Supplementary Appendix

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

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Supplementary Appendix

Multiple rare CNVs and phenotypic heterogeneity of genomic disorders

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SUPPLEMENTARY METHODS

Patient ascertainment and CNV definition

About 32,587 patients were ascertained and sent to Signature Genomics Laboratories by geneticists, pediatricians, and neurologists from more than 40 referral centers primarily throughout the United States. The ages of the ascertained cases ranged between 2 to 22 years. Based on self-reported ethnicity, about 75% are of European descent, 7% African or African-American, and 18% belonged to other or mixed ancestry[1]. We analyzed 72 large rare copy number variants (CNVs) within 39 genomic regions composed of 39 deletions and 33 reciprocal duplications. Mechanistically, these CNVs can be classified in to 25 recurrent and 14 nonrecurrent genomic events. While two broad groups of genomic disorders can be distinguished based on syndromic features and extensive phenotypic variability, these large CNVs fall into three categories: (a) rare CNVs associated with syndromic phenotypes, (b) rare CNVs associated with variable expressivity, and (c) rare CNVs of potential pathogenic significance (Figures S1-2, Table S1). These categories are defined below:

1. **CNVs previously known to be associated with syndromic phenotypes**. These individuals typically manifest with striking, clinically recognizable, core constellation of phenotypes (Figure S1). Clinical variability exists even within these disorders. Examples: 15q24 microdeletions[2]; Williams-Beuren syndrome[3]; Smith-Magenis syndrome[4]; Phelan-McDermid syndrome[5] (Figure S1).
2. **CNVs associated with variable expressivity and heterogeneity of clinical features.** These CNVs are known to be pathogenic, i.e., enriched in the case population compared with the general population controls. Extensive variability of phenotypic presentation, including variable expressivity as well as heterogeneity of phenotypes, has been noted. **Variable expressivity** refers to the range of phenotypes that can occur in different people with the same genotype. Even though ascertained from the same clinical cohort, individuals present with a range of presenting features (both in type and severity of phenotypes). For example, individuals with the 16p11.2 deletion show a range of clinical features from craniofacial dysmorphology, speech delays, and obesity, in addition to intellectual disability. **Phenotypic heterogeneity** refers to the involvement of the same genotype in different phenotypes. For example, the 1q21.1 deletion is associated with phenotypic heterogeneity. Individuals ascertained for distinct neuropsychiatric conditions were detected to carry the same genetic change. Individuals ascertained to carry a tetralogy of Fallot, a congenital heart disease, were enriched for the 1q21.1 deletion[6]. Similarly, individuals with

schizophrenia[7], intellectual disability[8], cataracts with normal intellect[8], and autism were also identified to carry the same 1q21.1 deletion. We use the term *phenotypic variability* as a global term to denote either or both of these features (Figure S2).

3. **Potentially pathogenic CNVs.** The role of these large CNVs in disease has not been well established due to extreme rarity and the lack of statistical power for a meaningful comparison. These are usually reciprocal duplications of known pathogenic rare CNVs or syndromic disorders. Examples include the 6q16 duplication, 15q24 duplication, and 15q13.3 BP4-BP5 duplication. The pathogenic association of these CNVs is unclear although it continues to remain a target of investigation. We included these CNVs to identify any enrichment in our large set of cases compared with controls and to find strong association for additional CNVs. Phenotypes associated with these CNVs are not syndromic and cases typically exhibit phenotypic variability similar to those with category 2 CNVs. For example, the pathogenic association of the smaller 15q13.3 duplication nested within BP4-BP5 (Hg18, 29.7-30.2 Mb) remains unclear, although it continues to remain a target of investigation[9]. We neither identified a strong enrichment of this CNV in 32,587 cases compared to 8,329 controls nor did we find increased frequency of large additional CNVs (p=0.36). We believe that testing for pathogenic association (as a single hit or with additional CNVs) of these loci was essential since this is one of the largest collections of cases and controls.

Breakpoint definition

While breakpoints of most recurrent events spanned within segmental duplications, the breakpoints of the nonrecurrent CNVs were variable. We only considered the extent of the unique regions and not the segmental duplications for genomic hotspot regions. For classical recurrent genomic disorders where atypical deletions or duplications have also been identified, such as Smith-Magenis syndrome/Potocki-Lupski syndrome[4,10], Williams-Beuren syndrome (del7q11.23), and 15q24 microdeletion[2,11], the common deletion region or the smallest region of overlap (including candidate genes such as *ELN* and *RAI1*) was considered as the inclusion criteria. Larger deletions and duplications in these regions usually encompass this critical hotspot region. Notably, phenotypic variability in these disorders can potentially be attributed to the size of the deletion conforming to the model of contiguous gene syndromes.

For the nonrecurrent regions, major candidate genes were included within the query. The Phelan-McDermid (del22q13.3) syndrome region contains *SHANK3* and the Wolf-Hirschhorn

syndrome region (del4p16) contains *WHSC1* and *WHSC2*. Three 17p13.3 pathogenic regions were identified: a region encompassing *YWHAE* only, a region encompassing *YWHAE* and *PAFAH1B1*, and the region containing only *PAFAH1B1*[12-14] (Figure S3). For the distal 22q11.2 CNVs, regions spanning breakpoints 4 and 6 or 5 and 6 or larger[15-17] were considered (Figure S4). The 1p36 deletions include the first 10 Mb region as reported previously[18]. Throughout the manuscript the genomic disorders are designated by the cytoband location followed by the candidate gene symbol in parenthesis. The gene symbol is intended to provide a quick landmark using one of the best candidate genes of the region to pinpoint to the specific CNV. Examples are the 16p11.2 genomic hotspot region containing *SH2B1*, the proximal 16p11.2 region with *TBX6* associated with autism, and the 17p11.2 Smith-Magenis syndrome/Potocki-Lupski syndrome region with *RAI1*.

CNV detection and validation

Our analysis for multiple CNVs was restricted to those carrying a pathogenic (genomic disorder) or potentially pathogenic CNV (72 total). We found that 2,312 individuals carried at least one of the 72 known disease-associated CNVs. We searched for another rare (<0.1%; i.e., seen in <8/8,329 controls), large CNV (>500 kb) at a second site (non-allelic). Detection and validation of the identified CNVs were performed in accordance with Clinical Laboratory Improvement Amendments (CLIA) certified protocols. Confirmation of abnormal array findings were carried out by fluorescence *in situ* hybridization (FISH), standard G-banded chromosome analysis, or a second array analysis, depending on the size of the observed CNV (Figure S7). Parental studies were conducted by G-banded analysis, FISH, or array analysis to determine the inheritance in all cases where parental samples were available. Data from a subset of parental calls confirmed 502 CNVs because a parent also carried the same variant. Since we focused on large, rare variants of pathogenic significance, our validation rates are higher than our previous precision estimate of 0.945 calculated for CNVs >150 kb in size[1] (Table S4).

Control CNV calls were obtained from 8,329 individuals that were not ascertained from any specific study but were ruled out for overt neurological disorders. Data were obtained from the following sources: HGDP[19,20]; NINDS (dbGaP accession number phs000089)[19,20], PARC/PARC2[21,22]; Stephanie London (parents of asthmatic children)[23]; FHCRC (pre-release data provided courtesy of A. Aragaki, C. Kooperberg and R. Jackson as part of an ongoing

genome-wide association study to identify genetic components of hip fracture in the Women's Health Initiative); InCHIANTI (data provided by InCHIANTI study of aging)[19,24]; and Wellcome Trust Case Control Consortium 2, National Blood Services Cohort (WTCCC2 NBS)[25]. Primarily, about 81.5% of the control individuals are Caucasian or European, 2% are African or African American, and 16.5% are of other or mixed ancestry, as described previously[1]. CNV comparisons to controls were made by testing if CNVs from our cases had a reciprocal overlap of 50% or more of their length with CNVs found in these 8,329 controls. For the Simons Simplex Collection autism analysis, proband (n=841), parent (n=1,651), and sibling (n=793) CNV calls were generated from Illumina 1M and 1M Duo arrays using the same algorithm as the control CNV data[1,26,27]. Rare CNV calls were defined by the presence of a 50% reciprocal overlapping CNV in less than 0.1% of both the sibling cohort (≤1/793) and the Wellcome Trust Case Control Consortium (WTCCC2) subpopulation (≤2/2090) of our control cohort. Quantitative phenotypes were obtained from published data[27].

Global analysis for enrichment of two large CNVs of unknown pathogenic significance in cases compared to controls

Analysis for enrichment for two large CNVs that are not known pathogenic variants was performed as follows. CNV calls from cases generated from oligonucleotide arrays (n=15,767 individuals) were utilized for this analysis. CNVs were first filtered to remove any known genomic disorder or reciprocal pathogenic CNVs. CNVs were also filtered to include only those detectable on single nucleotide polymorphism (550K, 10 probes) or Signature custom arrays (97K, 5 probes). This provided similar sensitivities for comparisons to control CNV calls. Further filtering was performed to remove calls observed in >0.1% of (>8/8,329) controls. The results from the comparison analysis (one-tailed p-values) are as follows:

1. Global analysis for enrichment for any large (500 kb) rare variant of unknown significance (VOUS): 2,142/13,739 cases and 503/8,148 controls, p=1.51E-103, OR=2.81; OR=2.53-3.11, 95% CI.
2. Enrichment for any two large CNVs (>500 kb) rare VOUS: 310/13,739 cases and 23/8,148 controls, p=2.11E-38, OR=8.16; OR=5.33-13.07, 95% CI.
3. Enrichment for any large CNVs conditioned on the presence of one large CNV (>500 kb) rare VOUS: 310/2,142 cases and 23/503 controls, p=2.9E-11; OR=3.53; OR=2.28-5.72, 95% CI.
4. Enrichment of second-site hits among nonsyndromic first hits vs. syndromic first hits:

1,509 cases have a nonsyndromic first hit and 857 cases have a syndromic first hit. 156/1,509 nonsyndromic cases have a second hit and 44/857 syndromic cases have a second hit, p=4.49E-6; OR=2.13; OR=1.50-3.08, 95% CI.

Sensitivity, specificity, positive predictive value, and likelihood ratio for carrying two large CNVs

We calculated sensitivity, specificity, and likelihood ratios for the genomic disorders significantly enriched for second-site CNVs and for any two large CNVs. Based on the published prevalence estimate of 2.3% for developmental delay and intellectual disability[28], we also calculated positive predictive value (Table S18).

We note that positive predictive value (PPV) is of little relevance in this context due to the following reasons:

1. Our case cohort consists of individuals with severe developmental delay or associated neurodevelopmental phenotypes while the controls were recruited for non-neurological phenotypes. Therefore, the prevalence estimates in the general population are not exactly reflected in our control population.
2. PPV is of relevance only when there is a high pretest probability or high prior for a disorder (e.g., abnormal ultrasound, positive family history, etc.). Therefore, in case of a prenatal screen without a strong prior for disease, testing for the presence of two large CNVs would be a weak test mainly because of low population prevalence. PPV estimates from our study are likely lower bounds of likelihood ratios because controls are a population sampling where issues of mild developmental delay have not been excluded.
3. Developmental delay/intellectual disability (DD/ID) is associated with extreme genetic heterogeneity. While CNVs account for only about 15-20% of the disease etiology, other genetic changes such as smaller CNVs (<500 kb) not evaluated in this study, single nucleotide changes, and repeat expansions can account for a sizable proportion of the DD/ID morbidity.

For our study, we find that positive likelihood ratio is a better pretest predictor of the DD/ID phenotype. The likelihood ratio can be used to estimate posttest probability from pretest probability. For example, the posttest probability of any randomly selected individual carrying two variants of unknown significance (VOUS) to have DD/ID is given by 7.99 (likelihood ratio) × 0.023 (prevalence of DD/ID in the population) = 0.18377. Note that the negative likelihood ratio is less informative and simply reflects the fact that a negative result is not very strong at predicting a lack of disease (given that the large number of cases is without two large CNV hits).

Evaluation of inheritance bias

Inheritance of autosomal first-hit CNVs: We expect 15.5 first-site events each to be inherited from father and mother; we observe 14 from the mother.

Calculation of binomial, two-sided probabilities for inheritance bias in first hits:

Probability of expecting 14 out of 31 = 0.123485

Probability of expecting 14 or more out of 31 = 0.7634

Probability of expecting more than 14 out of 31 = 0.63995

Inheritance of autosomal second-site CNVs: If we consider only autosomes for second-site hits, we expect 16.5 events each (total 33), but we observe 22 maternal and 11 paternal.

Calculation of binomial, two-sided probabilities:

Probability of expecting 23 out of 33 = 0.022531

Probability of expecting 23 or more out of 33 = 0.04

Probability of expecting more than 23 out of 33 = 0.0175

Co-inheritance of first and second hits: We next considered patterns of co-inheritance between first- and second-site CNVs. We asked if there are more individuals co-inheriting the two hits as opposed to carrying both hits from the same parent. In 12 cases (8 maternal, 4 paternal), the two events were inherited from the same parent, while in 12 cases events were inherited from different parents, suggesting no particular bias in co-inheritance.

Calculation of binomial, two-sided probabilities:

Probability of expecting 12 out of 24 = 0.16118

Probability of expecting 12 or more out of 24 = 0.58

Probability of expecting more than 12 out of 24 = 0.419

Phenotypic impact of carrying two or more large CNVs

Validating our previous observations[29], within cases carrying a pathogenic CNV associated with a specific clinical feature, occurrence of additional hits modified the severity or conferred additional clinical features. A few examples are noteworthy: the 560 kb 16p11.2 deletion and the 1.5 Mb 15q13.3 deletion are known to be enriched in approximately 1% of individuals with autism and epilepsy, respectively. Notably, patient GC23858 carries deletions on both 16p11.2 and 15q13.3 and has developmental delay, craniofacial features (plagiocephaly, high anterior

hair line, broad forehead, small pointed chin), behavioral features ("overly friendly and affectionate" and recent onset of aggression and oppositional behaviors without self-mutilation), and encephalopathy yet without autism-specific features. Similarly, no autistic features were documented in GC51323, carrying a 16p11.2 deletion and a 7 Mb deletion on chromosome 10q23. However, structural cardiac anomalies, craniofacial features, and vascular defects (Raynauds disease), distinct from published reports[30], were also documented in this individual. A combination of del16p11.2 and a 1.5 Mb del1q21.1 in GC36479 resulted in craniofacial defects, including asymmetric corneas, epicanthal folds, and zygomatic hypoplasia, speech delay, and aggressive behaviors. Microdeletions in 1q21.1 encompassing *GJA5* and *GJA8* were reported enriched in cases with intellectual disability, congenital cataracts, cardiac disease, and schizophrenia[7,8,31,32]. From our cohort, medical records of two other individuals with del1q21.1 and a second hit also indicate variable clinical presentations such as hypotonia (GC25163) and hemihypertrophy (GC24219). Thus, no common features were apparent in the three cases with del1q21.1 suggesting that the second hit contributes to variable phenotypes. While none of these two-hit cases with a 1q21.1 microdeletion were shown to have the associated congenital cataracts[8,33], congenital cataracts were documented in one carrier parent with 1q21.1 deletion. Of note, GC28231 carries a 1.5 Mb del17q12, previously associated with renal cysts and diabetes[34], and a maternally inherited 2 Mb duplication on Xp22.3, the patient also manifests with familial attention-deficit/hyperactivity disorder and Mayer-Rokitansky-Kuster-Hauser syndrome.

Although the frequency of second-site hits was low in individuals with syndromic disorders, clinical features were atypical or severe in these individuals. For example, developmental delay, short stature, autism features, absence of neural hypophysis, delayed puberty, and focal epilepsy were observed in an individual (GC32825) with a 22q13 (Phelan-McDermid syndrome) deletion and a 1.9 Mb 9p23 duplication; speech delay and visual impairment in a case (GC26098) with a 3.7 Mb dup15q11.2q13 and trisomy 21 are remarkable. Clinical features were also noted as severe in two cases with Prader-Willi syndrome: GC20500, carrying a 4.3 Mb deletion second hit on chr1p32 manifests with abnormal MRI and unresolved severe hypotonia[35], and GC29221, carrying a 948 kb duplication second hit on chr1p31.1 and has severe hypotonia and hypoglycemia. Features atypical for Williams-Beuren syndrome (WBS)[36] were also observed in the three cases with clinical data; for example, decreased mouth opening, forearm skeletal defects, and camptodactyly (GC40354), and additional neurological

manifestations such as Arnold-Chiari malformation and multiple cranial neuropathies (GC36775) and stroke (GC21414) were notable in the WBS cases with another large CNV second hit. Atypical clinical features were also noted from the medical records of individuals with a 22q11.2 (DiGeorge/VCFS) deletion.

Functional analysis for genes within first- and second-site CNVs

We performed functional enrichment analysis on first- and second-hit specific genes, excluding duplicated genes (>50% segmental duplication) from both cases with syndromic CNVs and variably expressive first hits. Genes residing within four sets of CNVs were analyzed: (a) syndromic first hits or primary genomic disorders, (b) second-site hits observed in individuals with syndromic first hits, (c) first-hit CNVs associated with phenotypic variability, and (d) additional CNV second-site hits observed in nonsyndromic first hits or CNVs associated with phenotypic variability. We observe more functions achieving significant enrichments in genes with second-site hits of phenotypically variable CNVs than the primary CNVs associated with phenotypic variability. Among these functions, a sizeable number are related to development. This suggests that the second-site CNVs are likely responsible for a significant functional deregulation in cases with variably expressive conditions. No functions were enriched for second hits from syndromic cases. Table S16 shows all functional categories and subcategories that satisfy the nominal significance after Benjamini-Hochberg correction for the four types of hits.

We sought to understand if there is an increase in the overall burden of large CNVs in individuals with syndromic disorders compared to those with variable features. We also included the data from controls. When all CNVs were included, we found no difference in the CNV burden between the two categories of genomic disorders. However, when we excluded primary CNVs or CNVs at first sites responsible for the major clinical features of genomic disorders (for example, we removed the 17p11.2 deletion associated with Smith-Magenis syndrome and the 16p11.2 deletion associated with various neurocognitive and neuropsychiatric disease), we found a higher CNV burden for second-site CNV co-occurring disorders associated with variable features compared to syndromic disorders. This is because the syndromic CNVs are the primary cause of the constellation of clinical features (syndromes) and these CNVs do not essentially have any additional CNVs at a second site.

SUPPLEMENTARY FIGURES

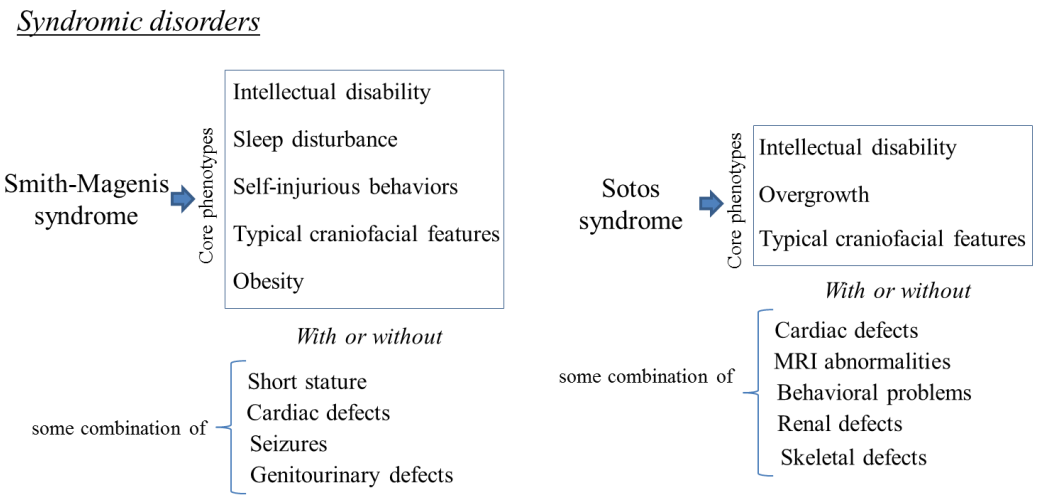

Figure S1

Figure S1. Phenotypic features associated with classical genomic disorders. Examples are shown for Smith-Magenis syndrome (17p11.2 deletion) and Sotos syndrome (5q35 deletion). Please note that these disorders are associated with core diagnostic phenotypes with or without a combination of additional, less common features.

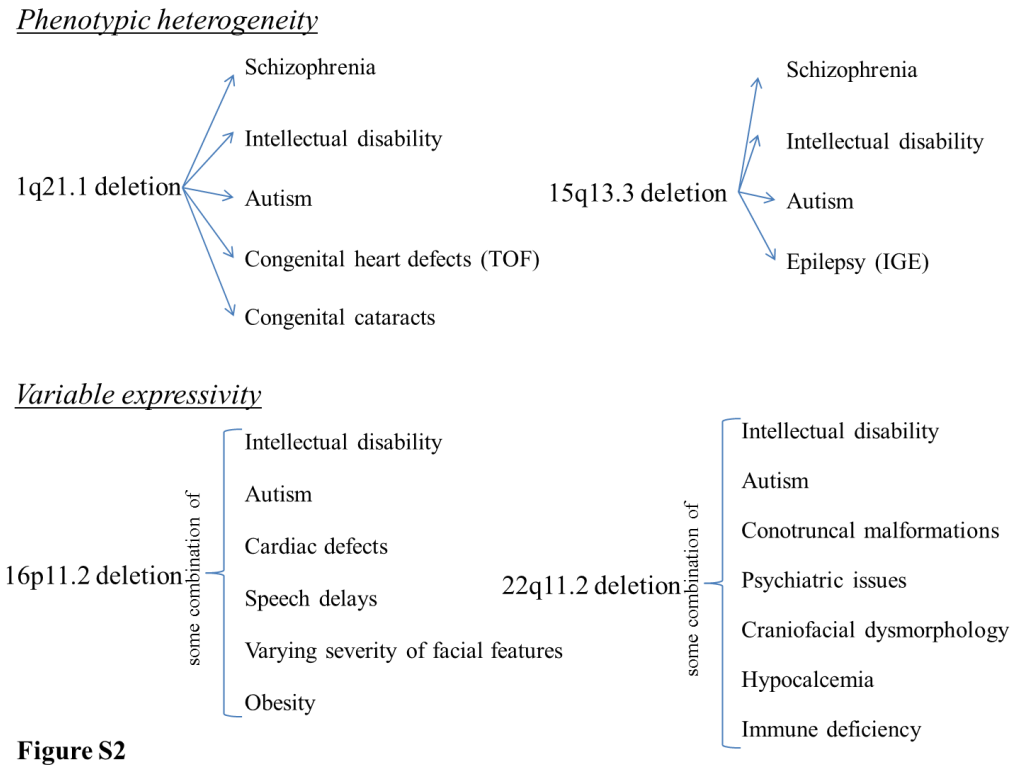

Figure S2

Figure S2. Definitions of phenotypic variability terms. CNVs with variable expressivity and phenotypic heterogeneity have been observed to be enriched in multiple case populations ascertained for different, nosologically distinct neurodevelopmental disorders. Examples for four such disorders are shown. Please note that variably expressive CNVs may also show extensive heterogeneity.

