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Short Report

A recurrent 1.71 Mb genomic imbalance at 2q13 increases the risk of developmental delay and dysmorphism

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Whole genome profiling such as array comparative genomic hybridization has identified novel genomic imbalances. Many of these genomic imbalances have since been shown to associate with developmental delay, intellectual disability and congenital malformation. Here we identified five unrelated individuals who have a recurrent 1.71 Mb deletion/duplication at 2q13 (Human Genome Build 19: 111,392,197-113,102,594). Four of these individuals have developmental issues, four have cranial dysmorphism. Literature review revealed 14 more cases that had similar genomic imbalances at 2q13. Many of them had developmental delay and dysmorphism. Taken together, 93% and 63% of individuals with this genomic imbalance displayed impaired developmental skills and/or abnormal facial features respectively. This copy number variant (CNV) has not been reported in normal control databases. We, therefore, propose that CNV in this region is a risk factor for developmental delay and dysmorphism.

Conflict of interest

The authors declare no conflicts of interest.

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Whole genome microarray scanning uncovered the widespread existence of copy number variant (CNV), defined as a greater than 1 kb segment of DNA that has variable copy number as compared to reference genome in normal humans (1–3). A large number of novel CNVs have also been discovered among individuals with clinical phenotypes and many of them are known to be associated with diseases (reviewed in Refs (4–6)). Those CNVs that have not been reported in the normal control databases, do not overlap with genomic regions that are known to be associated with disorders and do not involve genes with known dosage effect, are temporally classified as CNV of unknown significance (7). Currently, a significant portion of CNVs detected in patients belongs to this category. It is important yet challenging to establish association between a novel CNV and a clinical phenotype. Such study depends largely on case accumulation which requires a long-term effort.

Here, we present five unrelated children who had a 1.71 Mb deletion/duplication at chromosome 2q13, a CNV of unknown clinical significance. Four such individuals exhibited developmental disability (DD), of which, three carried the diagnosis of autism spectrum disorders (ASD). Further, four of the children had dysmorphic facial features. Although genomic imbalance in this region had been observed previously, its association with DD and facial abnormality was not established (8, 9). Based on the different occurrences of this genomic imbalance in patient and normal populations, we propose that the recurrent genomic imbalance at 2q13 is a novel genetic risk factor for DD.

Materials and methods

Study subjects

Individuals in this study were identified among 5523 consecutive samples with clinical indications of developmental delay, mental retardation and multiple congenital anomalies tested by clinical chromosomal microarray analysis between November 2006 and December 2009. Medical chart review was approved by the Institutional Review Board of the Children's Hospital Boston.

Chromosomal microarray analysis

aCGH was performed using Agilent 244K oligonucleotide CGH array microarray (G4411B) following the manufacturer's instructions [oligonucleotide array-based CGH for genomic DNA analysis protocol version 3 (Agilent Technologies, Palo Alto, CA)] and previously described method (10).

Results

Case 1

This individual was born at 39 weeks gestation by a cesarean section because of breech presentation. aCGH was performed at the age of 4 months for concerns of multiple dysmorphic facial features including hypertelorism, a broad and depressed face, and a prominent forehead, as well as multiple congenital anomalies including several ventricular septal defects, anteriorly placed anus and bilateral partial duplication of collecting system and bilateral bifid ureters. At age 2, no obvious developmental issue was noticed.

Case 2

This individual was born at 37 weeks gestation by cesarean section for breech presentation. Morphological features, including excess nuchal skin folds, wide-spaced nipples and a microphallus, were noticed at birth. At 7 h of life, he developed seizure and hypoglycemia.

aCGH was performed at age of 4 years for concerns of autism, staring episodes, abnormal electroencephalogram, panhypopituitarism associated with a ectopic posterior pituitary and absent infundibular stalk. He is status post-bilateral orchidopexy for undescended testicles, status post-tympanostomy tube insertion and status post-adenotonsillectomy. He has history of attention-deficit hyperactivity disorder (ADHD), obesity and obstructive sleep apnea syndrome.

