Genetics Corner: Familial Duodenal Atresia Due to Feingold Syndrome

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"A genetic consultation was requested for a preterm female with duodenal atresia that had been prenatally diagnosed by fetal ultrasound. Her family history was significant for duodenal atresia in her mother, her sister, and a deceased brother, who died in the immediate post-natal period after preterm delivery at 24 weeks gestation."

Case Summary:

A genetic consultation was requested for a preterm female with duodenal atresia that had been prenatally diagnosed by fetal ultrasound. Her family history was significant for duodenal atresia in her mother, her sister, and a deceased brother, who died in the immediate post-natal period after preterm delivery at 24 weeks gestation. She was admitted to the neonatal intensive care unit for surgical repair of her duodenal atresia and further evaluation. The patient was small for gestation age in all parameters: at 36 weeks 4 days gestational age, her birth weight was 1.77 kg. An echocardiogram showed a patent foramen ovale with fenestrations, mild right ventricular dilation, and hypertrophy with mildly elevated pulmonary pressures, but otherwise unremarkable.

The patient underwent exploratory laparotomy to repair a complete duodenal web and duodenoduodenostomy on day 6 of life. Oral feeding was begun on postoperative day 6, with uneventful advancement to full oral feeds and appropriate weight gain. Chromosomal microarray and chromosome analysis were normal. She had asymptomatic thrombocytopenia that was self-resolving. Her hearing screen was normal. Her newborn screen was normal. Cystic Fibrosis was indeterminate, but the California state protocol for *CFTR* gene panel testing identified no mutations.

The genetics team examined the infant after her surgical repair.

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Many dysmorphic features were appreciated, including microcephaly, short palpebral fissures, broad nose, thin upper lip, low anterior hairline, high palatal arch, bilateral clinodactyly of the little fingers, brachydactyly of the index and little fingers, each with single flexion creases, diminished distal flexion creases on the middle and ring fingers bilaterally, abnormal fisting with little fingers over-riding the ring fingers, thenar hypoplasia, left Sydney line, and right distal "hockey stick" crease (figures 1-3). The baby's facial and digital phenotype suggested Feingold syndrome in familial duodenal atresia. Maternal gene panel testing (gastrointestinal anomalies) had been sent one month before delivery and was in progress, so genetic testing on the infant was paused until the mother's results returned.

"The patient's mother (MOP) had a first pregnancy with a previous partner that ended in preterm premature rupture of the membranes (PPROM) and delivery of a male at approximately 24 weeks gestation, followed by neonatal demise in the first days of life. "

The family history was significant for the duodenal atresia in the mother and three of her offspring. The patient's mother (MOP) had a first pregnancy with a previous partner that ended in preterm premature rupture of the membranes (PPROM) and delivery of a male at approximately 24 weeks gestation, followed by neonatal demise in the first days of life. MOP's second pregnancy, conceived with her current partner, was also complicated by PPROM with the delivery of a male with duodenal atresia at 24 weeks and 2 days gestation, with neonatal demise on day 3 of life. No genetic testing was performed on either child. MOP's third pregnancy with the current partner was complicated by preterm delivery at 27 weeks, resulting in a female infant with duodenal atresia and microcephaly without other notable dysmorphic features. This child, our patient's full sister, had a surgical repair for duodenal atresia at approximately one month of age. Her chromosomal microarray was normal. She has a mild to moderate learning disability and receives intervention at school. There were no other similarly affected family members with duodenal atresia, dysmorphic features, digital anomalies, or intellectual disability. Both mother and father of the patient are of Hispanic ancestry from Mexico. Parental consanguinity was denied.

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Following the infant's discharge, the mother's genetic test results identified a heterozygous pathogenic variant in *MYCN*: c.302dup (p.Leu102Thrfs*164). This variant caused a frameshift and premature protein truncation. The pathogenic variant in *MYCN* confirmed this family's suspected diagnosis of autosomal dominant Feingold Syndrome. Targeted gene testing for this variant is planned in the infant and her affected sister on an outpatient basis.

