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A cross-comparison of cognitive ability across 8 genomic disorders

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Abstract

Genomic disorders result from rearrangement of the human genome. Most genomic disorders are caused by copy number variants (CNV), deletions or duplications of several hundred kilobases. Many CNV loci are associated with autism, schizophrenia, and most commonly, intellectual disability (ID). However, there is little comparison of cognitive ability measures across these CNV disorders. This study aims to understand whether existing data can be leveraged for a cross-comparison of cognitive ability among multiple CNV. We found there is a lack of harmonization among assessment instruments and little standardization for reporting summary data across studies. Despite these limitations, we identified a differential impact of CNV loci on cognitive ability. Our data suggest that future cross-comparisons of CNV disorders will reveal meaningful differences across the phenotypic spectrum, especially if standardized phenotypic assessment is achieved.

Introduction

Genomic disorders, resulting from copy-number variants (CNV) or structural rearrangements of the genome[1, 2], account for a significant amount of human morbidity and mortality.[3, 4] CNVs include copy number loss (deletions) and copy number gains (duplications).[5–7] Phenotypes vary between genomic disorders but often include multi-system impairments, such as cardiac malformations, characteristic craniofacial abnormalities, immune system impairment, metabolic dysregulation, and neurodevelopmental and psychiatric disorders.[8–11] There is an increase in the overall burden of large, rare CNV in individuals with these phenotypes, and large, rare CNV are more likely to contain genes with functional roles in neurodevelopmental pathways.[12–14] Rare CNV have been implicated in a variety of diseases, and are found to be increased in more severe developmental phenotypes associated with congenital abnormalities.[8, 15]

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A substantial number of CNV are associated with neurodevelopmental and psychiatric phenotypes. For example, there are at least 8 CNV with genome-wide significance for association with schizophrenia, including 1q21.1, 2p16.3, 3q29, 7q11.23, 15q13.3, distal 16p11.2, proximal 16p11.2, and 22q11.2.[16–18] Phenotypic heterogeneity has been observed among these CNV; in addition to schizophrenia, each locus may also be associated with autism, epilepsy, and additional neurodevelopmental sequelae.[19–21] Many CNV loci cause a degree of cognitive impairment, ranging from mild to severe.[22, 23] Few studies have compared the impact on cognitive ability across CNV loci.

There has been a consistent observation that while CNV occur in different parts of the genome and contain non-overlapping genes, they nevertheless are associated with an overlapping set of phenotypes.[24, 25] The hypothesis of convergent biology has been advanced as a way to explain these observations. On a genetic level, convergence can reflect a variety of degrees of similarity, ranging from evolutionary changes in the same genes but at different sites, to changes in the same pathways but within different genes.[26] Although different genes lie within these CNV loci, they may converge on the same pathways, resulting in shared phenotypes. To study the hypothesis of convergent biology, a first needed step is to have comprehensive, harmonized phenotyping data across a range of CNV, to enable cross-comparison.[27]

For many CNV, their impact on cognitive function is well-studied. In this review, we sought to ask whether this copious amount of existing data could be leveraged for cross-comparison of cognitive phenotypes. We conducted a thorough literature search across 11 CNV loci, harvesting data from 156 studies. We compared a) the instruments used in these studies and b) estimates of cognitive ability across CNV loci. Our study aims to draw a systematic comparison of cognitive measures across different genomic disorders, and document any barriers that may exist in using existing data to conduct cross-disorder comparisons of cognitive ability.

Methods

Literature Search Strategy

We selected a set of 11 CNVs known to be associated with intellectual disability and conducted a systematic literature search to identify eligible papers with data for analysis. These included 3q29 deletion, 7q11.23 deletion, 15q11.2 deletion (Angelman's Syndrome (AS)), 15q11.2 deletion (Prader-Willi Syndrome (PWS)), 16p11.2 deletion and duplication, 17p11.2 deletion, and 22q11.2 deletion. (Table 1).

Papers were identified in October 2020 via a PubMed literature search. We identified relevant studies with the search terms "*CNV name* and *cognitive ability*", or "*CNV name* and *IQ*". If a genomic disorder is well-known by an alternate name, we repeated all searches using the alternate name (ie: Williams Syndrome for 7q11.23 deletion). See supplemental table 2 for search details.