Case 3

This individual was born at 34 weeks gestation by cesarean section because of premature labor. She was enrolled in an Early Intervention Program with speech and language therapy, occupational therapy and physical therapy since the age of 3 years.

aCGH was performed at age 5.5 years for concerns of pervasive developmental disorder not otherwise specified (PDD-NOS) and macrocephaly. She also presented with symptoms of ADHD. She walked at 2 years of age and began talking at around the same time. At 6 years old, she ran but lacked coordination, and had trouble jumping on one foot.

Case 4

This individual is the product of an *in vitro* fertilization. He was delivered by normal vaginal delivery at 38 weeks gestation. He had transient tachypnea of newborn which was followed by pneumonia.

aCGH was performed at 15 months of age for concerns of developmental delays. He has macrocephaly and partial midline clefting of the upper lip. Scoliosis was noted at the thoracolumbar region. The penis appeared small. He has hypotonia throughout. Brain magnetic resonance imaging revealed slight molar tooth malformation appearance of the midbrain, a small vermis with abnormal cerebellar folia, and a midline vermian cleft with thickening of the superior cerebellar peduncles, suggestive of Joubert syndrome. Diagnostic sequencing of *NPHP1* and *AHI1* genes was normal.

Case 5

This individual was induced because he was late for dates and ultimately delivered by forceps assistance. His early developmental milestones

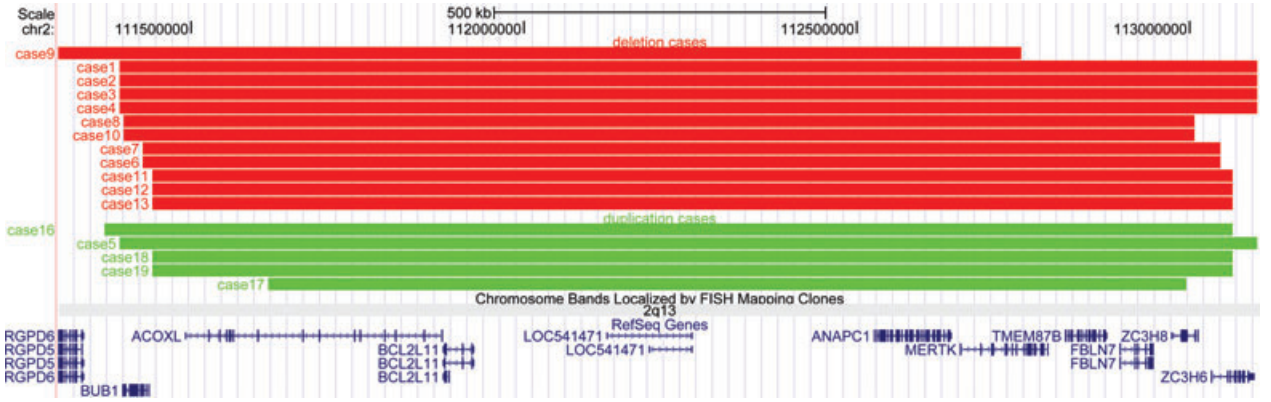

Fig. 1. Genome view of deletion cases (red colored, middle panel) and duplication cases (blue colored, bottom panel) relative to the genomic coordinates, RefSeq genes at 2q13 region, extracted from Human Genome Build 37 (hg19). RefSeq genes are as described in http://www.genome.ucsc.edu/.

were reached late in both language and motor spheres. He had hypospadias and plagiocephaly.

aCGH was performed at 6 years for concerns on PDD-NOS with mild hypotonia and diminished strength. He also had substantial difficulties in fine motor planning (e.g. handwriting).

Individuals 1–4 shared a similar deletion at 2q13 (Fig. 1). Individual 5 had a reciprocal duplication. The region is flanked by segmental duplications of about 76 kb in size and with >99% matched bases (110,552,944-110,586,660 and 113,112,671-113,188,294), which presumably mediated the rearrangement through non-allelic homologous recombination mechanism. The clinical features of the five children are summarized in Table 1. Individuals 2, 3 and 5 were diagnosed with ASD. Individuals 1 and 4 did not meet the age criteria for autism assessment, but individual 4 had some language and motor delays. Three of the four individuals with 2q13 deletion appeared to have large stature and overweight/obesity.

In addition to DD, hypotonia and cranial dysmorphic features were noted among them. All except individual 1 had hypotonia. Individual 1 had hypertelorism and macrocephaly, individuals 3 and 4 also had macrocephaly and individual 5 had deformational plagiocephaly. Some of these appeared to bear resemblance to their parents – individual 1's father also had hypertelorism and both parents of individual 4 had macrocephaly.