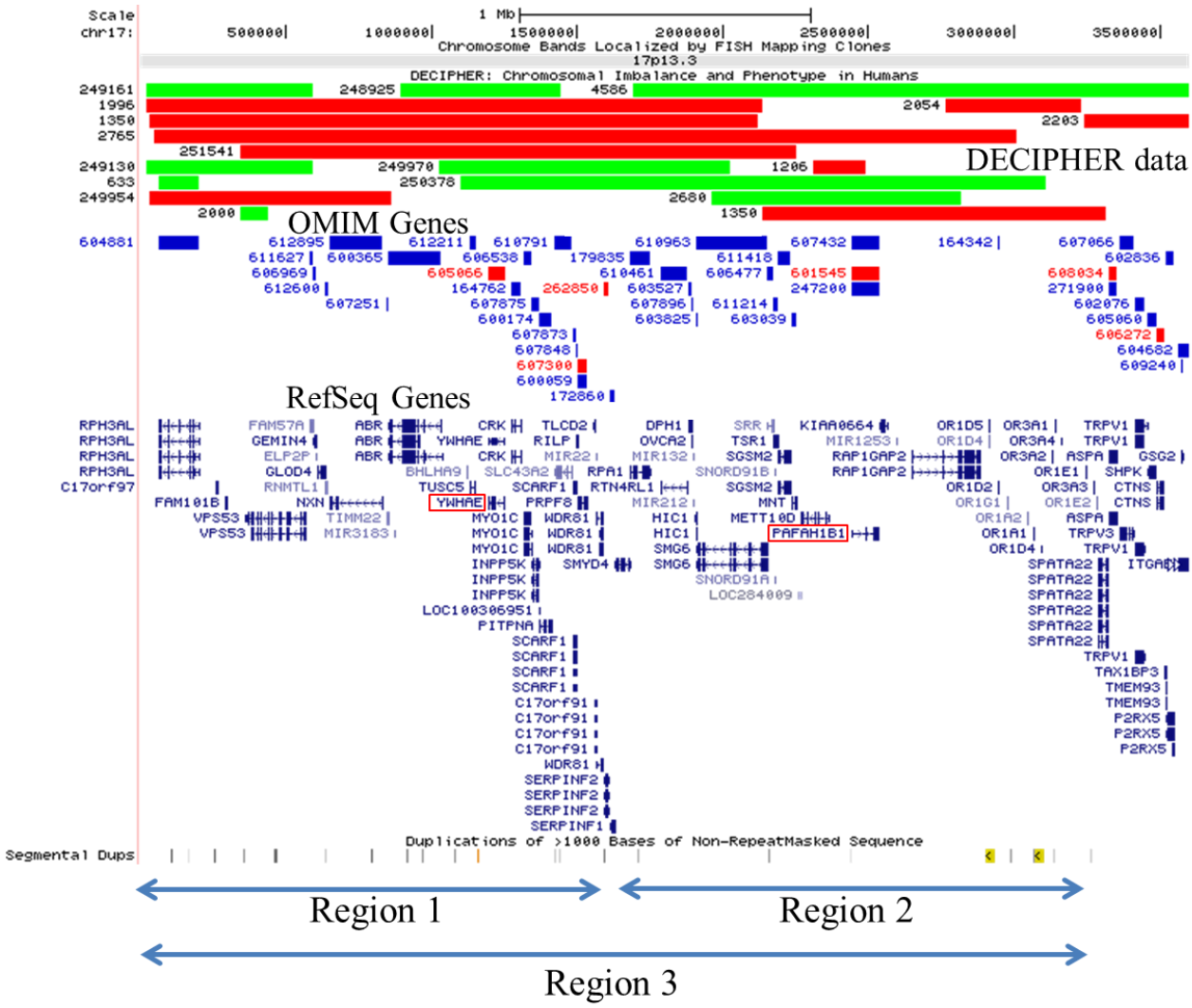

Figure S3. CNVs within 17p13.3 analyzed in this study for two hits.

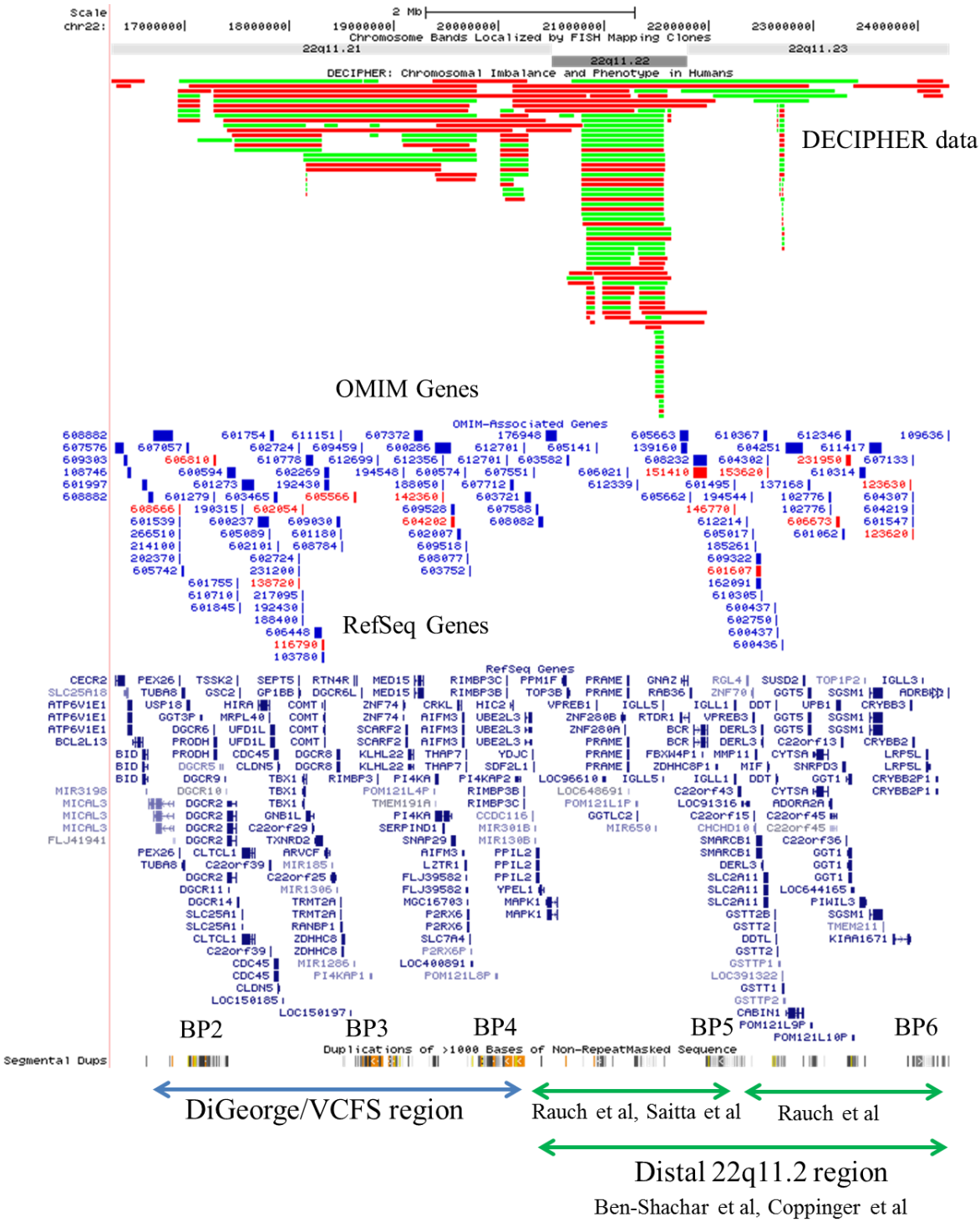

Figure S4. Distal 22q11.2 CNVs (green arrows) analyzed in this study for two hits. Please note that regions spanning breakpoints 4 and 6 or 5 and 6 or larger were considered in our study.

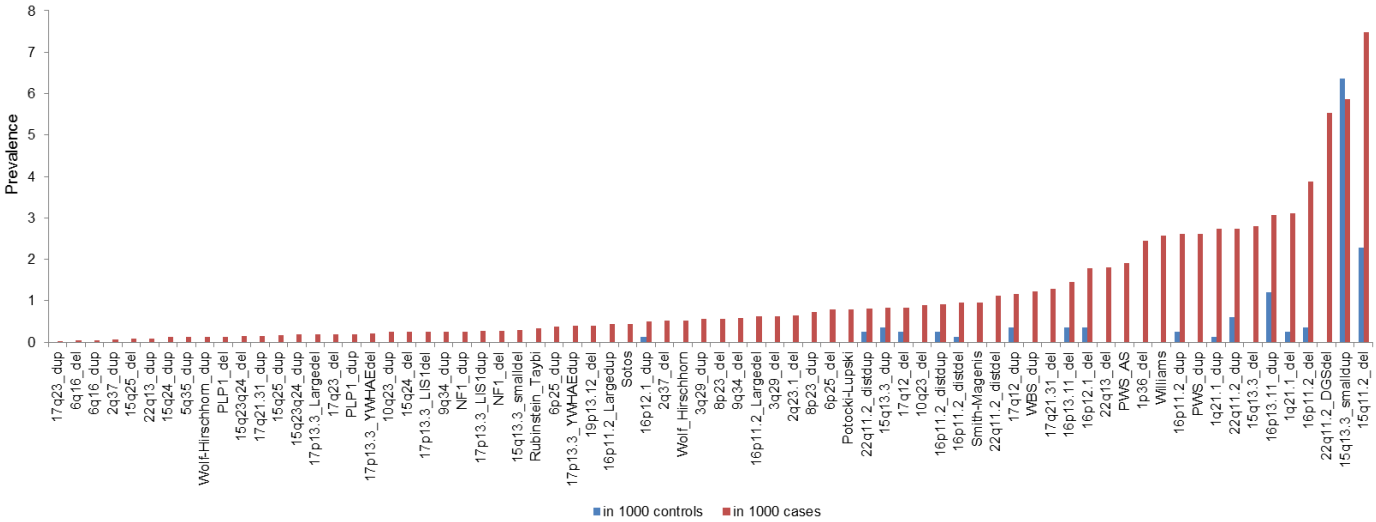

Figure S5. Prevalence of CNVs associated with neurodevelopmental disease in cases and controls. Note that this list also includes the smaller duplication encompassing *CHRNA7* on chromosome 15q13.3. The pathogenic association of this gene was unclear according to recent reports[9,37]. The denominator (total samples analyzed) for most of these CNVs is 32,587; however, for a subset of cases the number of samples analyzed is 23,380 (15q11.2, 15q13.3 smaller CNVs, 6q16 CNVs involving *SIM1*, 22q11.2 distal CNVs, *NF1* duplications, CNVs involving *PLP1*, and 15q25 CNVs).

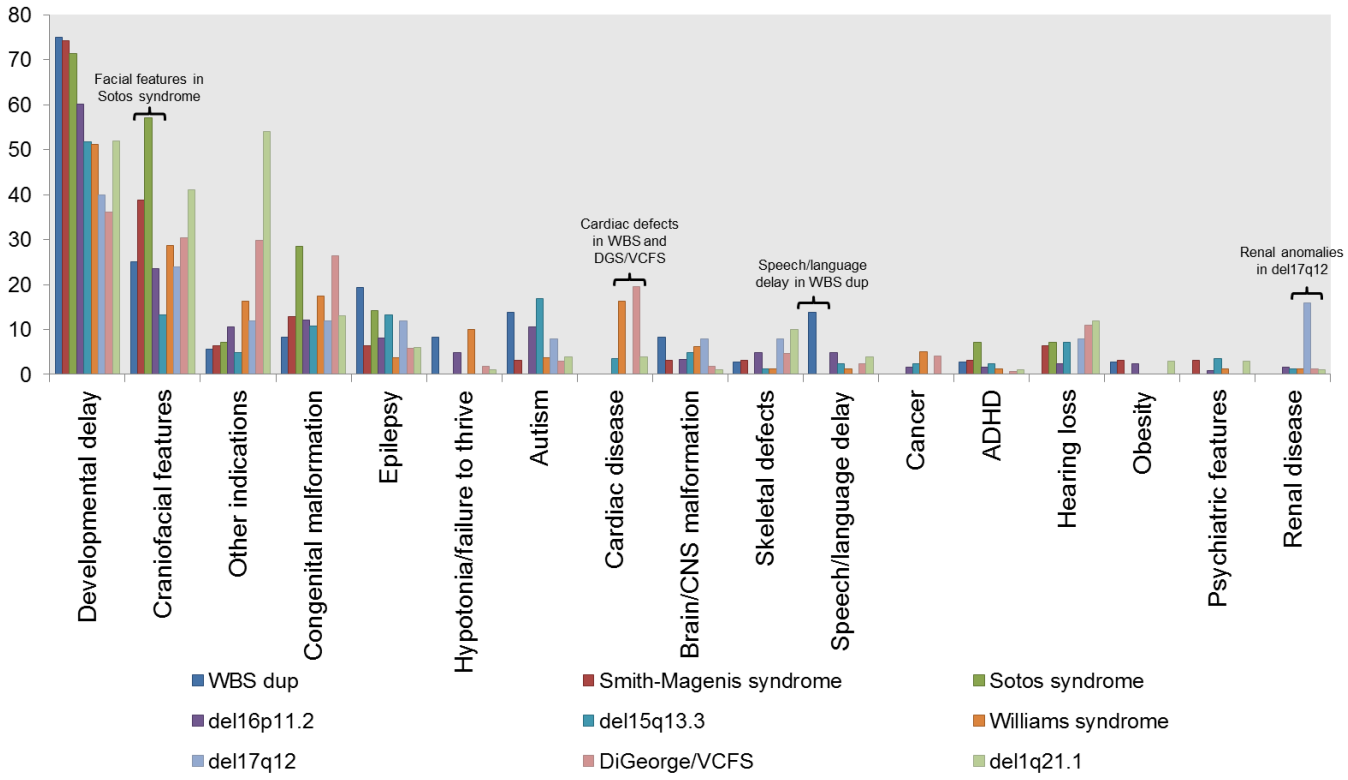

Figure S6. Frequency of clinical features of a representative set of genomic disorders. Shown are the major clinical indications for referral of individuals who carry a genomic disorder CNV. Only nine disorders are represented here. Note that some pathognomonic features are marked (e.g., facial features for Sotos, cardiac defects for WBS, and 22q11.2 deletion). We note that these are only indications for referral and are not comprehensive for full phenotype-genotype study.

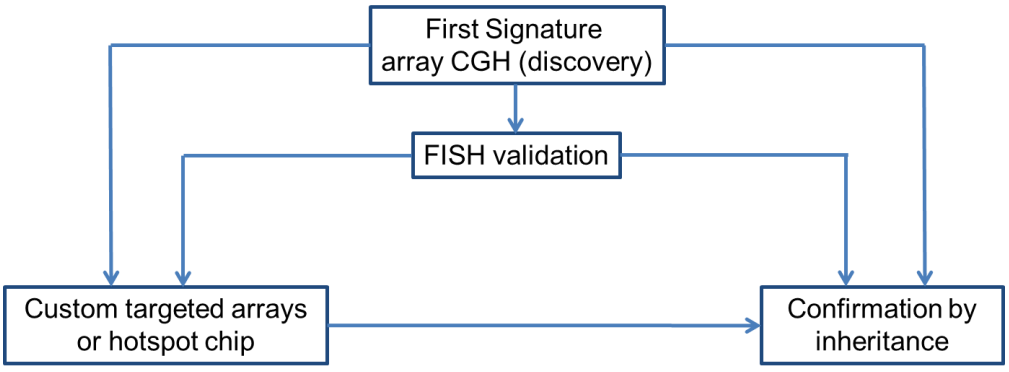

Figure S7. A flow chart for validation of discovered CNVs. Please note that the custom-targeted arrays and hotspot chips were designed for the NimbleGen platform. Hotspot chips target genomic hotspots, i.e. regions flanked by segmental duplications, at a high density (~2.6 kb) and a uniform density (~36 kb) in the genomic backbone[38].

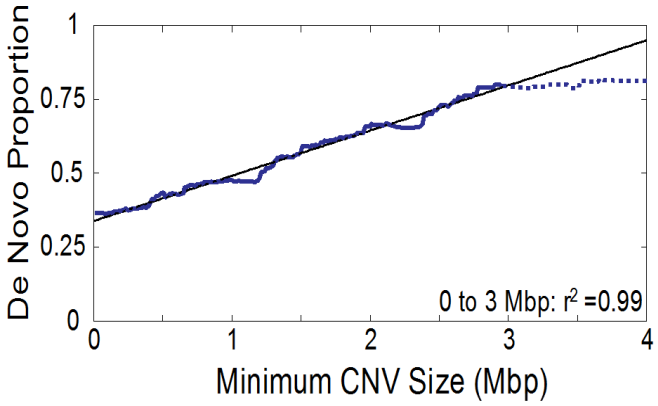

Figure S8. *De novo* rates and CNV size associated with genomic disorders.
We examined CNVs from 2,312 individuals for the frequency of *de novo* CNVs as a function of size. We excluded events due to unbalanced translocations and complex rearrangements. As expected, the proportion of *de novo* CNVs is strongly correlated with CNV size (r^2=0.99).

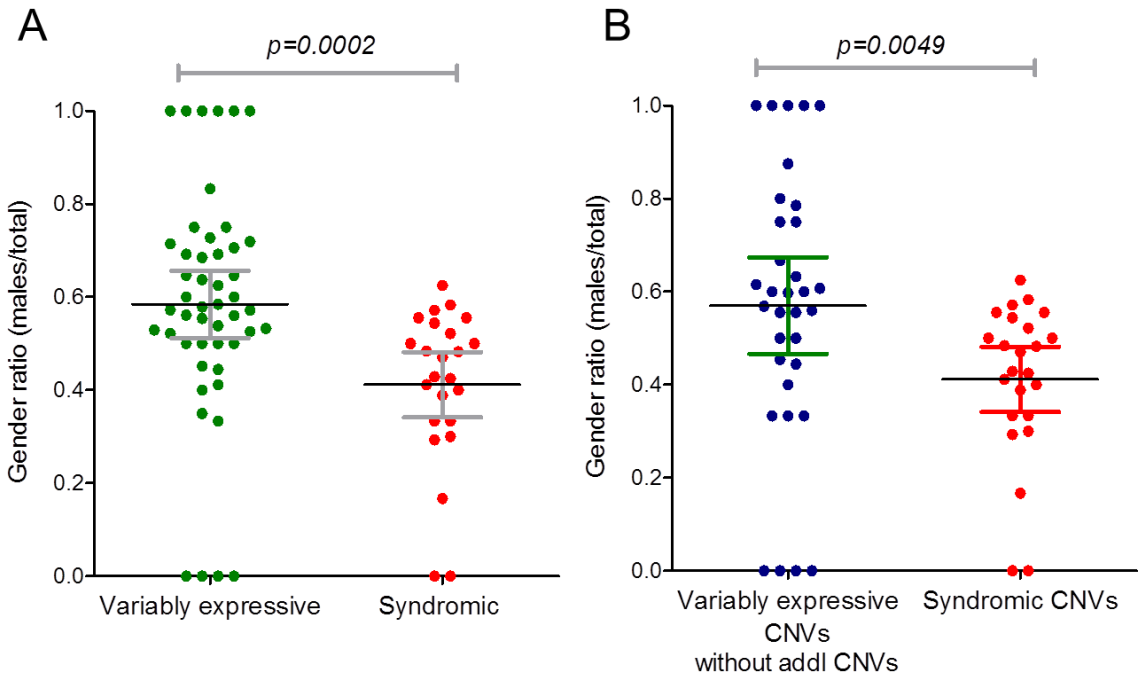

Figure S9. Gender bias towards males in disorders with phenotypic variability compared to syndromic disorders. The gender bias is based on the primary genomic disorders and is observed with or without the presence of the secondary CNVs, although we note that the effect is slightly greater in the presence of the secondary CNVs. Due to the limits of our assays, we are unable to detect most secondary damaging events including smaller CNVs or single nucleotide mutation within a coding or a regulatory element. It is important to note that syndromic CNVs show no gender bias while more phenotypically heterogeneous CNVs are more likely to be found among males—suggesting that males are a sensitized background.

