disclosure process and returnable CNVs underwent review by Geisinger’s Ethics Advisory Council, Clinical Oversight Committee, Genomics Council, and MyCode® Governing Board prior to implementation.

Three licensed certified genetic counselors experienced with NPD were responsible for contacting and counseling participants about results, facilitating cascade testing for relevant family members, and providing clinical guidance to other healthcare providers. Initiation of result notification occurred from March 2017 to March 2019. A disclosure session outline (eFigure 1) was developed to ensure consistency among genetic counselors and to guide psychosocial assessment of participants’ reactions. Particular consideration was given to reactions upon learning about a genetic NPD etiology and the effects of cognitive and psychiatric symptoms on the comprehension of information provided. Discussion included a description of the CNV, inheritance, knowledge of the associated clinical manifestations, the variable expressivity inherent to brain disorders, and the complex interplay between high-impact genomic variants and environmental factors. Personal medical and NPD histories and family histories were elicited, including participants’ experience with NPD and treatment history. Participants were asked for their thoughts about communicating with relatives about their result and about whether and how the result was valuable to them. Genetic counseling disclosure sessions were documented in participants’ EHR, with detailed three-generation pedigrees that include NPD and other brain disorders; relevant medical articles and healthcare guidelines were also provided to participants’ primary healthcare providers.

A mixed-methods approach was utilized to evaluate a sub-set of participants’ immediate responses to receiving NPD-related results, including qualitative analyses of written genetic counselor post-disclosure assessments of participant responses and audio recordings of in-person disclosure sessions. Retrospective chart reviews of disclosure session notes were conducted, if needed. The post-disclosure assessments were implemented initially to reduce participant burden and were eventually phased out after this analysis. Audio-recording of in-person disclosure sessions was implemented, with participant written consent (IRB #2017-0273), after results had been reported to the first group of 34 participants and remains on-going. Detailed thematic analysis of a larger dataset of audio-recorded transcripts, which is consistent with this subset, will be reported separately (Wain et al., in preparation), but major themes from preliminary analyses are reported here. Post-disclosure assessments were completed for all participants who also consented for audio-recorded sessions. Datasets (audio-recorded transcripts and genetic counselor post-disclosure assessments) were assessed independently using a grounded theory approach. Genetic counselor post-disclosure assessment data were available for both in-person and telephone disclosures (eFigure 1). For each dataset, two independent coders generated codes for themes and subthemes, with

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discussion to reach consensus and develop final codebooks. Themes derived from the genetic counselor assessments were also discussed with the entire GSC team.

We took our working definition of “personal utility” from Bunnik et al., 2015 who provide the following: “genomic information has personal utility if and only if it can reasonably be used for decisions, actions or self-understanding which are personal in nature.” They go on to clarify that “personal utility can be (indirectly) related to health and disease.” This definition informed our interpretation of identified themes which we determined to be related to personal utility.
eReferences.

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## eTable 1. Genomic Coordinates and Inclusion Criteria for Copy Number Variants