Study Selection

Papers matching search criteria were manually reviewed for eligibility. Inclusion criteria were: data measures on human subjects; reporting of cognitive data (Full-Scale IQ (FSIQ), verbal IQ (VIQ), or performance or non-verbal IQ (PIQ or NVIQ)); clear identification of the instrument used for measures of cognitive ability; a sample size > 20; and either open access or reasonable access through a typical University library. When multiple papers reported data using nested, overlapping sample sources, only the paper with the largest sample size was retained. See supplemental table 2 for literature search results.

Data Extraction and Management

For papers that met eligibility criteria, data were extracted from the paper and maintained in a local database. Extracted data included paper title, authors, year published, sample size, assessment instruments, and cognitive ability scores. In this primary literature, data summaries were reported in variable ways across studies. Measures of central tendency (e.g., mean or median) and variance (e.g., standard error or standard deviation) were extracted as reported. Data visualization was performed in R.

Computing Average IQ Scores

For each CNV, we calculated the overall average FSIQ, VIQ, and PIQ across all studies for that CNV, weighting each study by its sample size.

Cognitive Assessment

Measures of cognitive ability, such as IQ tests, have been shrouded in controversy, mainly due to accusations of cultural bias.[28] However, they are still considered the most effective form of assessing cognitive ability, and continue to be widely-used.[29] Although we compared cognitive ability assessed by different instruments in this study, it is important to note that all instruments are normed on a standard scale (mean = 100, standard deviation (SD) = 15). This means that for almost any of the commonly used instruments, a score that falls two SD below the mean (IQ < 70) indicates the presence of intellectual disability. Additionally, these scores can be used in multiple frameworks. We can use standard scores as a quantitative, dimensional measure to compare cognitive ability across CNVs. Alternatively, we can group people based on whether or not they have intellectual disability. Some common instruments include:

Wechsler Intelligence Scale ——Measures cognitive ability in verbal and non-verbal dimensions. It includes 11 subscales (6 verbal and 5 non-verbal) including general information, numeric memory, vocabulary, computing, comprehension and similarities, verbal intelligence and image completion, image adjustment, cube design, and component insertion[30] Different versions of the test may be administered based on the age of the test taker, including Wechsler Preschool and Primary Scale of Intelligence (WPPSI, ages 3–5 years), Wechsler Intelligence Scale for Children (WISC, 6–15 years), and Wechsler Adult Intelligence Scale (WAIS, 16 years and older).[31]

Kaufman Brief Intelligence Scale ––—Assesses verbal and non-verbal ability in people ages 4–90 years. Verbal scale measures verbal knowledge and riddles, while the nonverbal scale measures fluid intelligence (ability to think logically and solve novel problems).[32]

Differential Ability Scales ––—Assesses verbal and non-verbal ability in preschool and school-age children, ages 2.5–18 years. Verbal and non-verbal domains have different subtests depending on the age of test taker. For example, the non-verbal domain for older ages (3.5–7 years) includes matrices and copying, as well as pattern construction, while the younger ages (2.5–3.5 years) are tested on picture similarities.[33]

Bayley Scales of Infant and Toddler Development ––—an assessment for infants aged 1–42 months across three domains: cognitive, language, and motor skills.[34]

Leiter International Performance Scale ––—an assessment for children and adolescents aged 2–20 years.[35] Composed of two batteries: attention and memory (AM) and visualization and reasoning (VR). The AM battery is used for the assessment of attention and memory difficulties, while the VR battery is used to measure general intelligence.[36]

Ammons Quick Test ––—an assessment of verbal intelligence using picture identification in children and adults ages 2–90 years.[37]

Reynolds Intellectual Screening Test ––—an assessment of verbal and non-verbal intelligence in people aged 3–99 years.[38]

Results

Using our search criteria, we identified 156 eligible studies that reported cognitive ability scores. This included 1 paper on 3q29 deletion[39], 36 papers on 7q11.23 deletion[32, 40–74], 2 papers on 15q11.2 deletion (AS)[75, 76], 31 papers on 15q11.2 deletion (PWS)[56, 77–106], 6 papers on 16p11.2 deletion (proximal)[107–112], 4 papers on 16p11.2 duplication (proximal)[107, 109, 110, 112], 3 papers on 17p11.2 deletion[113–115], and 73 papers on 22q11.2 deletion syndrome.[74, 80, 116–186] Studies reporting cognitive scores for 1q21.1 deletion, 2p15p16.1 deletion, and 9q34 deletion were not identified. The total number of subjects evaluated for a given CNV across all publications for that CNV was variable and ranged from 32 subjects for the 3q29 deletion to 4,732 study subjects for the 22q11.2 deletion. For other CNV included in this review, total sample sizes were: 1,849 (7q11.23 deletion); 45 (15q11.2 deletion, AS); 1,836 (15q11.2 deletion, PWS); 354 (16p11.2 deletion (proximal)); 198 (16p11.2 duplication (proximal)); and 134 (17p11.2 deletion) (Table 1).