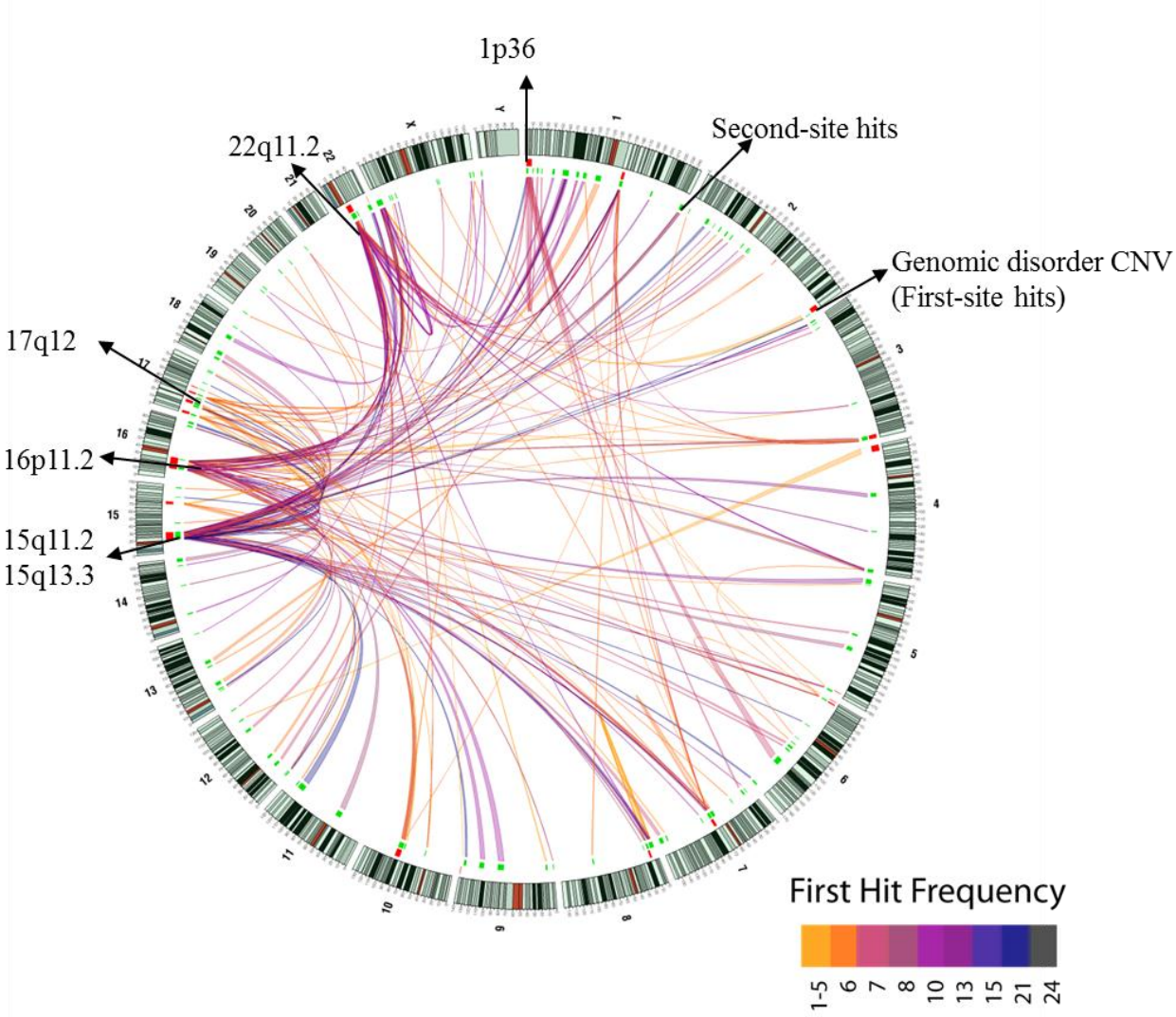

Figure S10. Distribution of second-hit CNVs in individuals with a genomic disorder.
A circos diagram (chromosomal ideograms arranged in a circle) representing the locations of the first-site CNVs and large second-site CNVs is shown. The first-site CNVs are depicted in red in the outer circle, and second-site CNVs are depicted in green in the inner circle. The first and second CNVs are connected by lines color-coded to represent the frequency of the first-site CNVs. Note that CNV regions, such as 16p11.2, 15q11.2, 15q13.3, and 22q11.2 regions, that are "hubs" for recurrent genomic disorder events are also shown.

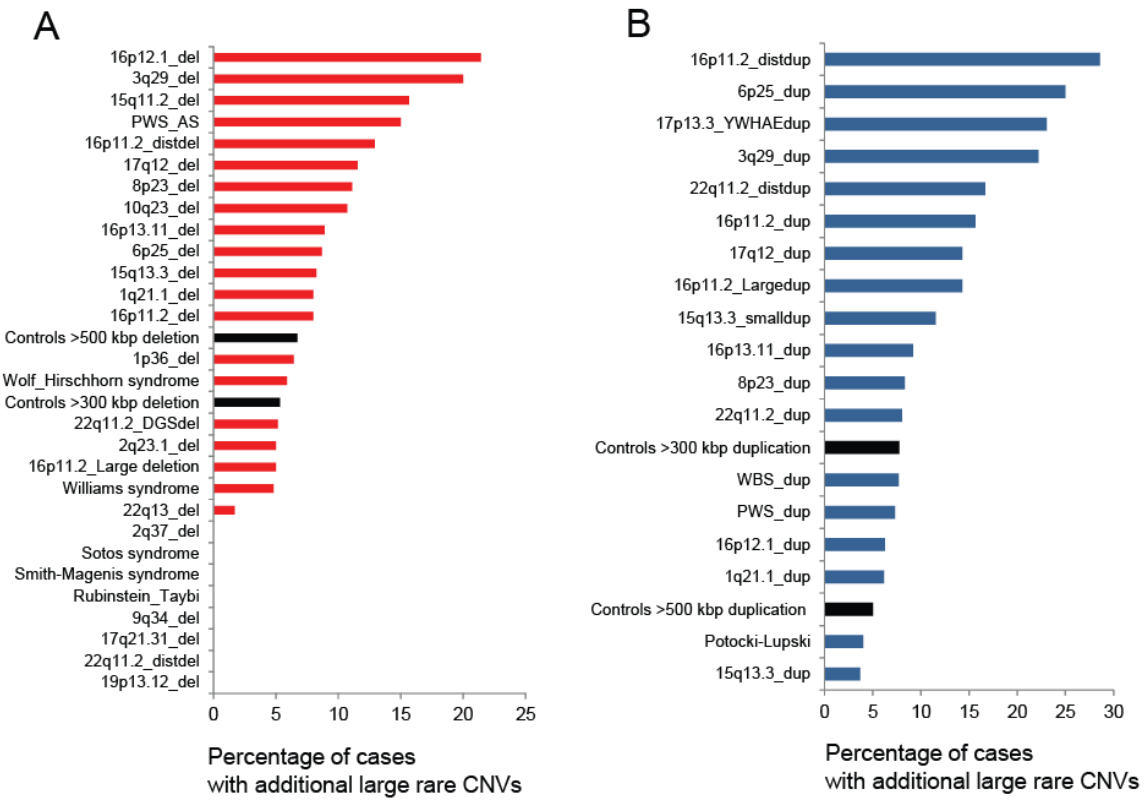

Figure S11. Frequency of additional large rare CNVs associated with neurodevelopmental disorders. The histograms depict the percentage of additional large rare CNVs in individuals who carry a (A) deletion or (B) duplication variant that is potentially pathogenic or known to be associated with a genomic disorder. Conditioning for controls was performed for both deletions and duplications, separately. The data for controls were conditioned for the presence of a first-hit CNV (i.e., either deletion or duplication first hit) and then the number of additional large CNVs (both deletions and duplications) was counted.

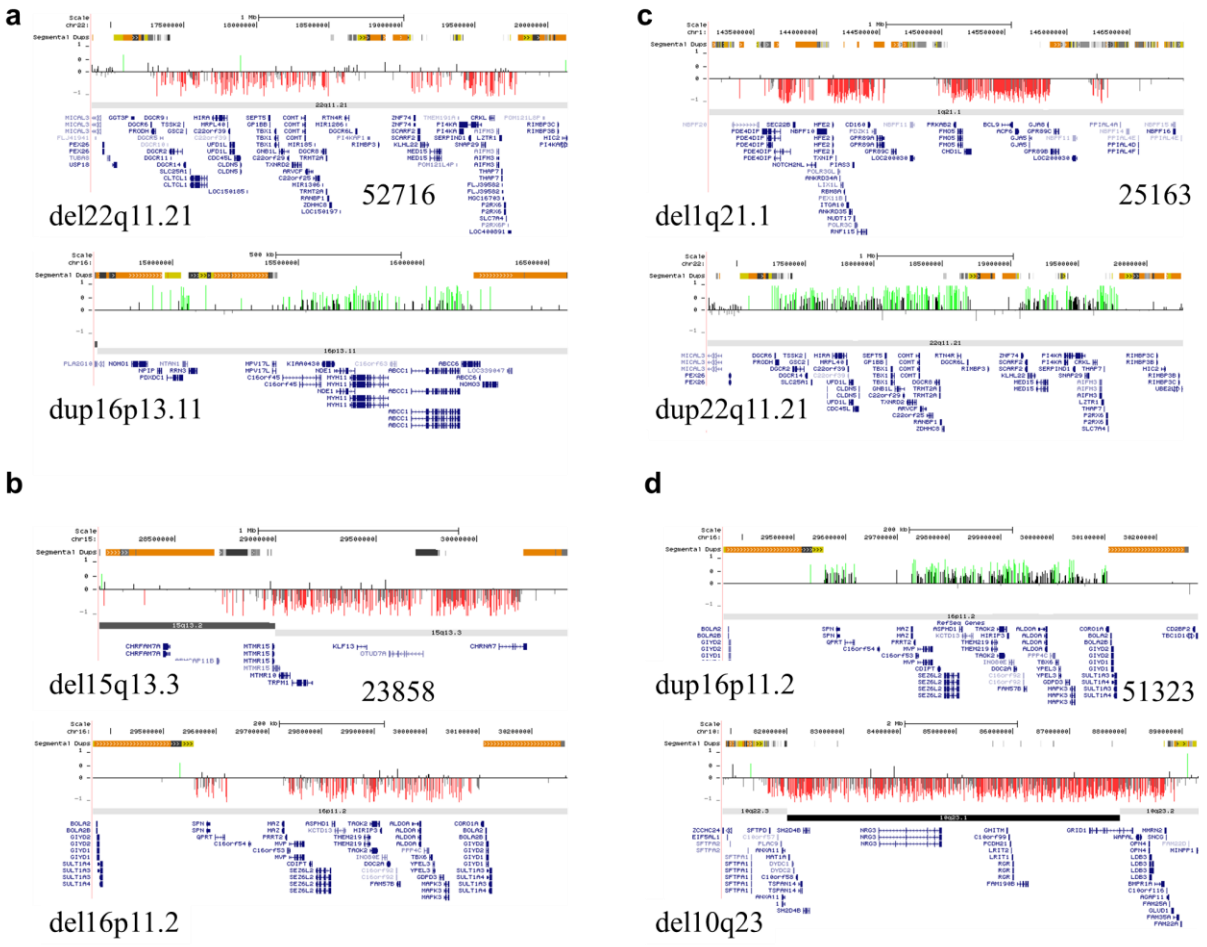

Figure S12. Representative examples of individuals with two rare CNVs both associated with a genomic disorder. Array CGH data embedded into a custom genome browser with genes and segmental duplications (orange bars) shown. Note that the probes with $\log_2$ ratios below a threshold of 1.5 standard deviations from the normalized mean $\log_2$ ratio denote deletions (red) and those greater than 1.5 standard deviations denote duplications (green). The numbers denote the sample identifiers of individuals.

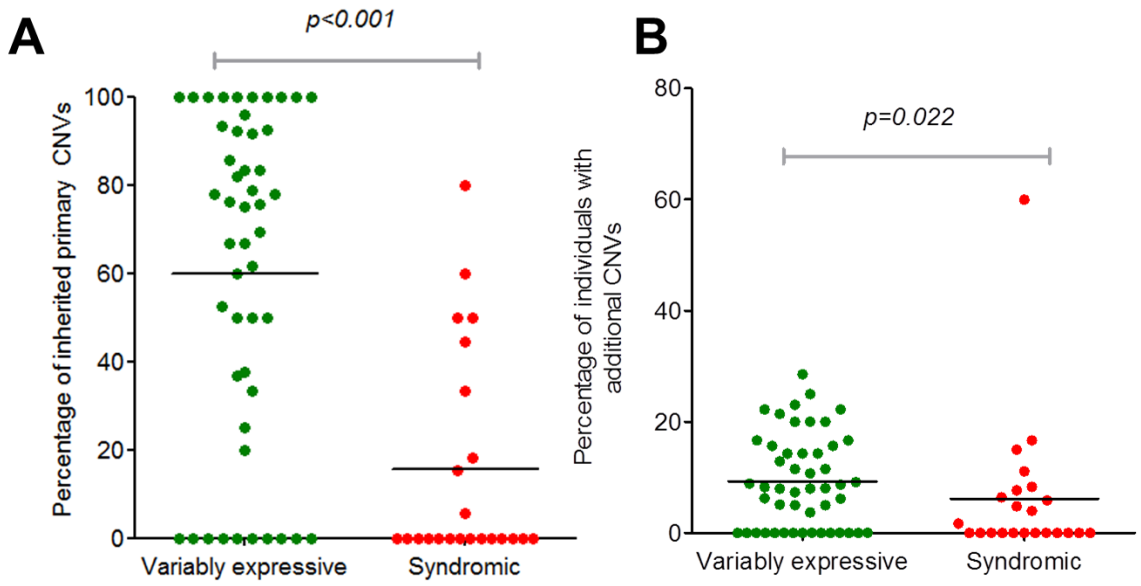

Figure S13. The frequency of inherited primary CNVs and additional CNVs is shown for the two categories of genomic disorders.
(A) We compared the frequency of the two metrics in genomic disorders associated with syndromic features with those with variable features. We found a significant difference. CNVs associated with variable expressivity had significantly higher inheritance rates (Mann Whitney test; $p<0.001$) and increased frequency of additional CNVs (Mann Whitney test, $p=0.0224$) compared to syndromic CNVs. (B) Next, to assess correlation, we compared the proportion of cases with inherited first-site CNVs to the percentage of individuals with second-site CNVs. When all the disorders were considered, the Spearman correlation is $r=0.5108$ with p-value <0.001. Taking into account the fact that some of the sample sizes were too small to derive any meaningful correlation, we then only selected disorders where at least 10 samples were available for evaluation. The Spearman correlation showed a value of $r=0.6641$, p-value <0.0001. The scatterplot for deletions only and duplications only is also shown in Figure S16.

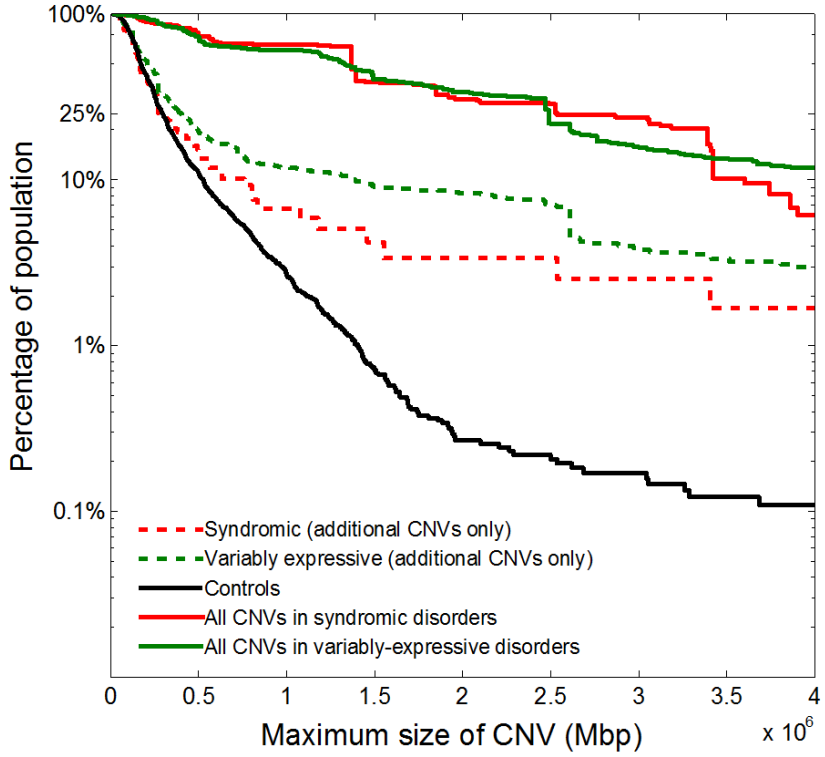

Figure S14. CNV burden at second sites for syndromic CNVs and CNVs with phenotypic variability.

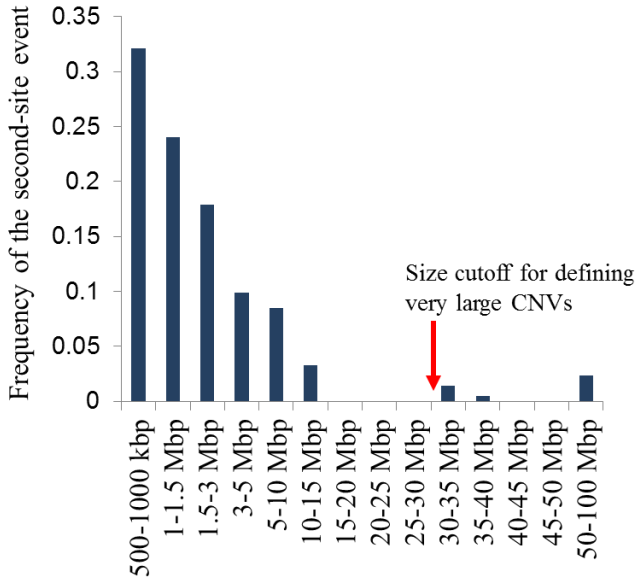

Figure S15. Size distribution of second-site CNVs. Note that most second-site CNVs (>95%) are within the 15 Mb range. The size distribution of second-site CNVs shows that about 5% of the variants are very large (e.g., Trisomy 21, Trisomy 18, XYY). We tested significant enrichment for very large variants at second sites. We chose a size cutoff of 30 Mb based on the size distribution of second-site CNVs.

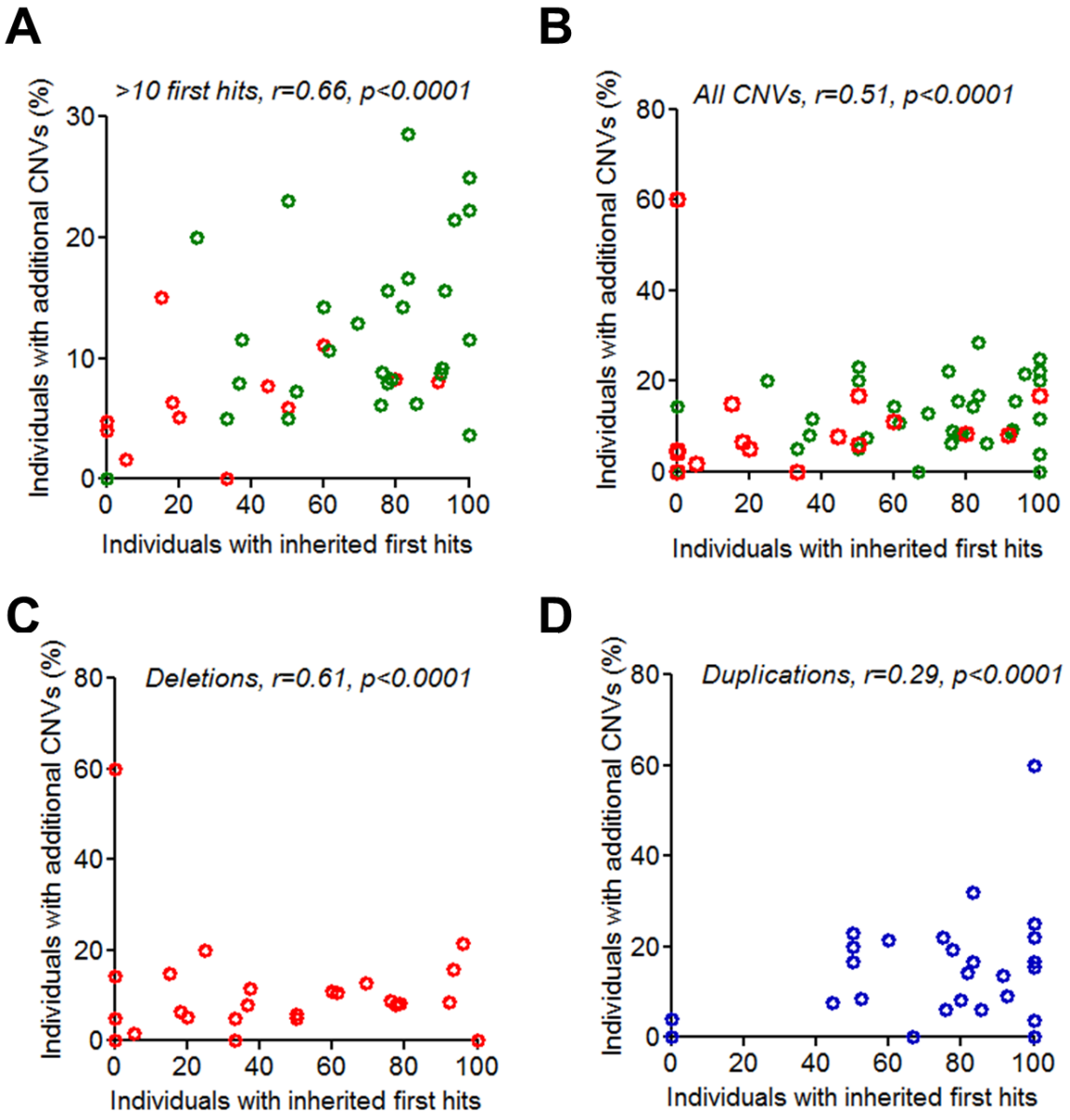

Figure S16. Scatterplots showing the relation between the frequency of inherited first hits and prevalence of additional CNVs for individuals.
(A) Data shown for only those genomic disorders where the number of samples is at least 10 for evaluation. (B) Data shown for all 72 genomic disorders. Note that red circles are CNVs associated with syndromic disorders and green circles are those associated with variable expressivity. Data for (C) deletions (red) and (D) duplications (blue) are also shown.

