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Microduplications of 1q32.1 associated with neurodevelopmental delay

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Abstract

Distal partial trisomies involving the region 1q32 have been associated with dysmorphic features and developmental delay.[1–11] To further define the critical region for developmental delay and to investigate the genotype-phenotype association of 1q trisomy syndrome, we report two patients with much smaller (3 Mb and 3.5 Mb in size) trisomic regions on 1q32.1. The two microduplications largely overlap and both patients exhibited cognitive and motor delays. Case 1 is a 5-year-old boy with global developmental delay, behavioral problems, pervasive developmental disorder not otherwise specified (PDD-NOS), staring spells, headaches, and paresthesias. Case 2 is a 14-year-old girl with seizures, cognitive and motor difficulties, and minor dysmorphic features. These two cases suggest that 1q32.1 region on distal arm of 1q and genes involved are critical to cognitive and motor development in a gene dosage sensitive manner and that other neurological features are variable within this syndrome.

Keywords

neurogenetics; developmental delay; duplication syndrome; 1q

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1. Methods of detection

1.1 Patient ascertainment

The two probands with 1q32.1 microduplication were seen in the Neurology Department at Children's Hospital Boston (CHB), and diagnostic chromosomal microarray (CMA) test were performed at the Genetic Diagnostic Laboratory at CHB as part of their clinical evaluations. After approval for the study was obtained from the Children's Hospital Boston Institutional Review Board, charts were reviewed for phenotypic information, including developmental history, presence or absence of seizures, examination findings, neuroimaging findings, and electroencephalogram (EEG) data.

1.2 Array-CGH

Whole genome oligonucleotide comparative genomic hybridization (CGH) array (Agilent 244K) were used to detect the 1q32.1 microduplications. The array is designed to detect copy number variants greater than 50 kb. Parental testing was performed when possible in individuals with copy number abnormalities of unknown or possible significance.

1.3 Chromosomal anomaly

In case 1, CMA testing revealed a 3.0 Mb duplication on 1q32.1 (chr1:200481206-203490056 hg19) and in case 2, the duplication is 3.5 Mb in size (chr1:200544702-204050423 hg19) (Figure 1).

1.4 Method of confirmation

In case 1, fluorescent in situ hybridization (FISH) was performed using probes (RP11-51H18) to confirm the duplication and identify the location of the duplicated material (Figure 2). FISH was not performed in case 2.

1.5 Causative of the phenotype

In case 1, the biological parental samples were examined and the duplication was found to be *de novo*. In addition to the 1q32.1 duplication, the proband also carried a 183 kb deletion at 2q34 which is found to be a familial variant inherited from father. This 2q34 deletion in our patient is much smaller than the one reported in Pescucci et al in 2003 which contains 47 genes. In contrast, the deletion in case 1 only contains the intronic sequences of the *ERCC4* gene. The main portion of this deletion was repeatedly observed in normal individuals as reported in Database of Genomic Variants (DGV), so we are quite certain this deletion is a benign polymorphism.

In case 2, the duplication on 1q32.1 is the only CNV in this individual and the inheritance of this duplication is not known since paternal sample was not available, but it is not inherited from mother. The two overlapping duplications were identified from over 8000 probands with neurodevelopmental delay that were examined by diagnostic CMA testing. Duplications in this region were not identified by diagnostic CMA testing in approximately 2000 probands with no developmental delay or neurologic phenotype reported. Compared to previously reported 1q trisomies, the duplications in our patients are much smaller. We searched for additional patients with CNV at 1q32.1 in DECIPHER (Database of Chromosomal Imbalance and Phenotype in Humans Using Ensembl Resources, Accessed on June 27 2011). No similar size duplications were identified. We also searched the DGV (Accessed on June 27 2011) to see if the duplication has ever been detected in normal individuals and found no similar duplications reported. Thus, the duplications at 1q32.1 are rare CNV that are likely causative in these cases.

