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CASE REPORT

Genomic characterization of chromosome 8 pericentric trisomy

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Key Clinical Message

We present a patient with trisomy 8p11.21q11.21 associated with language, gross motor, fine motor, and cognitive delay. Furthermore, using array-based comparative genomic hybridization, we identify the specific genes duplicated in our patient.

Keywords

Ankyrin, Array-based comparative genomic hybridization, Duplication chromosome 8p11.21q11.21, global developmental delay.

Introduction

Variation in gene copy number detected by array-based comparative genomic hybridization (aCGH) has led to a better understanding of the genetic basis of sporadic intellectual disability [1, 2]. Recently, we identified a patient where supranumerary DNA material was located on a marker chromosome, a structurally abnormal chromosome in which no part can be identified. Marker chromosomes are 10 times more likely to be found when a patient suffers from intellectual disability (ID) [3]. Moreover, in 80% of the cases, the DNA originates from the pericentromeric region [4].

Here, we present a patient with global developmental delay (DD) associated with a *de novo* 8p11.21q11.21 duplication found on a supranumerary marker chromosome for which gene-specific information was obtained using aCGH. Pham et al. [5] have recently used CGH to determine the level of mosaicism in patients with intellectual disability, which included the investigation of trisomy 8; however, the specific genes involved were not published.

Results

Case description

The propositus is a 3-year-old right-hand dominant girl who presented to a multidisciplinary neurodevelopment clinic with a question of developmental delay and hypotonia. Early spotting in the third week complicated the pregnancy however, no subsequent difficulties occurred. She was born at 41 weeks of gestation by vaginal vertex delivery. Apgar scores were 8 at 1 min and 9 at 5 min. The birth weight was 3935 grams. She had a stable neonatal course and was breastfed for the first 7 months of life. She presented with early emesis but with no history of reflux or aspiration. She did have a history of chronic respiratory congestion since early infancy and was subsequently diagnosed with asthma; which was treated with Flovent and Ventolin. She had a history of recurrent middle-ear infections requiring myringotomy tubes. Serial neuro-opthalmologic assessments were performed for mild intermittent exotropia, which had been improving. An MRI of her brain

