Familial Combined Factor V and VIII Deficiency with a novel missense mutation in LMAN1: Exploring the role of genotype, age, and blood group

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BACKGROUND

- Combined Factor V and VIII deficiency (F5F8D) is an autosomal recessive rare inherited bleeding disorder (estimated prevalence 1:1,000,000) resulting from mutations in either LMAN1 (lectin mannose binding 1) or MCFD2 (multiple coagulation factor deficiency 2).
- The proteins encoded by LMAN1 and MCFD2 work cooperatively to shuttle newly synthesized clotting factors V and VIII from the endoplasmic reticulum to the Golgi apparatus for further processing.
- Mutations in either LMAN1 or MCFD2 result in defective intracellular transport of Factors V and VIII, and patients with F5F8D have reduced levels of both clotting factors in the 5-30% range, with an associated mild to moderate bleeding phenotype.

CASE PRESENTATION

Patient A came to medical attention at age 66 when an elective coronary artery bypass grafting (CABG) procedure was complicated by perioperative coagulopathy requiring multiple plasma transfusions to achieve hemostasis.

- He was noted to have a baseline prolonged INR and APTT, and subsequent investigation identified both decreased Factor V and VIII activity.
- Other hemostasis testing was entirely normal including Factors II, X, von Willebrand Factor, and fibrinogen.
- He denied bleeding other than longstanding epistaxis.

Patient B, his son, underwent screening in light of his father's findings, and was found to have a prolonged APTT as well as mildly decreased Factor V and VIII activity.

Sanger sequencing identified a missense variant in LMAN1 (**HGVS nomenclature c.[47T>C];[47T>C] p.[(Leu16Pro)];[(Leu16Pro)]**) in both patients – homozygous in Patient A and heterozygous in Patient B.

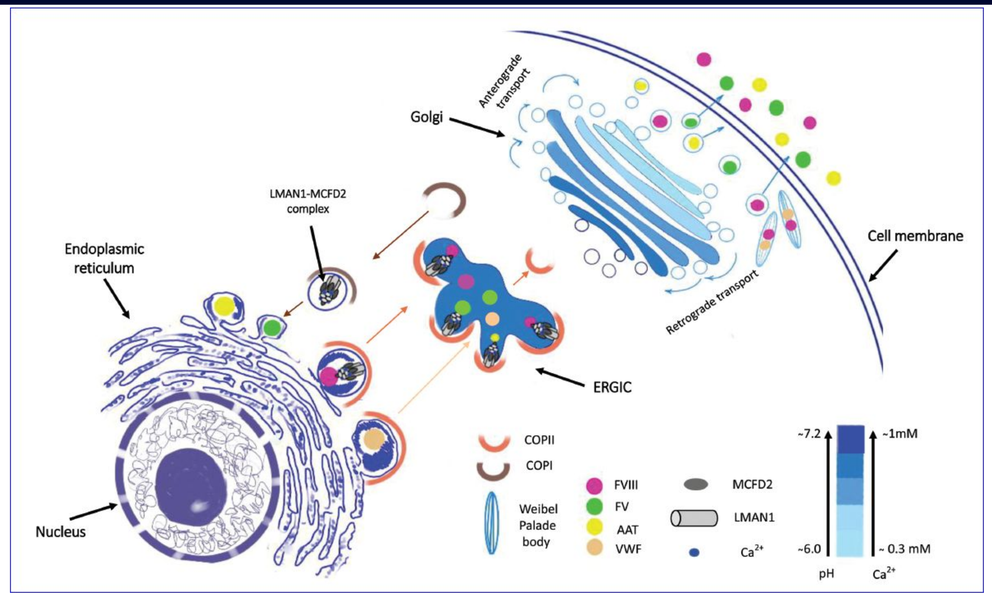
- This variant, not previously been reported, was deemed a variant of unknown significance.
- Neither patient had sequence variations in MCFD2.
- Patient A also underwent Sanger sequencing of Factor V with no sequence variations found.

CLINICAL AND LABORATORY DATA

	Patient A	Patient B	Reference Range
Age at diagnosis (years)	66	23	-
INR	1.5	1.1	0.9 - 1.2
APTT (seconds)	59	43	25 - 38
Factor V activity, PTT-based (U/mL)*	0.06 - 0.14	0.39 - 0.46	0.50 - 1.50
Factor VIII activity, one-stage (U/mL)*	0.32 - 0.44	0.39 - 0.40	0.50 - 1.50
vWF Antigen (U/mL)	1.51	0.65	0.50 - 1.50
vWF Activity, GP1b binding (U/mL)	1.54	0.42	0.50 - 1.50
Blood Group	A	O	-
LMAN1 mutation	Homozygous variant	Heterozygous variant	-
Bleeding Score (ISTH-BAT)	5	0	< 4

**Ranges provided where testing was performed more than once*

DISCUSSION



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Factor VIII: 0.32 - 0.44 U/mL

Older age: ⬆

Homozygous LMAN1 mutation: ⬇⬇

Factor V: 0.05 - 0.14 U/mL

Homozygous LMAN1 mutation: ⬇⬇

Patient A

Patient B

Factor VIII: 0.39 - 0.40 U/mL

Group O blood: ⬇

Heterozygous LMAN1 mutation: ?⬇

Factor V: 0.39 - 0.46 U/mL

Heterozygous LMAN1 mutation: ?⬇

DISCUSSION

F5F8D due to homozygous LMAN1 mutations is associated with Factor V and VIII activity 0.05 - 0.30 U/mL, with slightly higher levels as compared to F5F8D related to MCFD2 mutations. Neither patient had Factor VIII activity in this range, and despite their differing genotypes, both patients had similar results. Why?

- **Factor VIII has been shown to increase with age**
- **Group O blood has been shown to decrease levels of both Factor VIII and von Willebrand Factor**
- Murine models suggest that **heterozygous LMAN1 mutations may result in an intermediate phenotype**

Patient A's Factor V activity was within the expected range based on his homozygous LMAN1 mutation. In contrast, although his INR was 'within normal limits,' Patient B also had slightly decreased Factor V activity.

- **Unlike Factor VIII, Factor V is not reported to increase with age and is not known to vary with blood group.**
- As noted above, a heterozygous LMAN1 variant may account for Patient B's slightly decreased Factor V activity.

CONCLUSION

- These two cases highlight the complex relationship between multiple patient factors including age, genotype, and blood group which can affect the clinical endpoint of clotting factor activity.
- Assessment of Factor V activity and consideration for LMAN1/MCFD2 sequencing could be considered as adjunctive testing in patients with the clinical phenotype of mild Hemophilia A (Factor VIII deficiency) who are not found to have sequence variations in their Factor VIII gene.
- Further research is required to better delineate the implications of heterozygous mutations in LMAN1 or MCFD2.

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