| Copy Number Variant | Criteria                                      | Genomic Coordinates (GRCh38/hg38; Mb) |
|--------------------|-----------------------------------------------|---------------------------------------|
| 1q21.1 (GJA5) del/dup | Size >50% of critical region                   | chr1:147.11-147.92                    |
| 1q21.1 (GJA5 + TAR) del/dup | Size >50% of critical region                   | chr1:145.63-147.92                    |
| 3q29 del            | Size >50% of critical region                   | chr3:196.03-197.62                    |
| 5q35 (NSD1) del/dup | Size >50% of critical region                   | chr5:176.3-177.59                     |
| 7q11.23 (ELN) del/dup | Size >50% of critical region                   | chr7:73.33-74.73                     |
| 8p23.1 del/dup      | At least 1 Mb of critical region               | chr8:8.26-11.91                       |
| 10q23 del           | At least 1 Mb, including NRG3 and GRID1        | chr10:79.92-86.98                     |
| 15q11.2q13.1 BP1-3 del/dup | Full critical region, ~4 Mb                 | chr15:22.78-28.14                    |
| 15q13.3 del         | Size >50% of critical region                   | chr15:30.84-32.15                     |
| 15q24 del           | At least 1 Mb between the A-E intervals       | chr15:72.67-75.68                     |
| 16p13.11 del        | Size >50% of critical region                   | chr16:15.42-16.20                     |
| 16p11.2 distal del  | Size >50% of critical region                   | chr16:28.81-29.04                     |
| 16p11.2 del/dup     | Size >50% of critical region                   | chr16:29.64-30.19                     |
| 17p12 (PMP22) del/dup | Size >50% of critical region, affecting PMP22 | chr17:14.19-15.52                     |
| 17p11.2 (RAI1) del/dup | Size >50% of critical region                   | chr17:16.91-20.30                     |
| 17q11.2 (NF1) del/dup | Size >50% of critical region, affecting NF1   | chr17:30.78-31.94                     |
| 17q12 del/dup       | Size >50% of critical region                   | chr17:36.46-37.85                     |
| 17q21.31 (KANSL1) del | Size >50% of critical region                   | chr17:45.63-46.08                     |
| 22q11.2 del/dup (proximal, A-B) | Size >50% of critical region                   | chr22:18.92-20.29                     |
| 22q11.2 del/dup (proximal, A-D) | Size >50% of critical region                   | chr22:18.92-21.11                     |
| 22q11.2 distal del/dup | Size >50% of critical region                   | chr22:21.64-23.31                     |

Table adapted from Crawford K, Bracher-Smith M, Owen D, Kendall KM, Rees E, Pardiñas AF, et al. Medical consequences of pathogenic CNVs in adults: analysis of the UK Biobank. *J Med Genet* 2019;56:131–8.
**eTable 2. ICD-9 and ICD-10 Codes for Neuropsychiatric Disorders, Congenital Malformations, and Chromosomal Abnormalities**

### A. Neuropsychiatric Disorders (NPD)

| Disorder                        | ICD-9 Codes         | ICD-10 Codes |
|---------------------------------|---------------------|--------------|
| Intellectual Disabilities       | 317, 318.0, 318.1, 318.2, 319, 315.5, 315.8 | F70, F71, F72, F73, F78, F79, F88 |
| Communication Disorders         | 315.3, 315.31, 315.32, 315.34, 315.35, 315.39, 307.9 | F80.0, F80.1, F80.2, F80.4, F80.8, F80.81, F80.82, F80.89, F80.9, |
| Autism Spectrum Disorder        | 299.00, 299.80      | F84.*        |
| ADHD                            | 314, 314.0, 314.00, 314.01, 314.1, 314.2, 314.8, 314.9 | F90, F90.0, F90.1, F90.2, F90.8, F90.9 |
| Specific Learning Disorder      | 315.0*, 315.1, 315.2 | F81, F81.0, F81.2, F81.8, F81.81, F81.89, F81.9 |
| Motor Disorders                 | 315.4, 307.2, 307.20, 307.21, 307.22, 307.23, 307.3, 781.3 | F82, F98.4, F95, F95.0, F95.1, F95.2, F95.8, F95.9, R27.0, R27.8, R27.9 |
| Other Neurodevelopmental Disorders | 315.9        | F89         |
| Schizophrenia Spectrum and Other Psychotic Disorders | 295.*, 297.*, 298.*, 301.22 | F20.*, F21, F22, F23, F24, F25.*, F28, F29, F06.1 |
| Bipolar and Related Disorders   | 296.0*, 296.1*, 296.4*, 296.5*, 296.6*, 296.7, 296.8* | F30.*, F31.*, F34.0 |
| Depressive Disorders            | 296.2*, 296.3*, 311 | F32.*, F33.*, F34.1 |
| Anxiety Disorders               | 300.0, 300.00, 300.01, 300.02, 300.09, 300.2*, 309.21, 312.23 | F40.*, F41.*, F93.0, F94.0 |
| Obsessive-Compulsive and Related Disorders | 300.3, 300.7, 312.39 | F42.*, F45.22, F63.3 |
| Epilepsy                        | 345.*            | G40.*        |
| Cerebral Palsy                  | 343.*            | G80.*        |