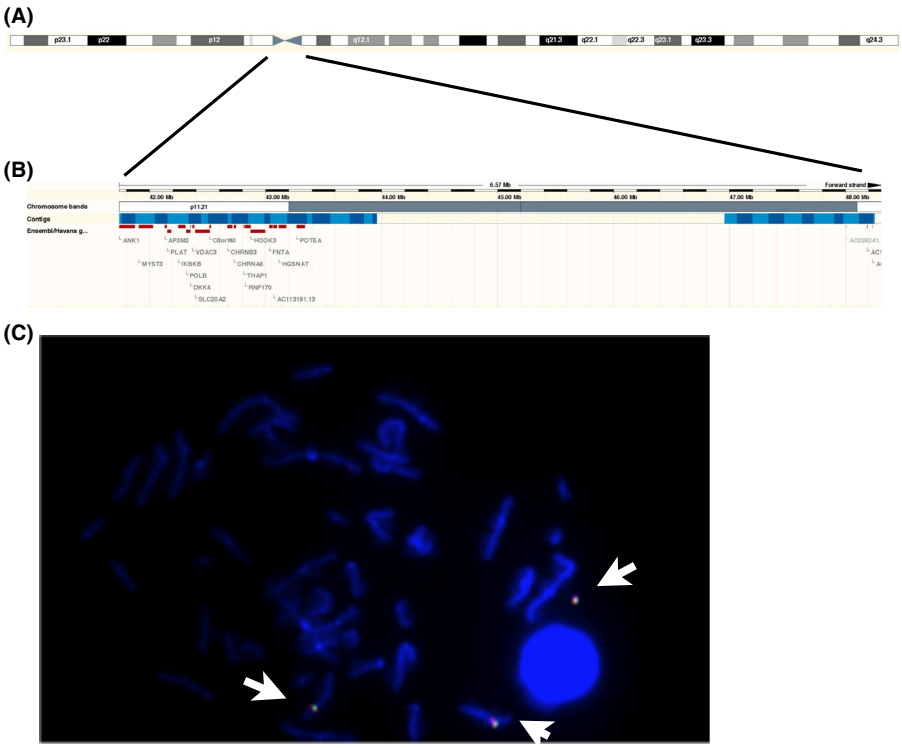

Figure 1. Duplication of pericentric region of chromosome 8. (A) Representation of the region of chromosome 8 that is present in the supernumerary marker chromosome 8. (B) The genes with increased copy number are illustrated. (C) FISH probe illustrating the supernumerary copy of chromosome 8 probe.

at 1 year of age showed normal brain structures with no evidence of agenesis of the corpus callosum.

Early in her second year of life, her parents were concerned when her walking milestone was delayed. She walked at the age of 23 months, but continued to have difficulties with balance and coordination and was quite a cautious child. Her first words were around the age of 8 months. Slow progress was made and by her assessment at 31 months of age she had approximately 30 single words and was not combining words into phrases. She had difficulties with pronunciation and remained unintelligible to unfamiliar people. In her fine motor skills, she was found to be severely delayed in both manipulation and skills required for self-care. She was not toilet trained. A decrease in pain sensation was also reported. She was very social, had a happy temperament and enjoyed a variety of play activities although at a younger developmental level than her chronological age. There was no regression and no signs of autism.

A formal assessment of her motor development using the Peabody Developmental Motor Scale (PDMS-2) at the age of 31 months indicated that she had a severe delay in fine and gross motor skills. On the Fine Motor Scales Subset, she scored less than the first percentile with overall skills equivalent to those of a 17-month-old in visual motor tasks and that of an 11-month-old in hand grasping skills. In the Gross Motor Scales Subset, she was at the second percentile and this gave her an age equivalent of 16 to 17 months. Her speech and language development was assessed using the Preschool Language Scales 4 (PLS-4) and was found to be at the first percentile for both auditory comprehension and expressed communications. Her overall cognitive abilities were assessed using the Bailey Scales of Infant and Toddler Development 3rd Edition Cognitive Scales, where she was found to be in the extremely low range at approximately the 17-month-old level, suggesting that she would learn at a slow rate and would require repeated learning opportunities to acquire new concepts.

Her family history revealed that both parents are healthy, nonconsanguinous and have completed university degrees. The only other pregnancy was that of a 4-year-old sister with normal developmental. A paternal uncle died at 6 years of age with a history of motor developmental disability and one of the father's cousins was diagnosed with autism.

On physical examination, the patient was very interactive with good eye contact. Her weight was 12.8 kg (25%), height was 93 cm (50%), and head circumference was 47.5 cm (30%), with a prominent forehead. Bilateral supranumerary nipples were present on general

examination and was otherwise normal. Her skin examination revealed a small midline hemangioma over the upper back. Generally decreased tone was revealed from her neurological examination and her deep tendon reflexes were 1+ in the upper and lower extremities. She could walk independently but fell quite often during the examination. She had a wide-based gait on assessment.

Molecular studies

Informed consent was obtained from the patient's parents for genetic studies. Karyotyping was performed at the University of Alberta Stollery Children Hospital cytogenetics laboratory with twenty metaphases at 550 GTG-banded resolution, revealing the presence of supernumerary chromosome marker in all five cells analyzed. This supernumerary chromosome was C-band negative and was not recognized by a fluorescence *in situ* hybridization (FISH) probe to the acrocentric chromosome short arms (acro p). This indicated that the marker chromosome was composed of euchromatic chromatin and was likely to contribute to the abnormal phenotype. Both parents had a normal karyotype. Further investigation with an array-based comparative genomic hybridization analysis, using 105K CMA OLIGO V7.2, was performed at the Baylor College of Medicine (http://www.bcm.edu/geneticlabs/cma/tables.html) by the Kleberg Cytogenetics Laboratory. Confirmatory FISH analyses, using the BAC clones RP11-589C21, RP11-465K16, and RP11-1134114 was also performed at the Baylor College of Medicine. It identified a duplication of chromosome 8p11.21q11.21 with minimal interval 41772739–48248222 representing a 6.475 Mb duplication of chromosome 8 (Fig. 1). The maximal duplication interval included 41739024–48312482 representing 6.573 Mb. The region included several genes ANK1, MYST3, AP3M2, PLAT, IKBKB, POLB, DKK4, VDAC3, SLC20A2, CBorf40, CHRNB3, CHRNA6, THAP1, RNF170, HOOK3, FNTA, FLJ23356, HGSNAT, and A26A1 (Table 1). Both parents were tested using the same FISH probes and did not show presence of the supranumerary chromosomal 8 material, indicating the *de novo* nature of the defect in the child.

