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Genetics Corner: Alpha Thalassemia X-Linked Intellectual Disability Syndrome in an Infant with Developmental Delay and DYS Recurrent Respiratory Failure Confirmed by Whole-Exome Sequencing

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Case Summary

A 13-month old boy with global developmental delay and dysmorphic features was admitted for increased work of breathing. He was born at 37 weeks gestation to a mother, G2P2, via emergency C-section for partial *abruptio placentae*. Other prenatal history was noncontributory. Maternal prenatal labs were negative. The prenatal US was normal. Mother had gestational diabetes that was controlled. She endorsed difficulty conceiving but denied miscarriage. He was admitted to the NICU for one week at an outside hospital due to respiratory difficulty requiring HFNC and feeding difficulties. At six months of age, he had developmental delay and hypotonia. He was referred for a developmental assessment, but his mother did not follow up.

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During this admission, his problems included esotropia, gastroesophageal reflux, dysphagia to thin liquids, malnutrition, left undescended testis and left inguinal hernia, microcytic anemia, and chronic constipation. A genetics consultation was requested. Following his discharge, he has three more hospitalizations for acute respiratory failure due to viral illness, requiring PICU admission and intubation on one of those occasions.

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Family History

The maternal family history was significant for several males with neurodevelopmental disorders. She reported a male first cousin, the son of her maternal aunt, with a diagnosis of spinal muscular atrophy. She also reported two brothers who were maternal uncles to the patient, who had severe developmental delay, both of whom died during childhood.

The patient has one healthy brother. The patient's father has three healthy children (female and male) from previous relationships. Mother is 30 years old, and the father is 46 years old; both are healthy (Fig 1. the family pedigree). Parents are of Hispanic ancestry from Mexico. Consanguinity was denied.

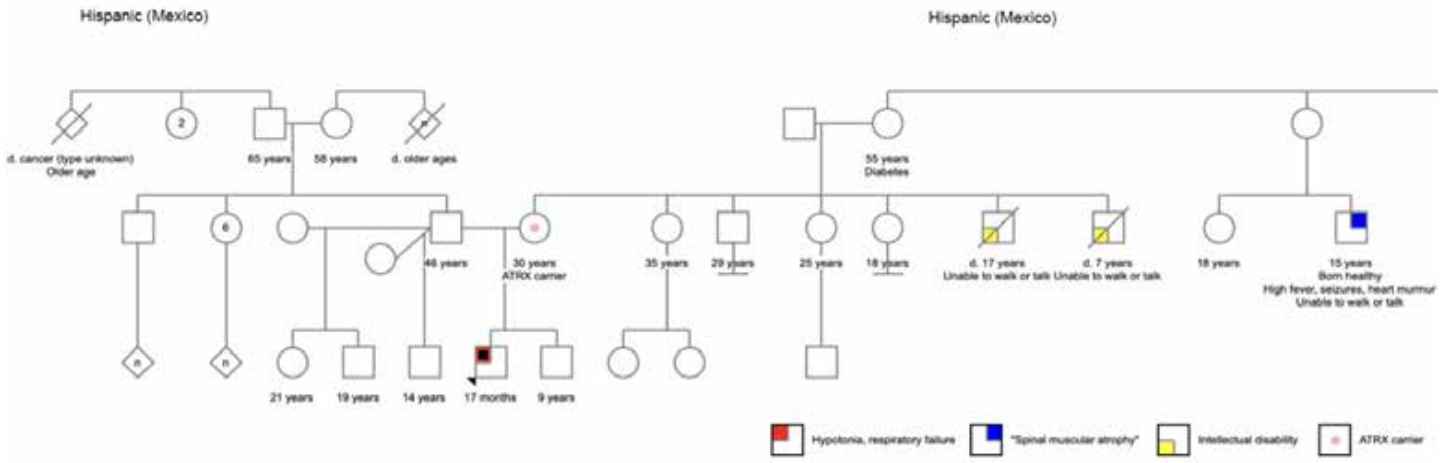
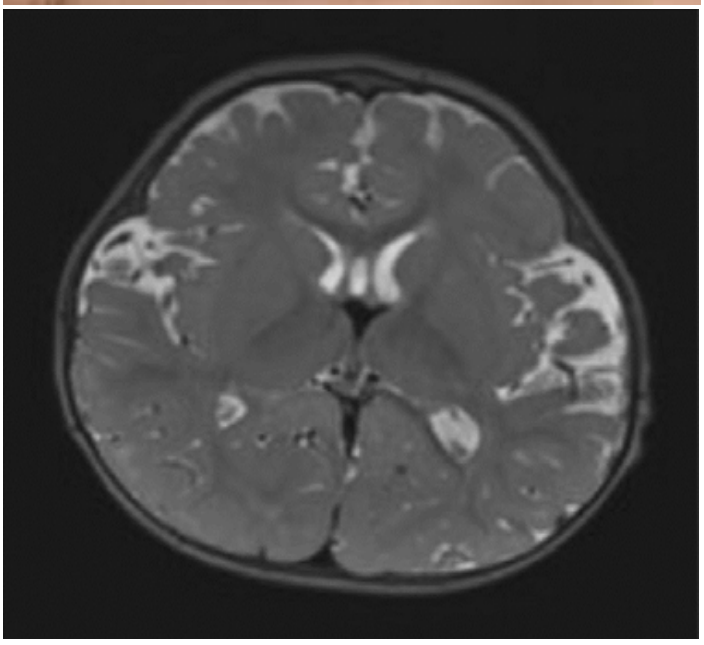