*Indicates wildcard character (none or any number)

### B. Congenital Malformation (CM)

| Malformation                  | ICD-9 Codes         | ICD-10 Codes |
|-------------------------------|---------------------|--------------|
| Central Nervous System        | 740.*, 741.*, 742.* | Q00.*, Q01.*, Q02, Q03.*, Q04.*, Q05.*, Q06.*, Q07.* |
| Cardiac                       | 745.*, 746.*, 747..0, 747.1, 747.2, 747.3, 747.4* | Q20.*, Q21.*, Q22.*, Q23.*, Q24.*, Q25.*, Q26.* |
| Cleft lip/palate              | 749.*             | Q35.*, Q36.*, Q37.* |
| Genital                       | 752.*             | Q50.*, Q51.*, Q52.*, Q53, Q53.1*, Q53.0*, Q53.2*, Q54.*, Q55.*, Q56.* |
| Renal/Urinary                 | 753.*             | Q60.*, Q61.*, Q62.*, Q63.*, Q64.* |

*Indicates wildcard character (none or any number)

### C. Chromosomal or Structural Abnormality

| Abnormality                   | ICD-9 Codes         | ICD-10 Codes |
|-------------------------------|---------------------|--------------|
| 758.*, 795.2, 279.11          | Q90.*, Q91.*, Q92.*, Q92.6*, Q93.*, Q95.*, Q96.*, Q97.*, Q98.*, Q99.*, D82.1, R89.8* |

