Monozygous twins with distal 5p duplication: a case report

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Abstract:

Duplications of the short arm of chromosome 5 are very rare, and their severity is highly variable. The few patients reported with duplication distal to 5p13.3 had milder psychomotor delays and short stature compared to those with duplications proximal to 5p13.3, the latter group being characterized by developmental delays, failure to thrive and seizures.[1]

We saw monochorionic diamnionic twin girls born to a 25-year-old primigravid mother and 28-year-old father for developmental delays, behavioral concerns, and multiple malformations (umbilical hernia, loose jointed fingers, pectus excavatum and Duane anomaly). SNP arrays revealed 2.9Mb duplication of 5p15.33p15.32 in both girls. In the DECIPHER database and one previously published case report, one finds similar duplications (ranging 1.07 to 2.42 Mb) that overlap in five genes*: MRPL36, NDUFS6, IRX4, IRX2* and *IRX1*. Though all patients have global developmental delays, the twins uniquely present with pectus excavatum and Duane anomaly. Their duplication exclusively contained the genes *LSINCT5* and *C5orf38*. Further, their family history suggests inheritance with incomplete penetrance. In conclusion, the overlapping five genes in all these cases may be related to their phenotype.

Table of features

Feature	Twin A	Twin B	Decipher 1	Decipher 2	Riordan
Duplication Size	2.902Mb	2.925Mb	1.07Mb	2.42Mb	N/A
Birth Weight	< 3rd	25th	N/A	N/A	50th
Head Circumference	95th	98th	N/A	N/A	N/A
Age Last Seen	10.5	10.5	N/A	N/A	8
Current Height	23rd	82nd	N/A	N/A	N/A
Current Weight	82nd	97th	N/A	N/A	N/A
Global Delays	X	X	X	X	X
Duane Anomaly	X	X	N/A	N/A	N/A
Pectus Excavatum	X	X	N/A	N/A	N/A
Joint Laxity	X	X	N/A	N/A	N/A
Café au lait spots	-	X	N/A	N/A	N/A
Short 5th finger	-	X	N/A	N/A	X
Dysmorphic features	-	Macrocephaly, nevus on right temple	Macrotia, prognathia, smooth philtrum	N/A	Wide palpebral fissures, midface hypoplasia, high arched palate, thin upper lip, smooth philtrum
Behavior	Outbursts, aggression, anxiety	-	Easily frustrated, inattentive	N/A	X
Other organ issues	Umbilical hernia	Thyromegaly, hemangiomas, umbilical hernia	N/A	N/A	Mild respiratory distress, tremors, hypertonia

Methods:

SNP microarray was performed using the Affymetrix Cytoscan HD platform including more than 2.6 million copy number markers with a median spacing of 880 bp. Total genomic DNA was extracted from lymphocytes, amplified by PCR, and hybridized to the Cytoscan HD genechip. Data were analyzed using the Affymetrix Chromosome Analysis Suite (ChaS) version 4.2.1 and interpreted based on the NCBI genome build hg19 (Genome Reference Consortium Human Build 37 [GRCh37]).

Riordan Patient

Case report:

Monozygous twin girls were born by Caesarean route at 36 weeks of gestation to a 25 year old gravida 1 para 1 woman and her 28 year old partner, the union not known to be consanguineous. The pregnancy was complicated by preeclampsia. Neonatal period for Twin A was notable for jaundice and low birth weight requiring a 2 week stay in the NICU; this period was unremarkable for Twin B. Features for both twin patients are described in Table 1 along with other patients found in the literature with similar chromosome 5 duplications.

Conclusions:

- All 5 cases have duplications that include a group of five genes (*MRPL36, NDUFS6, IRX4, IRX2* and *IRX1)* which demonstrates a possible relationship to their common phenotype of global developmental delays
- There were “behavior problems” in the twins’ father and maternal uncle, and “difficulty with comprehension” in the maternal grandfather. Incomplete penetrance with variable expressivity could account for this, but we were unable to investigate parental origin of the duplication.
- The Riordan patient’s mother and half brother had the same duplication and learning delays, which connotes variable expressivity.
- These twins are the only ones to present with Duane anomaly and pectus excavatum.
- They are also the only ones whose duplication contains the genes- *LSINCT5* and *C5orf38.*

-Further investigation into the phenotypic roles of these two genes should be done

References:

1. Riordan D, Vust A, Wickstrom DE, et al. Identification of a dup(5)(p15.3) by multicolor banding. *Clin Genet*. 2002;61(4):277-282. doi:10.1034/j.1399-0004.2002.610406.x

2.https://www.deciphergenomics.org/search/patients/results?q=5%3A1705102-4629789