Figure 1. The pedigree demonstrates an X-linked pattern of affected males related through females.

Physical examination

The geneticist noted dysmorphic facial features, microcephaly, hypotonia, pectus ex cavatum, global developmental delay, and failure to thrive with acute respiratory insufficiency. Head circumference and weight parameters were significantly below the 3rd %ile: weight Z-score -2.76, head circumference Z-score -2.76, length Z-score -0.70. The face was round with a flat profile, faint eyebrows, telecanthus, bilateral intermittent esotropia, short nasal bridge, upturned nasal tip, tented upper lip, and open mouth. He was mildly hypotonic with truncal instability but adequate head support. Mild genital anomalies were appreciated: undescended L testis and L inguinal hernia. Figure 2. illustrates the facial features during his acute illness at 13 months and a follow-up visit at 17 months. Brain MRI revealed brachycephaly but was otherwise essentially normal.



a) 13 months old b) 17 months old c) MRI of the brain (13 months)

Fig 2. Facial features and MRI of the brain.

"Alpha thalassemia X-linked intellectual disability syndrome (ATR-X) is a rare condition. Whole exome sequencing is a powerful tool for diagnosing such rare disorders."

ATRX syndrome (Alpha thalassemia X-linked intellectual disability syndrome, ATR-X) was suspected clinically based on the X-linked pattern of affected males in the family history and the child's characteristic facial features in the context of microcephaly, genital anomalies, and hypotonia.

Laboratory testing

Chromosome microarray and conventional metaphase chromosome analysis were normal. A whole-exome trio revealed a hemizygous pathogenic variant in *ATRX*: c.736C>T (p. Arg246Cys) (NM_000489.4). The mother was a heterozygous carrier for the same variant. This variant has been reported many times as causative for ATRX syndrome.

This confirmed Alpha thalassemia X-linked intellectual disability syndrome (OMIM 301040).

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Discussion

Clinical features of ATR-X

ATR-X syndrome is an X-linked intellectual disability disorder that almost exclusively presents in males. Affected males have variable intellectual disability, from mild to profound, and delayed development in speech and ambulation. Typically there is a characteristic pattern of facial features, microcephaly, and short stature. Most individuals also have hypotonia, gastrointestinal dysfunction, and under masculinized genitalia ranging from undescended testes to hypospadias, or normal-appearing female genitalia. Seizures occur in 30-40%. The Alpha-thalassemia for which the syndrome is named is present in about 75% of affected individuals - it is mild and typically does not require treatment. Osteosarcoma has been reported in 4 children with germline pathogenic variants, but the association with tumor predisposition has not been well defined. Other findings can include a characteristic neurobehavioral phenotype, minor skeletal anomalies, and less commonly ocular coloboma, cleft palate, cardiac defects, inguinal hernia, heterotaxy, and asplenia. Phenotypic variability in individuals with ATR-X syndrome is broad, even within the same family. This family's phenotypic variability might have obscured the X-linked inheritance pattern had we not considered that all affected males in the maternal lineage were more likely to have the same diagnosis: the diagnosis attributed to the mother's cousin, spinal cord muscular atrophy is only rarely X-linked.