*Indicates wildcard character (none or any number); ^Only R89.8 descriptions specifying abnormal genetic test/chromosomal analysis/karyotype were included
| Chr | Dosage | CNV | Total | ID | CD | ASD | ADHD | SLD | MD | OND | SCZ | BPD | OCD | EP | CP | Any NPD | Percent Affected |
|-----|--------|-----|-------|----|----|-----|------|-----|----|-----|-----|-----|-----|----|----|----------|------------------|
| 1   | Deletion | 1q21.1 (GJA5) | 59 | 2 | 2 | 0 | 2 | 1 | 0 | 0 | 3 | 4 | 0 | 0 | 0 | 11 | 18.6 |
| 1   | Duplication | 1q21.1 (GJA5) | 90 | 2 | 2 | 0 | 3 | 0 | 0 | 6 | 8 | 0 | 6 | 0 | 16 | 17.8 |
| 3   | Deletion | 3q29 (DLG1) | 4 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0.0 |
| 7   | Deletion | 7q11.23 (ELN) | 4 | 1 | 0 | 0 | 1 | 1 | 0 | 1 | 1 | 0 | 0 | 0 | 3 | 75.0 |
| 7   | Duplication | 7q11.23 (ELN) | 8 | 2 | 1 | 0 | 1 | 1 | 0 | 1 | 1 | 0 | 0 | 0 | 4 | 50.0 |
| 10  | Deletion | 10q23 (BMPR1A) | 1 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0.0 |
| 15  | Deletion | 15q11.2q13.1 BP1-3 (UBE3A) | 5 | 4 | 1 | 0 | 0 | 1 | 1 | 3 | 0 | 0 | 1 | 0 | 4 | 80.0 |
| 15  | Duplication | 15q11.2q13.1 BP1-3 (UBE3A) | 3 | 1 | 0 | 1 | 0 | 1 | 0 | 0 | 0 | 0 | 0 | 2 | 0 | 3 | 100.0 |
| 15  | Deletion | 15q13.3 (CHRNA7) | 55 | 2 | 1 | 1 | 2 | 1 | 1 | 1 | 1 | 3 | 11 | 0 | 15 | 27.3 |
| 15  | Deletion | 15q24 (SIN3A) | 2 | 2 | 0 | 1 | 1 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 2 | 100.0 |
| 16  | Deletion | 16p11.2 distal (SH2B1) | 28 | 0 | 2 | 0 | 0 | 0 | 0 | 0 | 0 | 1 | 0 | 0 | 3 | 10.7 |
| 16  | Deletion | 16p11.2 (TBX6) | 59 | 9 | 2 | 1 | 4 | 2 | 2 | 1 | 0 | 3 | 1 | 5 | 0 | 17 | 28.8 |
| 16  | Duplication | 16p11.2 (TBX6) | 63 | 2 | 1 | 2 | 6 | 3 | 1 | 1 | 4 | 10 | 1 | 4 | 0 | 21 | 33.3 |
| 16  | Deletion | 16p13.11 (MYH11) | 71 | 3 | 4 | 0 | 3 | 1 | 4 | 2 | 2 | 6 | 1 | 18 | 1 | 27 | 38.0 |
| 17  | Deletion | 17p11.2 (RAI1) | 4 | 4 | 2 | 1 | 2 | 0 | 0 | 0 | 0 | 0 | 3 | 1 | 4 | 100.0 |
| 17  | Deletion | 17p12 (PMP22) | 31 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 2 | 0 | 2 | 6.5 |
| 17  | Duplication | 17p12 (PMP22) | 38 | 0 | 1 | 0 | 1 | 0 | 0 | 0 | 2 | 4 | 1 | 2 | 0 | 9 | 23.7 |
| 17  | Deletion | 17q11.2 (NF1) | 3 | 0 | 0 | 0 | 1 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 1 | 33.3 |
| 17  | Duplication | 17q11.2 (NF1) | 4 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0.0 |
| 17  | Deletion | 17q12 (HNF1B) | 4 | 0 | 0 | 1 | 2 | 1 | 0 | 0 | 1 | 1 | 0 | 1 | 0 | 3 | 75.0 |
| 17  | Duplication | 17q12 (HNF1B) | 41 | 1 | 1 | 1 | 4 | 1 | 0 | 0 | 2 | 2 | 1 | 2 | 0 | 11 | 26.8 |
| 22  | Deletion | 22q11.2 (TBX1) | 23 | 13 | 11 | 1 | 6 | 2 | 5 | 2 | 5 | 2 | 0 | 4 | 0 | 17 | 73.9 |
| 22  | Duplication | 22q11.2 (TBX1) | 108 | 10 | 6 | 1 | 9 | 2 | 2 | 2 | 5 | 12 | 1 | 3 | 0 | 31 | 28.7 |
| 22  | Deletion | 22q11.2 distal | 1 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0.0 |
| 22  | Duplication | 22q11.2 distal | 1 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0.0 |
| All CNVs | | | 708 | 58 | 37 | 11 | 48 | 18 | 16 | 12 | 33 | 56 | 9 | 64 | 2 | 204 | 28.8 |

ID: Intellectual Disability; CD: Communication Disorder; ASD: Autism Spectrum Disorder; ADHD: Attention Deficit and Hyperactivity Disorder; SLD: Specific Language Disorder; MD: Motor Disorder; OND: Other Neurodevelopmental Disorder; SCZ: Schizophrenia and Related Disorder; BPD: Bipolar Disorder; OCD: Obsessive Compulsive Disorder; EP: Epilepsy; CP: Cerebral Palsy; CM: Congenital Malformation; NPD: Neuropsychiatric Disorder; * Includes one individual with 1q21.1 Duplication and 17p12 Deletion; ^ Includes one individual with 1q21.1 Deletion and 22q11.2 Duplication.

