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Recurrent Deletions and Duplications of Chromosome 2q11.2 and 2q13 are Associated with Variable Outcomes

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Copy number variation (CNV) in the long arm of chromosome 2 has been implicated in developmental delay (DD), intellectual disability (ID), autism spectrum disorder (ASD), congenital anomalies, and psychiatric disorders. Here we describe 14 new subjects with recurrent deletions and duplications of chromosome 2q11.2, 2q13, and 2q11.2–2q13. Though diverse phenotypes are associated with these CNVs, some common features have emerged. Subjects with 2q11.2 deletions often exhibit DD, speech delay, and attention deficit hyperactivity disorder (ADHD), whereas those with 2q11.2 duplications have DD, gastroesophageal reflux, and short stature. Congenital heart defects (CHDs), hypotonia, dysmorphic features, and abnormal head size are common in those with 2q13 deletions. In the 2q13 duplication cohort, we report dysmorphic features, DD, and abnormal head size. Two individuals with large duplications spanning 2q11.2–2q13 have dysmorphic features, hypotonia, and DD. This compilation of clinical features associated with 2q CNVs provides information that will be useful for healthcare providers and for families of affected children. However, the reduced penetrance and variable expressivity associated with these recurrent CNVs makes genetic counseling and prediction of outcomes challenging.

Key words: 2q11.2 deletion; 2q11.2 duplication; 2q13 deletion; 2q13 duplication; recurrent CNV; *FBLN7*; *TMEM87B*

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INTRODUCTION

Approximately 15–20% of children referred for chromosomal microarray analysis (CMA) testing have a clinically relevant CNV that in many cases explains their phenotype [Rudd et al., 2009; Cooper et al., 2011; Kaminsky et al., 2011]. However, for almost all pathogenic CNVs there are a range of phenotypic outcomes (variable expressivity) and/or unaffected family members who carry the same CNV (incomplete penetrance) [Deak et al., 2011; Moreno-De-Luca et al., 2013; Rosenfeld et al., 2013]. Thus, to capture the spectrum of features associated with a new genomic disorder, it is essential to evaluate multiple individuals with the same CNV. Deletions and duplications mediated by non-allelic homologous recombination (NAHR) are ideal for genotype-phenotype correlations because they have recurrent breakpoints in unrelated individuals [Stankiewicz and Lupski, 2010; Liu et al., 2011; Dittwald et al., 2013].

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Large duplications of the long arm of chromosome 2 have been described in children with DD, ID, microcephaly, short stature, and cleft lip and palate [Riegel and Schinzel, 2002; Ounap et al., 2005]. These duplications were originally identified by chromosome banding and span regions as large as 2q11.2–2q21. Six years ago, we reported seven patients with recurrent deletions and duplications of 2q11.2 and 2q13 [Rudd et al., 2009]. Based on CNV inheritance, normal variation in control CNV datasets, and genes within CNVs, we concluded that 2q11.2 CNVs were likely pathogenic whereas 2q13 CNVs had unknown clinical significance. Since then, similar CNVs have been reported in other studies of DD/ID, ASD, CHD, and schizophrenia [Cooper et al., 2011; Soemedi et al., 2012; Yu et al., 2012; Costain et al., 2013; Dittwald et al., 2013; Russell et al., 2014]. Here we present 14 new subjects with genomic imbalances of 2q11.2–2q13 and their phenotypes as compared to published cases, representing the largest study of chromosome 2q11.2–2q13 rearrangements to date.

MATERIALS AND METHODS

Human Subjects

This study was approved by the Institutional Review Boards at Emory University, Baylor College of Medicine, and The University of Michigan. Healthcare providers referred families to our research study after testing in diagnostic cytogenetics laboratories. We recruited 14 new subjects: five with deletions of 2q11.2, three with duplications of 2q11.2, three with deletions of 2q13, one with a duplication of 2q13, and two with different duplications of the intervening region between 2q11.2 and 2q13. We compared the clinical features from new subjects and previously reported subjects [Rudd et al., 2009; Yu et al., 2012; Russell et al., 2014]. Subjects range in age from six months to 17 years at the time of assessment and have various ethnic backgrounds. Informed consent was obtained from probands and their family members. Subjects 1, 4, 5, 7–10, 12–14 were consented at Emory University, Subjects 2, 3, and 6 were consented at Baylor College of Medicine, and Subject 11 was consented at The University of Michigan. Once informed consent was provided, medical records and clinical notes were obtained from primary care physicians and relevant specialists.