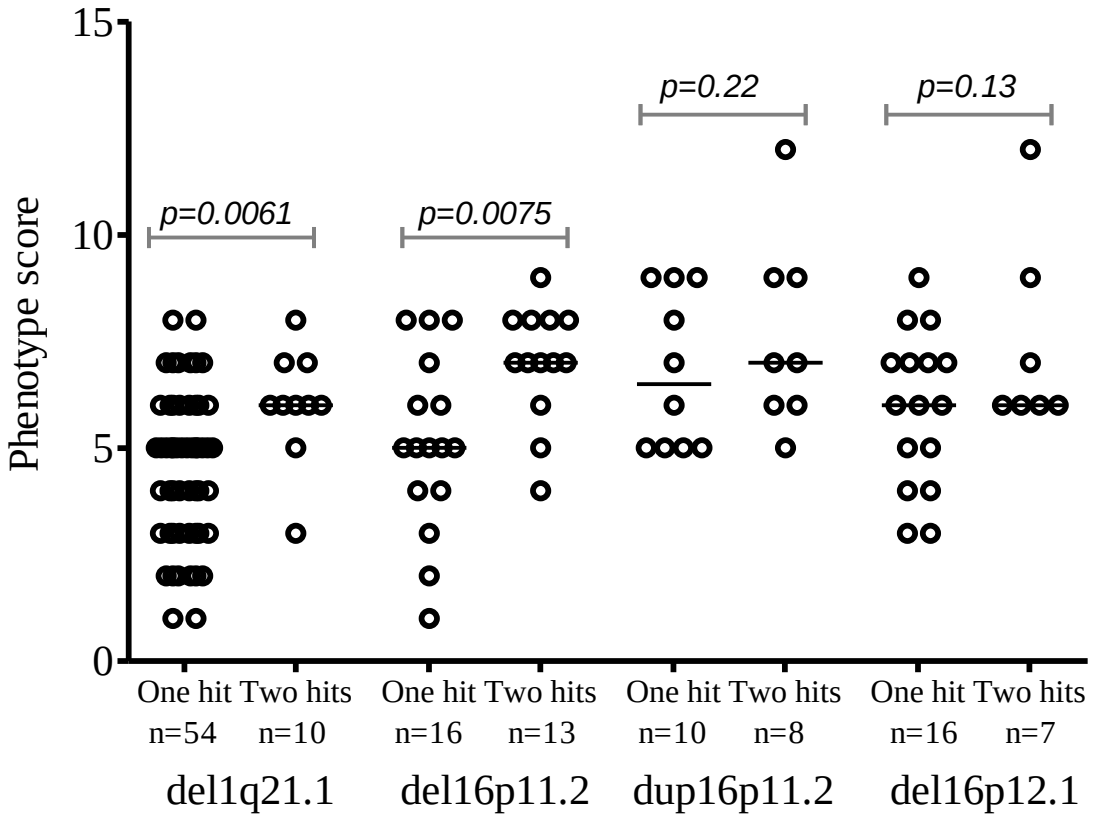

Figure S17. Scatterplot for phenotypic variability of four known genomic disorders (with and without additional large CNV) displayed in Figure 3A.

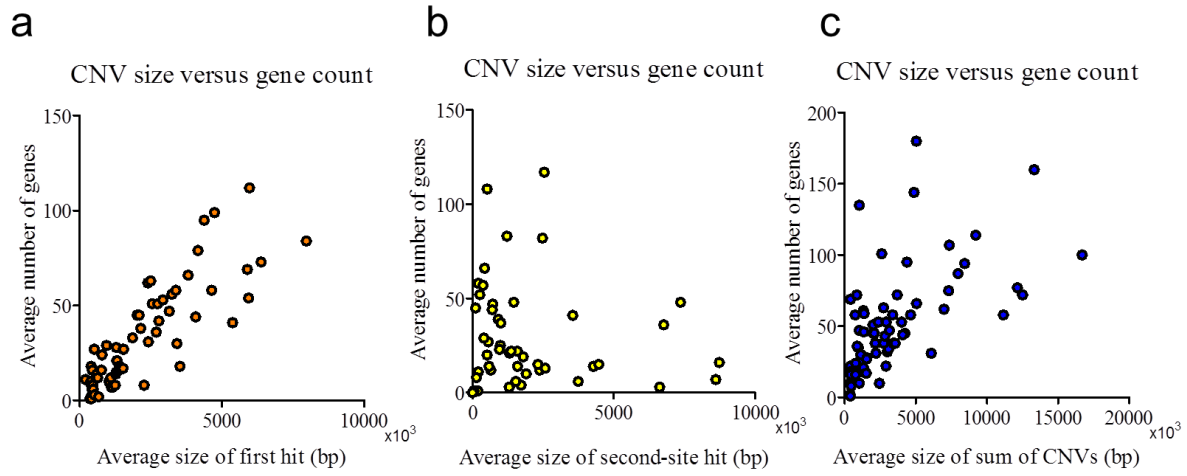

Figure S18. Gene counts as function of CNV size. (A) Correlation of average gene counts with average size of ascertained CNV. (B) Correlation of average gene counts with average size second-site CNVs. (C) Correlation of average gene counts with average size of combination of first- and second-site hits. A strong correlation was observed between the average CNV size and the average number of genes for first-hit CNV regions (Spearman correlation, r=0.85, p<0.0001) or both the hits were considered (Spearman correlation, r=0.65, p<0.0001).

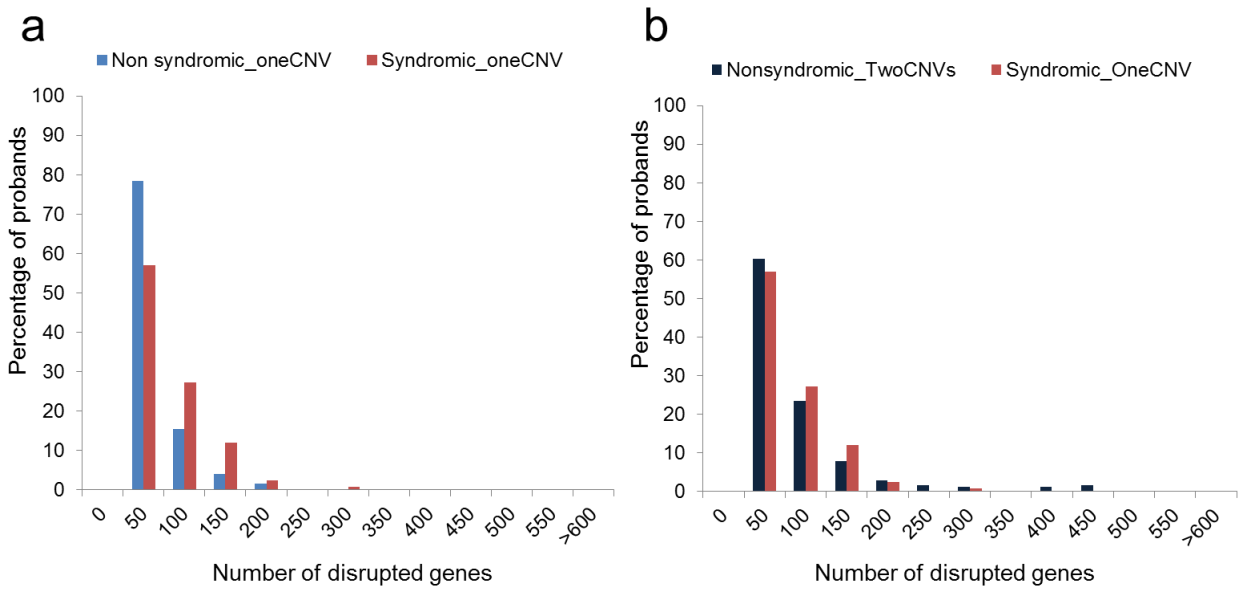

Figure S19. Proportion of probands with disrupted genes versus genomic disorder type. (A) A distribution of the proportion of probands (in percentage) and the number of disrupted genes is shown for CNVs with phenotypic variability compared to syndromic CNVs. Note, both duplications and deletions were considered here. A significantly increased number of genes as well as the percentage of probands with disrupted genes was observed for those carrying syndromic CNVs compared to variably expressive CNVs (Mann Whitney test, $p<0.001$). (B) The distribution of the proportion of probands and gene counts is shown when second-site CNVs were also included in the analysis. The addition of second-site CNVs to variably expressive CNVs results in no difference between the two groups (Mann Whitney test, $p=0.95$).

SUPPLEMENTARY TABLES

Table S1. Definition of syndromic and variably expressive disorders

Deletion CNVs	Category	Duplication CNVs	Category
1p36 deletion syndrome	syndromic		
1q21.1 deletion	variably expressive	1q21.1 duplication	variably expressive
10q23 deletion	variably expressive	10q23 duplication	potentially pathogenic
15q11.2 deletion	variably expressive		
Prader-Willi/Angelman	syndromic	PWS duplication	variably expressive
15q13.3 deletion	variably expressive	15q13.3 duplication	variably expressive
15q13.3 smaller deletion	variably expressive	15q13.3 smaller duplication	potentially pathogenic
15q24 deletion	syndromic	15q24 duplication	potentially pathogenic
15q24.2q24.3 deletion	syndromic	15q24.2q24.3 duplication	potentially pathogenic
15q25 deletion	variably expressive	15q25 duplication	potentially pathogenic
Rubinstein-Taybi deletion	syndromic		
16p13.11 deletion	variably expressive	16p13.11 duplication	variably expressive
16p11.2p12.1 deletion	variably expressive	16p11.2p12.1 duplication	variably expressive
16p12.1 deletion	variably expressive	16p12.1 duplication	potentially pathogenic
16p11.2 (SH2B1) deletion	variably expressive	16p11.2 (SH2B1) duplication	variably expressive
16p11.2 deletion	variably expressive	16p11.2 duplication	variably expressive
17p13.3 large deletion	syndromic		
17p13.3 (YWHAE) deletion	variably expressive	17p13.3 (YWHAE) duplication	variably expressive
17p13.3 (PAFAH1B1) deletion	syndromic	17p13.3 (PAFAH1B1) duplication	variably expressive
Smith-Magenis syndrome	syndromic	Potocki-Lupski syndrome	syndromic
NF1 deletion syndrome	syndromic	NF1 duplication	variably expressive
17q12 deletion	variably expressive	17q12 duplication	variably expressive
17q21.31 deletion	syndromic	17q21.31 duplication	potentially pathogenic
17q23 deletion	variably expressive	17q23 duplication	potentially pathogenic
19p13.12 deletion	variably expressive		
2q23.1 deletion	variably expressive		
2q37 deletion	syndromic	2q37 duplication	potentially pathogenic
DiGeorge/VCFS deletion	variably expressive	22q11.2 duplication	variably expressive
22q11.2 distal deletion	variably expressive	22q11.2 distal duplication	variably expressive
Phelan-McDermid syndrome	syndromic	22q13 duplication	variably expressive
3q29 deletion	variably expressive	3q29 duplication	variably expressive
Wolf-Hirschhorn	syndromic	WHS duplication	variably expressive
Sotos syndrome	syndromic	5q35 duplication	variably expressive
6p25 deletion	variably expressive	6p25 duplication	variably expressive
6q16 deletion	syndromic	6q16 duplication	variably expressive
Williams syndrome	syndromic	WBS duplication	syndromic
8p23.1 deletion	syndromic	8p23.1 duplication	syndromic
9q34 deletion	syndromic	9q34 duplication	variably expressive
PLP1 deletion	syndromic	PLP1 duplication	syndromic

Table S2. Definition of genomic disorders and potentially pathogenic CNVs analyzed in this study

Deletion	Chr	Start (hg18)	End (hg18)	Cases	Controls	p-value	Duplication	Cases	Controls	p-value	Candidate Genes	Reference
1p36 deletion syndrome	chr1	0.00	10.00	78	0	2E-08					*SKI, KCNAB2, MMP23, GABRD*	[18]
1q21.1 deletion	chr1	145.04	145.86	100	2	3E-08	1q21.1 duplication	81	1	2E-07	*GJA5, GJA8, CHD1L, HYDIN2*	[8,31]
10q23 deletion	chr10	81.95	88.79	28	0	0.002	10q23 duplication	5	0	0.3204	*NRG3, PCDH21, LRIT1,GRID1,BMPR1A*	[30]
15q11.2 deletion	chr15	20.35	20.64	166	19	2E-04					*NIPA1, NIPA2, CYFIP1*	[7,39]
Prader-Willi/Angelman	chr15	22.37	26.10	60	0	1E-06	PWS duplication	82	0	8E-09	*GABRB3, UBE3A, SNRPN*	[40]
15q13.3 deletion	chr15	28.92	30.27	85	0	4E-09	15q13.3 duplication	27	3	0.1135	*CHRNA7*	[41]
15q13.3 smaller deletion	chr15	29.80	30.24	7	0	0.203	15q13.3 smaller duplication	130	52	0.997	*CHRNA7*	[42]
15q24 deletion	chr15	70.74	72.15	8	0	0.162	15q24 duplication	4	0	0.4023	*EDC3, CYP1A1, ULK3, PTPN9*	[11]
15q24.2q24.3 deletion	chr15	73.76	75.99	5	0	0.32	15q24.2q24.3 duplication	6	0	0.2552	*UBE2Q2, ETFA, SCAPER, RCN2*	[2]
15q25 deletion	chr15	80.98	82.53	2	0	0.634	15q25 duplication	4	0	0.4023	*SH3GL3, BTBD1, HOMER2, CPEB1*	[1]
Rubinstein-Taybi deletion	chr16	3.69	3.89	10	0	0.103					*CREBBP1*	[43]
16p13.11 deletion	chr16	15.41	16.20	45	3	0.007	16p13.11 duplication	98	10	0.0015	*NDE1, MYH11, ABCC1*	[44,45]
16p11.2p12.1 deletion	chr16	21.44	29.01	20	0	0.011	16p11.2p12.1 duplication	14	0	0.0413	*UQCRC2, CACNG3, GTF3C1, ERN2*	[46]
16p12.1 deletion	chr16	21.85	22.34	56	3	1E-03	16p12.1 duplication	16	1	0.1115	*EEF2K, CDR2, POLR3E*	[29]
16p11.2 (*SH2B1*) deletion	chr16	28.73	28.96	31	1	0.006	16p11.2 (*SH2B1*) duplication	28	2	0.0401	*SH2B1*	[47,48]
16p11.2 deletion	chr16	29.56	30.11	125	3	1E-09	16p11.2 duplication	83	2	1E-06	*SEZ6L2, ALDOA, TBX6*	[49-51]
17p13.3 deletion	chr17	1.00	2.58	6	0	0.255					*YWHAE, PAFAH1B1*	[12-14]
17p13.3 (*YWHAE*) deletion	chr17	1.15	1.27	7	1	0.493	17p13.3 (*YWHAE*) duplication	13	0	0.0519	*YWHAE*	[12-14]
17p13.3 (*PAFAH1B1*) deletion	chr17	2.37	2.54	8	0	0.162	17p13.3 (*PAFAH1B1*) duplication	9	0	0.1289	*PAFAH1B1*	[12-14]
Smith-Magenis syndrome	chr17	16.73	18.24	31	0	9E-04	Potocki-Lupski syndrome	25	0	0.0034	*RAI1, TOM1L2, DRG2*	[4,52]
NF1 deletion syndrome	chr17	26.12	27.30	9	0	0.129	NF1 duplication	6	0	0.2552	*NF1, EVI2A, RNF135*	[53]
17q12 deletion	chr17	31.89	33.30	26	2	0.056	17q12 duplication	35	3	0.0346	*TCF2, LHX1, ACACA,HNF1β*	[34,54]
17q21.31 deletion	chr17	41.06	41.52	42	0	7E-05	17q21.31 duplication	5	0	0.3204	*CRHR, MAPT, KIAA1267*	[55]

17q23 deletion	chr17	55.64	57.66	6	0	0.255	17q23 duplication	1	0	0.7964	*BCAS3*, *PPM1D*, *TBX2*, *TBX4*	[56]
19p13.12 deletion	chr19	12.94	16.56	13	0	0.052					*MRI1*, *CACNA1A*, *NOTCH3*, *RLN3*	[57]
2q23.1 deletion	chr2	148.44	149.01	20	0	0.011					*MBD5*	[58]
2q37 deletion	chr2	239.37	242.12	17	0	0.021	2q37 duplication	2	0	0.6343	*HDAC4*	[59]
DiGeorge/VCFS deletion	chr22	17.40	18.67	175	0	5E-18	22q11.2 duplication	87	5	5E-05	*TBX1*, *COMT*	[60]
22q11.2 distal deletion	chr22	20.24	22.00	26	0	0.003	22q11.2 distal duplication	18	0	0.0166	*TOP3B*, *MAPK1*, *UBE2L3*, *BCR*	[15,17,61]
Phelan-McDermid syndrome	chr22	41.33	49.51	59	0	1E-06	22q13 duplication	3	0	0.5052	*SHANK3*, *HDAC10*, *WNT7B*	[62]
3q29 deletion	chr3	197.23	198.84	20	0	0.011	3q29 duplication	18	0	0.0166	*PAK2*, *DLG1*	[63,64]
Wolf-Hirschhorn	chr4	1.50	2.00	17	0	0.021	WHS duplication	4	0	0.4023	*WHSC1*, *WHSC2*	[65]
Sotos syndrome	chr5	175.65	176.99	14	0	0.041	5q35 duplication	4	0	0.4023	*NSD1*	[66]
6p25 deletion	chr6	0.10	6.00	23	0	0.005	6p25 duplication	12	0	0.0651	*TUBB2B*, *FOXC1*, *FOXF2*, *SLC22A23*	[67]
6q16 deletion	chr6	100.92	101.05	1	0	0.796	6q16 duplication	1	0	0.7964	*SIM1*	[68]
Williams syndrome	chr7	72.38	73.78	83	0	6E-09	WBS duplication	39	0	0.0001	*ELN*, *GTF2I*, *FKBP6*, *LIMK1*	[36,69]
8p23.1 deletion	chr8	8.13	11.93	18	0	0.017	8p23.1 duplication	24	0	0.0042	*CLDN23*, *MSRA*, *SOX7*, *GATA4*	[70]
9q34 deletion	chr9	136.95	140.20	18	0	0.017	9q34 duplication	8	0	0.1619	*EHMT1*	[71,72]
PLP1 deletion	chrX	102.30	113.30	3	0	0.505	*PLP1* duplication	6	0	0.2552	*PLP1*	[73]

Note that our study includes only pure terminal and interstitial CNVs. Unbalanced translocations and complex rearrangements were excluded. Shaded regions indicate nonhotspot CNVs.

Table S3. Clinical features observed in individuals with pathogenic CNVs

	DD/ID	Facial features	Renal disease	Epilepsy	Autism	ADHD	Cardiac anomalies	Brain malformation	Speech and language delay	Cancer	Failure to thrive	MCA	Obesity	Skeletal defects	Other indications
Sotos syndrome	71.43	57.14	0.00	14.29	0.00	7.14	0.00	0.00	0.00	0.00	0.00	28.57	0.00	0.00	7.14
10q23_dup	40.00	60.00	0.00	0.00	60.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	20.00	0.00
6p25.3_dup	36.36	45.45	0.00	0.00	0.00	0.00	0.00	9.09	0.00	0.00	0.00	18.18	0.00	0.00	36.36
10q23_del	39.29	42.86	0.00	10.71	7.14	0.00	3.57	7.14	3.57	3.57	7.14	10.71	0.00	0.00	10.71
22q11.2_distdel	42.31	42.31	0.00	7.69	0.00	0.00	3.85	0.00	0.00	0.00	0.00	46.15	0.00	15.38	3.85
15q13.3_smalldel	71.43	28.57	0.00	14.29	14.29	0.00	0.00	0.00	14.29	0.00	14.29	0.00	14.29	14.29	0.00
1q21.1_del	52.00	41.00	1.00	6.00	4.00	1.00	4.00	1.00	4.00	0.00	12.00	13.00	3.00	10.00	5.00
15q23q24_del	50.00	0.00	0.00	0.00	0.00	0.00	25.00	25.00	0.00	0.00	25.00	0.00	25.00	0.00	25.00
15q23q24_dup	66.67	33.33	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	33.33
15q24_del	75.00	25.00	0.00	12.50	25.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	12.50	12.50
15q24_dup	75.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	25.00	0.00	0.00	0.00	0.00
15q25_del	0.00	0.00	0.00	50.00	50.00	0.00	0.00	0.00	0.00	0.00	50.00	0.00	0.00	0.00	0.00
15q25_dup	100.00	33.33	0.00	33.33	33.33	0.00	0.00	0.00	0.00	0.00	33.33	33.33	0.00	0.00	0.00
Rubinstein_Taybi	30.00	40.00	0.00	0.00	0.00	0.00	10.00	10.00	0.00	0.00	0.00	30.00	0.00	0.00	30.00
16p12.1_del	66.67	38.89	0.00	11.11	5.56	1.85	12.96	5.56	3.70	3.70	16.67	25.93	0.00	3.70	14.81
Smith-Magenis	74.19	38.71	0.00	6.45	3.23	3.23	0.00	3.23	0.00	0.00	0.00	12.90	3.23	3.23	6.45
19p13.12_del	76.92	38.46	0.00	15.38	0.00	0.00	7.69	7.69	0.00	7.69	15.38	0.00	0.00	0.00	0.00
17q21.31_del	69.05	38.10	0.00	23.81	0.00	0.00	0.00	9.52	0.00	2.38	9.52	23.81	0.00	0.00	2.38
6q25.3_del	45.45	36.36	0.00	4.55	0.00	0.00	0.00	9.09	0.00	0.00	4.55	4.55	0.00	9.09	18.18
Wolf_Hirschhorn	52.94	35.29	5.88	11.76	0.00	5.88	11.76	0.00	0.00	0.00	0.00	11.76	5.88	0.00	17.65
1p36_del	56.41	34.62	0.00	19.23	2.56	1.28	1.28	1.28	1.28	0.00	6.41	11.54	1.28	6.41	7.69
Potocki-Lupski	76.00	32.00	0.00	8.00	12.00	0.00	4.00	0.00	12.00	0.00	16.00	8.00	0.00	4.00	0.00
1q21.1_dup	56.79	30.86	1.23	7.41	19.75	3.70	1.23	3.70	1.23	1.23	3.70	8.64	1.23	1.23	11.11
17p13.3_Largedel	0.00	16.67	0.00	16.67	0.00	0.00	0.00	50.00	0.00	0.00	33.33	16.67	0.00	0.00	0.00
17p13.3_LIS1del	25.00	62.50	0.00	37.50	0.00	0.00	0.00	0.00	0.00	0.00	0.00	12.50	0.00	0.00	0.00
17p13.3_LIS1dup	77.78	44.44	0.00	0.00	11.11	0.00	11.11	0.00	0.00	11.11	11.11	0.00	0.00	0.00	11.11
17p13.3_YWHAEdel	28.57	14.29	0.00	14.29	14.29	0.00	0.00	14.29	0.00	0.00	0.00	14.29	0.00	14.29	28.57