Discussion

Duplications of various regions of chromosome 8 have been described previously (Table 2). Five of these patients were diagnosed prenatally and 25 patients postnatally. Of the thirty patients reviewed, seven were nonmosaic. The associated phenotypes range from normal (14, 15, 18, 34, 36, 37) to anomalies consistent with trisomy 8 syndrome. Trisomy of the entire human chromosome 8 has been associated clinically with prominent forehead, hypertelorism, deep-set eyes, low set cupped ears, micrognathia, a broad nasal root, limb defects, urogenital disease, congenital heart disease, Rieger malformation [6, 7], and absence of the corpus callosum [8–13]. Of the 30 children reviewed, 18 (60%) were reported as having craniofacial anomalies. Table 3 summarizes the reported dysmorphic

Table 1. Genes included within the duplicated region. The genes involved in the duplicated area are listed with corresponding OMIM accession number. The role of the gene is listed. When available, a reference to the literature is described in the last column.

Gene	OMIM Number	Role	CNS References
ANK1	612641	Erythrocyte structure	ID [22]
MYST3	601408	Histone acetyltransferase	
AP3M2	610469	Clathrin adaptor	
PLAT	173370	Plasminogen activator	Fear conditioning [26]
IKBKB	603258	Activation of NFKB	
POLB	174760	DNA polymerase	
DKK4	605417	Antagonist of Wnt protein	
VDAC3	610029	Voltage-dep anion channel	Muscle mitochondria malformation [27]
SLC20A2	158378	Murine leukemia virus receptor	
CBorf40			
CHRNB3	118508	Neuronal Cholinergic receptor	Beta-3 subunit [28]
CHRNA6	606888	Neuronal Cholinergic receptor	Alpha polypeptide [29]
THAP1	609520	Atypical zinc finger proapoptotic	
RNF170			
HOOK3	607825	Endocytic pathway. Binding organels and microtubule	[30]
FNTA	134635	Posttranslational modifications:prenylation	RAS localization [31]
FLJ23356			
HGSNAT	610453	Lysosomal acetylation of heparan	MPS3 [32]
A26A1			

Table 2. Comparative analysis of the general features associated with partial chromosome 8 trisomy in previous studies and our patient.