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| Chr | Dosage | CNV                           | Total | Cleft Lip & Palate | Cardiac | CNS | Urinary | Genital | Any CM | Percent Affected |
|-----|--------|-------------------------------|-------|--------------------|---------|-----|---------|---------|--------|-----------------|
| 1   | Deletion | 1q21.1 (GJA5)                | 59    | 0                  | 3       | 2   | 0       | 1       | 6      | 10.2            |
| 1   | Duplication | 1q21.1 (GJA5)              | 90    | 1                  | 8       | 2   | 4       | 1       | 15     | 16.7            |
| 3   | Deletion | 3q29 (DLG1)                  | 4     | 0                  | 0       | 0   | 0       | 0       | 0      | 0.0             |
| 7   | Deletion | 7q11.23 (ELN)                | 4     | 0                  | 3       | 1   | 0       | 0       | 3      | 75.0            |
| 7   | Duplication | 7q11.23 (ELN)               | 8     | 0                  | 0       | 0   | 0       | 0       | 0      | 0.0             |
| 10  | Deletion | 10q23 (BMPR1A)               | 1     | 0                  | 0       | 0   | 0       | 0       | 0      | 0.0             |
| 15  | Deletion | 15q11.2q13.1 BP1-3 (UBE3A)   | 5     | 0                  | 1       | 1   | 0       | 3       | 4      | 80.0            |
| 15  | Duplication | 15q11.2q13.1 BP1-3 (UBE3A)  | 3     | 0                  | 0       | 0   | 0       | 0       | 0      | 0.0             |
| 15  | Deletion | 15q13.3 (CHRNA7)             | 55    | 2                  | 1       | 1   | 0       | 2       | 6      | 10.9            |
| 15  | Deletion | 15q24 (SIN3A)                | 2     | 0                  | 0       | 0   | 0       | 0       | 0      | 0.0             |
| 16  | Deletion | 16p11.2 distal (SH2B1)       | 28    | 0                  | 0       | 0   | 0       | 1       | 1      | 3.6             |
| 16  | Deletion | 16p11.2 (TBX6)               | 59    | 0                  | 3       | 2   | 1       | 0       | 5      | 8.5             |
| 16  | Duplication | 16p11.2 (TBX6)              | 63    | 0                  | 3       | 1   | 4       | 1       | 9      | 14.3            |
| 16  | Deletion | 16p13.11 (MYH11)             | 71    | 0                  | 4       | 0   | 0       | 2       | 6      | 8.5             |
| 17  | Deletion | 17p11.2 (RAI1)               | 4     | 0                  | 0       | 1   | 0       | 0       | 1      | 25.0            |
| 17  | Deletion | 17p12 (PMP22)                | 31    | 0                  | 1       | 2   | 0       | 0       | 3      | 9.7             |
| 17  | Duplication | 17p12 (PMP22)              | 38    | 0                  | 1       | 1   | 2       | 0       | 4      | 10.5            |
| 17  | Deletion | 17q11.2 (NF1)                | 3     | 0                  | 0       | 0   | 1       | 0       | 1      | 33.3            |
| 17  | Duplication | 17q11.2 (NF1)              | 4     | 0                  | 1       | 0   | 0       | 0       | 1      | 25.0            |
| 17  | Deletion | 17q12 (HNF1B)                | 4     | 0                  | 1       | 0   | 2       | 0       | 2      | 50.0            |
| 17  | Duplication | 17q12 (HNF1B)              | 41    | 0                  | 1       | 1   | 1       | 1       | 3      | 7.3             |
| 22  | Deletion | 22q11.2 (TBX1)               | 23    | 3                  | 10      | 0   | 1       | 0       | 11     | 47.8            |
| 22  | Duplication | 22q11.2 (TBX1)              | 108   | 1                  | 5       | 1   | 5       | 3       | 13     | 12.0            |
| 22  | Deletion | 22q11.2 distal               | 1     | 0                  | 0       | 0   | 0       | 0       | 0      | 0.0             |
| 22  | Duplication | 22q11.2 distal              | 1     | 0                  | 0       | 0   | 0       | 0       | 0      | 0.0             |
| All CNVs |          |                               | 708   | 7                  | 46      | 16  | 21      | 15      | 94     | 13.3            |