16p11.2_distdup	42.31	30.77	0.00	3.85	7.69	0.00	7.69	0.00	7.69	0.00	7.69	19.23	0.00	7.69	11.54
22q11.2_DGSdel	36.21	30.46	1.15	5.75	2.87	0.57	19.54	1.72	2.30	4.02	10.92	26.44	0.00	4.60	11.49
2q37_del	76.47	29.41	0.00	17.65	5.88	0.00	5.88	0.00	5.88	0.00	5.88	5.88	0.00	0.00	0.00
22q11.2_dup	54.88	29.27	2.44	9.76	9.76	1.22	6.10	2.44	1.22	0.00	9.76	12.20	2.44	6.10	6.10
17q21.31_dup	75.00	50.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	25.00	0.00	0.00	0.00
17q23_del	60.00	40.00	0.00	0.00	0.00	0.00	20.00	0.00	0.00	0.00	0.00	20.00	0.00	20.00	0.00
17q23_dup	100.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00
Williams	51.25	28.75	1.25	3.75	3.75	1.25	16.25	6.25	1.25	5.00	10.00	17.50	0.00	1.25	15.00
15q11.2_del	56.97	28.48	0.61	12.73	7.88	1.21	6.67	3.64	2.42	1.82	8.48	16.36	1.21	4.24	5.45
8p23_del	27.78	27.78	0.00	0.00	0.00	0.00	33.33	0.00	0.00	0.00	5.56	33.33	0.00	0.00	0.00
15q13.3_smalldup	50.00	26.92	0.00	5.38	10.00	2.31	9.23	1.54	2.31	3.08	7.69	18.46	0.77	3.08	10.77
16p13.11_dup	55.10	25.51	2.04	6.12	10.20	3.06	5.10	4.08	4.08	2.04	4.08	16.33	1.02	7.14	13.27
WBS_dup	75.00	25.00	0.00	19.44	13.89	2.78	0.00	8.33	13.89	0.00	8.33	8.33	2.78	2.78	5.56
17p13.3_YWHAEdup	66.67	25.00	0.00	8.33	0.00	0.00	0.00	0.00	8.33	0.00	0.00	8.33	0.00	8.33	16.67
16p11.2_dup	56.79	24.69	0.00	17.28	9.88	4.94	2.47	8.64	0.00	1.23	3.70	9.88	0.00	1.23	9.88
PWS_AS	48.28	24.14	0.00	8.62	1.72	0.00	0.00	0.00	0.00	0.00	29.31	1.72	0.00	0.00	13.79
22q13_dup	66.67	0.00	0.00	0.00	0.00	0.00	0.00	33.33	0.00	0.00	0.00	0.00	0.00	0.00	0.00
17q12_del	40.00	24.00	16.00	12.00	8.00	0.00	0.00	8.00	0.00	0.00	8.00	12.00	0.00	8.00	8.00
16p11.2_del	60.16	23.58	1.63	8.13	10.57	1.63	0.00	3.25	4.88	1.63	4.88	12.20	2.44	4.88	7.32
2q37_dup	50.00	50.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	50.00	0.00	0.00	0.00	0.00
3q29_del	64.71	23.53	0.00	5.88	5.88	0.00	0.00	0.00	11.76	0.00	5.88	5.88	0.00	5.88	11.76
16p11.2_Largedel	75.00	20.00	0.00	10.00	0.00	0.00	0.00	5.00	0.00	0.00	0.00	10.00	0.00	0.00	15.00
5q35_dup	75.00	50.00	0.00	0.00	0.00	0.00	25.00	0.00	25.00	0.00	50.00	0.00	0.00	0.00	0.00
17q12_dup	68.57	20.00	0.00	28.57	8.57	2.86	11.43	5.71	2.86	0.00	5.71	8.57	2.86	2.86	2.86
6q16_del	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	100.00
6q16_dup	100.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00
16p13.11_del	51.11	20.00	2.22	13.33	0.00	4.44	0.00	8.89	6.67	4.44	2.22	15.56	4.44	4.44	15.56
16p12.1_dup	37.50	18.75	0.00	0.00	12.50	0.00	0.00	0.00	6.25	0.00	6.25	25.00	0.00	0.00	31.25
15q13.3_dup	51.85	18.52	0.00	14.81	7.41	0.00	3.70	3.70	3.70	0.00	3.70	11.11	3.70	0.00	18.52
3q29_dup	41.18	17.65	0.00	0.00	5.88	0.00	5.88	0.00	0.00	0.00	5.88	23.53	0.00	0.00	23.53
9q34_dup	50.00	25.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	12.50	12.50	37.50

NF1_del	44.44	33.33	0.00	0.00	0.00	0.00	0.00	0.00	11.11	0.00	0.00	11.11	0.00	0.00	33.33
NF1_dup	80.00	60.00	0.00	0.00	0.00	0.00	0.00	0.00	20.00	0.00	0.00	20.00	0.00	0.00	60.00
PLP1_del	66.67	100.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	66.67	0.00	0.00	0.00
PLP1_dup	83.33	83.33	0.00	16.67	0.00	0.00	0.00	0.00	0.00	0.00	33.33	0.00	0.00	0.00	33.33
22q11.2_distdup	29.41	17.65	0.00	11.76	11.76	0.00	0.00	0.00	0.00	0.00	5.88	11.76	0.00	5.88	29.41
8p23_dup	43.48	17.39	4.35	8.70	0.00	13.04	8.70	8.70	0.00	4.35	0.00	8.70	0.00	0.00	26.09
9q34_del	50.00	16.67	5.56	16.67	11.11	0.00	0.00	5.56	0.00	0.00	5.56	11.11	0.00	0.00	5.56
PWS_dup	62.20	15.85	0.00	15.85	12.20	0.00	1.22	4.88	1.22	0.00	4.88	4.88	0.00	0.00	17.07
16p11.2_Largedup	30.77	15.38	0.00	0.00	0.00	0.00	7.69	0.00	0.00	0.00	23.08	23.08	0.00	0.00	23.08
2q23.1_del	65.00	15.00	0.00	20.00	20.00	0.00	0.00	0.00	0.00	0.00	10.00	0.00	0.00	0.00	10.00
16p11.2_distdel	53.57	14.29	0.00	10.71	3.57	3.57	0.00	14.29	3.57	3.57	17.86	3.57	10.71	0.00	17.86
22q13_del	75.86	13.79	0.00	13.79	13.79	0.00	1.72	1.72	8.62	1.72	6.90	10.34	0.00	1.72	3.45
15q13.3_del	52.38	13.10	1.19	13.10	16.67	2.38	3.57	4.76	2.38	2.38	7.14	10.71	0.00	1.19	2.38
Wolf-Hirschhorn_dup	50.00	25.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	25.00	0.00	0.00	0.00	25.00

Table S4. Validation of a subset of discovered CNVs

	By inheritance	FISH	Custom high-density arrays
First hits	430	111	123
Second-site hits	72	102	142
Total	502	213	265

Table S5. Breakdown of second-site CNVs into deletions and duplications

Genomic disorder	dups	Average dup size	dels	Average del size
10q23_del	1	519978	1	1315482
10q23_dup	1	512635		
15q11.2_del	13	2088120	14	2594920
15q13.3_del	2	813698	5	1094647
15q13.3_dup	1	678757		
15q13.3_smalldup	6	25811245	11	5013081
15q23q24_del	3	1135951		
15q23q24_dup	1	1194973		
16p11.2_del	3	914379.7	6	4464526
16p11.2_distdel	3	1746438	1	5827240
16p11.2_distdup	5	1365762	3	970842.3
16p11.2_dup	4	16011213	7	5235663
16p11.2_Largedel	1	1028180		
16p11.2_Largedup	2	711599		
16p12.1_del	8	12341838	6	7184092
16p12.1_dup	1	720235		
16p13.11_del	4	1277145	1	3120996
16p13.11_dup	1	2170259	5	3625364
17p13.3_LIS1dup			2	1070477
17p13.3_YWHAEdel	1	1552215		
17p13.3_YWHAEdup	1	1238104	2	6244557
17q12_del	1	1423745		
17q12_dup	3	921252.7	2	940139
1p36_del	5	1291010	1	9905415
1q21.1_del	1	1079218	3	5613658
1q21.1_dup			5	19704287
22q11.2_DGSdel	6	865691.3	3	1400713
22q11.2_distdup	2	2015337	1	1238104
22q11.2_dup	3	26552845	5	4483501
22q13_del	1	1916240		
2q23.1_del	1	4258493		
3q29_del	1	1137742	2	1486219

3q29_dup	1	630290	3	1433689
6p25_del	1	3432802	1	584036
6p25_dup	3	4121820		
8p23_del			2	4855380
8p23_dup	1	553068	1	1238104
PLP1_dup	1	786523		
Potocki-Lupski	1	1456967		
PWS_AS	5	1403445	4	3393042
PWS_dup	4	10004246	3	1361306
WBS_dup	1	1244519	2	2557433
Williams	3	830458	1	2486671
Wolf_Hirschhorn	1	1180370		
Total	108		103	

Table S6. List of cases where both large CNVs were associated with genomic disorders

		Ascertained CNV (first hit)		Second-site CNV	
ID	Clinical indication	Genomic Disorder	Inheritance	Genomic Disorder	Inheritance
10538	Developmental Delay, Seizure Disorder, Short Stature, Microcephaly	NF1 deletion syndrome	Unknown	15q11.2 deletion	Unknown
14963	Kyphosis	17p13.3 (*YWHAE*) duplication	Unknown	16p13.11 duplication	Unknown
20880	Failure to thrive	Prader-Willi/Angelman syndrome	De Novo	1q21.1 deletion	Maternal
21683	Multiple Congenital Anomalies	22q11.2 DiGeorge/VCFS deletion	Unknown	15q11.2 deletion	Unknown
23022	Borderline newborn screening, Failure to thrive, Altered mental status	16p11.2 deletion	Unknown	16p11.2 distal duplication	Unknown
23858	Encephalopathy	15q13.3 deletion	Unknown	16p11.2 deletion	Unknown
24219	Developmental Delay	Williams region duplication	Paternal	1q21.1 deletion	Paternal
24781	Developmental Delay	PWS/AS duplication	Unknown	16p12.1 deletion	Maternal
25163	Not Specified	1q21.1 deletion	Unknown	22q11.2 duplication	Maternal
25870	Developmental Delay, Dysmorphic Features, Seizure Disorder, Multiple Congenital Anomalies	22q11.2 DiGeorge/VCFS deletion	Unknown	3q29 duplication	Unknown
27419	Dysmorphic Features, Multiple Congenital Anomalies, Failure to thrive, Congenital stenosis of aortic valve	Williams syndrome	Unknown	15q11.2 deletion	Unknown
28304	Multiple Congenital Anomalies	Williams syndrome	Unknown	15q13.3 small duplication	Unknown
29163	Dysmorphic Features, Developmental Delay	PWS/AS duplication	Maternal	16p11.2 distal deletion	Unknown
31441	Heart defect	8p23.1 deletion	Unknown	15q13.3 small duplication	Unknown
31576	Lack of Coordination, cystic kidney disease, nystagmus	22q11.2 duplication	De Novo	17q12 deletion	De novo

31898	Developmental Delay, Dysmorphic Features, Seizure Disorder	16p12.1 deletion	Paternal	22q11.2 duplication	Maternal, Paternal
33128	Developmental Delay, mental retardation, autistic features, convulsive disorder, microcephaly	Phelan-McDermid syndrome	Unknown	15q11.2 deletion	Unknown
33459	Autistic Spectrum Disorder	PWS/AS duplication	Unknown	22q11.2 distal deletion	Unknown
33529	Aberrant subclavian artery	22q11.2 DiGeorge/VCFS deletion	Unknown	3q29 deletion	Unknown
34299	Developmental Delay, Dysmorphic Features, Seizure Disorder	Prader-Willi/Angelman syndrome	Unknown	16p11.2 distal deletion	Unknown
36479	Developmental Delay	1q21.1 deletion	Unknown	16p11.2 deletion	Unknown
37709	Multiple Congenital Anomalies	22q11.2 DiGeorge/VCFS deletion	Unknown	15q11.2 deletion	Unknown
38663	Developmental Delay, Dysmorphic Features	Williams syndrome	Unknown	17p13.3 (*LIS1*) duplication	Maternal
39259	Autistic Disorder	15q13.3 deletion	Maternal	16p12.1 deletion	Maternal
40354	Developmental Delay, Dysmorphic Features	Williams syndrome	Unknown	16p13.11 duplication	Maternal
42267	Dysmorphic Features	16p11.2 deletion	Unknown	3q29 deletion	Unknown
42275	Encephalopathy	Williams syndrome	Unknown	16p11.2 distal duplication	Maternal
43001	Attention deficit disorder of childhood with hyperactivity, Failure to thrive, Microcephaly	6p25 deletion	Unknown	16p11.2 duplication	Unknown
43248	Developmental Delay, Multiple Congenital Anomalies	17q21.31 duplication	Unknown	16p11.2 deletion	Unknown
44153	Developmental Delay, Dysmorphic Features	16p13.11 deletion	Unknown	22q11.2 distal duplication	Unknown
46810	Developmental delay	16p11.2 duplication	Unknown	15q13.3 small duplication	Maternal
49557	Feeding difficulty	16p11.2 distal deletion	Unknown	1q21.1 duplication	Unknown
51323	Developmental Delay, Dysmorphic Features	10q23.1 deletion	Unknown	16p11.2 duplication	Unknown

51967	Developmental Delay, Delayed milestones	Prader-Willi/Angelman syndrome	Unknown	Williams region duplication	Unknown
52609	Cystic kidneys, Absent bladder and small stomach, Patient deceased	15q13.3 deletion	Unknown	17q12 deletion	Maternal
52716	Dysmorphic Features, Speech delay, Small stature	22q11.2 DiGeorge/VCFS deletion	Unknown	16p13.11 duplication	Unknown
55326	Dysmorphic Features, Multiple Congenital Anomalies, Bilateral Hand, Contractures, Bilateral clubfeet, Growth delay	16p11.2 distal duplication	Unknown	15q13.3 duplication	Unknown
57872	Developmental Delay, Hypotonia	PWS/AS duplication	Unknown	16p11.2 duplication	Unknown
60452	TOF, Speech delay	22q11.2 DiGeorge/VCFS deletion	Unknown	Williams region duplication	Unknown
60918	Developmental Delay, Mental Retardation, Central Nervous System Disorder	1q21.1 duplication	Unknown	22q11.2 duplication	Unknown
63335	Developmental Delay, Overgrowth, Delayed Milestones	15q13.3 deletion	Maternal	15q11.2 deletion	Maternal
67345	Mixed development disorder, Microcephalus	1q21.1 deletion	Unknown	3q29 deletion	Unknown
68390	ADHD, Seizures, Mild Dysmorphic features	8p23 duplication	Unknown	16p13.11 deletion	Maternal
69470	Delayed milestones	1q21.1 deletion	Unknown	15q11.2 deletion	Unknown
73180	Developmental delay, Dysmorphic features	15q23q24 duplication	Unknown	1q21.1 duplication	Unknown

Note that the designation of first hit or second hit is based on the rarity and penetrance (severity) of the CNV[1].

Table S7. List of individuals carrying more than two large CNVs

ID	SEX	Inheritance	Genomic disorder	Chr	Start	Stop	CNV	Inheritance	Size
29386	Male	Paternal	16p13.11_del	chr12	126,798,089	127,973,176	chr12	maternal	1,175,087
29386	Male	Paternal	16p13.11_del	chr7	68,274,398	70,872,555	chr7	paternal	2,598,157
31441	Male	Unknown	15q13.3_smalldup	chr8	9469354	11895875	chr8	unknown	2426521
31441	Male	Unknown	15q13.3_smalldup	chr8	1659939	6907722	chr8	unknown	5247783
40242	Female	Paternal	15q13.3_smalldup	chr9	14,200,803	66,245,169	chr9	de novo	52044366
40242	Female	Paternal	15q13.3_smalldup	chr9	204,366	14,129,729	chr9	de novo	13925363
40822	Male	Paternal	22q11.2_dup	chr18	39,703,953	45,137,422	chr18	de novo	5,433,469
40822	Male	Paternal	22q11.2_dup	chr4	186,656,427	188,142,936	chr4	maternal	1,486,509
42977	Male	Maternal	16p12.1_del	chr9	75,805,226	84,795,201	chr9	paternal (inversion carrier)	8,989,975
42977	Male	Maternal	16p12.1_del	chr9	105,958,680	112,691,549	chr9	paternal (inversion carrier)	6,732,869
43670	Male	Unknown	16p12.1_del	chr3	5,411,510	6,088,506	chr3	maternal	676,996
43670	Male	Unknown	16p12.1_del	chr14	20,805,673	22,308,694	chr14	unknown	1,503,021
44153	Female	Unknown	16p13.11_del	chr20	61,086,010	61,915,632	chr20	unknown	829,622
44153	Female	Unknown	16p13.11_del	chr22	20,128,774	23,289,893	chr22	unknown	3,161,119
46609	Male	Unknown	1q21.1_dup	chr13	56,112,951	114,103,243	chr13	unknown	57,990,292
46609	Male	Unknown	1q21.1_dup	chr13	18,448,674	56,269,250	chr13	unknown	37,820,576
57860	Male	Unknown	PWS_dup	chr18	11,690,934	17,148,187	chr18	unknown	5,457,253
57860	Male	Unknown	PWS_dup	chr5	178,486,666	179,522,156	chr5	unknown	1,035,490
66566	Female	Unknown	1p36_del	chr1	17,157,085	18,965,927	chr1	unknown	1,808,842
66566	Female	Unknown	1p36_del	chr6	116,357,416	126,262,831	chr6	unknown	9,905,415
69285	Female	Unknown	15q11.2_del	chr9	133,267,694	136,385,775	chr9	unknown	3,118,081
69285	Female	Unknown	15q11.2_del	chr2	30,044,284	33,934,019	chr2	unknown	3,889,735

Table S8. Comparison of frequency of at least two large CNVs between cases with a genomic disorder and population controls

Genomic Disorder	Cases with two hits	Cases without two hits	Controls with second hits	Controls without second hits	Fisher's exact p value	OR (95% CI)
15q11.2_del	26	140	18	276	0.00093	2.841 (1.443 - 5.704)
16p11.2_dup	13	70	21	374	0.00217	3.296 (1.445 - 7.279)
16p11.2_distdup	8	20	69	733	0.00257	4.237 (1.555 - 10.51)
15q23q24_del	3	2	9	126	0.00444	19.866 (2.017 - 265.662)
16p12.1_del	12	44	9	126	0.00453	3.787 (1.36 - 10.938)
3q29_dup	4	14	21	374	0.01800	5.051 (1.114 - 18.063)
17p13.3_YWHAEdup	3	10	21	374	0.03470	5.3 (0.873 - 22.767)
PWS_AS	9	51	9	126	0.05962	2.458 (0.813 - 7.439)
3q29_del	4	16	9	126	0.06721	3.46 (0.698 - 14.305)
6q25.3_dup	3	9	69	733	0.08169	3.532 (0.601 - 14.588)
16p13.11_dup	9	89	21	374	0.11797	1.798 (0.7 - 4.267)
17q12_dup	4	31	21	374	0.13557	2.292 (0.538 - 7.414)
16p11.2_distdel	4	27	18	276	0.14535	2.264 (0.52 - 7.585)
15q13.3_smalldup	15	115	69	733	0.17748	1.385 (0.711 - 2.549)
17p13.3_LIS1dup	2	7	69	733	0.18236	3.029 (0.301 - 16.32)
16p11.2_Largedup	2	12	21	374	0.18251	2.956 (0.302 - 14.667)
22q11.2_dup	7	80	21	374	0.22526	1.557 (0.54 - 3.965)
22q11.2_distdup	2	16	21	374	0.26455	2.22 (0.233 - 10.497)
15q23q24_dup	1	5	21	374	0.28876	3.542 (0.072 - 33.78)
PLP1_dup	1	5	21	374	0.28876	3.542 (0.072 - 33.78)
17q12_del	3	23	9	126	0.30156	1.818 (0.295 - 8.04)
PWS_dup	6	76	21	374	0.31174	1.405 (0.449 - 3.756)
10q23_del	3	25	9	126	0.33942	1.674 (0.273 - 7.352)
10q23_dup	1	4	69	733	0.36546	2.651 (0.053 - 27.283)
17q21.31_dup	1	4	69	733	0.36546	2.651 (0.053 - 27.283)
WBS_dup	3	36	21	374	0.36798	1.483 (0.27 - 5.335)

8p23_del	2	16	9	126	0.37989	1.742 (0.169 - 9.569)
8p23_dup	2	22	21	374	0.38525	1.617 (0.173 - 7.354)
17p13.3_YWHAEdel	1	6	9	126	0.40711	2.314 (0.046 - 22.73)
16p13.11_del	4	41	9	126	0.41569	1.363 (0.291 - 5.21)
15q13.3_del	7	78	9	126	0.42620	1.255 (0.381 - 3.962)
16p11.2_del	10	115	9	126	0.43008	1.216 (0.427 - 3.515)
6q25.3_del	2	21	18	276	0.43579	1.458 (0.154 - 6.799)
1q21.1_del	8	92	9	126	0.44207	1.216 (0.392 - 3.703)
1q21.1_dup	5	76	21	374	0.46239	1.171 (0.335 - 3.326)
Wolf_Hirschhorn	1	16	9	126	0.70626	0.876 (0.019 - 7.096)
2q23.1_del	1	19	18	276	0.72447	0.808 (0.018 - 5.702)
Potocki-Lupski	1	24	21	374	0.74998	0.743 (0.017 - 5.038)
16p11.2_Largedel	1	19	9	126	0.75985	0.738 (0.016 - 5.882)
1p36_del	4	74	9	126	0.76892	0.758 (0.165 - 2.833)
15q13.3_dup	1	26	21	374	0.77540	0.686 (0.016 - 4.622)
Williams	4	79	9	126	0.80113	0.71 (0.154 - 2.65)
22q11.2_DGSdel	8	167	9	126	0.85413	0.672 (0.219 - 2.022)
22q13_del	1	58	9	126	0.97604	0.243 (0.005 - 1.823)
15q13.3_smalldel	0	7	18	276	1.00000	0 (0 - 11.508)
15q24_del	0	8	9	126	1.00000	0 (0 - 9.73)
15q24_dup	0	4	21	374	1.00000	0 (0 - 28.341)
15q25_del	0	2	9	126	1.00000	0 (0 - 79.066)
15q25_dup	0	4	21	374	1.00000	0 (0 - 28.341)
16p12.1_dup	0	16	21	374	1.00000	0 (0 - 5.012)
17p13.3_Largedel	0	6	9	126	1.00000	0 (0 - 13.868)
17p13.3_LIS1del	0	8	9	126	1.00000	0 (0 - 9.73)
17q21.31_del	0	42	9	126	1.00000	0 (0 - 1.599)
17q23_del	0	6	9	126	1.00000	0 (0 - 13.868)
17q23_dup	0	1	21	374	1.00000	0 (0 - 688.942)

19p13.12_del	0	13	9	126	1.00000	0 (0 - 5.569)
22q11.2_distdel	0	26	9	126	1.00000	0 (0 - 2.635)
22q13_dup	0	3	69	733	1.00000	0 (0 - 26.031)
2q37_del	0	17	9	126	1.00000	0 (0 - 4.148)
2q37_dup	0	2	21	374	1.00000	0 (0 - 97.373)
5q35_dup	0	4	21	374	1.00000	0 (0 - 28.341)
6q16_del	0	1	9	126	1.00000	0 (0 - 545.65)
6q16_dup	0	1	69	733	1.00000	0 (0 - 412.204)
9q34_del	0	18	9	126	1.00000	0 (0 - 3.899)
9q34_dup	0	8	69	733	1.00000	0 (0 - 6.362)
NF1_del	0	9	9	126	1.00000	0 (0 - 8.466)
NF1_dup	0	6	21	374	1.00000	0 (0 - 16.089)
PLP1_del	0	3	9	126	1.00000	0 (0 - 37.348)
Rubinstein_Taybi	0	10	18	276	1.00000	0 (0 - 7.47)
Smith-Magenis	0	31	9	126	1.00000	0 (0 - 2.191)
Sotos	0	14	9	126	1.00000	0 (0 - 5.13)
Wolf-Hirschhorn_dup	0	4	21	374	1.00000	0 (0 - 28.341)

*One-tailed p-valued for Fisher's exact test; confidence intervals (CI) were derived from two-tailed Fisher's exact test. Note that the controls were conditioned to carry a large CNV (>500 kb or >300 kb) deletion or duplication (to match the genomic disorder) as the first-hit CNV and then the number of second-site CNVs (both deletions and duplications) were counted. Filters were applied to only include variants <0.1% frequency and <50% segmental duplication content.