Chromosomal Microarray Analysis (CMA)

Deletions and duplications were detected by microarray analysis of DNA extracted from peripheral blood. Most subjects were tested with a version of the EmArray oligonucleotide array [Baldwin et al., 2008]. Agilent microarray design identifier (AMADID) numbers correspond to custom array designs (Agilent Technologies, Santa Clara, CA). Subject 10 was tested using the EmArray Cyto6000 version 2 (AMADID 0246141) and Subjects 9, 12, and 13 were tested with the EmArray Cyto60K (AMADID 0246121); both are based on the NCBI36/hg18 genome assembly. Subject 1 was tested using EmArray Cyto (AMADID 0275741), an Oxford Gene Technology (OGT) array based on the GRCh37/hg19 genome assembly. Subjects 4–7 were tested using the Affymetrix CytoScan HD array and Subjects 11 and 14 were tested using the Illumina CytoSNP-850K BeadChip, both based on the GRCh37/hg19 genome assembly. Subjects 2 and 3 were tested using the 180k CMA-HR, based on the NCBI36/hg18 genome assembly. Coordinates from arrays using the NCBI36/hg18 build were converted to GRCh37/hg19 using the LiftOver tool (http://genome.ucsc.edu) [Kent et al., 2002].

DNA digestion, labeling, purification, hybridization, array scanning, and analysis were performed following manufacturers' instructions. To determine the inheritance of CNVs, fluorescence in situ hybridization (FISH) analysis was performed on peripheral blood samples from parents using standard cytogenetic procedures with probes corresponding to the proband's CNV.

RESULTS

2q11.2 Deletions

Speech delay, ADHD, and dysmorphic features are common in children with deletions of chromosome 2q11.2 (Fig. 1; Table I). Subject 1's father carries the 2q11.2 deletion, and describes "trouble in school" and two nephews with ADHD. Subject 2's deletion occurred de novo and Subject 3's deletion was maternally inherited. Subjects 4 and 5 are brothers with the same 2q11.2 deletion, but their parents have not been tested. The 2q11.2 deletion is not present in databases of normal CNV [Itsara et al., 2009; Shaikh et al., 2009; Macdonald et al., 2014].

2q11.2 Duplications

DD, dysmorphic features, gastroesophageal reflux, and short stature are present in individuals with 2q11.2 duplications (Table II). The three children who were assessed exhibited frontal bossing with other minor facial features. Subject 6 has begun growth hormone therapy. Her mother does not carry the duplication; her father had learning difficulties and short stature, but was not available for testing. Subject 7 inherited her duplication from her unaffected mother, and her half-brother (Subject 8) carries the same 2q11.2 duplication. Both children have short stature, feeding difficulties, and gastroesophageal reflux with vomiting. One duplication of 2q11.2 was reported in an individual from the 1000 Genomes project [Consortium et al., 2010]; however, 2q11.2 duplications are not found in other databases of normal CNV [Itsara et al., 2009; Shaikh et al., 2009; Macdonald et al., 2014].