	Marker Freq (%)	Marker formation	Age at diagnosis	Gender	Lt/Wt/OFC (%tile)	Reported clinical features
Current Study [2015]	100	8p11.21q11.21	3 years	F	50/25/30	Moderate DD, Hypotonia, Prominent forehead, Intermittent exotropia, Bilateral supernumerary nipples, Single hemangioma
Allen and Hodgkin [1983]	–	8p21-pter	Birth	F	<3/<3/3	Mild DD, Hypotonia, Hydrocephalus, Craniofacial anomalies, VSD, Coarctation of aorta
Blennow et al. [1993]	40–72	Ring centromeric	1 year	F	–	Motor retardation, Hypotonia, Craniofacial anomalies, Bilateral pes equinovarus, Narrow shoulders, Accessory nipple, Severe hearing deficit
Daniel et al. [1993]	50	–	7 years	M	Normal	ID Craniofacial anomalies, Hyperextensibility of elbows and MP joints, Clawing second –fifth toes
Plattner et al. [1993]	95	Ring centromeric	Prenatal	M	75/80/80	Moderate DD, Craniofacial anomalies, Deep palmar crease, Mildly hypoplastic widely spaced nipples
Digilio et al. [1994] Patient 1	73	Isodicentric 8p;8p	14 month	F	25/<3/25–50	Mild DD, Agenesis corpus callosum, Craniofacial anomalies, Valvular pulmonary stenosis, Secundum ASD, Camptodactyly, Deep plantar crease, Flat angioma
Digilio et al. [1994] Patient 2	–	Isodicentric 8p;8p	2 month	M	-/<3/10	Moderate DD, Hypertonis. Agenesis corpus callosum, Cystic tumor in occiptal region, VSD with persistent left superior vena cava, Empty scrotum, Short distal phalanges, Hypoplastic nails, Palmar furrows, Varus deformity of right foot, Short metatarsals, Cutaneous syndactyly of second and third toes, Advanced bone age, 13 paired ribs, " Bone within bone" image in vertebral bodies, Asymmetric ossification of femoral heads, Single hemangioma
Melnyk and Dewald [1994]	100	8p11.2-q11.2	15 month	F	25/75/<5	Moderate DD, Hypotonia, Seizure, Craniofacial anomalies
Ohashi et al. [1994]	100	Submetacentric	2 years	F	25/25/97	ID Craniofacial anomalies, Patent ductus arteriosus with pulmonary hypertension,
Butler et al. [1995]	41	Pericentric	3 days	F	95/90/60	Mild DD, Craniofacial anomalies, Hydronephrosis, Vesicouretral reflux, Low ureter insertion, Absent clitoris, Bilateral fifth finger, Clinodactyly, Sprengel deformity, Long slender trunk
Gravholt and Friedrich [1995]	48–67	Centromeric	7 years	F	–	–
Sasagawa et al. [1995]	100	P11-q11	10 years	M	–	ID Monorchidism, Cryptorchidism
Spinner et al. [1995]	68	Pericentric p11-q11	7 months	M	90/-/90	Mild DD, Craniofacial anomalies, Malrotation kidneys, Thickened extrarenal pelvis, Hydronephrosis, Camptodactyly, Overlap of toes, Malalignment of feet, Hypoplastic

(*Continued*)

Table 2. Continued.

	Marker Freq (%)	Marker formation	Age at diagnosis	Gender	Lt/Wt/OFC (%tile)	Reported clinical features
						patellae, Deep plantar crease, Extra lumbar vertebrae, Bifid vertebrae, Hypoplastic iliac bones, Advanced bone age, Long slender trunk, Anteriorly placed anus
Rothenmund et al. [1997] II-1	10	Pericentric	30 years	M	>95/25/90	Long slender trunk, Myopia
Rothenmund et al. [1997] III-1	98	Pericentric	4 years	F	90/75/40	Moderate DD, Autistic behaviour, Duplicated thumb, Long slender trunk
Rothenmund et al. [1997] III-2	97	Pericentric	Birth	F	75/50/10	Mild DD, Coarctation of aorta, Long slender trunk
Starke et al. [1999]	54	8p11-q11	Prenatal	F	–	Unilateral slightly enlarged ureter, Prenatal U/S of echogenic bowel
Batanian et al. [2000] Patient 1	72	8cen-p12	5 years	M	45/50/80	Moderate DD, ADHD, Seizure, Craniofacial anomalies, Small scrotum, Hypermobility, Long slender trunk
Batanian et al. [2000] Patient 2	100	8cen-p21	10 years	F	>98/>98/98	Moderate DD, Seizure, Aggressive behaviour, Craniofacial anomalies, Anomalous pulmonary venous return, Precocious puberty, ITP, JODM
Batanian et al. [2000] Patient 3	50	Dup (8cen-p21)	Prenatal	F	75/75/75	Hydrocephalus, Craniofacial anomalies, Hypoplastic toenails, Multiple hemangiomas
Tonk et al. [2000] Patient 1	100	Pericentric	7.5 months	F	25/25/25	Mild DD, Hypotonia, Craniofacial anomalies, Two hemangiomas
Tonk et al. [2000] Patient 2	100	Pericentric	6 months	M	>95/>95/>95	Moderate DD, Hypotonia, Agenesis corpus callosum, Craniofacial anomalies, Single hemangioma
Daniel and Malafiej [2003] Case 2	34	Ring with 8ptel signal	21 years	F	Short	ID Infertile, Central obesity
Daniel and Malafiej [2003]Case 3	27	Ring negative with pantelomeric probe	31 years	F	–	–
Daniel and Malafiej [2003]Case 6	54	Ring negative with pantelomeric probe	9 years	F	–	Severe DD, ADD, Mild ataxia, Craniofacial anomalies
Loeffler et al. [2003]	70	8p12-q12	16 years	F	>40/75/-	Mild DD, Craniofacial anomalies, Renal hypoplasia, Duplicated collecting system, Bertin column, Muellerian aplasia, Small phalanges of fingers, Minor toe anomalies, Deep plantar creases, Scoliosis, Congenital hip dysplasia, Sacral hypoplasia, Absent os coccyx, Glaucoma
Herry et al. [2004] Patient 1	76	Pericentric	29 years	M	–	Mild DD
Herry et al. [2004] Patient 2	50	Inversion duplication (8)(p23pter)	Postnatal	M	–	–
Gole and Biswas [2005]	50	Pericentric	Prenatal	F	–	U/S of echogenic bowel
Bettio et al. [2008]	96	Pericentric p11.21-q11.21	Prenatal	F	25/10–25/95	Mild DD, ADHD, Flat occiput, Right supernumerary nipple