CM: Congenital Malformation; CNS: Central Nervous System; NPD: Neuropsychiatric Disorder; * Includes one individual with 1q21.1 Duplication and 17p12 Deletion; ^ Includes one individual with 1q21.1 Deletion and 22q11.2 Duplication.
### Table 5. Combined Congenital Malformation and Neuropsychiatric Diagnoses by Copy Number Variant

| Chr | Dosage | CNV | Total | Any NPD | Any CM | Any NPD or CM | Percent Affected (NPD or CM) |
|-----|--------|-----|-------|---------|--------|---------------|------------------------------|
| 1   | Deletion | 1q21.1 (GJA5) | 59    | 11      | 6      | 14            | 23.7                         |
| 1   | Duplication | 1q21.1 (GJA5) | 90    | 16      | 15     | 24            | 26.7                         |
| 3   | Deletion | 3q29 (DLG1) | 4     | 0       | 0      | 0             | 0.0                          |
| 7   | Deletion | 7q11.23 (ELN) | 4     | 3       | 3      | 4             | 100.0                        |
| 7   | Duplication | 7q11.23 (ELN) | 8     | 4       | 0      | 4             | 50.0                         |
| 10  | Deletion | 10q23 (BMPR1A) | 1     | 0       | 0      | 0             | 0.0                          |
| 15  | Deletion | 15q11.2q13.1 BP1-3 (UBE3A) | 5 | 4       | 4      | 4             | 80.0                         |
| 15  | Duplication | 15q11.2q13.1 BP1-3 (UBE3A) | 3 | 3       | 0      | 3             | 100.0                        |
| 15  | Deletion | 15q13.3 (CHRNA7) | 55 | 15      | 6      | 19            | 34.5                         |
| 15  | Deletion | 15q24 (SIN3A) | 2     | 2       | 0      | 2             | 100.0                        |
| 16  | Deletion | 16p11.2 distal (SH2B1) | 28 | 3       | 1      | 4             | 14.3                         |
| 16  | Deletion | 16p11.2 (TBX6) | 59 | 17      | 5      | 20            | 33.9                         |
| 16  | Duplication | 16p11.2 (TBX6) | 63 | 21      | 9      | 26            | 41.3                         |
| 16  | Deletion | 16p13.11 (MYH11) | 71 | 27      | 6      | 30            | 42.3                         |
| 17  | Deletion | 17p11.2 (RAI1) | 4     | 4       | 1      | 4             | 100.0                        |
| 17  | Deletion | 17p12 (PMP22) | 31    | 2       | 3      | 4             | 12.9                         |
| 17  | Duplication | 17p12 (PMP22) | 38 | 9       | 4      | 10            | 26.3                         |
| 17  | Deletion | 17q11.2 (NF1) | 3     | 1       | 1      | 2             | 66.7                         |
| 17  | Duplication | 17q11.2 (NF1) | 4     | 0       | 1      | 1             | 25.0                         |
| 17  | Deletion | 17q12 (HNF1B) | 4     | 3       | 2      | 3             | 75.0                         |
| 17  | Duplication | 17q12 (HNF1B) | 41 | 11      | 3      | 14            | 34.1                         |
| 22  | Deletion | 22q11.2 (TBX1) | 23 | 17      | 11     | 19            | 82.6                         |
| 22  | Duplication | 22q11.2 (TBX1)* | 108 | 31      | 13     | 39            | 36.1                         |
| 22  | Deletion | 22q11.2 distal | 1 | 0       | 0      | 0             | 0.0                          |
| 22  | Duplication | 22q11.2 distal | 1 | 0       | 0      | 0             | 0.0                          |
| All CNVs |       |       | 708 | 204     | 94     | 250           | 35.3                         |

CM: Congenital Malformation; NPD: Neuropsychiatric Disorder; * Includes one individual with 1q21.1 Duplication and 17p12 Deletion; ^ Includes one individual with 1q21.1 Deletion and 22q11.2 Duplication.
A genetic counselor results disclosure session outline was used to guide sessions, promote consistency between genetic counselors, and to standardize participant response assessment for post-session data analysis.