2q13 Deletions

Eleven subjects have 1.62–1.71-Mb deletions of chromosome 2q13 flanked by the same cluster of segmental duplications. Patient 2's atypical 1.35-Mb deletion partially overlaps the common 2q13 deletion region, but is shifted distally (Fig. 2) [Russell et al., 2014]. Both regions are distal to the smaller 2q13 CNV that includes the *NPHP1* gene [Konrad et al., 1996]. Congenital heart defects (7/12), dysmorphic features (10/12), hypotonia (7/12), and abnormal head size (9/12) are common in those with 2q13 deletions (Table III). Cognitive impairment or ASD was reported in 4 of the 7 subjects who were evaluated; however, several subjects in our study were less than two years of age at the time of assessment so their abilities could not be determined. Five

FIG. 1. Features of subjects with 2q CNVs. Subjects 6-8 have duplications of 2q11.2. A: Subject 6 at 10 years. B: Subject 7 at 21 months. C–D: Subject 8 at 21 months and three years, respectively. E: Subject 1 (2q11.2 deletion) at four years. F: Subject 12 (2q13 duplication) at eight years.

out of eight males with 2q13 deletions in our combined studies exhibited hypogonadism or hypospadias [Yu et al., 2012; Russell et al., 2014]. One 1.71-Mb deletion of 2q13 has been described in the CHOP study of normal CNV [Shaikh et al., 2009], and a similar 2q13 deletion was described in one individual from the Cooper et al. control group [Cooper et al., 2011]. The atypical distal deletion of 2q13 has not been described in databases of normal CNV [Russell et al., 2014].

TABLE I. Clinical Features of Subjects with Deletions of Chromosome 2q11.2

	Patient 2	Subject 1	Subject 2	Subject 3	Subject 4 (Family 1)	Subject 5 (Family 1)	Total
Reference	Rudd et al. [2009]	This study	This study	This study	This study	This study	
Age at assessment	16 yrs	4 yrs	4 yrs, 10 mos	7 yrs, 1 mos	17 yrs	15 yrs	
Gender	M	M	M	F	M	M	
Ethnicity	–	Caucasian	–	Caucasian	African American	African American	
Size of CNV	1.25 Mb	1.25 Mb	913 kb	913 kb	1.61 Mb	1.60 Mb	
Coordinates	96,766,561–98,013,866	96,766,565–98,013,954	96,739,309–97,652,262	96,739,309–97,652,262	96,097,383–97,703,370	96,097,383–97,693,317	
Inheritance	Unknown	Paternal	De Novo	Maternal	Unknown, familial	Unknown, familial	
DD/ID	–	+	+	–	+	+	4/6
ASD	–	+	–	–	+	+	3/6
Speech delay	–	+	+	+	–	+	4/6
ADHD	+	+	+	+	–	–	4/6
Hypotonia	–	+	+	–	–	+	3/6
Dysmorphic features	+	Midface hypoplasia, coarse features, hypertelorism, depressed nasal bridge	Malformed ears, midface hypoplasia	Malformed ears	–	–	4/6
Skeletal	Scoliosis	–	Pectus excavatum	–	Mild scoliosis	Kyphoscoliosis, kyphosis, lordosis, microcephaly	4/6
Other clinical findings	Café-au-lait spots, aortic coarctation	Recurrent ear infections, hip joint hypermobility	Inversion of the foot, recurrent ear infections	Inversion of the foot, uncontrolled eating	Encephalopathy, sleep problems, mood disorder, aggression, mild motor delays	Encephalopathy, asthma, ichthyosis, chiari malformation, mood disorder, aggression	

+, feature present; –, feature absent; DD, developmental delay; ID, intellectual disability; ASD, autism spectrum disorder; ADHD, attention deficit hyperactivity disorder.
Genomic coordinates for chromosome 2 are based on the GRCh37/hg19 build of the human genome.

2q13 Duplications

Four subjects have a duplication of 2q13 that is reciprocal to the common 2q13 deletion. Dysmorphic features, DD, and microcephaly are common findings in this group (Table IV). Two of our subjects with 2q13 duplications are members of the same family (Fig. 3). Patient 4 [Rudd et al., 2009] has a nephew (Subject 12) with DD, learning disabilities, and dysmorphic features. Subject 12's mother, who also carries the duplication, reported difficulty with math, but strengths in expressive language and reading. She also described some difficulties with fine motor skills and visual integration. Duplications of this region of chromosome 2q13 are not reported in normal CNV databases [Itsara et al., 2009; Shaikh et al., 2009; Macdonald et al., 2014].