facial features. Starke [14] described a patient with a trisomy limited to the pericentromere region, which did not contain euchromatic material that was clinically asymptomatic at 9 months of age. Gole [15] presented another case of 8 pq centromeric material, but with a small amount of euchromatin, that was also clinically asymptomatic at 5 months of age. Extension of duplication beyond the pericentromere to 8p11.22 (short arm) or to 8q11.22 (long arm) has been associated with developmental delay, attention difficulty and autism. Based on review

Table 3. Specific dysmorphic facial features associated with partial chromosome 8 trisomy.

Dysmorphic Facial Feature	Number of Children with given feature among children with reported craniofacial anomalies 18 (%)
Eyes	
Deep set	4 (22)
Epicanthal folds	6 (33)
Upslanting palpebral fissures	3 (17)
Hypertelorism	5 (28)
Long eyelashes	1 (6)
Strabismus	2 (11)
Nose	
Upturned tip	5 (28)
Wide nasal bridge	6 (33)
Mouth	
Downturned corners	2 (11)
Long philtrum	3 (17)
High arched palate	4 (22)
Ears	
Low set	8 (44)
Abnormal helix	11 (61)
Head & Neck	
Prominent forehead	8 (44)
Micrognathia	2 (11)
Short Neck	3 (17)
Abnormal skull shape	5 (28)
Excess nuchal skin	2 (11)

of reported clinical findings in children with partial trisomy 8, it appears patients receiving this diagnosis should have a full screening assessment for possible associated anomalies of the cardiac (6 of 30 reviewed patients), renal (4 of 30 reviewed patients), genitourinary (6 of 30 reviewed patients), skeletal (10 of 30 reviewed patients), and dermatologic (6 of 30 reviewed patients) systems.

More recently, reports using focal *in situ* hybridization (FISH) of older patients with marker chromosome containing at least the centromeric region identified variable semiology ranging from isolated growth retardation [16] to association with cutaneous anomalies, ankylosed large joint, clubfoot, absent or hypoplastic patellae, brachydactyly, deep set eye, prominent nasal tip, everted lower lip, and small jaw. In addition, cryptorchidism and deep longitudinal plantar or palmar skin furrows were observed. Psychomotor retardation was usually mild to moderate and affected most severely expressive language skills [17–21].

