Prenatally diagnosed RASA1 deletion: an incidental finding that uncovers a family history

Laura Kline, MS, CGC; June Dennen, MS, MSW, CGC; Stuart Schwartz, PhD, FAMC/G
1Labcorp Women’s Health and Genetics, Laboratory Corporation of America® Holdings, Research Triangle Park, NC, 2University of Maryland St. Joseph Medical Center, Towson, MD

1. Introduction

• Red birthmarks (hemangiomas) occur in ~40% of newborns and appear when an overgrowth of angioblastic cells is present on the skin. While the majority resolve without intervention, some can persist and may require additional medical care.

• A subset of patients may have an underlying genetic condition: autosomal dominant capillary malformation-arteriovenous malformation syndrome (CM-AVM). The RASA1 gene is responsible for 50% of cases with CM-AVM, the majority of which are resulting in haploinsufficiency.

• The phenotype is characterized by the presence of small capillary malformations on the face and limbs with or without AVMs, arteriovenous fistulas (AVFs), and rarely Parkes Weber syndrome. Other findings may include lymphatic malformations and cardiac outflow tract anomalies.

• In severe cases, medical management may include a multidisciplinary team including dermatology, cardiology, radiology, surgery and/or orthopedics. Penetrance of the condition is 90-99%. Familial inheritance is noted in 70% of cases, however larger deletions encompassing RASA1 are usually de novo and have additional phenotypic effects from involvement of other pathogenic genes, namely MPF2C.

2. Methods

• SNP microarray methodology: SNP microarray analysis was performed using the Affymetrix (now Applied Biosystems®) Microarray Analysis Cytoscan® HD platform which uses over 743,000 SNP probes and 1,953,000 NIP probes with a median spacing of 0.88 kb. 250 ng of total genomic DNA was digested with NspI and ligated to NspI adaptors, respectively, and amplified using Titanium® Taq with a GeneAmp® PCR System 9700. PCR products were purified using AMPure® beads and quantified using NanoDrop® 8000. Purified DNA was fragmented and biotin labeled and hybridized to the Affymetrix (now Applied Biosystems®) Microarray Analysis Cytoscan® HD GeneChip®. Data was analyzed using Chromosome Analysis Suite. The analysis is based on the GRCh37/hg19 assembly.

• qPCR methodology: qPCR analysis was performed using the QuantStudio® 3 Real Time PCR system (Applied Biosystems®) in conjunction with the VeriF algorithm. The Fast STR8 Green qPCR Master Mix (2X) (Thermo Scientific®). All samples were run in triplicate. To determine copy number, primers specific to an amplicon within a CNV were designed using the GRCh37/hg19 assembly.

3. Case Report

We present the case of a proband whose mother was a 23-year-old primigravida who presented for genetic counseling at 11 weeks 6 days gestation secondary to absent nasal bone and increased nuchal translucency (1.8mm) on ultrasound. The mother reported a family history of distant relatives with intellectual and physical disabilities due to an unbalanced translocation, however no records could be obtained. The mother also had a notable personal history of Long QT syndrome (molecular testing confirmed). The mother opted for chorionic villus sampling (CVS). Aneuploidy FISH and SNP microarray were ordered on CVS to rule out any significant copy number or copy neutral imbalances in the fetus. Fetal diagnosis for Long QT was declined.

4. Results

• Aneuploidy FISH reported normal karyotype.

• SNP microarray run on cultured villi revealed an interstitial deletion of chromosome 5, at band 5q34-33 that involved 3 genes, including whole gene deletion of RASA1 but not MPF2C.

• Results of parental qPCR testing revealed the father of the pregnancy carried the same 5q deletion involving RASA1. Maternal analysis was normal.

• No evidence seen on SNP microarray of imbalance related to verbal family history of translocation.

• Baby delivered without issue, minor hemangiomas but no outstanding features.

• Postnatal referral to pediatric genetics recommended after delivery, and formal evaluation of child is pending, as well as paternal family follow-up.

5. Discussion

• Potential follow-up discussion uncovered a seemingly benign family-history reported by the father of the pregnancy, who described a large hemangiomma on his tongue in childhood that interfered with the ability to close his mouth, along with other orthodontic complications including tongue-lie, wide spaced teeth, and under-bite.

• The father’s mother, maternal aunt, and niece also had red raised birthmarks. Additionally, the niece had wide spaced teeth, tongue-lie, and an abnormal upper lip frenulum.

• As previously described by Wooderchak-Donahue et. al (see references), prior studies of RASA1 have thus far only detected mutations and small exonic deletions within and on the promoter end of RASA1. Full gene deletions have only been seen to exist as part of a large contiguous gene deletion involving MEF2C, which presents with intellectual disability, behavioral abnormalities, and stenotopic movements akin to Rett syndrome. As such, all prior contiguous gene deletions have been de novo.

• This appears to be the first described case of an inherited RASA1 whole gene deletion without contiguous deletion involving MEF2C. Therefore, whole gene deletions may be anticipated to have the same high inheritance percentage as mutations of RASA1 when MEF2C is not included.

References