We observed significant variability in the assessment instruments used to measure cognitive ability. The Wechsler Intelligence scales (WAIS, WISC, WASI, WPPSI) are the most widely used across studies (Fig. 1, Table S1). However, the Kaufman Brief Intelligence Test has also been administered in a substantial number of study subjects, particularly for the 7q11.23 deletion and 15q11.2 deletion (PWS). Some CNV studies assessed IQ using multiple cognitive assessment instruments, but failed to specify how many subjects were evaluated with each instrument. Across the 8 CNV included in this review, only 2 (15q11.2 deletion

(AS) and 17p11.2 deletion) reported cognitive scores with a single instrument (Fig. 1). The variety of instruments used to measure cognitive ability demonstrates the challenges of retrospective data comparison, both within and across disorders.

Figure 2 shows a comparison of FSIQ scores across the CNV included in this study. Within a single CNV, there can be wide variation across studies. For example, FSIQ mean estimates for the 22q11.2 deletion range from a low of 53[178] to a high of 88.[174] Careful examination of the primary papers does not reveal a clear reason for these differential estimates. Despite this variability, some conclusions can be drawn across CNV. 17p11.2 deletion subjects appear to have the lowest FSIQ estimates among the CNV included in this study, and 16p11.2 deletion and 16p11.2 duplication subjects appear to have the highest. All cognitive data estimates included in this review, across all studies, report FSIQ scores below the population mean IQ of 100 (Fig. 2). As the studies within each CNV are ordered chronologically (from earliest to most recent), we did not notice any temporal changes in FSIQ within the CNV.

Though we studied 8 CNV, only 6 contained studies that reported VIQ and PIQ scores (Fig. 3, 4). Inter and intra-CNV VIQ and PIQ scores across studies also showed consistency, but largely mirror the results for FSIQ. 17p11.2 deletion appears to have the lowest PIQ and VIQ, while 16p11.2 deletion and duplication subjects appear to have the highest (Fig. S1, S2). We also did not notice any temporal changes in VIQ or PIQ within CNV across the studies (Fig. S1, S2).

Weighted mean FSIQ, VIQ, and PIQ scores across CNV also showed consistency, with all scores falling below population mean (3q29 deletion = 73, 7q11.23 deletion = 66, 15q11.2 deletion (AS) = 76, 15q11.2 (PWS) = 66, 16p11.2 deletion = 82, 16p11.2 duplication = 86, 17p11.2 deletion = 50, 22q11.2 deletion = 71). Mean VIQ scores also fell below population mean (7q11.23 deletion = 70, 15q11.2 deletion (PWS) = 68, 16p11.2 deletion = 81, 16p11.2 duplication = 86, 17p11.2 deletion = 55, 22q11.2 deletion = 74). Mean PIQ scores followed a similar trend (7q11.23 deletion = 66, 15q11.2 deletion (PWS) = 65, 16p11.2 deletion = 85, 16p11.2 duplication = 81, 17p11.2 deletion = 55, 22q11.2 deletion = 71) (Fig. 3).

Discussion

In this study, we sought to compare the impact of a diversity of CNV loci on cognitive ability, using existing data culled from the literature. We document significant challenges in this endeavor. One such challenge is the range of instruments used, with little harmonization within and across loci, as shown in Figure 1. Because many instruments are normed and scored on the same scale, this lack of harmonization presents a minor barrier to cross-comparison. A second challenge is the lack of standardization in data reporting; this is a more significant barrier that obscures our ability to conduct cross-disorder comparisons. Despite these barriers, our analysis reveals a differential impact of CNV loci on cognitive ability.