2. Clinical description

We report 2 cases of duplications in chromosome 1q32.1, 3 Mb and 3.5 Mb in size. Reports of distal partial trisomies involving the region 1q32 have shown association with dysmorphic features and developmental delays as summarized in Table 1. Micro-duplications as found in the following two cases are not previously reported in the literature. The clinical presentations of both cases include developmental delay with cognitive and motor difficulties.

2.1 Case 1

Case 1 is a 5-year-old boy with global developmental delay, behavioral problems, PDD-NOS, staring spells, headaches, and paresthesias. He was born at full term with no prenatal or perinatal complications. Birth weight was 3.6kg (56th percentile), and birth length and head circumference are unknown. He had global developmental delay without regression. He developed two word phrases at 3 years and walked at 2 years. He preferred to play alone and had difficulty with social skills. He had sensory seeking behaviors, repetitive hand mannerisms, and repetitive and compulsive behaviors. He was irritable and had aggressive behavior.

Neuropsychological evaluation was performed at 4 ½ years of age. Autism Diagnostic Observation Schedule (ADOS) was consistent with autism spectrum disorder, and he was diagnosed with PDD-NOS. He was also diagnosed with Anxiety Disorder, Not Otherwise Specified. Verbal and nonverbal skills were in the low average range/slower learning range using the Differential Ability Scale, Second Edition. Kaufman Survey of Early Academic and Language Skills (KSEALS) testing showed low average knowledge.

Additional neurologic symptoms that occurred at 3 years of age include staring spells without other features to suggest seizures, migraine headaches, and paresthesias of the hands. Staring spells and headaches persisted but paresthesias resolved.

Physical examination at 4 years (by neurology and genetics clinics) revealed normal growth parameters except overweight: head circumference 51cm (59th percentile), height 106cm (61st percentile), and weight 22.5kg (98th percentile, +2.0 SD). Ears were mildly everted. There were no dysmorphic features. Neurologic exam revealed irritability and verbal output limited to rare sentences. The remainder of the neurologic and systemic exams was normal.

Routine EEG was normal. MRI spine was normal. MRI brain showed small non-specific subcortical white matter T2 hyperintensities in the frontal and parietal lobes bilaterally and a larger focus in the right occipital lobe, which were not enhancing. A lysosomal enzyme screen was normal, and there were no positive inflammatory or infectious markers to explain the white matter changes on MRI. It is possible that white matter changes contribute to the developmental phenotype, and they may be related to the underlying genetic abnormality.

The proband's father had learning difficulties including dyslexia for which he required special education, and paternal aunt had intellectual disability, severity and etiology unknown. The proband's mother also had learning difficulties, for which she received special education services, and epilepsy (details unknown). One brother and one maternal half-sister are healthy and developmentally normal. Another maternal half-sister has attention deficit hyperactivity disorder (ADHD). Parents are non-consanguineous.

2.2 Case 2

Case 2 is a 14-year-old right-handed girl with a history of developmental delay, cognitive and motor difficulties, and myoclonic epilepsy. She was born at 34 weeks' gestation by

vaginal delivery with normal weight and length: weight was 3.2kg (97th percentile) and length 43 cm (20th percentile), head circumference unknown. There were no perinatal complications.

She had delayed early developmental milestones, primarily with regards to motor skills. She walked at 26 months chronologic age. Physical therapy evaluation at 12 years revealed decreased body awareness and coordination and difficulty with motor planning for new skills. She has had difficulty with fine motor tasks and dexterity. She also has had academic difficulties, and at age 12, she was reading at a third grade level. Neuropsychological exam was completed at age 12 years, 10 months. On the WISC-IV, her full scale IQ was 50 (<0.1 percentile), with scores fairly consistent across the indexes. On the Comprehensive Test of Nonverbal Intelligence she had a nonverbal intelligence quotient in the very poor range. Speech language evaluation also at the same time indicated significant difficulty with receptive and expressive language.