Table S9. List of large second-site CNVs >30 Mb in size

		Large second-site CNV				
ID	**Primary genomic disorder**	**Chr**	**Start**	**Stop**	**Size**	**Comment**
38091	15q13.3_smalldup	chr13	18454945	114109838	95,654,893	mosaic trisomy 13
66683	22q11.2_dup	chr18	131,491	76,114,684	75,983,193	Trisomy 18
24333	16p11.2_dup	chr11	75,265,230	134,431,368	59,166,138	large segment of 11q inserted into 11p
46609	1q21.1_dup	chr13	56,112,951	114,103,243	57,990,292	Large mosaic terminal 13q deletion
40242	15q13.3_smalldup	chr9	14,200,803	66,245,169	52,044,366	Abnormal chromosome 9: terminal deletion and the rest of the short arm is duplicated.
52882	16p12.1_del	chr9	199,254	38,751,949	38,552,695	Unbalanced translocation: inherited a supernumerary chromosome made up of 9p, 9cen, 15p - mom is balanced carrier
46609	1q21.1_dup	chr13	18,448,674	56,269,250	37,820,576	Mosaic monosomy 13/large del(13q)
26098	PWS_dup	chr21	13,925,877	46,914,885	32,989,008	Trisomy 21
34937	16p12.1_del	chr21	14,429,720	46,912,065	32,482,345	Trisomy 21
30323	16p12.1_del	chr5	98,042,952	128,161,233	30,118,281	30 Mb 5q interstitial deletion

It is worth noting that (1) many of the very large events exist in mosaic state leading to unclear diagnostic interpretations and thus may be properly thought of as a secondary hit and (2) the ascertained genomic disorder CNV can actually be a modifier of the phenotype due to the larger event. It is therefore quite possible that these large chromosomal abnormalities (especially mosaic events) can go unnoticed without the presence of a second hit, i.e. the primary CNVs, thus they may be clinically important and relevant to the model.

Table S10. Comparison of frequency of at least two large CNVs (<30 Mb) between cases and population controls

Genomic Disorder	Cases with two hits	Cases without two hits	Controls with second hits	Controls without second hits	Fishers exact p-value	OR	Lower	Upper
15q11.2_del	27	139	18	276	0.00051	2.97	1.52	5.94
16p11.2_distdup	8	20	69	733	0.00257	4.24	1.55	10.51
15q23q24_del	3	2	9	126	0.00444	19.87	2.02	265.66
16p11.2_dup	12	71	21	374	0.00536	3.00	1.28	6.73
3q29_dup	4	14	21	374	0.018	5.05	1.11	18.06
17p13.3_YWHAEdup	3	10	21	374	0.0347	5.30	0.87	22.77
16p12.1_del	9	47	9	126	0.04363	2.67	0.88	8.10
3q29_del	4	16	9	126	0.06721	3.46	0.70	14.31
6p25_dup	3	9	69	733	0.08169	3.53	0.60	14.59
PWS_AS	8	52	9	126	0.10806	2.14	0.68	6.65
17q12_dup	4	31	21	374	0.13557	2.29	0.54	7.41
16p11.2_distdel	4	27	18	276	0.14535	2.26	0.52	7.58
17p13.3_LIS1dup	2	7	69	733	0.18236	3.03	0.30	16.32
16p11.2_Largedup	2	12	21	374	0.18251	2.96	0.30	14.67
16p13.11_dup	8	90	21	374	0.19873	1.58	0.59	3.87
22q11.2_distdup	2	16	21	374	0.26455	2.22	0.23	10.50
15q23q24_dup	1	5	21	374	0.28876	3.54	0.07	33.78
PLP1_dup	1	5	21	374	0.28876	3.54	0.07	33.78
17q12_del	3	23	9	126	0.30156	1.82	0.29	8.04
10q23_del	3	25	9	126	0.33942	1.67	0.27	7.35
15q13.3_smalldup	13	117	69	733	0.3508	1.18	0.58	2.24
22q11.2_dup	6	81	21	374	0.35716	1.32	0.42	3.52
10q23_dup	1	4	69	733	0.36546	2.65	0.05	27.28
17q21.31_dup	1	4	69	733	0.36546	2.65	0.05	27.28
8p23_del	2	16	9	126	0.37989	1.74	0.17	9.57
8p23_dup	2	22	21	374	0.38525	1.62	0.17	7.35

17p13.3_YWHAEdel	1	6	9	126	0.40711	2.31	0.05	22.73
16p13.11_del	4	41	9	126	0.41569	1.36	0.29	5.21
15q13.3_del	7	78	9	126	0.4262	1.26	0.38	3.96
16p11.2_del	10	115	9	126	0.43008	1.22	0.43	3.52
1q21.1_del	8	92	9	126	0.44207	1.22	0.39	3.70
PWS_dup	5	77	21	374	0.47217	1.16	0.33	3.28
WBS_dup	2	37	21	374	0.63219	0.96	0.11	4.20
1q21.1_dup	4	77	21	374	0.64186	0.93	0.22	2.85
Wolf_Hirschhorn	1	16	9	126	0.70626	0.88	0.02	7.10
2q23.1_del	1	19	18	276	0.72447	0.81	0.02	5.70
Potocki-Lupski	1	24	21	374	0.74998	0.74	0.02	5.04
16p11.2_Largedel	1	19	9	126	0.75985	0.74	0.02	5.88
1p36_del	4	74	9	126	0.76892	0.76	0.16	2.83
6p25_del	1	22	18	276	0.77125	0.70	0.02	4.86
15q13.3_dup	1	26	21	374	0.7754	0.69	0.02	4.62
Williams	4	79	9	126	0.80113	0.71	0.15	2.65
22q11.2_DGSdel	8	167	9	126	0.85413	0.67	0.22	2.02
22q13_del	1	58	9	126	0.97604	0.24	0.01	1.82
15q13.3_smalldel	0	7	18	276	1	0.00	0.00	11.51
15q24_del	0	8	9	126	1	0.00	0.00	9.73
15q24_dup	0	4	21	374	1	0.00	0.00	28.34
15q25_del	0	2	9	126	1	0.00	0.00	79.07
15q25_dup	0	4	21	374	1	0.00	0.00	28.34
16p12.1_dup	0	16	21	374	1	0.00	0.00	5.01
17p13.3_Largedel	0	6	9	126	1	0.00	0.00	13.87
17p13.3_LIS1del	0	8	9	126	1	0.00	0.00	9.73
17q21.31_del	0	42	9	126	1	0.00	0.00	1.60
17q23_del	0	6	9	126	1	0.00	0.00	13.87
17q23_dup	0	1	21	374	1	0.00	0.00	688.94

19p13.12_del	0	13	9	126	1	0.00	0.00	5.57
22q11.2_distdel	0	26	9	126	1	0.00	0.00	2.64
22q13_dup	0	3	69	733	1	0.00	0.00	26.03
2q37_del	0	17	9	126	1	0.00	0.00	4.15
2q37_dup	0	2	21	374	1	0.00	0.00	97.37
5q35_dup	0	4	21	374	1	0.00	0.00	28.34
6q16_del	0	1	9	126	1	0.00	0.00	545.65
6q16_dup	0	1	69	733	1	0.00	0.00	412.20
9q34_del	0	18	9	126	1	0.00	0.00	3.90
9q34_dup	0	8	69	733	1	0.00	0.00	6.36
NF1_del	0	9	9	126	1	0.00	0.00	8.47
NF1_dup	0	6	21	374	1	0.00	0.00	16.09
PLP1_del	0	3	9	126	1	0.00	0.00	37.35
Rubinstein_Taybi	0	10	18	276	1	0.00	0.00	7.47
Smith-Magenis	0	31	9	126	1	0.00	0.00	2.19
Sotos	0	14	9	126	1	0.00	0.00	5.13
Wolf-Hirschhorn_dup	0	4	21	374	1	0.00	0.00	28.34

Table S11. Inheritance for second-site variants within autosomes

First CNV/Second CNV	*De novo*	Maternal	Paternal	Total first-site CNVs
De Novo	5	6	4	15
Maternal	3	8	3	14
Paternal	5	8	4	17
Total second-site CNVs	13	22	11	

Table S12. Inheritance pattern of primary CNVs (genomic disorders) and second-site CNVs

	First-hit CNVs (genomic disorders)					Second-site CNVs				
	De Novo	Maternal	Paternal	Unknown	Grand Total	De novo	Maternal	Paternal	Unknown	Grand Total
10q23_del	5	3	5	15	28		1		2	3
10q23_dup		2	1	2	5		1			1
15q11.2_del	1	10	4	151	166	1	5		20	26
15q13.3_del	7	18	8	52	85		1		6	7
15q13.3_dup		6	5	16	27				1	1
15q13.3_smalldel		1		6	7					
15q13.3_smalldup		6	6	118	130	2	1	1	11	15
15q23q24_del	4			1	5	1	1	1		3
15q23q24_dup		1		5	6				1	1
15q24_del	5			3	8					
15q24_dup		1		3	4					
15q25_del				2	2					
15q25_dup	1			3	4					
16p11.2_del	31	18		76	125		1		9	10
16p11.2_distdel	4	6	3	18	31		1	1	2	4
16p11.2_distdup	1	4	1	22	28		1	2	5	8
16p11.2_dup	6	13	8	55	83	2	1		10	13
16p11.2_Largedel	4	2		14	20				1	1
16p11.2_Largedup	2	2	1	9	14		1		1	2
16p12.1_del	1	19	5	31	56	1	5	1	4	12
16p12.1_dup	1	4	2	9	16			1		1
16p13.11_del	5	9	7	24	45			1	3	4
16p13.11_dup	3	18	19	58	98		2	1	6	9
17p13.3_Largedel	2			4	6					
17p13.3_LIS1del				8	8					
17p13.3_LIS1dup	1	3		5	9			1	1	2
17p13.3_YWHAEdel	3			4	7				1	1
17p13.3_YWHAEdup	4	2	2	5	13				3	3

17q12_del	5	3		18	26	1			2	3
17q12_dup	2	6	3	24	35			1	4	5
17q21.31_del	10			32	42					
17q21.31_dup	1		1	3	5				1	1
17q23_del	1			5	6					
17q23_dup	1				1					
19p13.12_del	2			11	13					
1p36_del	9	2		67	78		1		4	5
1q21.1_del	8	15	13	64	100	1	1	1	5	8
1q21.1_dup	10	22	9	40	81	1			4	5
22q11.2_DGSdel	16	2	2	155	175	1	2		6	9
22q11.2_distdel	8			18	26					
22q11.2_distdup	1	3	2	12	18				3	3
22q11.2_dup	2	16	6	62	87	1	1		5	7
22q13_del	17	1		41	59				1	1
22q13_dup			2	1	3					
2q23.1_del	1		1	18	20			1		1
2q37_del	2		1	14	17					
2q37_dup		2			2					
3q29_del	3	1		16	20				4	4
3q29_dup		5	3	10	18	1	2		1	4
5q35_dup		1		3	4					
6p25_del	1	5	7	10	23		1		1	2
6p25_dup		3	3	6	12		2		1	3
6q16_del				1	1					
6q16_dup			1		1					
8p23_del	2	3		13	18				2	2
8p23_dup	2	4	4	14	24		2			2
9q34_del	9			9	18					
9q34_dup	2	3	1	2	8					
NF1_del				9	9					

NF1_dup	1	1	1	3	6					
PLP1_del				3	3					
PLP1_dup	1	1		4	6			1		1
Potocki-Lupski	4			21	25				1	1
PWS_AS	11	1	1	47	60	1	2		6	9
PWS_dup	10	9	2	61	82	1			5	6
Rubinstein_Taybi	1			9	10					
Smith-Magenis	4			27	31					
Sotos	1			13	14					
WBS_dup	5	3	1	30	39			1	2	3
Williams	6			77	83		2		2	4
Wolf_Hirschhorn	1		1	15	17				1	1
Wolf-Hirschhorn_dup	1			3	4					

Table S13. Phenotypic data on individuals with additional rare CNVs

Subject ID	GC25163[a]	GC27875	GC35416	GC36479[a]	GC67345	GC20500
First CNV	1q21.1 del	1q21.1 del	1q21.1 del	1q21.1 del	1q21.1 del	PW/AS del dn
Second CNV	22q11.21 dup mat	47,XYY	3p12.3p11.2 del (chr3:76807356-88278201)	16p11.2 del	3q29 del	1p32.1p31.3 del dn (chr1:59515650-63779925)
Sex	M	M	M	M	M	M
Age	2y	4y	4y8m	10y	8y	3y
Growth percentiles	Wt, Ht, OFC nl	Wt 90th-97th; Ht 97th **(1)**; OFC -1 SD	Wt 3rd **(1);** Ht 50th; OFC -3.2 SD **(1)**	Wt <3rd**(1)**; Ht 5th; OFC nl	FTT **(1)**; Wt 10th; Ht 25th-50th; OFC -2.7 SD **(1)**	Ht, Wt, & OFC Nl
Neurological features						
Developmental delay	Mild delays **(1)**	Mild motor & speech delays **(1)**	Motor & speech delays **(1)**	Motor delay; poor speech **(1)**	IQ 90; speech delay **(1)**	Moderate motor & severe speech delays **(1)**
Behavior problems	-	-	-	Aggression **(1)**	ADHD; some sensory issues **(1)**	-
Tone	Hypotonia **(1)**	Nl	Hypotonia **(1)**	Nl	Nl	Persistent hypotonia **(1)**
Other		Unilateral HL **(1)**				Periventricular porencephalic change, posterior thinning of CC **(1)**
Dysmorphic features	Nondysmorphic	Ptosis; small ears **(1)**	Prominent ear inner helix; prominent knees **(1)**	Midface hypoplasia; epicanthal folds; allergic shiners; Down syndrome-like **(2)**	Bitemporal narrowing; thin nose; epicanthal folds; rotated ears; absent antitragus; small philtrum; high palate **(2)**	Light pigmentation; widow's peak; triangular face; high palate **(2)**
Congenital anomalies	-	Hydronephrosis **(1)**; undescended testicle; inguinal hernia	VSD **(1)**	Hypoplastic patellae; posterior iliac horns **(1)**	-	Undescended testicle
Other features		Strabismus		Strabismus	Hypothyroidism; rectal prolapsed	-
Family history	Mother has psychiatric issues and LD **(1)**	Father had CHD **(1)**	Father has similar ears	Mother has nail patella syndrome and ID **(1)**	Mother has MVP	Cousin with OCA
Total score	**3**	**6**	**6**	**7**	**6**	**5**

[a]Rosenfeld et al., 2012[75]. Phenotypic scores are shown adjacent to the phenotypes observed in each of these individuals.

Subject ID	GC29221	GC22848	GC27397	GC37514	GC57860
First CNV	PW/AS del	PWS dup pat	PWS dup	PWS dup	PWS dup (mosaic)
Second CNV	1p31.1 dup mat (chr1:79829666-80777741)	6q16.1q16.3 del dn (chr6:98471672-100234320)	Xp22.31 del (chrX:6467202-8091950)	2q12.2q12.3 del (chr2:106295688-107769685)	5q35 dup (mosaic) (chr5:178486666-179522156); 18p11.21q11.1 dup (mosaic) (chr18:11690934-17148187)
Sex	F	M	F	M	M
Age	2y1m	21m	8m	11y	2y8m
Growth percentiles	Wt 58th; Ht 18th; OFC -0.7 SD	Wt >99th; Ht >99th; OFC 98th **(2)**	Wt 25th-50th; Ht >97th **(1);** OFC -1.3 SD	Wt 10th-25th; Ht 10th; OFC +0.4 SD	Wt 75th-90th; Ht 50th-75th; OFC -0.8 SD
Neurological features					
Developmental delay	Global **(1)**	Global **(1)**	None yet	Mild ID; global delays **(1)**	Global **(1)**
Behavior problems	-	+, unspecified **(1)**	NA	ASD; Anxiety; ADHD; trichotillomania; Tourette syndrome **(1)**	-
Tone	Hypotonia **(1)**	Hypotonia **(1)**	Nl	Nl	Nl
Other	Nl MRI				
Dysmorphic features	Almond-shaped PF; mild micrognathia; bitemporal narrowing **(1)**	Frontal bossing; deep-set eyes; upslanting PF; protruding ears; widened nasal bridge; bulbous nasal tip; small nares; micrognathia **(2)**	Nondysmorphic	Nondysmorphic	Preauricular pit; frontal bossing; borderline low-set ears **(1)**
Congenital anomalies	-	-	-	-	2-3 toe syndactyly; mottled skin hypopigmentation
Other features	Required G-tube **(1)**	-	-	-	
Family history	Mother had TEF & duodenal atresia; Father had undescended testicle **(2)**	Father has ADHD and auditory processing disorder; mom has Kawasaki syndrome, heart aneurysm **(2)**	NS	NS	Mother has LD **(1)**
Total score	**6**	**9**	**1**	**2**	**3**

Phenotypic scores are shown adjacent to the phenotypes observed in these individuals.

Subject ID	GC26112	GC29386	GC44153	GC5609[b]	GC9460[c]
First CNV	15q13.3 del mat	16p13.11 del pat	16p13.11 del	16p11.2 del dn	16p11.2 del
Second CNV	1q44 del mat (chr1:245985930-247189904); Xp22.31 del (chrX:6472947-8039507)	7q11.22 dup pat (chr7:68274398-70872555); 12q24.32 dup mat (chr12:126798089-127973176)	22q11.2 distal dup; 20q13.33 dup (chr20:61086010-61915632)	Yq12 del pat (chrY:57428366-57747284)	5q21.3q22.2 del (chr5:106638415-112236540)
Sex	F	M	F	M	F
Age	9y3m	1y	14y	7y	22y
Growth percentiles	Wt 75th; Ht 75th; OFC -1.1 SD	NS	Wt 50th-75th; Ht >97th**(1);** OFC unknown	Wt 97th **(1);** Ht 82nd; OFC >97th **(1)**	Wt >97th **(1);** Ht 10th-25th; OFC 50th-75th
Neurological features					
Developmental delay	Mild ID; IQ 56 **(1)**	DD	LD; mild DD **(1)**	IQ 66; speech and motor delays **(1)**	Mild ID **(1)**
Behavior problems	-	NS	Tantrums; self-pinching **(1)**	PDD-NOS; ADHD; outbursts; OCD-like **(1)**	-
Tone	Nl	NS	Nl	Mild hypotonia **(1)**	Hypotonia **(1)**
Other	Mild HL **(1)**			Apraxia; heat intolerance	Epilepsy **(1)**; hypernasal speech
Dysmorphic features	Short philtrum; full lips **(1)**	NS	Tall forehead; ptosis; downturned mouth; retrognathia; long neck **(2)**	Turricocephaly; midface hypoplasia; flat occiput; frontal bossing; boxy, overfolded helices; low-set ears **(2)**	Downslanting PF; low-set, rotated ears; frontal bossing; downturned mouth; unerupted teeth **(2)**
Congenital anomalies	-	NS	Mild scoliosis	Pectus excavatum	-
Other features	-	NS	-	Delayed closure of AF; suspected mitochondrial disorder	Strabismus; FAP
Family history	2 half sibs (NT) with ADHD & behavior problems	Father had DD and LD; mother has dyslexia & memory problems but cognitively normal	Half-brothers with LD or schizophrenia	Father is healthy; brother (NT) has mitochondrial disease **(1)**	NS
Total score	**3**	Not calculated	**5**	**8**	**6**

[b]Previously reported in Rosenfeld et al., 2010[50]. [c]Previously reported Heald et al.[74]. Phenotypic scores are shown adjacent to the phenotypes observed in each of these individuals.