Parental aCGH were performed in three cases. All of which (individuals 1, 3 and 4) indicated familial inheritance. Family histories of DD were noted for individuals 3 and 4 – both parents of individual 3 required special education and numerous DD/neurological issues were noted in the family of individual 4.

Discussion

We observed four individuals with a recurrent 1.71 Mb microdeletion at 2q13 from about 5523 cases for clinical diagnostic aCGH testing. Two had ASD. The other two did not meet the age criteria for autism assessment, but one had developmental delays. This microdeletion has not been reported in over 7000 normal individuals recorded in the Database of Genomic Variants (accessed in August 2010) including 2026 healthy children in CHOP CNV database (cnv.chop.edu). The 2q13 deletion is significantly enriched in patient population ($p = 0.04$, χ^2 test with Yates' correction). We therefore propose that this microdeletion is probably clinically relevant.

Ten deletion cases had been reported in the literature (8, 9, 11) and the DECIPHER database (Table 2). Although features of developmental delay and dysmorphism are often documented (8, 9, 11), an analysis of its CNV–phenotype association has not been made and this CNV has not been categorized as pathogenic.

Bisgaard et al. (11) reported two brothers who inherited the 2q13 deletion from their mother (#14, Table 2). Both had significant psychomotor delay and similar mild dysmorphic features. Because the carrier mother was phenotypically normal, the authors concluded that the 2q13 deletion is a normal variant.

Rudd et al. (9) reported the detection of three 2q13 deletions among 2419 samples from patients referred for aCGH testing (#11–13, Table 2). One had severely impaired speech and language skills, and mild facial features; another had intra-uterus growth retardation, and significant dysmorphic facial features including microcephaly, micrognathia, low-set ear, neck webbing and multiple malformations involving congenital heart defect,

Table 1. Clinical features of five children with a 1.71 Mb genomic imbalance at 2q13

	Case 1	Case 2	Case 3	Case 4	Case 5
Age/gender	2/F	6/M	6/F	2/M	6/M
2q13 loss or gain/inheritance	Loss/maternal	Loss/unknown	Loss/maternal	Loss/paternal	Gain/unknown
Additional CNV/inheritance	Gain 2p22: 32480016-33189373/maternal	None	Gain 22q11.21: 17270271 – 19891514/paternal	None	None
Height/weight percentile	56.5th/85th	>97th/>97th	75–90th/90–95th	96th/99th	Not available
Developmental feature	Normal	ASD	PDD-NOS	Developmental delays	PDD-NOS
Cranial/facial dysmorphism	Hypertelorism, macrocephaly (OFC>97th)	None	Macrocephaly (OFC>98th)	Macrocephaly (OFC>97th), partial cleft of upper lip	Plagiocephaly
Muscle tone	Normal	Hypotonia	Hypotonia	Hypotonia	Mild hypotonia
Other clinical features	Ventricular septal defects, hip displacement, anterior anus displacement	Abnormal EEG, panhypopituitarism and large stature, obesity, seizure, glucose control issue, small testes, microphallus, wide-spaced nipples excess nuchal skin folds	Lacking coordination to jump/run	Large stature, scoliosis, small-appearing penis, molar tooth malformation	Hypospadias
Mother's features	None	Not mentioned	Required special education	Macrocephaly	Not mentioned
Father's features	Hypertelorism	Not mentioned	Required special education	Macrocephaly	Not mentioned

Table 2. Clinical features of ten previously reported cases with genomic loss at 2q13