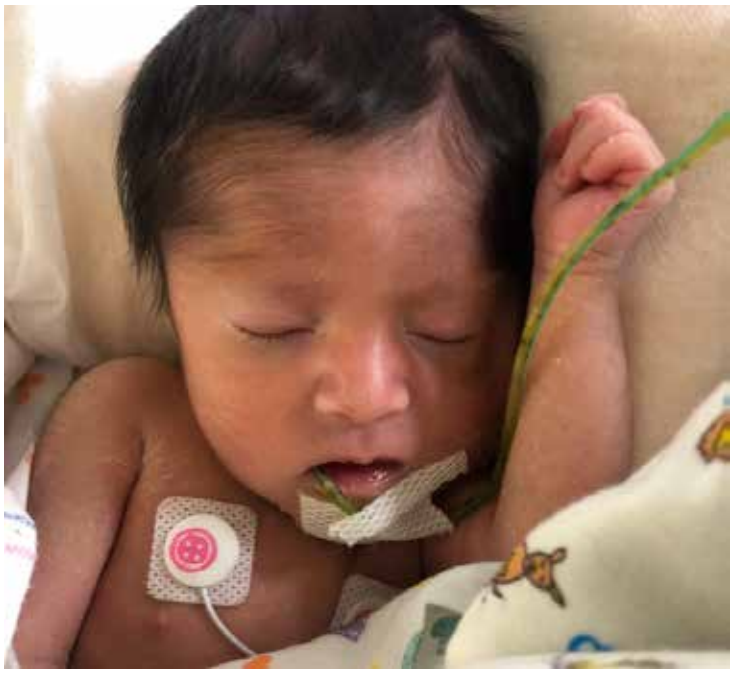

Figure 1: Face with dysmorphic features - short palpebral fissures, broad nose, thin upper lip, low anterior hairline.

Figure 2: Ears (left and right, respectively) with minor helical irregularities, pointed superior folding of the ear.

Figure 3: Left hand with abnormal fisting of pinky over the ring finger. Single crease or flexion of pointer and pinky fingers consistent with mesobrachydactyly. Clinodactyly of the pinky finger is observed. Faint distal flexion creases are noted on the middle and ring fingers. Sidney's line is seen on the palm.

Assessment and Counseling:

Duodenal atresia is a congenital absence or complete closure of the first portion of the small intestine (lumen of the duodenum). It is the leading cause of intestinal obstruction in newborns, occurring in approximately 1 in 10,000 live births.[1] Duodenal atresia is usually sporadic, although it can also be reported with genetic and chromosomal syndromes. About 1/3 of individuals with duodenal atresia have Down syndrome. It is also one of the many diabetic embryopathies associated with maternal diabetes.

Isolated, non-syndromic duodenal atresia is usually not inherited in a Mendelian single-gene fashion but given significant dysmorphic features, digital hypoplasia, and microcephaly, with a positive family history of duodenal atresia, our patient's presentation indicated a syndromic and inherited form of duodenal atresia. Her dysmorphic features are compatible with Feingold Syndrome Type 1 (OMIM # 164280): microcephaly, short palpebral fissures, and short index and little fingers.

Differential diagnoses:

- Down syndrome (OMIM # 190685) is highly associated with duodenal atresia; other clinical exam features include upslanting palpebral fissures, Simian creases, widely spaced big toes, hypotonia, etc. A normal NIPT does not completely rule out Trisomy 21; a karyotype is needed to rule out a balanced translocation that the microarray would not detect.
- VACTERL association (or VATER syndrome) should also be considered. There are many different causes of this syndrome, including genetic and environmental factors. It is typically seen as sporadic and nonfamilial; no single gene disorder has been implicated. However, microcephaly and the specific facial features would be atypical for VATER/VACTERL.

