Identification of *BRCA1* Biallelic Pathogenic Variants in a Fanconi Anemia Patient and the Clinical Implications of Variant Location

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Introduction: Fanconi anemia subtype S (FA-S) is an extremely rare, autosomal recessive disorder caused by biallelic pathogenic mutations in *BRCA1* and is characterized by physical abnormalities, developmental delay, and increased chromosomal breakage. The rarity of FA-S is likely due to embryonic lethality and cases resulting in live birth may be the result of some level of retained functional BRCA1 protein.

Clinical Description: A 2-year-old female was referred for genetic consultation due to the clinical presentation of microcephaly, coloboma, duodenal web, colpocephaly, multiple café-au-lait spots, poor growth, and developmental delay. A molecular diagnosis of FA was confirmed by abnormal chromosome breakage testing. Genetic testing by exome and cancer panel identified two *BRCA1* pathogenic mutations: c.191G>A (p.C64Y) and c.3991C>T (p.Q1331*). Pathogenic alterations in other FA-associated genes were not identified.

Discussion: *BRCA1* c.191G>A is a missense alteration at a cysteine residue critical for protein folding and function. *BRCA1* c.3991C>T is a nonsense alteration in exon 11 and is expected to result in nonsense-mediated decay and loss-of-function. Multiple literature-reported FA-S patients also have loss-of-function variants in exon 11. This exon undergoes natural alternative splicing resulting in in-frame transcripts with partial or complete loss of this exon. The proteins resulting from these alternative transcripts may retain partial function. Because these alternative events splice-out the loss-of-function alterations, and may be partially functional, the result may be a hypomorphic effect explaining the enrichment of exon 11 loss-of-function variants in this patient and in other literature FA-S patients.

Conclusions: Two pathogenic *BRCA1* alterations, including a loss-of-function variant in exon 11 were identified in a 2-year-old proband with FA-S. The enrichment of pathogenic variants in FA-S patients in alternatively spliced exons, such as exon 11, may be evidence that loss-of-function alterations in these exons are hypomorphic and may have atypical risks relative to traditional pathogenic alterations.