Our comparisons revealed that the 16p11.2 deletion and 16p11.2 duplication tend to have the smallest effect on FSIQ, VIQ, and PIQ, compared to the other CNV loci included in this

analysis (Fig. 2, S1, S2). This was true when examining measures at the individual study level, as well as weighted estimates (Fig. 3). In contrast, we found the 17p11.2 deletion is estimated to depress cognitive ability scores to a great extent than any of the other CNV included in this study. This is consistent with previously reported literature, as 17p11.2 deletion is known to be associated with lower cognitive ability scores.[113]

The lack of harmonization in cognitive assessment instruments makes a cross comparison difficult, due to instruments using different scales and methods to develop an IQ score.[187] CNV cross-comparison would be facilitated if the same instruments were used to measure cognitive ability. Minimally, the instruments used must be explicitly defined. There were multiple studies that we came across in our literature search that were excluded because the cognitive measurement instruments were not identified. It is also important that all studies report the same measures of central tendency and variation when measuring cognitive ability, to allow for a more uniform comparison. An ideal solution is for investigators to make the raw data available upon publication, either in the supplement, or through a public-facing database like NDAR (https://nda.nih.gov/about.html). By making this raw data public, it would allow future studies to download the data for their own analysis, thereby aiding in reproducibility.[188]

This is one of the first cross-comparisons of cognitive ability in CNV disorders, a paradigm that has previously been suggested as important for study.[27, 189] The overlap of these neuropsychiatric phenotypes, within and between these CNV, warrants a cross-disorder analysis, as it may identify biologically defined subcategories of these neuropsychiatric phenotypes.[27] Additionally, a cross-comparison like this allows for a global overview of cognitive ability among CNV; despite these CNV originating on different loci, they all share a common phenotype of intellectual disability. Thus, a cross-comparison highlights the fact that thousands of CNV risk factors converge on a limited number of diagnoses[190],and that these risk factors overlap with loci that contribute to these disorders.[17] Additionally, this type of cross comparison shows evidence of genotype-specific effects on severity of intellectual disability, allowing us to draw a genotype-phenotype association.[191]

The limitations of this study include, as mentioned earlier, a lack of harmonization among assessment instruments, as well as different measures of central tendency and variation being reported. Ascertainment bias is also a major limitation of this study; carriers of incompletely penetrant CNV may appear phenotypically normal, and hence their cognitive performance may not be captured in the primary literature.[192] As a result, only people with severe cognitive and developmental delays are more likely to be referred for a clinical genetics test.[191] This would skew our results, as the IQ scores that are reported in the primary papers may over-represent the most severely-affected individuals.

This study presents a promising direction forward into understanding cognitive ability among people with CNV, as it reveals a differential impact of CNV loci on cognitive ability. This study also allows for identification of subcategories of these neuropsychiatric phenotypes, and can be applied to other shared phenotypes aside from cognitive ability. Future studies should ensure consistent, harmonized data collection efforts are being conducted. Additionally, to control for ascertainment bias, studies should conduct

population-level analyses of large samples of individuals, such as birth cohorts or health system registries. This will hopefully allow for a more uniform cross-comparison of cognitive ability across CNV to be performed, which will ultimately allow us to better understand the biology and mechanisms of these disorders. This type of study also plays a role into preventative medicine, as it allows us to inform clinicians what to expect when treating patients with these CNV, with the goal of improving the lives of those living with these disorders.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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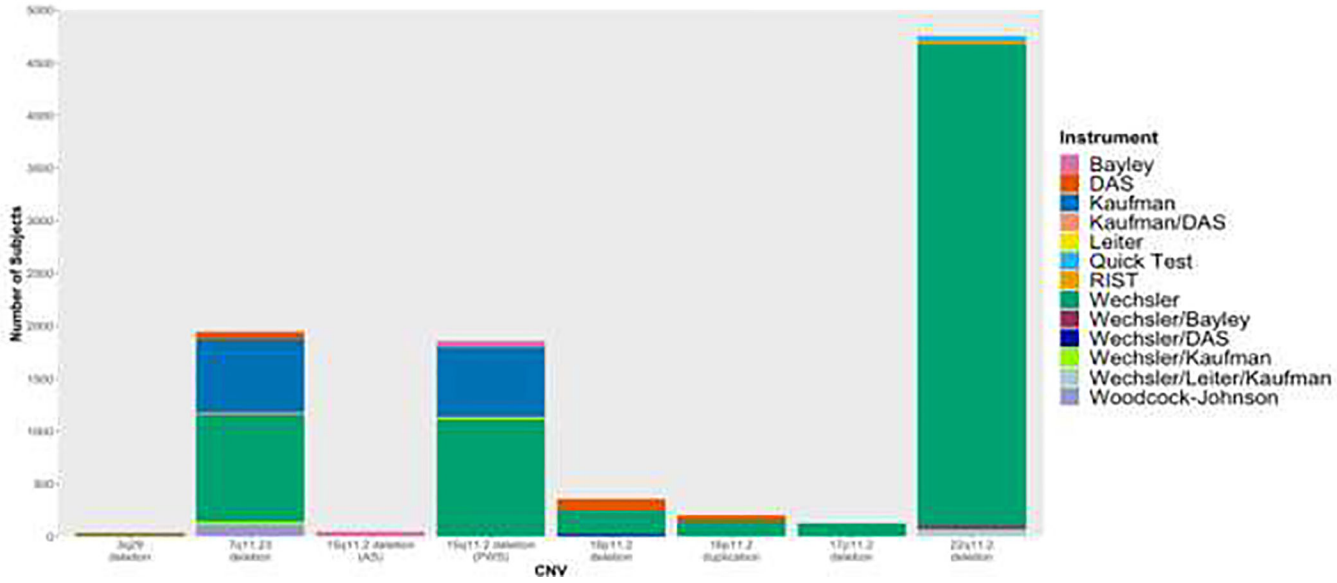