2q11.2–2q13 Duplications

Two subjects have large duplications between the common CNV regions in chromosome 2q11.2 and 2q13. Subject 13 has a 9.22-Mb duplication of 2q11.2–2q13 (hg19, chr2:102,327,289–111,548,995) and subject 14 has a 3.33-Mb duplication of 2q12.2–2q13 (hg19, chr2:107,132,930–110,465,307) (Fig. 2). The distal breakpoint of both duplications lies in a cluster of segmental duplications in 2q13, but the proximal breakpoints are different. Subject 14's duplication is flanked by paralogous segmental duplications in 2q12.2 and 2q13, whereas Subject 13's proximal 2q11.2 breakpoint is not bounded by segmental duplications. Developmental delay, hypotonia, and various dysmorphic features were present in Subjects 13 and 14. As for the parents of our subjects who also carry these duplications, Subject 13's mother reported fainting spells and chest pain with suspected mitral valve prolapse. Subject 14's father is reportedly healthy, though he did not finish high school for unspecified reasons.

DISCUSSION

In this study, we describe 14 new subjects with pathogenic CNVs involving chromosome 2q11.2, 2q13, and 2q11.2–2q13 and compare their features to others in the literature. Evaluating multiple individuals with the same CNV can shed light on the range of phenotypes associated with a deletion or duplication.

Chromosome 2q13 deletions are the most common CNV in our study, and between our subjects and others, a consistent phenotype is beginning to emerge. Dysmorphic features, cranial abnormalities, DD, and CHD are the most common features. In all of the

TABLE II. Clinical Features of Subjects with Duplications of Chromosome 2q11.2

	Patient 1	Subject 6	Subject 7 (Family 2)	Subject 8 (Family 2)	Total
Reference	Rudd et al. [2009]	This study	This study	This study	
Age at assessment	16 mos	10 yrs	13 months	10 years	
Gender	M	F	F	M	
Ethnicity	Indian	Hispanic	Caucasian	Caucasian	
Size of CNV	1.47 Mb	1.38 Mb	1.49 Mb	Not determined	
Coordinates	96,545,351–98,013,866	96,734,646–98,118,200	96,732,520–98,225,552	FISH confirmed	
Inheritance	De novo	Unknown	Maternal	Maternal	
DD/ID	+	+	+	NA	3/3
Hypotonia	+	−	+	NA	2/3
Dysmorphic features	+	Prominent forehead, flattened nasal bridge, protuberant ears	Prominent forehead, triangular face, epicanthal folds, short philtrum, high arched palate	NA	3/3
Short stature	+	+	+	+	4/4
Skeletal	Macrocephaly, dolicocephaly, frontal bossing	Microcephaly (2nd% tile), scoliosis, frontal bossing	Frontal bossing, mild leg asymmetry	NA	3/3
Gastroesophageal reflux	+	+	+	+	4/4
Other clinical findings	Café-au-lait spots	FTT, low weight (<5th% tile), joint pain, hypermobility, speech delay	Feeding difficulties, reflux with vomiting, FTT, low weight (5th% tile), PFO	Feeding difficulties, reflux with vomiting, eosinophilic esophagitis, ADHD	
Other cytogenetic findings	inv(Y)(p11.2q11.2)				

FTT, failure to thrive; NA, not assessed; PFO, patent foramen ovale.
Genomic coordinates for chromosome 2 are based on the GRCh37/hg19 build of the human genome.

families where parents were tested, the 2q13 deletion was inherited. However, little or no phenotypic information was available from the parents who carried the deletion. The 2q13 deletion is enriched in other cohorts of individuals with DD/ID [Bisgaard et al., 2007; Cooper et al., 2011], ASD [Szatmari et al., 2007], and CHD [Soemedi et al., 2012] as compared to controls, consistent with a pathogenic CNV. Recent knockdown experiments in zebrafish point to two genes involved in the 2q13 deletion phenotype. Abnormal head size and dysmorphic features may be due to heterozygous loss of *FBLN7* since depletion of this gene leads to craniofacial defects in fish. In addition, knockdown of *FBLN7* or *TMEM87B* individually and synergistically recapitulated heart abnormalities in fish [Russell et al., 2014].