The proband developed myoclonic epilepsy. Her initial seizure semiology consisted of upward eye deviation, limpness and unresponsiveness occurring only in the setting of fever from 18 months to 3 years of age. At 4 to 5 years of age, she developed bilateral upper extremity myoclonic seizures, up to 40 times per day. EEG at 10 years of age showed generalized spike and slow wave discharges, and myoclonic seizures were associated with spike and wave discharges. Her seizures have persisted despite multiple anti-epileptic medications, with the most recent frequency one per day. She had a normal MRI brain at 6 years of age, and normal karyotype and Fragile X testing.

Physical exams have shown normal growth parameters, at 10yrs 9 months length 138.1 cm (27th percentile), weight 51.8kg (93rd percentile), head circumference 52cm (34th percentile). She has minor dysmorphic features including outer canthal distance >97th percentile, small teeth, and a single palmar crease in the right hand. Neurologic examination was significant for emotional immaturity, difficulty following directions, bilateral tight heel cords and difficulty with tandem gait. She had otherwise normal neurologic and systemic exams.

Family history is significant for a paternal half-brother with febrile seizures and learning disabilities. Parents are non-consanguineous.

3. Discussion

We present two cases of 1q32.1 micro-duplications detected by clinical CMA testing. The most notable shared feature of these cases is neuro-developmental delay and on-going intellectual disability. One case presented with features of PDD, and the other case presented with intractable myoclonic epilepsy.

There are reported cases of larger simple partial 1q duplications involving the region 1q32. [1–11] There are more reports of 1q duplications associated with unbalanced translocations. [5] Of the simple partial 1q duplications involving the region 1q32, developmental delay and mental retardation are common phenotypic features. Brain malformations and epilepsy are reported in some cases. Other phenotypic features often include growth retardation, microcephaly, congenital heart disease, large fontanelles, laryngomalacia, and dysmorphic features, including prominent forehead, pointed chin, flat nasal bridge, downslanting palpebral fissures, low set posteriorly rotated ears with abnormal pinnae, cleft of high arched palate, and overlapping toes. Tables 1 and 2 include our cases and a summary of many of the reported cases in the literature.

Many genes located in the duplicated region are expressed in the brain including *KDM5B*, *NAV1*, *KIF21B*, *UBE2T*, *PPR1R12B*, and *SYT2*. One or a combination of these genes could be responsible in a dose sensitive manner for the neurodevelopmental phenotypes of our patients.

We searched the DECIPHER database (Database of Chromosomal Imbalance and Phenotype in Humans Using Ensembl Resources) to see if any similar duplications were reported. While no similar size duplications were reported in the database, there are several patients with much smaller duplications (160 and 385Kb) or deletions (920, 454 and 281Kb) that were clustered at chr1:202,269,935-202,724,206 (Figure 1). All duplication cases had many other CNVs in the genome and some of the genomic variants were larger and more likely to be responsible for the patients' phenotypes. Thus, smaller duplications at 1q32.1 are less likely to be pathogenic. In addition, we observed similar clustering of benign CNV in the Database of Genomic Variants (DGV) database at the same location (Figure 1), further demonstrating its non-pathogenic nature of those smaller duplications. This evidence makes brain expressed genes within this small region, *PPP1R12B*, *SYT2* and *UBE2T* less likely candidate genes for patients' phenotype of developmental delay and intellectual disability.