- There are also reports of small bowel atresia in other syndromes, such as Fryns syndrome (OMIM % 229850) and Martinez-Frias syndrome (OMIM % 601346). One could also consider Thrombocytopenia-Absent Radii or TAR (OMIM # 274000) given thrombocytopenia, as duodenal atresia has been rarely associated with TAR.

"Feingold syndrome (FS) is a rare, genetic, congenital malformation syndrome characterized by microcephaly, facial dysmorphisms, digital anomalies, and mild-moderate learning disability.2,3 Synonymous names include Brunner-Winter syndrome and Oculo-digito-esophago-duodenal (ODED) syndrome, among many others. "

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- Type 1: the presence of GI atresia
- Type 2 (OMIM # 614326): absence of GI atresia

FS1 is a rare diagnosis, with a prevalence of less than 1 in 1,000,000.[3] To date, 69 families with 116 affected individuals having three or more phenotypic features of FS1 have been reported.[2] Penetrance appears to be 100%; however, expression widely varies. The most consistent phenotypic feature was digital anomalies, including brachymesophalangy and toe syndactyly, found in up to 97-100% of patients, while microcephaly was seen in 89%.[4] GI atresia was the most common significant congenital anomaly seen in 55% of cases; renal and cardiac anomalies were also significantly frequent (18% and 15%, respectively).

Diagnosis of FS is established through clinical findings. A heterozygous pathogenic variant in *MYCN* is identified through molecular genetic testing, single-gene or multigene panel testing, or even comprehensive genomic testing. Celli et al. looked at 4 pedigrees affected by FS, specifically at familial syndromic esophageal atresia.[5] Mapping revealed evidence for haploinsufficiency of genes in 2p24-p23. This locus has also been confirmed by Van Bokhoven et al.[6]

MYCN is part of the MYC proto-oncogene family, a class of transcription favors often implicated in many cancers due to amplification or overexpression through activating the mTOR pathway.[7] Alternatively, the *MYCN* mutation in FS1 is a loss of function resulting in truncation of growth in multiple organ systems. The Li et al. team out of the Koo lab used the zebrafish model to study FS1 and *MYCN* function in organogenesis. *MYCN* was expressed in the central nervous, pharyngeal arches, and digestive systems. Knock-out studies resulted in multiple developmental defects, including a shorter intestine with a narrowed lumen and fewer enteric neurons. This is highly consistent with duodenal atresia in FS1 and our patient. Shortened intestine length and central nervous system expression can help to explain findings of microcephaly and intrauterine growth restriction, as well as the risk of intellectual disability in the future. An important topic addressed in the Li study was using L-leucine and Rheb to activate the mTOR pathway, rescuing intestinal size. This could be a potential in-utero treatment option for patients with FS1.

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The *MYCN* variant found via MOP's testing is likely inherited by her two daughters in an autosomal dominant fashion, with a recurrence risk is as high as 50% in future pregnancies. Our patient and her sister should be tested for the same variant. MOP should be counseled regarding the high risk of recurrence and how the disease expressivity can range from mild features to the full spectrum of FS1.

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Practical applications:

1. Suspect Feingold syndrome when duodenal atresia or tracheoesophageal fistula occurs in a first-degree relative of an affected infant. Take a careful family history to document any GI atresias in the family. 60% of patients with Feingold syndrome have an affected parent.
2. The clinical presentation of FS includes gastrointestinal atresia, digital anomalies, facial dysmorphisms, symmetric intrauterine growth restriction, and mild to moderate intellectual disability. Gastrointestinal atresia is the most common primary medical concern in FS, warranting immediate surgical intervention.
3. Pay attention to minor anomalies, for example, digital abnormalities. They may be very helpful in establishing a rare diagnosis, especially in the absence of other significant anomalies.

4. Appreciate that many syndromes are underdiagnosed. Suspect a syndromic or genetic etiology when a parent and child have the same anomaly.

5. *GeneReviews* recommends chromosomal microarray analysis to identify large deletions and a combination of gene-targeted testing and comprehensive genomic testing depending on the patient and family phenotype.

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