Figure 1. Cognitive assessment instrument used across CNV studies.

Bars are proportional to number of study subjects that have been evaluated across studies with corresponding instrument. Studies that used any form of the Wechsler Intelligence Scale (WAIS, WASI, WISC, WPPSI) were grouped together under “Wechsler.” Studies that used multiple instruments but did not specify how many subjects were administered each instrument were grouped together with all instruments specified.

aDifferential ability scales

bReynolds Intellectual Screening Test

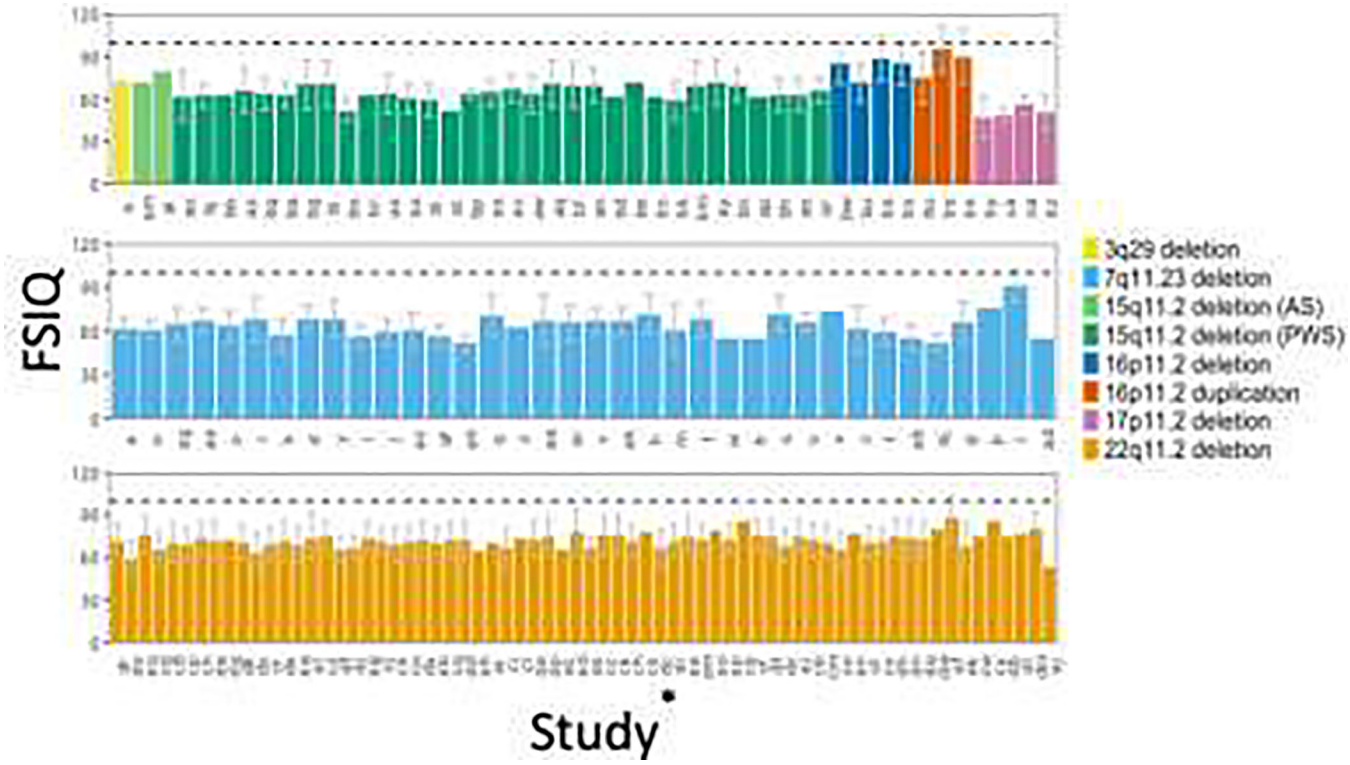

Figure 2. FSIQ measures across studies for 8 CNV.

