Variant-Specific Drug Responses in FH: an *Ex Vivo* Pilot Study

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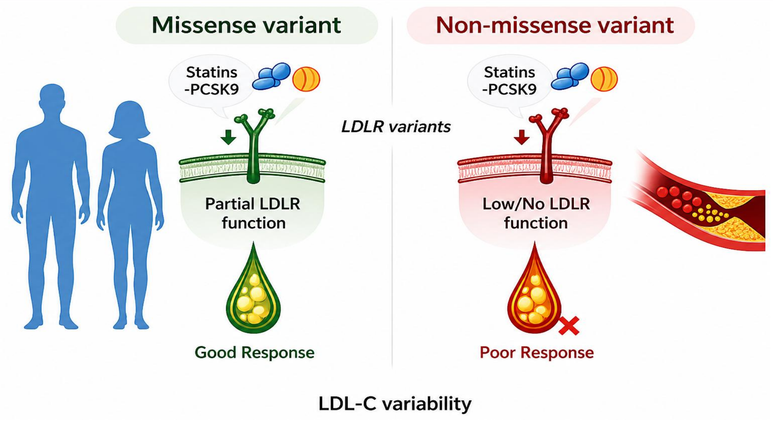
Background on Familial Hypercholesterolaemia

- Common inherited disorder causing high LDL-cholesterol from birth
- Primarily caused by pathogenic variants in the *LDLR* gene, impairing LDL clearance
- Autosomal semi-dominant inheritance pattern
- Untreated FH significantly increases the risk of premature atherosclerotic cardiovascular disease
- LLTs are effective but their efficacy depends on residual LDLR function



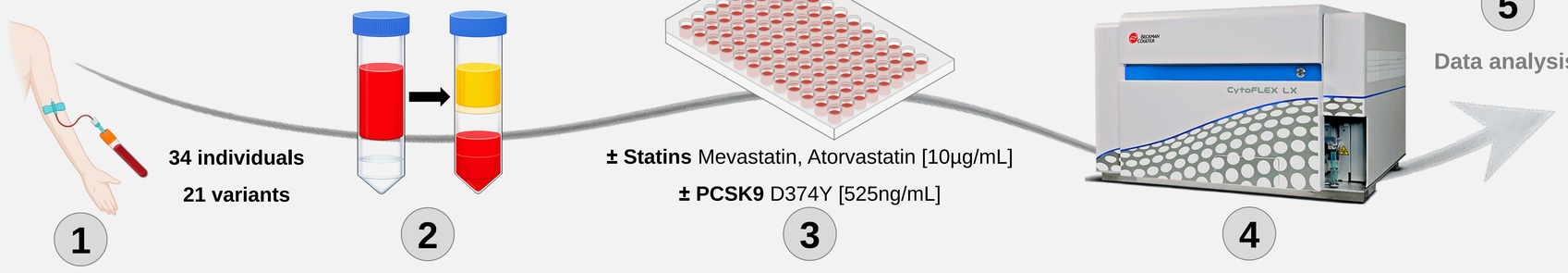
Does *LDLR* variant type influence cellular response to lipid-lowering therapies?

Aim

To determine whether *LDLR* variant type (missense vs non missense) predicts differential response to statins and PCSK9 modulation using patient-derived lymphocytes.

Experimental workflow

EPHF Estudo Português de Hipercolesterolemia Familiar



Results

Individual variant LDLR integrated functional activity score in FH patients

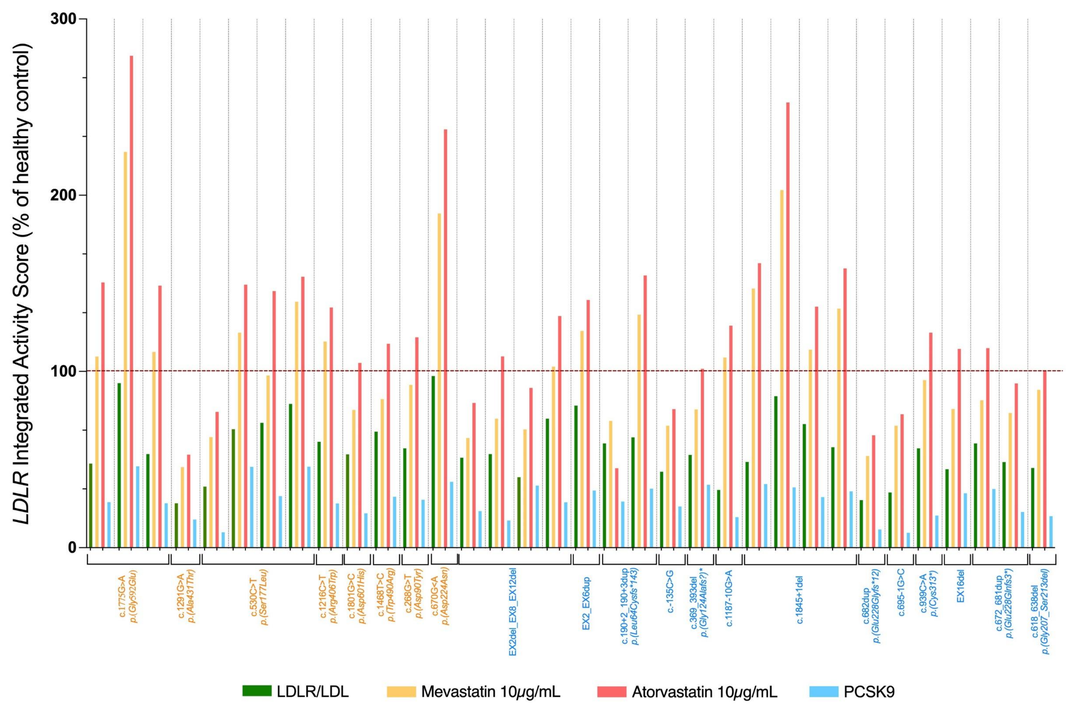


Figure 1. Each cluster of bars represents the integrated activity score (IAS) for an individual *LDLR* variant from one or more patients, calculated as the normalised composite of surface expression and LDL uptake relative to healthy controls, under basal conditions and after treatment (mevastatin or atorvastatin or PCSK9-D374Y). Variants are grouped by variant type (orange, missense; blue, non-missense). 21 different variants were studied in 34 individuals.