Dysmorphic features and DD, but not CHDs, are present in those with the reciprocal duplication of 2q13. These data suggest that haploinsufficiency, but not triplosensitivity, of 2q13 cause CHDs. Within Family 3, there is variable expressivity of the 2q13 duplication in three individuals with DD, learning disabilities, and/or dysmorphic features. Duplications of 2q13 have been reported in other children with DD, congenital anomalies, dysmorphic features, and/or ASD [Cooper et al., 2011]. Two subjects with 2q13 duplications have also been described in a schizophrenia cohort [Costain et al., 2013]. All three of the subjects in our studies inherited their duplications, as did three from Cooper et al., and others have unknown inheritance [Cooper et al., 2011; Yu et al., 2012; Costain et al., 2013]. In addition, 2q13 duplications are not reported in normal CNV databases [Itsara et al., 2009; Shaikh et al., 2009; Macdonald et al., 2014]. This, along with the segregation of the duplication in Family 3, suggests that 2q13 duplications are pathogenic with variable expressivity.

Deletions and duplications of 2q11.2 are also considered pathogenic. The 2q11.2 deletion is significantly enriched in children with developmental delay as compared to controls [Coe et al., 2014]. In our cohort, the deletion was inherited from a mildly affected parent (Subject 1), de novo (Subject 2), or present in two similarly affected siblings (Family 1), consistent with pathogenicity. The 2q11.2 duplication was found to be de novo (Patient 1) or present in siblings with similar clinical presentations (Family 2). The short stature observed in all four children with 2q11.2 duplications is striking and prompted other genetic testing. Subject 7 was