	Case 6	Case 7	Case 8	Case 9	Case 10	Case 11	Case 12	Case 13	Case 14	Case 15
Reference	DECIPHER Pt 250127	DECIPHER Pt 251377	DECIPHER Pt 252425	DECIPHER Pt 250370	DECIPHER Pt 252474	Patient #6 in [9]	Patient #5 in [9]	Patient #7 in [9]	Family #3 brothers 1 and 2 in [11]	NAAR026-A6-3102.002 in [8]
Size and type of 2q13 imbalance/inheritance	1.62 Mb loss/maternal	1.62 Mb loss/unknown	1.61 Mb loss/unknown	1.45 Mb loss/*de novo*	1.61 Mb loss/unknown	1.62 Mb loss/paternal	1.62 Mb loss/unknown	1.62 Mb loss/unknown	Loss/maternal	1.38 Mb loss/unknown
Coordinates (hg18)	111142809–112762656	111142808–112762656	111115715–112724494	111008549–112463408	111115715–112724294	111158601–112782250	111158601–112782250	111158601–112782250	Not specify	111333000–112712000
Additional CNV/inheritance	Gain chr1: 245457485–246645245/paternal	None	Gain chr1: 751796 - 5311663/unknown	None	None	None	None	None	None	None
Developmental feature	Developmental delay/mental retardation	Developmental delay/mental retardation	No specific information (affected)	No specific information (affected)	No specific information (affected)	Severe impaired speech/language skills	No information	Intra-uterus growth retardation	Developmental delay	ASD
Cranial/facial dysmorphism	Microcephaly	Macrocephaly, dolichocephaly microstomia, small and depressed nose, micrognathia	No information	No information	No information	Mild face retraction, widely spaced teeth	No information	Microcephaly, low-set ears, micrognathia, neck webbing	Micrognathia, upslanting palpebral fissure, high nasal bridge	No information
Muscle tone	No information	No information	No information	No information	No information	No information	No information	Hypotonia	Hypotonia	No information
Other clinical features	Hypoglycemia hydrocephalus/large ventricles, non-specific	Scoliosis, pyloric stenosis, broad hand/wide feet, large epiphyses/advanced bone age, brisk reflexes.	No information	No information	No information	Broad feet with short toes	Congenital heart disease, sleep apnea, seizure	Rocker-bottom feet, congenital heart disease, esophageal atresia, small penis, inguinal hernia, agenesis of corpus callosum, apnea	Brother 1: seizure, 5th finger clinodactyly, broad feet; brother 2: hypoglycemia, respiratory insufficiency	No information
Mother's feature	Normal	No information	No information	No information	No information	Normal	No information	No information	Normal	No information
Father's feature	Normal	No information	No information	No information	No information	Normal	No information	No information	No information	No information

esophageal atresia and inguinal hernia. A third exhibited severe congenital heart defect, as well as seizure and sleep apnea. The authors concluded that the clinical significance of this genomic imbalance was emerging with uncertain significance.

Five cases of 2q13 deletion were described in the DECIPHER database (#6–10, Table 2). No clinical information was provided for three of them except that they were affected, the other two had developmental delay. One of the individuals had a *de novo* 2q13 deletion, one had inherited deletion, and the rest had no inheritance information. The *de novo* nature of 2q13 deletion added further evidence supporting the causal role of this deletion in the patient's condition. The fact that the parents of several individuals (#3 and 4, Table 1) were also affected suggested the potential cosegregation of CNV with phenotypes in these families. However, phenotypic discordance among those with inherited genomic imbalances did not necessarily rule out the contributory role of the genomic imbalance to the phenotype.

The reciprocal duplication has also been reported (Table 3). The one in the DECIPHER database (#16, Table 3) did not have detailed clinical information. The other three (#17–19) had developmental delays. In our facilities, we observed one (#5, Table 1) who was diagnosed with ASD. Of all these five patients, four had dysmorphic features (Tables 1 and 3). But unlike deletion, the duplication has been detected in 1/876 normal controls (9). This suggests that the duplication had less penetrance.

Of a total of 19 cases with 2q13 imbalances, documentations of developmental features were available on 14. Out of these 14 cases, 93% (13 of 14) had various degree of developmental delay and five had confirmed ASD diagnosis. It is unclear whether ASD was assessed in the other individuals. Therefore, while our analysis suggests that 2q13 imbalance increases the risk of developmental delay, the exact correlation between ASD and 2q13 deletion/duplication remains to be determined.

In addition to developmental issues, we noted various cranial facial dysmorphism in four of the children we described and eight individuals from the literature (9) and DECIPHER database (Tables 2 and 3). Taken together, at least 12 of 19 (63%) (cases without dysmorphism information were also included in the total case) individuals who had genomic imbalance at 2q13 exhibited some cranial facial dysmorphism. Although some features such as macrocephaly/microcephaly appeared more frequently, no consistent pattern was noticed.