Study indicator on x-axis corresponds to study ID indicator in Table S1. If more than one study for a CNV, studies were listed chronologically from earliest to most recent, or left to right. Dashed black line indicates population mean IQ of 100.

*See Table S1 for study indicators for each study

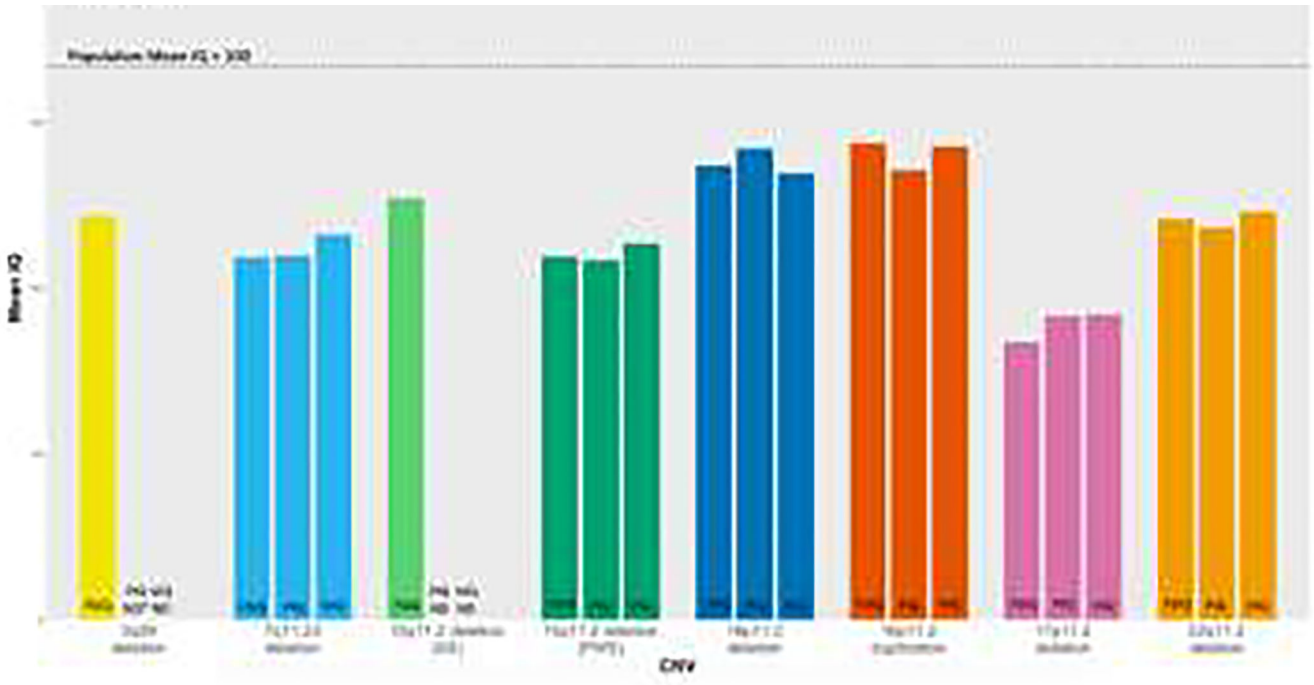

Figure 3. Weighted mean FSIQ, VIQ, and PIQ across CNV studies.

3q29 deletion and 15q11.2 deletion (AS) did not contain studies that reported sample VIQ or PIQ scores. See methods for computation of weighted mean IQ scores.

*Not Determined

Table 1.

Number of studies and study subjects among CNVs

CNV	Number of Studies	Total Number of Study Subjects
1q21.1 deletion	-	-
2p15p16.1 deletion	-	-
3q29 deletion	1	32
7q11.23 deletion	36	1,849
9q34 deletion	-	-
15q11.2 deletion (AS)[a]	2	45
15q11.2 deletion (PWS)[b]	31	1,836
16p11.2 deletion (proximal)	6	354
16p11.2 duplication (proximal)	4	198
17p11.2 deletion	3	134
22q11.2 deletion	73	4,732

[a] Angelman's Syndrome

[b] Prader-Willi Syndrome