Test strategy

Targeted genetic testing and chromosomal microarray are diagnostic in 15.3–52% of patients with microcephaly, while whole-exome sequencing (WES) has been shown to provide an underlying explanation in 29% of previously evaluated and undiagnosed patients (1). Genetic testing is a common next step in patients with developmental delay and intellectual disability.

Data from the Human Gene Mutation Database suggests that more than ninety percent of variants reported in *ATRX* are detectable through sequence analysis, though some gross deletions and duplications have been reported (2). ATR-X syndrome has also been linked to a unique and highly specific methylation signature (3). The clinician can determine which testing route is most appropriate based on the clinical circumstances. Although ATR-X was suspected, WES was chosen as the best testing option considering that there might not be other opportunities for testing after discharge.

His feeding problems and respiratory issues in the newborn period were likely attributed to sequelae of a difficult delivery due to abruptio placentae. In retrospect, these problems may have been the earliest expression of his neurodevelopmental delay. Nevertheless, such nonspecific signs were not sufficient to raise suspicion for an underlying disorder, and it is unlikely that the family history had been documented in the record at that time. This would be a difficult diagnosis to make in the newborn period or anytime prior to recognizing developmental delay at age six months.

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Differential Diagnosis

Genes of interest in the differential diagnosis of ATR-X syndrome, especially when alpha thalassemia is identified, include *HBA1* and *HBA2, MECP2,* other genes in the Xq28 region, and *RPS6KA3*. *HBA1* and *HBA2* are genes associated with hemoglobin H disease

(HbH). HbH is an autosomal recessive condition that is not associated with intellectual disability. Unlike HbH, patients with ATR-X syndrome are expected to have a normal alpha-globin genotype. *MECP2* duplication syndrome is an X-linked neurodevelopmental disorder that causes profound intellectual disability, developmental delay, infantile hypotonia, and other symptoms also seen in ATR-X syndrome. However, while microcephaly occurs in 75-85% of patients with ATR-X syndrome, it is not a consistent feature of *MECP2* duplication syndrome. Coffin-Lowry syndrome (CLS), an X-linked intellectual disability syndrome caused by pathogenic variants in *RPS6KA3,* has phenotypic overlap with ATR-X, including some of the dysmorphic facial features: a large open mouth, prominent lips, short stature, microcephaly, and musculoskeletal anomalies. Other CLS signs not present in ATR-X syndrome include short, soft hands with wide, tapered fingers, hyperextensible skin and fingers, and stimulus-induced drop attacks (4).

Molecular Genetics

ATRX encodes a transcription factor that functions in the binding and separating of double-stranded DNA during transcription. ATRX protein may be involved in chromatin remodeling and the regulation of gene expression during development. Mutations in *ATRX* have also been shown to cause changes in DNA methylation (3). Changes in *ATRX* may disrupt the transcription and chromatin structure of other genes. Pathogenic variants involving the zinc finger domain are associated with more severe genital anomalies and psychomotor delay, while those affecting the helicase domain correlate with a milder phenotype (6). Pathogenic variants in *ATRX* cause downregulation of alpha-globin expression, leading to alpha thalassemia in patients with ATR-X syndrome. ATRX is also thought to play a critical role in brain development and sex differentiation (7,8).

Inheritance

The condition is inherited in an X-linked manner. As a carrier of the *ATRX* pathogenic variant, the mother has a 50% chance of transmitting this allele to her offspring each pregnancy. Males who inherit the pathogenic variant will be affected but will not reproduce. Females who inherit the pathogenic variant will be carriers, and although rarely clinically affected, they will be able to pass this on to their children. This underscores the importance of making the diagnosis as early as possible. Genetic counseling should be offered to all affected families.

