The Genetics Corner: Pathogenic variants in *DOCK6* mimic congenital viral infection in an SGA infant with VSD and intracranial calcifications

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Case Summary:

This baby girl was born to an 18-year old primigravida at 35 weeks three days' gestation by planned induction of labor for oligohydramnios and IUGR. Fetal ultrasound examination revealed a single umbilical artery and a VSD. Mother had irritable bowel syndrome with abdominal pain and vomiting during pregnancy treated with amitriptyline, omeprazole (Prilosec), ondansetron HCl (Zofran) until two months gestation. She denied teratogenic exposures. Apgar scores were 7 and 9. Birth weight 1925g (9th %ile), length 40.1 cm (<3rd %ile), head circumference 30 cm (11th %ile). The placenta was small (266 grams, < 3rd %ile) with mild decidual arteriopathy but no infarctions or significant inflammatory changes.

The initial physical exam revealed mild micrognathia, a loud 2/6 holosystolic murmur, bilateral sandal gaps between the first and second toes, and a deep groove on the plantar surface of each foot. She had a high-pitched shrill cry and unusual posturing of the extremities: wrists flexed, and hands were held above the shoulders, ankles crossed, with generalized hypertonia and clonus at the ankles.

There was a large perimembranous type VSD with a left ventricle to right atrial shunt and a persistent superior vena cava on echocardiogram. The brain MRI revealed "mildly enlarged lateral ventricular bodies and atria with periventricular subependymal foci of T1 shortening suggesting calcification and scattered subarachnoid hemorrhage versus areas cortical calcification. Findings are consistent with intrauterine TORCH infection." A dilated eye exam by the ophthalmology consultant was normal. Chromosome microarray, Zika and TORCH titers, serum PCR for Zika, and urine PCR for CMV were negative.

The family history was significant for VSD and atrial fibrillation in the paternal grandmother, paternal great grandfather, and paternal great uncle (paternal grandmother's brother). The father had ADHD and bipolar disorder.

Because of the baby's abnormal neuro exam and CNS calcifications, the initial plan to order a cardiac gene panel was changed to a whole-exome sequencing test (Baylor). This test revealed two likely pathogenic variants in *DOCK6*, the gene responsible for the autosomal recessive Adams-Oliver syndrome 2 (OMIM 614219). The infant had two variants that caused premature truncation of the gene product: a novel variant c.3737_3738del (p.S1246Cfs*2) and c.1987C>T (p.Q663*).

At a return outpatient visit a four months of age, the VSD appeared to be closing spontaneously. The baby was less irritable, and her resting tone was normal without unusual posturing of the extremities. She had an area of scalp alopecia that had not been appreciated during the newborn exam. There were no digital anomalies except mild syndactyly of toes 2 and 3 and the previously noted sandal gap.

The mother provided an additional family history that the father also had an area of scalp alopecia at the vertex.

Discussion:

This child, who was small for gestational age, had features that

suggested a congenital viral infection: a septal heart defect, an abnormal neurological examination, and intracranial calcifications. When viral titers and PCR tests were negative, whole-exome sequencing revealed two likely pathogenic variants in *DOCK6*. This gene is responsible for the autosomal recessive condition, Adams-Oliver syndrome 2 (AOS2, OMIM 614219).

Adams and Oliver described their eponymous syndrome in 1945 (AOS, OMIM 100300) as a phenotype comprised primarily of aplasia cutis congenita (ACC) and transverse terminal defects of the limbs. AOS is now considered a heterogeneous disorder with at least six responsible genes: AOS1, 3, 5, and 6 are autosomal dominant, and AOS2 and AOS4 are autosomal recessive traits.

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AOS was initially thought to be a disorder of vascular neogenesis, but evidence now points to genes that impair the actin cytoskeleton's formation. *DOCK6*, the dedicator of cytokinesis 6 gene, encodes an atypical guanine exchange factor (GEF) known to activate two members of the Rho GTPase family of signaling proteins: Cdc42 and Rac1. Both Cdc42 and Rac1 induce actin polymerization in the cytoskeleton. Shaheen *et al.* (2011) have shown that the *DOCK6* mRNA expression profile is consistent with the AOS2 phenotype with expression in the distal developing limb bud in the mouse. Inactivating mutations in *DOCK6* are likely to impair actin-cytoskeleton organization, but the mechanism of action responsible for alopecia, cardiac defects, and intracranial calcifications has not been elucidated.

In AOS, the ACC is usually in the midline, parietal or occipital region of the scalp. Structures underlying these skin defects (skull bones, meninges, sinus) may also be involved. The transverse terminal limb defects are typically limb truncation defects affecting the distal phalanges or entire digits (true ectrodactyly). Syndactyly, most commonly of second and third toes, can also be seen. Interestingly, this child has an uncommon and milder presentation of the limb defects associated with AOS, but not all patients with AOS have transverse limb defects (Dudoignon *et al.* 2020). To complicate matters, our patient's scalp defect was initially missed, so none of the classic features of AOS were evident that would have suggested the diagnosis.

The clinical features of AOS are highly variable and include cardio-

vascular malformations, brain abnormalities, and vascular defects such as cutis marmorata and dilated scalp veins. Our patient is one of the about 20% of patients with AOS who have congenital heart defects, including septal defects (Snape *et al.* 2008). Dudoignon and colleagues (2020) reviewed the clinical features of 29 patients with AOS, including three with variants in *DOCK6*, and their patient nine who had intrauterine growth retardation, intracranial calcifications, and cardiac anomalies (valvulopathy) was similar to our patient.

Sukalo *et al.* (2015) described ten patients with biallelic pathogenic variants in *DOCK6* and abnormal structural brain anomalies. The most common CNS anomalies were ventriculomegaly, periventricular leukomalacia, calcifications, and hypoplasia or atrophy of the corpus callosum. They described developmental delay and seizures. Ocular findings associated with AOS2 include optic nerve hypoplasia, microphthalmia, retinal detachment. Sukalo and colleagues conclude that *DOCK6* mutations are "strongly associated with structural brain abnormalities, ocular anomalies, and intellectual disability, thus suggesting that *DOCK6*-linked disease represents a variant of AOS with a particularly poor prognosis."

Both parents should be tested specifically for these two *DOCK6* variants in order to establish the phase of the variants as *cis* or *trans*: when the phase is *cis*, both variants are inherited from the same parent, whereas *in trans*, the variants are inherited on separate chromosomes, one from each parent. Parental testing will

establish the biallelic nature of these variants in this patient and allow informed counseling regarding recurrence risks for future offspring born to these parents.

Practical Applications:

1. Select gene testing that is appropriate to the patient. Whole exome sequencing was the better option and more appropriate than a cardiac gene panel for this infant with a congenital cardiac anomaly who also had poor overall growth and evidence of major CNS anomalies.
2. Consider a genetic etiology for the small for gestational age infant with intracranial calcifications when congenital infections such as TORCH and Zika have been ruled out.
3. Examine each infant carefully for minor anomalies, in this case, alopecia of the scalp, which was initially missed.
 - a. Minor anomalies can define the phenotype and guide testing choices.
 - b. Had we identified the infant's scalp defect prior to ordering gene testing, we might have chosen a more focused and less costly gene panel that was specific for Adams-Oliver syndrome.
4. Examine the parents and ask for information about even seemingly minor anomalies.

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