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-ophthalmologic assessments were performed for mild intermittent exotropia, which had been improving. An MRI of her brain
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 development. 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 supranumery nipples were present on general

![Figure 1. Duplication of pericentric region of chromosome 8.](image_url)
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                     |                          |
| IKBKB     | 603258      | Activation of NFkB                        | Fear conditioning [26]   |
| 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 organel 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      | 8p1.12.1q11.21   | 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/<3/3        | 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, Hypertensibility 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, Agenesia 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, Hypertorisis. Agenesia corpus callosum, Cystic tumor in occipital region, VSD with persistent left superior vena cava, Empty scrotum, Short distal phalanges, Hyposplastic 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, Hydrenephrosis, Vesicouretal 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, Hydrenephrosis, Camptodactyly, Overlap of toes, Malalignment of feet, Hypoplastic |

(Continued)
Table 2. Continued.

| Marker | Freq (%) | Marker formation | Age at diagnosis | Gender | Lt/W/W/OFC (%tile) | Reported clinical features |
|--------|----------|------------------|------------------|--------|-------------------|----------------------------|
| Rothenmund et al. [1997] II-1 | 10 | Pericentric | 30 years | M | >95/25/90 | patellae, Deep plantar crease, Extra lumbar vertebrae, Bifid vertebral, Hypoplastic iliac bones, Advanced bone age, Long slender trunk, Anteriorly placed anus |
| 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, Prenatal episode of tachyarrhythmia, Multiple hemangiomas |
| 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, Agensis corpus callosum, Craniofacial anomalies, Single hemangioma |
| Brian and Malafiej [2003] Case 2 | 34 | Ring with 8ptel signal | 21 years | F | Short | ID Infertile, Central obesity |
| Brian and Malafiej [2003] Case 3 | 27 | Ring negative with pantelomeric probe | 31 years | F | – | – |
| Brian 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 | >40/75/75 | 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 8p 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
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), skeletal (10 of 30 reviewed patients), genitourinary (6 of 30 reviewed patients), craniofacial (18% of reviewed patients), and dermatologic (6 of 30 reviewed patients).

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 (APSM2), PLASMINOGEN ACTIVATOR, TISSUE (PLAT), INHIBITOR OF KAPPA LIGHT CHAIN GENE ENHANCER IN B CELLS, KINASE OF, BETA (IKBKBN), POLYMERASE, DNA, BETA (POLB), DICKOPF, 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 (CHRN3), 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-acetyltansferase) 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. CHRN3 (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 phenotype 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.

| Table 3. Specific dysmorphic facial features associated with partial chromosome 8 trisomy. |
|---------------------------------------------|---------------------------------------------|
| Number of Children with given feature among children with reported craniofacial anomalies 18% (| |
| Dysmorphic Facial Feature | Number of Children |
| 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) | |
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. FLT4 (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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