Subject ID	GC23022	GC23391[b]	GC23858	GC28324[b]
First CNV	16p11.2 del	16p11.2 del	16p11.2 del	16p11.2 del
Second CNV	16p11.2 distal dup	Xp22.31 dup mat (chrX:6472947-8039507)	15q13.3 del	1q25.2q25.3 del mat (chr1:178294383-178749915)
Sex	M	M	M	M
Age	4.5m	8y8m	10y	10y9m
Growth percentiles	Wt <3rd; Ht <3rd **(1);** OFC <3rd **(1)**	Wt >97th **(1);** Ht 50th; OFC 50th	IUGR **(1);** Wt 25th-50th; Ht 25th-50th; OFC unknown	Wt 25th; Ht 50th; OFC 90th
Neurological features				
Developmental delay	DD **(1)**	Mild global delays **(1)**; low-average cognition	Global; greatest delays in speech **(1)**	Global **(1)**
Behavior problems	NA	ADHD; frustration **(1)**	Stereotypies; aggression; ADHD **(1)**	PDD-NOS; delayed sleep; ADHD; aggression **(1)**
Tone	Hypotonia **(1)**	Nl	Nl	Slightly decreased **(1)**
Other	Borderline Chiari I **(1)**; mild prominence of ventricular system; neonatal abstinence syndrome with seizure-like activity **(1)**; tongue fasciculations		Poor articulation; seizures at 2y **(1)**	Apraxia
Dysmorphic features	Irregular skull; high anterior hairline; frontal bossing; telecanthus; upslanting PF; ptosis; blue sclera; flat nasal bridge; severe maxillary hypoplasia; short septum; deep and long philtrum; thick lips; wide mouth; high palate; protruding tongue; short neck **(2)**	Brachycephaly; mild ptosis; cleft in columella; downturned mouth; dental crowding; high palate; low posterior hairline; short neck; hypoplastic pinnae; Darwin's tubercles **(2)**	Small, pointed chin; large ears; high anterior hairline; frontal bossing; positional plagiocephaly **(2)**	Small mouth; dental crowding; small, pointed chin; malar hypoplasia; synophrys; long PF; iris heterochromia; thickened ears; long philtrum; short nose; thin upper lip; short palate; nuchal webbing; low posterior hairline **(2)**
Congenital anomalies	Hypertrophic cardiomyopathy **(1)**; inguinal hernias	Iris colobomas **(1)**	-	Narrow chest; prominent scapulae; sloping shoulders; thoracic kyphosis; valgus great toes
Other features	History of multiple prenatal exposures; Suspected fatty acid oxidation defect	-	-	-
Family history	Maternal substance abuse	Mother and father have LD **(2)**	Mother and father have LD; father has stutter **(2)**	Mother has depression; father has ADHD, depression, OCD, LD, unusual speech; sister has ADHD; maternal and paternal family histories of psychiatric disorders **(3)**
Total score	**9**	**8**	**8**	**8**

[b]Previously reported in Rosenfeld et al., 2010[50]. Phenotypic scores are shown adjacent to the phenotypes observed in each of these individuals.

Subject ID	GC36901	GC49331	GC47954	GC51237
First CNV	16p11.2 del dn	16p11.2 del dn	16p11.2 del	16p11.2 del
Second CNV	8p22 dup mat (chr8:16556893-17088556)	3q12.3q13.31 del dn (chr3:102541653-115356619)	2p14 dup mat (chr2:65498785-67148304)	12p13.33 del (chr12:1034078-1772563)
Sex	F	M	F	M
Age	8y11m	10.5y	4y9m	8y11m
Growth percentiles	Wt 90th; Ht 75th; OFC +2.3 SD **(1)**	Wt 75th-90th; Ht 75th; OFC 75th	Wt 60th; Ht 15th; OFC 50th	Wt 50th; Ht 25th; OFC +1.0 SD
Neurological features				
Developmental delay	Global **(1)**	Global delays; IQ in extremely low range with borderline performance and processing speed **(1)**	Expressive language delay; special ed preschool **(1)**	Severe speech delays; LD **(1)**
Behavior problems	ADHD; mood swings **(1)**	ASD **(1)**	Hyperactive **(1)**	Fidgety and active
Tone	Nl	Nl	Nl	Nl
Other	Poor coordination; difficulty following directions	Poor balance		
Dysmorphic features	High anterior hairline; frontal bossing; downslanting PF; arched eyebrows; high palate **(2)**	Facial asymmetry; laterally displaced inner canthi; wrinkled earlobes; long nasal root; frontal bossing; midface hypoplasia; small chin; prominent gums with large central incisors **(2)**	Mild jaw asymmetry	Long PF; midface hypoplasia; prominent ears with absence of antihelical fold **(2)**
Congenital anomalies	Pectus excavatum; 2-3 toe syndactyly	Mild left ventricular hypertrophy **(1)**; scoliosis requiring surgery **(1)**; 2-3 toe syndactyly	Subglottic stenosis; possible tracheolaryngealmalacia **(1)**	Retinal coloboma; CP with fistula **(2)**
Other features	Strabismus	-	Required G-tube feedings **(1)**	-
Family history	Father and brother have bipolar disorder **(2)**	Mother with possible scoliosis **(1)**	Mother is healthy; maternal half sister (2p14 dup + 15q24.2 dup) with cleft palate and short stature	Father had LD **(1)**; mother has seizures at 29y **(1)**; paternal family history of CP
Total score	**7**	**7**	**4**	**7**

Phenotypic scores are shown adjacent to the phenotypes observed in each of these individuals.

Subject ID	GC61119	GC21897	GC24333	GC26056	GC27819	GC38700
First CNV	16p11.2 del	16p11.2 dup	16p11.2 dup dn	16p11.2 dup	16p11.2 dup dn	16p11.2 dup
Second CNV	13q12.12 del (chr13:22442669-23767410); Xp22.33p22.32 dup (chrX:943551-4369605)	5p15.33p15.2 del (chr5:131946-8452568); 5p15.2 dup (chr5:8511592-9888817)	11q13.2q25 dup dn (chr11:75265230-134431368)	4q28.1q28.2 dup (chr4:128184801-129319376)	Xp22.33 del mat (chrX:793600-1466649); Yp11.32 pat (chrY:701-523227)	22q11.21 dup
Sex	F	F	M	M	M	F
Age	9.5m	9y1m	1y3m	9y8m	3.5y	2m
Growth percentiles	Wt <3rd **(1);** Ht 3rd-10th; OFC 25th-50th	Wt 10th-25th; Ht 50th-75th; OFC +0.2 SD	IUGR **(1)**; Wt 75th; Ht 3rd-10th	Wt & Ht 50th-75th; OFC -1.2 SD	Ht <3rd; OFC nl **(1)**	FTT: Ht <3rd; OFC <3rd **(2)**
Neurological features						
Developmental delay	Motor delay **(1)**	DD, IQ 83 **(1)**	Global **(1)**	Global **(1)**	-	None yet
Behavior problems	NA	ADHD **(1)**	NA	ASD; aggression; ADHD **(1)**	-	NA
Tone	Nl	Hypotonia **(1)**	Hypotonia **(1)**	Nl	Nl	Nl
Other		Mild pontine hypoplasia **(1)**	Agenesis of CC; bilateral HL; seizures **(3)**		Bilateral HL **(1)**	
Dysmorphic features	Brachycephaly; midface hypoplasia; downturned mouth; low-set ears; long & tapered fingers; abnormal thumb **(2)**	Short forehead; epicanthal folds; broad nasal bridge **(2)**	Round face; frontal bossing; epicanthal folds; hypertelorism; broad nose; shallow nasal bridge; micrognathia; preauricular pits **(2)**	Hypertelorism; downslanting PF; prominent nose; prominent ears **(2)**	Overfolded superior helices; epicanthal folds; grey sclera; narrow palate **(2)**	Hypertelorism; long philtrum; broad nasal bridge; prominent antihelix; epicanthal folds; ptosis; bitemporal narrowing **(2)**
Congenital anomalies	Scoliosis; unilateral renal agenesis **(1)**	-	Atrial septal defect **(1)**; inguinal hernias	-	Langer mesomelic dysplasia with Madelung deformity **(1)**	PDA **(1)**
Other features		-	-	-	-	-
Family history	NS (adopted)	NS	Parents healthy	Brother has CHARGE (no dups) **(1)**	Mother has Madelung deformity; father has Leri-Weill dyschondrosteosis **(2)**	Parents healthy; two sisters with LD, one with PFO **(1)**
Total score	**5**	**6**	**9**	**5**	**7**	**6**

Phenotypic scores are shown adjacent to the phenotypes observed in each of these individuals.

Subject ID	GC39824	GC51323	GC66870	GC67970	GC36941
First CNV	16p11.2 dup	16p11.2 dup	16p11.2 dup mat	16p11.2 dup	17p13.3 dup mat (chr17:769429-1503504)
Second CNV	1q31.3 del (chr1:193467178-195327851)	10q22.3q23.2 del (chr10:81674576-88837361)	21q11.2q21.3 del (chr21:14406100-27742431)	22q11.21q11.22 del (chr22:19408946-20797677)	13q12.3q13.2 del (chr13:29128098-33885086)
Sex	F	M	F	M	M
Age	12y	16y	11m	2y4m	9y
Growth percentiles	FTT **(1)**; Wt 10th; Ht 3rd-10th; OFC -2.2 SD **(1)**	Ht 25th-50th	Ht 3rd-10th **(1)**; OFC -2.2 SD **(1)**	Ht <3rd; Wt <3rd; OFC -4.8 SD **(2)**	FTT; microcephaly **(2)**
Neurological features					
Developmental delay	Mild ID, IQ 68 **(1)**	Nonverbal LD; speech delay **(1)**	Global **(1)**	Global; 22m level at 27m **(1)**	Global **(1)**
Behavior problems	ODD; PTSD **(1)**	Attention problems **(1)**	NA	-	Anger management issues **(1)**
Tone	Nl	Hypotonia **(1)**	Mixed low & high **(1)**	Hypotonia **(1)**	Nl
Other			Staring/jerking spells when excited **(1)**	Epilepsy **(1)**	Unilateral HL **(1)**
Dysmorphic features	Metopic prominence; hypertelorism; prominent nose with depressed columella; small hands **(2)**	Triangular face; long nose; upslanting PF; epicanthal folds; malar hypoplasia; retrognathia **(2)**	Low-set ears; broad nasal bridge; high palate; hypertelorism **(2)**	Epicanthal folds; short, downslanting PF; small ears; bulbous nose; smooth philtrum, thin upper lip; synophrys; high palate; small mouth **(2)**	Upslanting PF, pointed chin, large ears, midface hypoplasia; high palate; underbite **(2)**
Congenital anomalies	-	Large VSD; pulmonary valve stenosis; left pulmonary artery hypoplasia **(1)**; restricted extension & pronation at knees & elbows; hypospadias; inguinal hernia	Sacral dimple	Bilateral ectrodactyly; VSD; imperforate anus; hypospadias; small testes **(3)**	-
Other features	-	Raynaud's disease	Early teeth eruption (3m)	Strabismus; prenatal cocaine exposure	-
Family history	Mother has ID **(1)**; maternal half sibs have DD	Father with TOF **(1)**	Mother and brother have bipolar disorder; brother also has ADHD **(2)**	Mother has addiction problems; father incarcerated **(2)**	Mother has CL/P, unilateral HL, LD, mild dysmorphisms **(1)**
Total score	**7**	**7**	**9**	**12**	**8**

Phenotypic scores are shown adjacent to the phenotypes observed in each of these individuals.

Subject ID	GC14963	GC28231	GC24512	GC27522	GC43248	GC26098
First CNV	17p13.3 dup (chr17:1235314-2183796)	17q12 del dn	17q12 dup mat	17q12 dup	17q21.31 dup	Trisomy 21
Second CNV	16p13.11 dup	Xp22.33 dup mat (chrX:249740-1435195)	15q21.1 dup (chr15:43533276-44587071)	20p12.3p12.2 (chr20:8346087-9364411)	16p11.2 del	PW/AS dup
Sex	M	F	F	M	F	F
Age	13y	18y	13y	14y8m	21y	4y3m
Growth percentiles	NS	NS	Wt & Ht nl; mild macrocephaly **(1)**	Ht 90th; OFC +1.0 SD	Wt >97th **(1);** Ht 3rd-10th; OFC -1.9 SD **(1)**	Wt 3rd; Ht <3rd **(1)**
Neurological features						
Developmental delay	NS	NS	Moderate to severe ID **(1)**	In special ed; speech delay **(1)**	Mild ID; global delays **(1)**	DD; DQ 1y at 3y; nonverbal **(1)**
Behavior problems	NS	NS	Anxiety **(1)**	ADHD; Tourette syndrome **(1)**	-	Autistic features; meets 6/12 DSM-IV criteria **(1)**
Tone	NS	NS	Hypotonia **(1)**	Nl	Slightly low **(1)**	Hypotonia **(1)**
Other			Seizures **(1);** muscle weakness	Movement disorder		Visual impairment
Dysmorphic features	NS	NS	Nondysmorphic	Nondysmorphic	Small mouth; low-set ears; low posterior hairline**;** cranium smaller for size **(2)**	Low-set ears; short and thick neck **(1)**
Congenital anomalies	2 small VSDs and mild enlargement of aorta; bilateral Morgagni hernias; hiatal hernia; T12 hemivertebra	MRKH syndrome; polycystic kidneys	-	-	Leg length discrepancy; PIP finger contractures **(1)**; 2-3 toe syndactyly; scoliosis	VSD **(1)**
Other features	NS	NS	-	Osteochondroma on right femur **(1)**	Psoriatic arthritis	GERD; cataracts **(1)**
Family history	NS	NS	NS	Mother and twin brother with Tourette syndrome **(2)**; HL in father, post-infection	NS	Two brothers have ASD and 15q duplication **(1)**
Total score	Not calculated	Not calculated	**5**	**5**	**7**	**8**

Phenotypic scores are shown adjacent to the phenotypes observed in each of these individuals.

Subject ID	GC24222	GC33289	GC35334	GC38025	GC52716	GC51723
First CNV	22q11.21 del dn	22q11.21 del	22q11.21 del	22q11.21 del dn	22q11.21 del	22q11.21 del
Second CNV	1p31.1 del mat (chr1:77111613-79777881)	8p23.2 dup (chr8:3560165-4820819)	3q23 dup (chr3:140543531-141271442)	13q34 dup mat (chr13:113086471-113644014)	16p13.11 dup	2q11.2 del (chr2:96107157-97035122)
Sex	M	M	M	F	F	M
Age	6y	3y3m	11m	2m (deceased)	2y3m	3y4m
Growth percentiles	FTT; microcephalic **(2)**	Ht & Wt <3rd; OFC -2.2 SD **(2)**	Wt <3rd **(1)**; Ht 3rd; OFC -1.6 SD	Wt, Ht, OFC nl	Ht, Wt, & OFC <3rd **(2)**	Wt 97th; OFC 97th **(2)**
Neurological features						
Developmental delay	Global, with severe speech delay **(1)**	Speech delay: nonverbal **(1)**	None yet	NA	Global **(1)**	Speech delay **(1)**
Behavior problems	ADHD: ODD; autistic features **(1)**	Sleep issues **(1)**	NA	NA	-	-
Tone	Hypotonia **(1)**	Nl	Nl	NS	Nl	Nl
Other			Moderate mixed HL **(1)**	NS		Frontal lobe atrophy; HL **(2)**
Dysmorphic features	Midface hypoplasia; wide central incisors **(1)**	Small jaw; frontal bossing; flat nasal bridge; downslanting PF; nipples flat, small, and wide-spaced **(2)**	Retrognathia; small, cupped, malformed right ear **(1)**	Low-set ears with folded helices **(1)**	Low-set ears; short neck; small nose; upslanting PF; shallow nasal bridge; small mouth; micrognathia **(2)**	Micrognathia, low-set ears; blepharophimosis **(2)**
Congenital anomalies	CP **(1)**; VPI; sacral dimple; triphalangeal thumbs **(1)**; right aortic arch **(1)**; hypospadias; umbilical hernia; small testes	Abnormal heart valves **(1)**; inguinal hernia; overlapping and small toes	CP; left clubfoot; right multicystic, dysplastic kidney **(2)**	Severe CHD (TOF, absent pulmonary valve, VSD) butterfly vertebrae, 13 rib pairs; supernumerary nipple **(2)**	Blocked lacrimal ducts	Cryptorchidism
Other features	-	Mild hypothyroidism	Exotropia		Strabismus; chronic lung disease (prematurity)	Strabismus; retinopathy **(1)**; astigmatism
Family history	Mother has LD **(1)**; maternal half sib has CHD and contractures	Mom's ht @ 25th; dad's ht @ 10th	Father has CP and LD; mother has renal problems **(2)**	Noncontributory	Mother has bicornate uterus **(1)**	Parents healthy
Total score	**10**	**7**	**7**	**3**	**6**	**8**

Phenotypic scores are shown adjacent to the phenotypes observed in each of these individuals.

Subject ID	GC31576	GC32825	GC21414	GC36775
First CNV	22q11.21 dup dn	22q13.33 del (chr22:49469317-49525124)	WBS del dn	WBS del dn
Second CNV	17q12 del dn	9p23 dup (chr9:10105547-12021787)	20q11.21 dup mat (chr20: 29329161-30057216)	1p22.2p22.1 dup mat (chr1: 91839688-92600349)
Sex	M	M	F	F
Age	26m	18y	2y	3y2m
Growth percentiles	Ht 30th; OFC +1.0 SD	Short stature **(1)**	Wt 25th-50th; Ht 75th; OFC 5th-10th	Wt 30th; Ht 30th; OFC 40th
Neurological features				
Developmental delay	Motor delays **(1)**	DD; expressive language severely limited **(1)**	DD: mild motor delay, speech delay, hoarse voice **(1)**	Moderate-severe global DD **(1)**; severe speech delay; at 3y testing 9-13m developmentally; below average cognition
Behavior problems	-	Autism; ADHD; anxiety **(1)**	-	-
Tone	Hypotonia **(1)**	Mild hypotonia **(1)**	Nl	Mild hypotonia **(1)**
Other	Unsteady gait	Focal epilepsy; mild asymmetry of hippocampi; small gliosis in frontal lobe; absence of neural hypophysis **(2)**		Acquired Chiari I malformation but initially small cerebellum **(1);** gait ataxia,
Dysmorphic features	Nondysmorphic	Nondysmorphic	Periorbital fullness; flat nasal bridge; upturned nose; bilateral epicanthal folds; stellate irides, wide-spaced small teeth; full lower lips **(2)**	Broad brow; bitemporal narrowing; periorbital fullness; short nose; full nasal tip; malar hypoplasia; long philtrum; full lips; wide mouth **(2)**
Congenital anomalies	Cystic kidneys **(1)**; vesicoureteral reflux	-	CHD: supravulvular aortic & pulmonic stenosis, hypoplastic pulmonary arteries, moderate MVP, bilateral ventricular hypertrophy **(1)**	Coarcation of aorta **(1)**
Other features	Vertical nystagmus	Delayed puberty	Ankyloglossia; deceased after a post-surgical stroke	Post-surgical cranial neuropathies; esotropia; G-tube; GERD
Family history	Parents healthy	Noncontributory	Brother with mild speech delay; father with tall stature, LD, manic depressive illness and MVP **(2)**	Mother, father, and twin sister are healthy
Total score	**3**	**6**	**6**	**6**

Phenotypic scores are shown adjacent to the phenotypes observed in each of these individuals.

Subject ID	GC40354	GC37873	GC24219[a]
First CNV	WBS del dn	WBS dup	WBS dup pat
Second CNV	16p13.11 dup mat	1p36.33p36.32 dup (chr1:1989073-3233592)	1q21.1 del pat
Sex	M	M	F
Age	14y	4y10m	2y8m
Growth percentiles	SGA; Wt >95th**(1);** Ht 10th-25th; OFC +1.6 SD	Wt >95th**(1);** Ht 25th; OFC +4.0 SD **(1)**	Wt >99th **(1)**; Ht 61st; OFC 50th
Neurological features			
Developmental delay	Moderate ID; decreased speech **(1)**	DD; poor speech **(1)**	Severe speech delays **(1)**
Behavior problems	Stereotypies; usually quiet and shy but sometimes overly friendly; noise aversion **(1)**	-	-
Tone	Nl	NS	Hypotonia **(1)**
Other	Nl MRI	Ptosis	Febrile seizure; unilateral HL **(1)**; high pain tolerance
Dysmorphic features	Low anterior hairline; short philtrum; full lips; skin tags on neck; spots on tongue **(2)**	Frontal bossing; low-set ear with notched helix; broad nasal root; prominent central incisors **(2)**	Bilateral ptosis
Congenital anomalies	Radioulnar synostosis; PIP finger camptodactyly **(2)**	-	Duane syndrome; PDA **(1)**
Other features	-	-	Hemihypertrophy; chronic low-grade fevers
Family history	Mother is healthy	Father macrocephalic; mother has similar ears	Father has ADHD, congenital cataracts, chronic fevers, speech delay **(1)**
Total score	**7**	**4**	**6**

[a]Rosenfeld et al., 2012[75]. [b]Previously reported by Rosenfeld et al., 2010[50]. [c]Previously reported Heald et al.[74].