Of the remaining brain expressed genes, *KDM5B* is a histone lysine demethylase. Histone lysine demethylases play a role in stem cell maintenance, neural differentiation, development, and disease.[12,13] In humans, mutations in *KDM5C*, a similar histone lysine demethylase, are associated with X-linked mental retardation.[12,13] *NAV1* is a gene belonging to the neuron navigator family, expressed predominantly in the nervous system during development.[14] *Nav1* associates with microtubules plus ends and as such is involved in growth cone dynamics of dendrites and axons in migrating neurons. *KIF21B* belongs to a family of plus end-directed kinesin motor proteins.[15] Though there are no clinical associations known with *KIF21B*, there are clinical associations with mutations of related kinesin genes including Charcot-Marie Tooth disease type 2A (*KIF1Bβ*), congenital fibrosis of the extra-ocular muscles (CFEOM1) (*KIF21A*), hereditary spastic paraplegia (*KIF5*), and schizophrenia (*KIF17*). Thus, these three genes that play a role in neurodevelopment may either individually or in combination due to dosage effect be responsible for the phenotype of developmental delays and intellectual disability seen in our two cases.

The two cases reported here who shared similar duplications and phenotypes, supporting 1q32.1 as critical region on 1q for neurodevelopment. These cases suggest a novel genomic disorder at 1q32.1 region.

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Highlights

- Large partial trisomies of chromosome 1q are associated with developmental delays.
- We describe two probands with 1q32 micro-duplications and developmental delays.
- We propose possible candidate genes in the region including *KDM5B*, *NAV1*, and *KIF21B*.

Figure 1. UCSC Genome Browser view of 1q32.1. The top panel shows the two duplications reported here. Refseq genes, DECIPHER cases and Database of Genomic Variants (DGV) cases are shown below the custom track.

Figure 2. FISH confirmation of the 1q32.1 duplication. Chromosome 1 centromere specific alpha-satellite probe D1Z5 (green signals) was used as control probe. 1q32.1 region specific probe RP11-51H18 (red signals) showed increased signal on a metaphase chromosome 1 and three separate signals in an interphase nucleus.

Table 1

Overview of the clinical features of cases in the literature of pure partial 1q duplication involving 1q32 and the two cases presented here.

	Steffensen et al. 1977	Palmer et al. 1977	Lungarotti et al. 1979	Schinzel et al. 1979	Clark et. al 1994	Duba et al. 1997	Sillen et al. 1998	Schorry et al. 1998 Patient #1	Schorry et al. 1998 Patient #2	Nowaczyk et al. 2003	Utine et al. 2007 Patient #1	Utine et al. 2007 Patient #2	Balasubramanian et al. 2009	Case 1	Case 2
Duplicated region	1q31q43 ~44	1q31-q32	1q32-q42	1q25-q32	1q32-qter	1q32-qter	1q31q41	1q31.1-q32.1	1q31.1-q32.1	1q32q44	1q31q43~44	1q23q31.3~32	Inverted 1q32.1 q44	1q32.1	1q32.1
Age at last report	6 wks (died)	22 months	7 months	4 months (died)	1 day (died)	46 months	20 years	5 ½ years	17 months	9 months	Fetus (autopsy)	45 days	9 ½ months	5 years	14 years
Developmental delay?	NA	?	Severe	+	NA	Severe	Severe	–	–	Severe	NA	NA	Moderate	+	+
Intellectual disability	NA	?	NA	NA	NA	Severe	Severe	–	Unknown	Unknown	NA	NA	NA	+	+
Seizures?	–	***	+	–	–	–	***	–	–	–	NA	–	–	–	+
Hypotonia?	–	?	–	+	?	?	+	–	?	?	NA	?	?	–	–
Autistic features?	NA	NA	NA	NA	NA	–	+	–	–	–	NA	NA	NA	+	–
Brain malformations	–	Unknown	Unknown	Unknown	+	–	Unknown	+	Unknown	+	–	+	–	–	–
Head size	Normal	Micro	Micro	Not reported	Macro	Micro	Normal	Micro (5%)	Normal	Normal	Normal	Normal	Normal	Normal	Normal
Growth delay	Low birth weight	+	Low birth weight	+	Birth Wt 10%	+	–	+	IUGR,?	+	–	–	–	–	–
Large fontanelle, wide sutures	+	–	+	–	+	+	–	–	–	–	–	–	+	–	–
Cardiac anomalies	+	–	–	+	+	+	–	–	–	+	+	+	–	–	–
Tracheo-esophageal anomalies	–	–	–	–	–	+	–	–	–	+	–	–	+	–	–
Lower GI anomalies	–	–	–	–	+	+	–	–	–	–	+	–	–	–	–
Genitourinary anomalies	–	–	+	–	+	+	+	–	–	+	+	–	–	–	–
Renal anomalies	–	–	–	–	+	+	–	–	–	+	+	–	–	–	–
Ophthalmologic anomalies	–	+	–	–	–	+	–	–	–	–	–	–	–	–	–
Cleft lip and/or palate	–	–	–	–	–	+	–	–	–	–	+	–	–	–	–
Dysmorphisms§	+	+	+	+	+	+	+	+	+	+	+	+	+	–	+