LDLR integrated functional activity

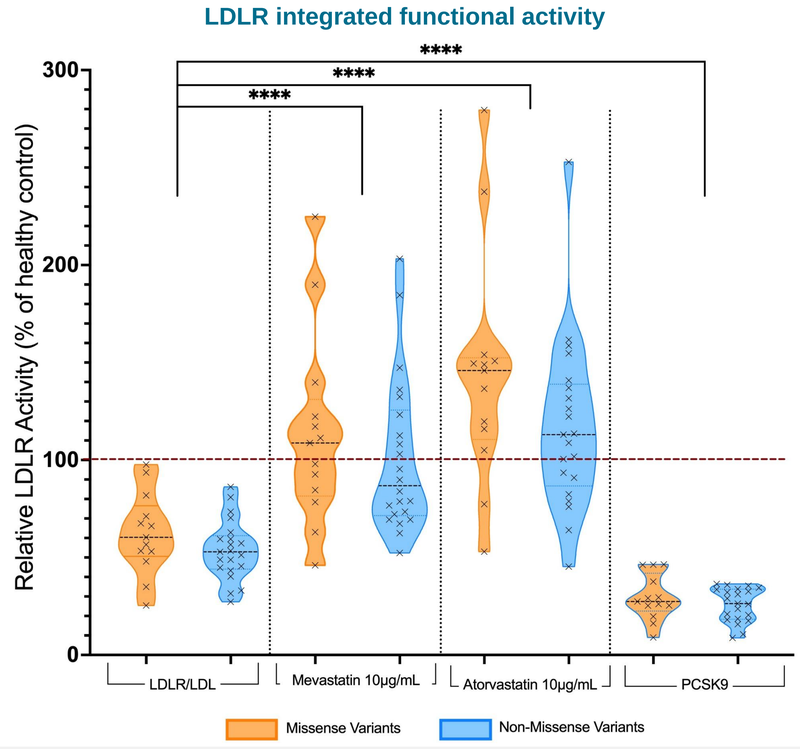


Figure 2. IAS in PBMCs from patients with genetically confirmed FH (N = 34), stratified by variant type (missense, n = 13; non-missense, n = 21). Data are displayed as violin plots with individual data points; horizontal lines indicate the median. Both statins significantly increased LDLR IAS compared with basal conditions and PCSK9 decreased IAS ($p < 0.0001$).

Correlation between atorvastatin- and mevastatin-induced LDLR responses

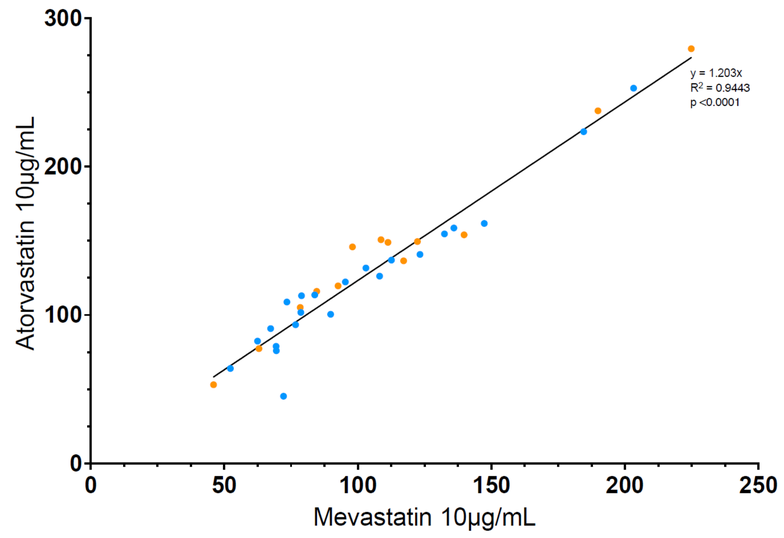


Figure 3. Each data point represents an individual FH patient; orange symbols indicate missense variants and blue symbols indicate non-missense variants. Linear regression was performed through the origin on the full cohort regardless of variant type. Atorvastatin significantly outperformed mevastatin ($y = 1.203x$, $R^2 = 0.9443$, $p < 0.0001$).

Conclusions

- Heterogeneous phenotypes and statin responses were observed across variants and individuals
- Statin responsiveness appears similar across *LDLR* variant type
- Variant type has been shown to constrain maximal LDLR rescue, with reduced activity observed in non-missense variants
- Current variant classification does not fully capture functional heterogeneity
- Atorvastatin provides a stronger functional rescue than mevastatin
- Patient-derived lymphocyte assays provide a feasible *ex vivo* model to assess drug responsiveness

Future Perspectives

- Expand the cohort to ~200 samples to validate the observed trends and improve statistical power
- Refine variant-specific functional profiles to improve interpretation
  (*e.g.* functional LDLR % activity groups [0-30%; 30-70%])
- Correlate *ex vivo* functional profiles and responses with clinical lipid profiles and treatment outcomes
- Perform analysis by allele type

Take home message

Variant type constrains maximal LDLR functional response; larger cohort and refined variant stratification are needed to clarify its impact on statin responsiveness

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