+: feature present; -: feature absent; ADHD: attention deficit hyperactivity disorder; ASD: autistic spectrum disorder; CC: corpus callosum; CHD: congenital heart defect; CL/P: cleft lip and palate; CP: cleft palate; DD: developmental delay; del: deletion; dn: *de novo;* dup: duplication; FAP: familial adenomatous polyposis; FTT: failure to thrive; GERD: gastroesophogeal reflux disease; HL: hearing loss; ht: height; ID: intellectual disability; IQ: intelligence quotient; IUGR: intrauterine growth retardation; LD: learning disability; m: months; mat: maternal; MRI: magnetic resonance imaging; MRKH: Mayer-Rokitansky-Kuster-Hauser syndrome; MVP: mitral valve prolapse; NA: not applicable; nl: normal; NT: not tested; NS: not specified; OCD: obsessive compulsive disorder; ODD: oppositional defiant disorder; OFC: occipitofrontal circumference; pat: paternal; PDA: patent ductus arteriosus; PDD-NOS: pervasive developmental disorder, not otherwise specified; PF: palpebral fissures; PFO: patent foramen ovale; PIP: proximal interphalangeal; PTSD: posttraumatic stress disorder; SD: standard deviation; SGA: small for gestational age; TEF: tracheoesophageal fistula; TOF: tetralogy of Fallot; VPI: velopharyngeal insufficiency; VSD: ventricular septal defect; wt: weight; y: years

Table S14. Checklist for objective evaluation of clinical features

Modified de Vries scoring (this study)	Score
Dysmorphic facial features	max 2
Microcephaly/macrocephaly	1
Growth	max 1
FTT/IUGR/short stature	1
Tall stature	1
Obesity	1
Developmental delay/motor delay/speech delay	1
Abnormal behaviors	max 1
ADHD	1
Schizophrenia	1
Aggression	1
Autism	1
Sleep disturbance	1
Hypotonia/Hypertonia	1
Epilepsy/seizures	1
Congenital anomalies	max 3
MRI/brain abnormalities	1
Kidney and urinary tract defects	1
Musculoskeletal features	1
Cardiac defects	1
Congenital diaphragmatic hernia	1
Cataracts	1
Hearing loss	1
Coloboma	1
Cleft lip and/or palate	1
Family history	max 3
Father	1
Mother	1
Full sibling(s)	1
TOTAL	max 14

de Vries Scoring	Score
Mild-Moderate developmental delay	1
Severe developmental delay	2
Pre-natal onset growth retardation	2
Post-natal growth abnormalities	max 2
Microcephaly	1
Short stature	1
Macrocephaly	1
Tall stature	
≥2 Facial dysmorphic features	2
Non-facial dysmorphism and congenital abnormalities	1-2
Family history of MR	1
TOTAL	10

Please note the phenotypic scoring system has been modified from de Vries et al.[76]. Short stature was defined as height <5th percentile, IUGR/growth retardation defined as <5th percentile, obesity defined as weight >95th percentile, and tall stature defined as height >95th percentile. Dysmorphic features include hypertelorism, nasal abnormalities, eye abnormalities, dental anomalies, asymmetry of face, midface hypoplasia, high arched palate, chin anomalies, palpebral fissure anomalies, features of the lip and philtrum, malar bones, shape of face, and jaw abnormalities. Mild dysmorphic features get 1 point.

Table S15. Penetrance of clinical features in individuals with one CNV compared to those with two CNVs

	16p11.2 duplication		16p11.2 deletion		1q21.1 deletion		16p12.1 deletion	
	One CNV	Two CNVs	One CNV	Two CNVs	One CNV	Two CNVs	One CNV	Two CNVs
Facial features	0.800	1.000	0.625	0.923	0.796	0.800	0.813	1.000
Microcephaly	0.300	0.500	0.000	0.154	0.519	0.600	0.438	0.143
Macrocephaly	0.000	0.000	0.125	0.154	0.000	0.000	0.000	0.000
Growth retardation/IUGR/short stature	0.600	0.625	0.1875	0.385	0.407	0.600	0.438	0.286
Obesity	0.100	0.000	0.125	0.308	0.074	0.200	0.000	0.143
Developmental delay/intellectual disability features								
Developmental delay/motor delay	0.600	0.625	0.6875	0.846	0.481	0.500	0.625	0.857
Speech and expressive language delay	0.700	0.625	0.75	0.846	0.130	0.500	0.625	0.714
Intellectual disability	0.200	0.125	0.3125	0.462	0.204	0.200	0.188	0.143
Behavioral abnormalities								
Autism spectrum disorder	0.100	0.125	0.125	0.231	0.093	0.000	0.125	0.000
Other abnormal behaviors	0.500	0.500	0.5625	0.538	0.185	0.300	0.438	0.286
Hypotonia	0.300	0.500	0.3125	0.385	0.204	0.600	0.313	0.429
Hypertonia	0.100	0.125	0.0625	0.000	0.019	0.000	0.063	0.143
Epilepsy/seizures	0.000	0.375	0.0625	0.231	0.130	0.000	0.188	0.571
Congenital anomalies								
MRI/brain abnormalities	0.400	0.250	0.1875	0.077	0.111	0.000	0.063	0.429
Kidney defects	0.400	0.125	0.250	0.077	0.093	0.100	0.250	0.143
Musculoskeletal features	0.200	0.125	0.125	0.231	0.278	0.100	0.125	0.143
Cardiac defects	0.100	0.500	0.1875	0.154	0.204	0.500	0.375	0.286
Congenital diagphragmatic hernia	0.100	0.000	0.000	0.000	0.000	0.000	0.000	0.000
Hearing loss	0.000	0.125	0.125	0.000	0.056	0.200	0.125	0.143
Family history	0.900	0.750	0.4375	0.615	0.296	0.400	0.625	0.857
Father	0.500	0.250	0.125	0.385	0.185	0.200	0.313	0.286
Mother	0.500	0.375	0.3125	0.462	0.093	0.200	0.438	0.857
siblings	0.500	0.375	0.1875	0.231	0.130	0.000	0.125	0.286

Table S16. Significantly enriched functional categories for genes within first hits and second-site only hits

Row Labels	NonSynSecHits	NonSynFirstHits	SynFirstHits	SynSecHits
Antigen Presentation (min p-value)	0.0316	0.423	0.371	0.0696
proliferation	0.0316	-	-	-
Behavior (min p-value)	0.252	0.423	0.00991	0.0777
anxiety	-	-	0.0211	-
behavior	-	0.423	0.0261	-
learning	-	0.423	0.0261	-
panic-like anxiety	-	-	0.00991	-
Cancer (min p-value)	0.000591	0.0216	0.0626	0.0682
cancer	0.0145	0.0216	0.313	-
carcinoma	0.102	0.0269	0.303	-
neoplasia	0.0145	0.0316	0.262	-
solid tumor	0.0694	0.0248	0.303	-
tumorigenesis	0.000591	0.0244	0.301	-
Carbohydrate Metabolism (min p-value)	0.158	0.423	0.0487	0.0696
release	-	-	0.0487	-
Cardiovascular Disease (min p-value)	0.234	0.0216	0.0146	0.0696
DiGeorge syndrome	-	0.0226	-	-
mitral regurgitation	-	-	0.0458	-
stroke	-	0.0216	0.0307	-
Williams-Beuren syndrome	-	-	0.0146	-
Cardiovascular System Development and Function (min p-value)	0.128	0.423	0.0346	0.0682
cardiac output	-	-	0.0346	-
Cell Death (min p-value)	0.0145	0.423	0.371	0.0682
apoptosis	0.0145	0.423	0.371	0.0696
cell death	0.0145	0.423	0.371	0.0682
Cell Morphology (min p-value)	0.0745	0.423	0.0231	0.0696
blebbing	-	-	0.0283	-
branching	-	-	0.0231	-
Cell Signaling (min p-value)	0.185	0.423	0.0492	0.0737
accumulation	-	0.423	0.0492	-
Cell-To-Cell Signaling and Interaction (min p-value)	0.0286	0.25	0.0184	0.0682
cell-cell adhesion	0.0286	-	-	-
contact repulsion	-	-	0.0184	-
Cellular Assembly and Organization (min p-value)	0.0785	0.323	0.0111	0.0696
branching	-	-	0.0231	-
neuritogenesis	0.171	-	0.0111	-
Cellular Development (min p-value)	0.0145	0.423	0.0231	0.0682
branching	-	-	0.0231	-
developmental process	0.0321	-	0.371	-

differentiation	0.0145	0.423	0.371	0.0682
Cellular Function and Maintenance (min p-value)	0.0179	0.359	0.139	0.0696
homeostasis	0.0179	0.423	0.371	-
Cellular Growth and Proliferation (min p-value)	0.0146	0.25	0.262	0.0682
proliferation	0.0146	0.25	0.262	0.0696
Cellular Movement (min p-value)	0.0276	0.359	0.0184	0.0696
contact repulsion	-	-	0.0184	-
migration	0.0276	0.423	0.371	0.0696
Connective Tissue Disorders (min p-value)	0.0157	0.423	0.165	0.0696
osteoarthritis	0.0157	-	-	-
Developmental Disorder (min p-value)	0.0145	0.00169	7.78E-05	0.0696
brachydactyly mental retardation syndrome	-	0.0366	0.0146	-
DiGeorge syndrome	-	0.0226	-	-
Down's syndrome	0.0145	-	-	-
macrocephaly	-	0.00169	-	-
mental retardation	-	-	7.78E-05	-
Prader-Willi syndrome	-	0.423	0.0146	-
Williams-Beuren syndrome	-	-	0.0146	-
X-linked mental retardation	-	-	0.0146	-
Embryonic Development	0.0145	0.423	0.0531	0.0682
development	0.0145	0.423	0.0531	0.0696
organogenesis	0.0145	0.423	0.288	0.0696
Endocrine System Disorders	0.307	0.423	0.0146	0.0696
hypercalciuria	-	-	0.0211	-
Williams-Beuren syndrome	-	-	0.0146	-
Gene Expression	0.0459	0.423	0.316	0.0893
transcription	0.0459	-	-	-
Genetic Disorder	0.0145	0.0216	1.58E-07	0.0696
alcoholism	-	0.423	0.0187	-
Alzheimer's disease	-	-	0.0346	-
anorexia nervosa	-	-	0.0211	-
attention deficit hyperactivity disorder	-	-	0.0216	-
bipolar I disorder	-	-	0.0146	-
brachydactyly mental retardation syndrome	-	0.0366	0.0146	-
DiGeorge syndrome	-	0.0226	-	-
Down's syndrome	0.0145	-	-	-
mental retardation	-	-	7.78E-05	-
osteoarthritis	0.0157	-	-	-
panic disorder	-	-	0.0146	-
Prader-Willi syndrome	-	0.423	0.0146	-
schizoaffective disorder	-	-	0.00329	-
schizophrenia	-	0.423	0.00678	-
schizophreniform psychosis	-	-	0.0487	-

stroke	-	0.0216	0.0307	-
Williams-Beuren syndrome	-	-	0.0146	-
X-linked hereditary disease	-	-	1.58E-07	-
X-linked mental retardation	-	-	0.0146	-
Hematological System Development and Function	0.0145	0.281	0.139	0.0682
differentiation	0.0145	-	-	0.0696
hematopoiesis	0.0321	-	-	-
proliferation	0.0316	-	-	0.0696
quantity	0.0408	0.423	-	0.0682
Hematopoiesis	0.0145	0.281	0.139	0.0696
differentiation	0.0145	-	-	0.0696
hematopoiesis	0.0321	-	-	-
Immune Cell Trafficking	0.0276	0.423	0.288	0.0696
migration	0.0276	-	-	-
Inflammatory Disease	0.0157	0.423	0.274	-
osteoarthritis	0.0157	-	-	-
Inflammatory Response	0.0316	0.25	0.0707	0.0682
proliferation	0.0316	-	-	-
Lipid Metabolism	0.0145	0.423	0.0413	0.0696
dephosphorylation	-	-	0.0413	-
efflux	0.0145	-	-	-
release	0.205	-	0.0487	-
translocation	0.0284	-	0.371	0.0696
Molecular Transport	0.0145	0.0366	0.0487	0.0696
accumulation	-	0.423	0.0492	0.0696
efflux	0.0145	0.423	-	0.0893
release	0.205	0.423	0.0487	-
translocation	0.0284	0.423	0.371	0.0696
transport	0.252	0.0366	0.288	0.0737
Nervous System Development and Function	0.0886	0.359	0.0111	0.0682
branching	-	-	0.0231	-
contact repulsion	-	-	0.0184	-
neuritogenesis	0.171	-	0.0111	-
Neurological Disease	0.112	0.00169	7.78E-05	0.0696
Alzheimer's disease	-	-	0.0346	-
attention deficit hyperactivity disorder	-	-	0.0216	-
bipolar I disorder	-	-	0.0146	-
brachydactyly mental retardation syndrome	-	0.0366	0.0146	-
delirium	-	0.423	0.0033	-
dementia	-	0.423	0.0216	-
dyssomnia	-	0.423	0.0146	-
epilepsy	-	-	0.0287	-
epileptic seizure	-	-	0.0243	-

insomnia	-	-	0.0184	-
macrocephaly	-	0.00169	-	-
mental retardation	-	-	7.78E-05	-
neurodegenerative disorder	-	0.423	0.0107	-
psychomotor agitation	-	-	0.0287	-
schizoaffective disorder	-	-	0.00329	-
schizophrenia	-	0.423	0.00678	-
schizophreniform psychosis	-	-	0.0487	-
sedation	-	-	0.0399	-
sleep disorder	-	-	0.0112	-
stroke	-	0.0216	0.0307	-
X-linked mental retardation	-	-	0.0146	-
Nucleic Acid Metabolism	0.307	0.423	0.0492	0.0696
accumulation	-	0.423	0.0492	-
Nutritional Disease	-	-	0.0211	-
anorexia nervosa	-	-	0.0211	-
Organ Development	0.0145	0.423	0.0531	0.0696
development	0.0145	0.423	0.0531	0.0696
organogenesis	0.0145	0.423	0.288	0.0696
Organismal Development	0.0145	0.423	0.0531	0.0682
development	0.0145	0.423	0.0531	0.0696
organogenesis	0.0145	0.423	0.288	0.0696
Organismal Injury and Abnormalities	0.19	0.253	0.000555	0.0696
fibromyalgia	-	-	0.0211	-
intracranial hemorrhage	-	-	0.000555	-
postoperative pain	-	-	0.0107	-
subarachnoid hemorrhage	-	0.423	0.0033	-
Williams-Beuren syndrome	-	-	0.0146	-
Post-Translational Modification	0.0368	0.423	0.371	0.0696
cleavage	0.0368	-	-	0.0777
Protein Degradation	0.0368	-	-	0.0777
cleavage	0.0368	-	-	0.0777
Protein Synthesis	0.0368	0.423	0.371	0.0696
cleavage	0.0368	-	-	0.0777
Psychological Disorders	0.267	0.423	0.00329	-
addiction	-	0.423	0.0146	-
alcoholism	-	0.423	0.0187	-
anorexia nervosa	-	-	0.0211	-
attention deficit hyperactivity disorder	-	-	0.0216	-
bipolar I disorder	-	-	0.0146	-
dyssomnia	-	0.423	0.0146	-
generalized anxiety disorder	-	-	0.0261	-
insomnia	-	-	0.0184	-

panic disorder	-	-	0.0146	-
psychosis	-	-	0.0146	-
schizoaffective disorder	-	-	0.00329	-
schizophrenia	-	0.423	0.00678	-
schizophreniform psychosis	-	-	0.0487	-
sleep disorder	-	-	0.0112	-
substance-related disorder	-	0.423	0.0111	-
Skeletal and Muscular Disorders (min p-value)	0.0157	0.0216	0.0146	0.0696
brachydactyly mental retardation syndrome	-	0.0366	0.0146	-
fibromyalgia	-	-	0.0211	-
osteoarthritis	0.0157	-	-	-
stroke	-	0.0216	0.0307	-
Small Molecule Biochemistry (min p-value)	0.0145	0.146	0.0413	0.0696
accumulation	-	0.423	0.0492	0.0696
dephosphorylation	-	0.423	0.0413	-
efflux	0.0145	0.423	-	0.0893
release	0.205	0.423	0.0487	-
translocation	0.0284	-	0.371	0.0696
Tissue Development (min p-value)	0.000958	0.304	0.0111	0.0682
branching	-	-	0.0231	-
cell-cell adhesion	0.0286	-	-	-
development	0.000958	0.304	0.0154	0.0696
neuritogenesis	0.171	-	0.0111	-
Tissue Morphology (min p-value)	0.0145	0.423	0.288	0.0682
quantity	0.0145	0.423	0.371	0.0682

*The p-values are from Fisher's exact test and are corrected for multiple testing (Benjamini-Hochberg method).

Table S17. List of prenatal cases and CNVs identified

ID	SEX	INDICATION	Genomic Disorder
73612	Male	Abnormal ultrasound, Oligohydramnios	17q23_del
72998	Female	Abnormal ultrasound, Enlarged cisterna magna , Cardiac defect	22q11.2_DGSdel
72100	Male	Abnormal ultrasound, Diaphragmatic hernia and heart defect, Karyotype normal but suspicious of 8p	8p23_del
71676	Female	De novo marker chromosome-mosaic	8p23_dup
71374	Female	Abnormal ultrasound, Hydrops, Paternally inherited translocation, Advanced maternal age	16p13.11_del
64057	Female	Nuchal Translucency 6mm	17p13.3_YWHAEdel
63588	Female	Symmetric IUGR, Bilateral club feet	16p11.2_distdel
62904	Male	Advanced maternal age, Abnormal mosaic karotype	16p11.2_Largedup
62593	Female	Abnormal maternal serum screen, Multiple Congenital Anomalies	22q11.2_DGSdel
62420	Male	Stillborn infant with dandy walker malformation	6p25_del
62326	Male	Abnormal maternal serum screen, Septated cystic hygroma 6.5mm	16p11.2_distdup

62311	Female	Abnormal maternal serum screen, Advanced maternal age, Teralogy of fallot, Increased nuchal translucency	22q11.2_DGSdel
62270	Male	Fetal arachnoid cyst versus glioependymal cyst in the midline of the brain	15q11.2_del
62031	Male	Cystic hygroma	PWS_dup
61829	Male	Increased nuchal translucency (6.5 mm), Advanced maternal age, Abnormal maternal serum screen	16p11.2_dup
53273	Female	Ventriculomegaly, abnormal cerebellum	10q23_del
52686	Male	Abnormal ultrasound, Fetal hypoplastic left heart, Hydrocephalus, Endocardial fibroclastogies	17p13.3_LIS1dup
49142	Female	Abnormal ultrasound, Agenesis of corpus callosum, Dandy walker variant, Small right eye	15q13.3_smalldup
48261	Male	Multiple Congenital Anomalies	16p13.11_dup
47873	Male	Abnormal ultrasound, Hydrocephalus with aquductal stenosis	15q13.3_smalldup
47335	Female	Fetal cystic hygroma	2q23.1_del
46949	Male	Hereditary Disease in Family	17p13.3_YWHAEdup
46609	Male	Abnormal ultrasound, Abnormal karyotype, Cystic hygroma, Multiple fetal anomalies	1q21.1_dup
45976	Female	Absent nasal bone on fetal u/s, 46,XX,?var(17)(p11.2p11.2)	Smith-Magenis
45842	Female	Advanced maternal age, Abnormal maternal serum screen, Increased risk chromosomal abnormality, Abnormality seen on ultrasound, cystic hygroma	22q11.2_DGSdel
44418	Male	Multiple Congenital Anomalies bilateral absent fibulae, short tibiae, external rotation of feet, horseshoe kidney	16p13.11_del
43243	Female	Abnormal ultrasound: micrognathia, microcephaly, absent corpus callosum, severe hypoplasia of the frontal lobes; abnormal fetal MRI	16p13.11_del
42702	Female	Tetralogy of Fallot, polyhydramnios	22q11.2_DGSdel
42524	Male	Polydactyly on ultrasound	1q21.1_del
40806	Male	Advanced Maternal Age, Abnormal U/S, CHD, echogenic bowel, ambiguous genitalia	8p23_dup
39789	Female	Slight nuchal thickening, hypoplastic left heart, intraabdomenal cyst	Rubinstein-Taybi
39289	Female	Abnormal Ultrasound, Hemiventebrae, Cardiac defect, enlarged bladder, ambiguous genitalia, 2-vessel cord, growth lag	16p13.11_dup
39127	Female	6q23q25 deletion	6q16_del
39012	Male	Fetal multicystic renal dysplasia, pulmonary hypoplasia, mild craniofacial dysmorphism,	22q11.2_dup
38869	Female	VSD, AV canal defect, multicystic dysplastic kidney, Abnormal Ultrasound, Normal Karyotype	22q11.2_DGSdel
37607	Female	Family History of a son with PDD, increased risk for Down syndrome by maternal serum screen	16p13.11_dup
36837	Male	Abnormal ultrasound	1q21.1_dup
34410	Male	Abnormal ultrasound, Anencephaly and VSD	15q11.2_del
28112	Male	Abnormal Karyotype	15q13.3_smalldup
21294	Female	Diaphragmatic Hernia, Complex Heart Defect	8p23_del

The following cases have additional large CNVs: sample 72100 also has another large 4.4 Mb deletion on chr8: 2444745-6907722; sample 46609 has additional CNVs on chr13: 56112951-114103243 and chr13:18448674-56269250.

Table S18. Sensitivity, specificity, PPV and other measures for prognostic utility

	Sensitivity	Specificity	PPV	Likelihood Ratio Positive	Likelihood Ratio Negative	Odds Ratio
15q11.2_del	0.1566	0.9388	0.0568	2.56 (1.45-4.52)	0.89 (0.84-0.97)	2.84 (1.44-5.70)
16p11.2_dup	0.1566	0.9468	0.0649	2.95 (1.54-5.64)	0.89 (0.81-0.98)	3.3 (1.45 - 7.28)
16p11.2_distdup	0.2857	0.9140	0.0725	3.32 (1.77-6.22)	0.78 (0.62-0.99)	4.24 (1.55-10.51)
15q23q24_del	0.6000	0.9333	0.1748	9 (3.47-23.37)	0.43 (0.15-1.26)	19.87 (2.02-265.66)
16p12.1_del	0.2143	0.9333	0.0703	3.21 (1.43-7.19)	0.84 (0.73-0.97)	3.79 (1.36-10.93)
3q29_dup	0.2222	0.9468	0.0896	4.18 (1.60-10.91)	0.82 (0.64-1.05)	5.05 (1.36-10.93)
17p13.3_YWHAEdup	0.2308	0.9468	0.0927	4.34 (1.48-12.73)	0.81 (0.64-1.05)	5.34 (0.87-22.77)
Enrichment for 500 kb rare VOUS	0.1560	0.9383	0.0561	2.53 (2.30-2.77)	0.9 (0.89-0.90)	2.81 (2.53-3.11)
Enrichment of 2+ 500 kb rare VOUS	0.0226	0.9972	0.1584	7.99 (5.24-12.19)	0.98 (0.97-0.98)	8.16 (5.33-13.07)

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