"Four months after discharge, he returned for a follow-up evaluation. He was responding to physical and occupational therapy with improvement in gross and fine motor domains. He continued to have slow weight gain and feeding difficulties. He was referred for feeding therapy and an evaluation with a gastroenterologist to consider gastrostomy-tube placement."

Postscript –Follow up at 17 months

Four months after discharge, he returned for a follow-up evaluation. He was responding to physical and occupational therapy with improvement in gross and fine motor domains. He continued to have slow weight gain and feeding difficulties. He was referred for feeding therapy and an evaluation with a gastroenterologist to consider gastrostomy-tube placement. He had a left orchidopexy and herniaplasty. Corrective lenses had been prescribed for esotropia.

Practical Applications

1. Pay attention to the family history. The pattern of affected males provided an essential clue to the diagnosis. The X-linked pattern of affected males in the maternal lineage framed and narrowed the differential diagnosis and led us to focus on X-linked disorders that caused dysmorphic features and intellectual disability.
2. Use the pattern of anomalies to narrow the differential diagnosis further. ATR-X is one of the few X-linked disorders in which dysmorphic features, microcephaly, and genital anomalies coexist.
3. Consider an underlying genetic problem when a term newborn has unexplained feeding problems. A genetics evaluation can help identify the underlying etiology, and sometimes a common presenting problem, like poor feeding, can be the first sign of a rare syndrome.
4. Consider a genetic disorder in any of these situations: a positive family history of intellectual disability or developmental delay, esp more than one affected male is noted in the maternal lineage; dysmorphic features in a newborn with other anomalies, even minor anomalies (undescended testis), and whenever there is unexplained poor feeding in an otherwise healthy term infant.
5. Finally, be willing to consider trio whole-exome sequencing when a genetic disorder is suspected. It is a powerful tool for the diagnosis of rare disorders.

References

1. *Hanzlik E, Gigante J. Microcephaly. Children (Basel). 2017;4(6):47. Published 2017 Jun 9. doi:10.3390/children4060047*
2. *Stenson PD, Mort M, Ball EV, et al. The Human Gene Mutation Database: towards a comprehensive repository of inherited mutation data for medical research, genetic diagnosis and next-generation sequencing studies. Hum Genet. 2017;136(6):665-677. doi:10.1007/s00439-017-1779-6*
3. *Schenkel LC, Kernohan KD, McBride A, et al. Identification of epigenetic signature associated with alpha thalassemia/mental retardation X-linked syndrome. Epigenetics Chromatin. 2017;10:10. Published 2017 Mar 10. doi:10.1186/s13072-017-0118-4*
4. *Hahn JS, Hanauer A. Stimulus-induced drop episodes in Coffin-Lowry syndrome. Eur J Med Genet. 2012;55(5):335-337. doi:10.1016/j.ejmg.2012.03.004*
5. *Uhlén M, Fagerberg L, Hallström BM, et al. Proteomics. Tissue-based map of the human proteome. Science. 2015;347(6220):1260419. doi:10.1126/science.1260419*
6. *Badens C, Lacoste C, Philip N, et al. Mutations in PHD-like*

domain of the ATRX gene correlate with severe psychomotor impairment and severe urogenital abnormalities in patients with ATRX syndrome. Clin Genet. 2006;70(1):57-62. doi:10.1111/j.1399-0004.2006.00641.x

7. *Timpano S, Picketts DJ. Neurodevelopmental Disorders Caused by Defective Chromatin Remodeling: Phenotypic Complexity Is Highlighted by a Review of ATRX Function. Front Genet. 2020;11:885. Published 2020 Aug 11. doi:10.3389/fgene.2020.00885*
8. *Tang P, Park DJ, Marshall Graves JA, Harley VR. ATRX and sex differentiation. Trends Endocrinol Metab. 2004;15(7):339-344. doi:10.1016/j.tem.2004.07.006*

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