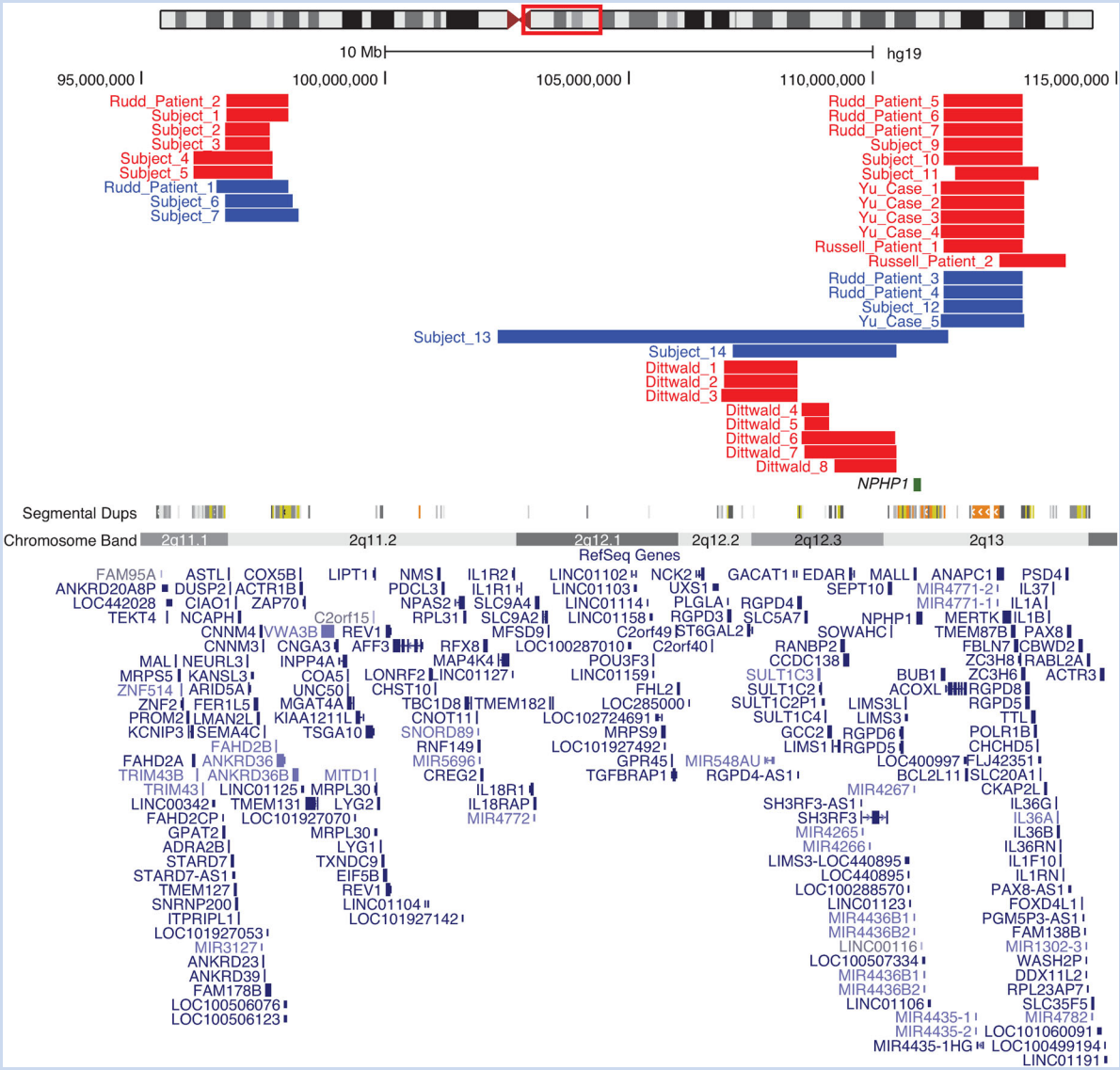

FIG. 2. CNVs in chromosome 2q11.1–2q13. Minimum CNV sizes are represented by red (deletion) or blue (duplication) bars and segmental duplications are shown below. The recurrent *NPHP1* deletion/duplication region is shown in green. RefSeq genes (blue) are indicated at the bottom. This figure was made with the PDF/PS tool on the UCSC genome browser (GRCh37/hg19) [Kent et al., 2002].

referred for Russell-Silver testing and Patient 1 was referred for *FGFR3* sequencing; both tests were negative.

Dittwald et al. recently described eight patients with deletions of the 2q12.2–2q13 region [Dittwald et al., 2013]. These deletions are 502 kb–1.91 Mb, lie between paralogous segmental duplications, and overlap the larger duplications in Subjects 13 and 14. Like Subjects 13 and 14, several of the patients with deletions exhibited DD and dysmorphic features. Our Subject 14 and Dittwald et al.'s patient 1 have temporal bone narrowing and Subject 13 has dolichocephaly and frontal bossing. Since all three of these CNVs overlap, it is possible that they include a gene involved in cranial development. However, none of the genes within the smallest region of overlap have been implicated in craniofacial development. Some of the deletions reported by Dittwald et al. are present in databases of normal CNV, but the larger duplications in Subjects 13 and 14 are not [Itsara et al., 2009; Shaikh et al., 2009; Macdonald et al., 2014].

Like other recurrent CNVs [Deak et al., 2011; Moreno-De-Luca et al., 2013; Rosenfeld et al., 2013], deletions and duplications of 2q11.2 and 2q13 exhibit incomplete penetrance and variable expressivity. It is possible that parents who carry the same CNV as their affected child have milder clinical presentations that were not recognized during childhood. On the other hand, affected children may carry additional "second hit" CNVs that exacerbate penetrance of the phenotype [Girirajan et al., 2012]. Patient 5 has a 2q13 deletion and an unbalanced translocation between chromo-

