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Splice Site Mutation in VEGFC is Associated With Milroy-Like Primary Lymphoedema

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Introduction:
Milroy Disease is an autosomal dominant condition and 70% of cases are caused by mutations in VEGFR3. A patient, who had screened negative for VEGFR3, presented with Milroy-Like Primary Lymphoedema and was screened for mutations in VEGFC. VEGFC is a ligand for VEGFR3.

Methods:
Sanger sequencing the DNA of the proband identified a heterozygous c.361+5 G>A variant in the VEGFC intronic region after exon 2. Further screening of the parents revealed that this variant was inherited from the mother who also shows mild symptoms. To test the effects of this mutation, blood was collected using PAXgene Blood RNA Tubes and RNA extraction was carried out. cDNA was then generated via RT-PCR for the mother and the proband. Primers were designed spanning exons 1 to 3 of VEGFC and the cDNA was sequenced to understand the effect the variant has on splicing.

Results:
Analysis of the Sanger sequencing trace of the cDNA identified that there was a heterozygous deletion of exon 2. The signal of the trace was very low which suggests a haploinsufficiency phenotype.

Conclusion:
The variant identified in the intronic region of VEGFC in the proband results in disruption to splicing leading to a deletion of exon 2. The low signal of mutant VEGFC in Sanger sequencing trace suggests that there could be low expression of VEGFC. This low expression could lead to disruption in vessel formation causing the edema in this patient.