COMPLEX PHENOTYPE OF HYPERCHOLESTEROLAEMIA IN A FAMILY WITH BOTH ABCG8 AND APOB MUTATIONS

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Background: Familial Hypercholesterolemia (FH) is the most common of all genetic hypercholesterolaemias with defects in *LDLR, APOB* and *PCSK9* accounting for the majority of cases. However, there are other rare disorders like sitosterolaemia that can present the same phenotype. Both can cause premature atherosclerosis but have distinctive dietetic and therapeutic intervention.

Patient/Proband

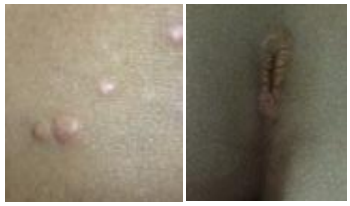
5 year-old referred for:

✓ xanthoma

✓ severe hypercholesterolemia

✓family history of hypercholesterolemia

Lipid profile	(mg/dL)
LDL	391
HDL	34
TG	89



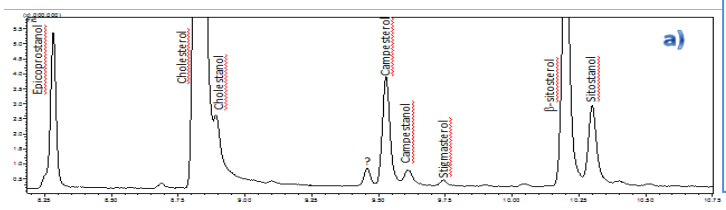
Initial Diagnosis: FH

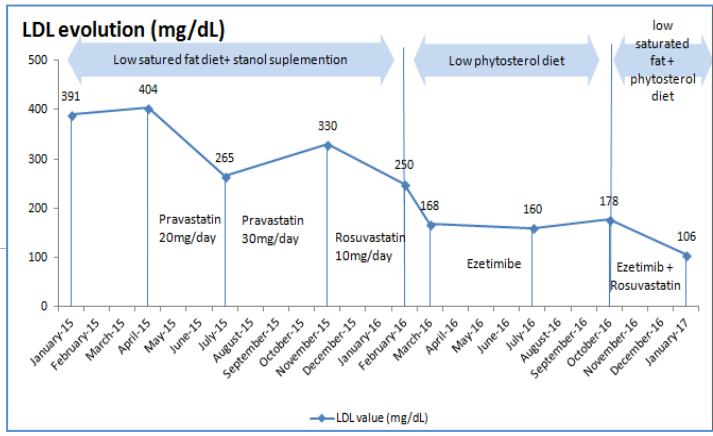
Treatment: low saturated fat diet + stanol supplementation + statin

….but lack of mutations *LDLR*, *APOB* (2 fragments of exons 26 and 29) and *PCSK9* genes questioned the diagnosis

Sitosterolemia?

- **Sterol Chromathography:** high plasma levels of sitosterol and presence of phytosterols
- ***ABCG8* gene analysis:** mutation (c.1974C>G, p.(Tyr658*) in homozygosity
- **Treatment:** low phytosterol diet + ezetimibe

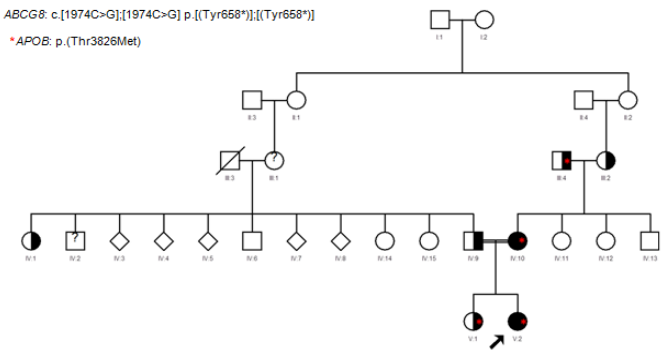




Re-sequencing of FH genes

- heterozygous variant in exon 26 of ***APOB* gene** (c.11477C>T, p.(Thr3826Met)
  → pathogenicity confirmed by functional studies (data not reported)

Family studies: same mutations in several elements



Follow-up

1.Cardiovascular and subclinical atheroesclerosis assessment:

- pre-hypertension with non-dipping pattern
- intima–media thickness (IMT) in P50-75.

2. Control of LDL levels:

- combined dietary and therapeutic intervention (sitosterolemia and familial hypercholesterolaemia)

Comments: Correct diagnosis of the various causes of hypercholesterolaemia is important because of the different dietary and pharmacological interventions in the prevention of atherosclerosis.

References: Ajagbe BO, Othman RA, Myrie SB. Plant Sterols, Stanols and Sitosterolemia. *J AOAC Int*. 2015 May-Jun; 98(3):716-23. Albert W et al. Familial hypercholesterolaemia in children and adolescents: gaining decades of life by optimizing detection and treatment. *European Heart Journal* 2015; 36:2425-2437. Othman RA, Myrie SB, Jones PJ. Non-cholesterol sterols and cholesterol metabolism in sitosterolemia. *Atherosclerosis* 2013; 231(2):291–9.