TABLE III. Clinical Features of Subjects With Deletions of Chromosome 2q13

	Patient 5	Patient 6	Patient 7	Subject 9	Subject 10	Subject 11	Patient 1	Patient 2	Case 1	Case 2	Case 3	Case 4	Total
Reference	Rudd et al. [2009]	Rudd et al. [2009]	Rudd et al. [2009]	This study	This study	This study	Russell et al. [2014]	Russell et al. [2014]	Yu et al. [2012]	Yu et al. [2012]	Yu et al. [2012]	Yu et al. [2012]	
Age at assessment	4 yrs	2 yrs	d. <1 yr	<1 yr	5 yrs	6 mos	2 mos (d. 6 mos)	3 yrs	2 yrs	6 yrs	6 yrs	2 yrs	
Gender	M	M	M	F	M	M	F	M	F	M	F	M	
Ethnicity	Caucasian	Hispanic	Caucasian/ Hispanic	Caucasian	Caucasian	Caucasian	African–American	African–American	–	–	–	–	
Size of CNV	1.62 Mb	1.62 Mb	1.62 Mb	1.62 Mb	1.62 Mb	1.70 Mb	1.62 Mb	1.35 Mb	1.71 Mb	1.71 Mb	1.71 Mb	1.71 Mb	
Coordinates	111,442,131–113,065,779	111,442,131–113,065,779	111,442,131–113,065,779	111,442,176–113,065,741	111,442,131–113,065,779	111,675,789–113,378,322	111,442,131–113,065,779	112,592,088–113,937,615	111,392,198–113,102,594	111,392,198–113,102,594	111,392,198–113,102,594	111,392,198–113,102,594	
Inheritance	Unknown	Paternal	Unknown	Paternal	Paternal	De Novo	Maternal	Unknown	Maternal	Unknown	Maternal	Paternal	
DD/ID	NA	–	NA	NA	+	NA	NA	+	–	–	+	+	4/7
ASD	NA	–	NA	NA	NA	NA	NA	NA	–	+	+	NA	2/4
Speech delay	–	+	NA	NA	+	NA	NA	+	–	–	+	–	3/8
Hypotonia	–	–	+	–	+	+	+	–	–	+	+	+	7/12
Dysmorphic features	+	+	+	+	+	–	+	+	+	+	–	+	10/12
CHD	TAPVR, VSD, PDA, heterotaxy, aortic coarctation	–	VSD, PFO, 2/6 murmur	AVSD, HLV, ASD, aortic coarctation, hypoplastic aortic arch, 2/6 murmur	Ventricular hypertrophy, slight murmur	–	HLV, ASD, PDA, DORV, PA, 2/6 murmur	TOF, VSD, PA, RSAA, 2/6 murmur	VSD	–	–	–	7/12
Skeletal	–	–	Microcephaly (<1st% tile)	Microcephaly (2nd% tile)	Microcephaly	Macrocephaly	Microcephaly (Slight)	Microcephaly (Mild), absent right 5th metatarsals/ phalanges	Macrocephaly	–	Macrocephaly	Macrocephaly, scoliosis	9/12
Other clinical findings		GERD, hypopigmented spots	Esophageal atresia, hypogonadism, stiff joints,	GERD, short stature (<5th% tile)	Dysphagia, recurrent bronchitis, 7th nerve palsy	Hypospadias, seizures, sleep apnea	Cleft lip/palate, stiff Joints	Hypospadias, bronchomalacia	Anterior anus displacement, hip displacement	Hypogonadism, tall stature, obesity, seizures, panhypopituitarism	Lack of coordination	Tall stature, hypogonadism, molar tooth malformation	
Other cytogenetic findings			der(1) t(1;9) (q43;p21.3). arr[hg18] 1q43q44 (237,788,353) ×1,9p24.3p21.3 (194,193–22,076857)×3						arr[hg19] 2p22(32,480,016–33,189,373)×3		arr[hg19] 22q11.21 (17,270,271–19,891,514)×3		

CHD, congenital heart defect, TAPVR, total anomalous pulmonary venous return; VSD, ventricular septal defect; PDA, patent ductus arteriosis; AVSD, atrioventricular septal defect; HLV, hypoplastic left ventricle; ASD, atrial septal defect; DORV, double outlet right ventricle; PA, pulmonary atresia; TOF, tetralogy of fallot; RSAA, right-sided aortic arch; GERD, gastroesophageal reflux disorder.
Genomic coordinates for chromosome 2 are based on the GRCh37/hg19 build of the human genome.

