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Supplemental Data

Heterozygous Loss-of-Function Mutations in *DLL4* Cause Adams-Oliver Syndrome

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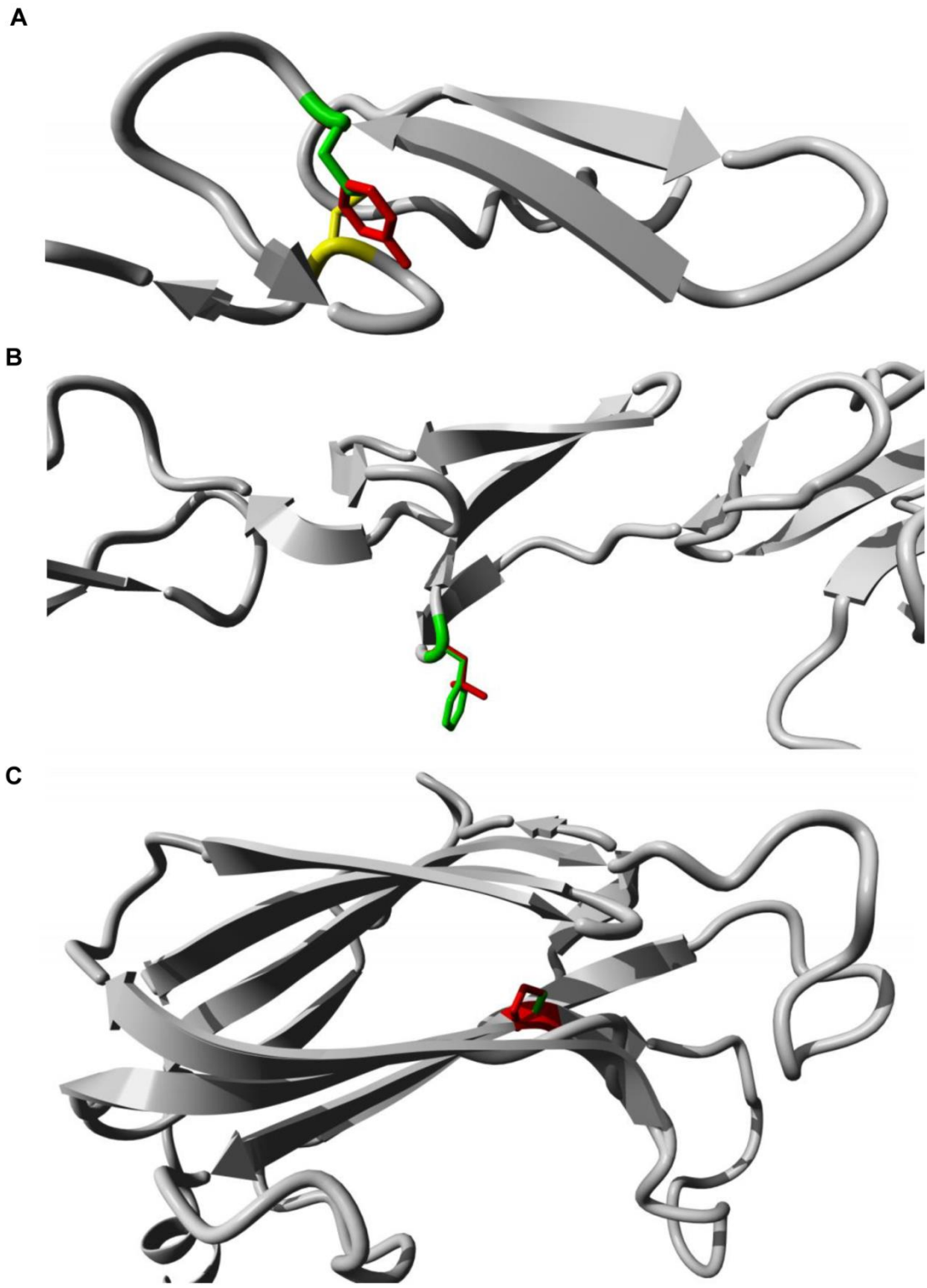

Figure S1. Modeling of *DLL4* variants

The structure of the protein domains is shown in grey and the wild type side chain is shown in green. The mutant side chain is depicted in red.

(A) 5th EGF-like domain with the p.Cys390Tyr variant. The disulfide bridge is shown in yellow.

(B) DSL domain with the p.Phe195Leu variant.

(C) MNNL domain with the p.Ala121Pro variant.

Table S1: *DLL4* mutation overview

Family	cDNA change	Protein change	Mutation Type	Domain	Proposed mechanism	Remarks
1	c.1660C>T	p.Gln554*	Nonsense	Intracellular domain	LOF, NMD	
2	c.1672C>T	p.Arg558*	Nonsense	Intracellular domain	LOF, NMD	Decreased penetrance
3	c.1365C>G	p.Cys455Trp	Cysteine replacing	EGF-like 7	LOF	
4	c.1169G>A	p.Cys390Tyr	Cysteine replacing	EGF-like 5	LOF	
5	c.1168T>C	p.Cys390Arg	Cysteine replacing	EGF-like 5	LOF	Variable expression
6	c.556C>T	p.Arg186Cys	Cysteine creating	DSL-domain	LOF	
7	c.799C>A	p.Pro267Tyr	Missense	EGF-like 2	LOF	Decreased penetrance
8	c.361G>C	p.Ala121Pro	Missense	MNNL-domain	LOF	
9	c.583T>C	p.Phe195Leu	Missense	DSL-domain	LOF	

LOF = Loss of function

NMD = Nonsense mediated decay