* with hypoglycemia

*** after cardiac arrest.

§ See Table 2 for description of dysmorphic features.

Table 2

Overview of the reported dysmorphisms of cases in the literature of pure partial 1q duplication involving 1q32 and the two cases presented here.

Dysmorphisms							
	Ears	Eyes	Nose	Face/mouth	Neck/Torso	Extremities	
Steffensen et al. 1997	Low set, posteriorly rotated	Microphthalmia Antimongoloid slant	Low, flat bridge	Triangular shape Midface hypoplasia Microstomia	Redundant nuchal skin folds Widely spaced nipples	Digits long and dysplastic	
Palmer et al. 1977	Low set, posteriorly rotated	Microphthalmia Narrow palpebral fissures		Small mouth. High arched palate.			
Lungarotti et al. 1979	Poorly modeled helix Deep conchae Hypoplastic lobes		Small with rounded tip	Triangular face. Long philtrum. High arched palate	Widely spaced nipples	Bilateral single palmar crease Over-riding toes	
Schinkel et al. 1979	Dysmorphic	Deep-set	Broad nasal bridge	Small mouth High-arched palate Receding mandible			
Clark et. Al 1994	Low-set, posteriorly rotated Malformed	Short palpebral fissures			Short neck	Tapered, incurved index and 5th fingers Short great toes	
Duba et al. 1997	Low set, posteriorly rotated	Downslanting palpebral fissures	Broad, pointed Flat nasal bridge		Widely spaced nipples	Polydactyly Long and over-riding toes	
Sillen et al. 1998	Low set	Downslanting palpebral fissures	Large, beaked	Long philtrum Thin upper lip	Hypertrichosis	Polydactyly	
Schorry et al. 1998 Patient #1	Simplified helices	Microphthalmia Narrow, upslanting palpebral fissures	Flat nasal bridge	Small mouth, thin lips			
Schorry et al. 1998 Patient #2		Narrow palpebral fissures				Mild clinodactyly Wide gap between toes 1 and 2 bilaterally	
Nowaczyk et al. 2003	Round Unfolded helices	Hypertelorism			Widely spaced nipples	Over-riding toes	
Uitene et al. 2007 Patient #1	Low set, posteriorly rotated Poorly formed.			Micrognathia		Polydactyly Toes long and overriding	
Uitene et al. 2007 Patient #2	Over-folded upper helices	Narrow palpebral fissures Hypertelorism	Wide flat nasal bridge	Long face Long smooth philtrum Micrognathia High palate		Long fingers and toes	
Balasubramanian et al. 2009	Low set, posteriorly rotated	Downslanting palpebral fissures.		Groove between forehead and nasal bridge	Pectus excavatum Hypertrichosis	Single palmar crease 3rd toes small Over-riding toes	
Case 1							

Dysmorphisms					
Ears	Eyes	Outer canthal distance wide	Nose	Face/mouth	Neck/Torso
				Small teeth	
					Extremities
Case 2					Single palmar crease