TABLE IV. Clinical Features of Subjects With Duplications of Chromosome 2q13

	Patient 3	Patient 4 (Family 3)	Subject 12 (Family 3)	Case 5	Total
Reference	Rudd et al. [2009]	Rudd et al. [2009]	This study	Yu et al. [2012]	
Age at assessment	3 yrs	13 yrs	8 yrs	6 yrs	
Gender	M	M	M	M	
Ethnicity	Caucasian	Caucasian	Caucasian	–	
Size of CNV	1.62 Mb	1.62 Mb	1.62 Mb	1.71 Mb	
Coordinates	111,442,131–113,065,779	111,442,131–113,065,779	111,442,131–113,065,779	111,392,198–113,102,594	
Inheritance	Paternal	Paternal	Maternal	Unknown	
DD/ID	+	+	+	+	4/4
ASD	–	+	–	+	2/4
Hypotonia	+	–	NA	+	2/3
Dysmorphic features	+	+	+	–	3/4
Skeletal	Microcephaly (Mild)	Microcephaly (Mild)	NA	Plagiocephaly	3/3

Genomic coordinates for chromosome 2 are based on the GRCh37/hg19 build of the human genome.

somes 1 and 9 [Rudd et al., 2009]. Two patients with 2q13 deletions reported in Yu et al. also carry additional CNVs. Case 1 has a 709-kb duplication of chromosome 2p22 and Case 3 has a 2.62-Mb duplication of chromosome 22q11.21, which overlaps with the 22q11.2 Duplication syndrome critical region [Yu et al., 2012]. It is possible that these additional CNVs contribute to or modify the phenotypes of those with 2q13 deletions. Since none of the CNVs in our study are common in databases of normal variation, it is unlikely that they are benign variants without phenotypic consequences.

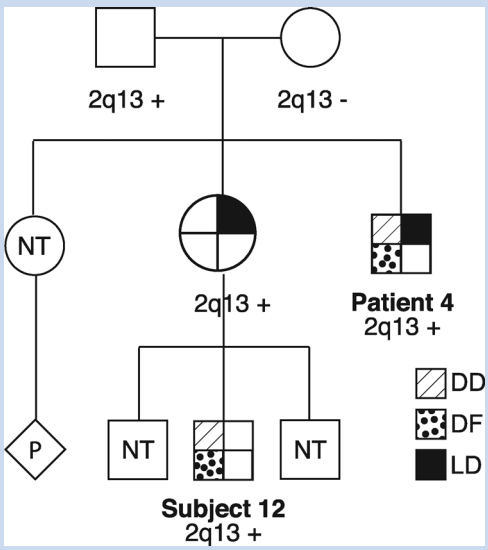

FIG. 3. 2q13 duplication family. Variable phenotypes associated with the 2q13 duplication in Family 3. Those tested for the duplication are indicated by 2q13 + or 2q13—for positive and negative results, respectively. Subject 12's brothers and aunt were not tested (NT). DD = developmental delay, LD = learning disability, DF = dysmorphic features.

Though we have expanded the phenotypes associated with these genomic rearrangements of 2q11.2 and 2q13, without a recognizable set of specific features, clinical diagnosis of microdeletions and microduplications of the long arm of chromosome 2 is not possible. However, this "genotype-first" approach is fast becoming the new standard for diagnosis of children with DD/ID, ASD, and congenital anomalies [Watson et al., 2014]. Though these CNVs exhibit variable expressivity, recognizing the spectrum of associated features and conditions is helpful for parents and healthcare providers. Detecting clinically relevant CNVs early is important to monitor conditions, anticipate future difficulties, and potentially intervene at a young age.

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