For the first time in pericentromeric chromosome 8 duplication, array-based comparative genomic hybridization allows the identification of specific genes involved within the duplicated area. Our patient's duplication involves ANKYRIN 1 (*ANK1), HISTONE ACETYLTRANSFERASE MYST 3 (MYST3), ADAPTOR-RELATED PROTEIN COMPLEX 3, MU-2 SUBUNIT (AP3M2), PLASMINOGEN ACTIVATOR, TISSUE (PLAT), INHIBITOR OF KAPPA LIGHT CHAIN GENE ENHANCER IN B CELLS, KINASE OF, BETA (IKBKB), POLYMERASE, DNA, BETA (POLB), DICKKOPF, XENOPUS, HOMOLOG OF, 4 (DKK4), VOLTAGE-DEPENDENT ANION CHANNEL 3(VDAC3), SOLUTE CARRIER FAMILY 20 (PHOSPHATE TRANSPORTER) MEMBER 2 (SLC20A2), CBorf40, CHOLINERGIC RECEPTOR, NEURONAL NICOTINIC, BETA POLYPEPTIDE 3 (CHRNB3), CHOLINERGIC RECEPTOR, NEURONAL NICOTINIC, ALPHA POLYPEPTIDE 6 (CHRNA6), THAP DOMAIN-CONTAINING PROTEIN 1 (THAP1), RING FINGER PROTEIN 170 (RNF170), HOOK, DROSOPHILA, HOMOLOG OF, 3 (HOOK3), FARNESYLTRANSFERASE, CAAX BOX, ALPHA (FNTA), PROTEIN KINASE-LIKE PROTEIN SGK196 (FLJ23356), HEPARAN-ALPHA-GLUCOSAMINIDE N ACETYLTRANSFERASE (HGSNAT), PROTEIN ANKYRIN DOMAIN FAMILY, MEMBER A, TRANSCRIPT VARIANT 2 (A26A1)*.

Although several genes are contained within the duplicated region for our patient, several genes have already been linked to neuronal function previously. Ankyrin mutation was identified in one patient with intellectual disability [22]. The molecular mechanism linking Ankyrin to ID remains unclear since, so far, the role of ankyrin has been mostly explored with erythrocyte shape. *HGSNAT* (heparan-alpha-glucosaminide N-acetyltransferase) has been linked to a storage disease named mucopolysaccharide type 3 causing neurodevelopmental disability. HGSNAT is responsible for lysosomal acetylation of heparan. *MYST3* encodes a histone acetyltransferase that has not been previously linked to developmental disability or congenital malformation. *CHRNB3* (Cholinergic receptor, nicotinic, beta 3) and *CHRNA6* (cholinergic receptor, nicotinic, alpha 6) both encode subunits of neuronal cholinergic receptors. They have not been linked to human neurological disorders yet. *THAP1* (THAP domain-containing, apoptosis associated protein 1) encodes an atypical zinc finger proapoptotic protein. Zinc finger-containing transcription factors have recently been linked to intellectual disability [23] and dystonia [24]. THAP1 has been directly linked with torsion dystonia-6 in multiple cases. Other genes such as *PLAT* (plasminogen activator, tissue), *POLB* (DNA polymerase B), *DKK4* (dickkopf -Xenopus laevis- homolog 4), *SLC20A2* (solute carrier family 20 (phosphate transporter), member 2) have not been linked to neuronal phenoytpe or human intellectual disability disorders so far. *HOOK3* (hook homolog 3) was initially identified in *Drosophila* as a linker between organelles and microtubules. Although no published report links *HOOK* to neurological disorder, it is possible

its role in endocytosis and microtubule-dependent transport participate in neuronal function. Zeng [25] and others have shown that cargo transport along microtubule was taking place in neurons. *FNTA* (farnesyltransferase alpha) has been linked to posttranslational modification leading to proper Ras localization.

In summary, to our knowledge, our patient is the first case of developmental delay in isolation with nonmosaic trisomy of chromosome 8p11.21q11.21 for which aCGH allowed to identify several candidate genes involved in neuronal function that could explain the patient's clinical phenotype. Further reports with overlapping duplication will be required to dissect more precisely the specific genotype–phenotype correlation of each gene. All in all, our report indicates that 8p11.21q11.21 trisomy should be considered in children with developmental delay.

Conflict of Interest

The authors have no conflict of interest.

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