While both deletions and duplications are associated with developmental delay and nonspecific dysmorphism, contrasting phenotypes may exist between patients with the microdeletion and the reciprocal duplication. For example, large body habitual (tall stature, overweight and macrocephaly) were more frequently observed in microdeletion patients; microcephaly and thin body build were more commonly seen in microduplication patients. Such contrasting phenotypes require more cases for validation.

Some individuals carry additional genomic imbalances which could modify the phenotype and/or affect overall penetrance. Individual 1 inherited a 709 kb gain at 2p22 from her mother. Her mother also had the 2q13 loss. Individual 3 inherited the 1.71 Mb loss at 2q13 from her mother, and the 2.62 Mb gain at 22q11.21 from her father. The 22q11.21 gain is known to impair development (12). Both her parents required special educations, which could potentially be caused by the genomic imbalances at 2q13 and 22q11.21. The developmental issues experienced by individual 3 could be the additive effect of genomic imbalances at 2q13 and 22q11.21. Individual 6 inherited a 1.19 Mb gain at 1q44 from a mentally healthy father, and a 1.62 Mb loss at 2q13 from a mentally healthy mother. The combination of two CNVs may exacerbate mental impairment, representing a two-hit model (13). Individual 8 had a 4.56 Mb gain at 1p36 of possible clinical significance.

In the 19 individuals described here, the smallest overlapping genomic imbalance at 2q13 was mapped to the 1.13 Mb at 111,616,529-112,746,937(hg19) (Fig. 1). Of all the genes encoded in this region, *BCL2L11* and *ACOXL* had been linked to neurodevelopment and dysmorphism (14–19). *BCL2L11* encodes an anti-apoptotic protein, Bcl2-like protein which might have a role in neuronal apoptosis. Autistic individuals have been shown to have decreased Bcl2 expression, suggesting increased apoptosis might increase the risk of autism (14–16). *ACOXL* encodes acyl-coenzyme A oxidase-like 2, a protein that is responsible for fatty acid oxidation. Alteration of *ACOXL* gene expression can affect fatty acid metabolism, which has been suggested to play a role in neurodevelopment (17–19).

In summary, we presented five new cases of 1.71 Mb genomic imbalances at 2q13 and revealed 14 similar genomic imbalances at 2q13 from literature and database. Our analysis shows that the 1.71 Mb CNV at 2q13 poses increased risk for DD and cranial facial dysmorphism. This finding added the 2q13 imbalance to a growing number

Table 3. Clinical features of four previously reported cases with genomic gain at 2q13

	Case 16	Case 17	Case 18	Case 19
Reference	DECIPHER Pt 254017	2 individuals from the family 3020 in [8]: NAAR022-E8-3020.004 NAAR035-D5-1014-D5-P1	Patient #3 in [9]	Patient #4 in [9]
Size and type of 2q13 imbalance/ inheritance	1.70 Mb gain/unknown	1.38 Mb gain/familial	1.62 Mb gain/paternal	1.62 Mb gain/paternal
Coordinates (hg18)	111085360–112782191	111333000–112712000	111158601–112782250	111158601–112782250
Additional CNV/inheritance	None	None	None	None
Developmental feature	No information	ASD	Severe developmental delay	Mild developmental delay, apraxia, ADHD, anxiety, Tourette syndrome
Cranial/facial dysmorphism	Microcephaly, cleft palate	No information	Prominent nose with bulbous nasal tip, mild microcephaly with bitemporal narrowing unusual ear pit, dental crowding	Hypertelorism, small mouth with arched palate, small jaw and dental crowding
Muscle tone	No information	No information	Hypotonia	No
Other clinical features	Thin body build	No information	Congenital hypomyelinating neuropathy, severe scoliosis, joint contractures, retinitis pigmentosa, bilateral cryptorchidism	Primary IgG-2 subclass deficiency, mild unilateral sensorineural hearing loss, 5th digit clinobrachydactly
Mother's feature	No information	No information	Normal	Normal
Father's feature	No information	No information	Normal	Normal

of genomic imbalances that have recently been recognized as genetic risk factors for DD (20, 21). Identification of the genetic basis for DD will help better understand the pathophysiology of the condition and allow for better counseling and management.

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