GENETIC ARCHITECTURE OF INHERITED DYSLIPIDEMIAS IN THE MAPA GENOMA BRAZIL COHORT

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INTRODUCTION

Dyslipidemias often result from a complex interplay of genetic and environmental factors. Inherited dyslipidemias are a heterogeneous group of disorders caused by germline variants that disrupt lipid metabolism, leading to abnormal blood levels of cholesterol and/or triglycerides. With the increasing availability of next-generation sequencing (NGS), the identification of individuals with inherited dyslipidemias has expanded. However, data on the prevalence and spectrum of causative variants in the Brazilian population remain limited. Genetic diagnosis can improve risk stratification, guide therapeutic decisions, and enable cascade testing of at-risk relatives.

OBJECTIVES

To establish a national registry of patients with clinical suspicion of monogenic dyslipidemias, with a focus on genotypic characterization and genotype–phenotype correlations.

METHODS

Patients with phenotypes suggestive of inherited dyslipidemia were recruited from cardiology centers across Brazil. All participants received genetic counseling and underwent whole-exome sequencing (WES). Variant interpretation was performed by clinical geneticists following ACMG guidelines. When necessary, family members were also clinically assessed and tested via Sanger sequencing.

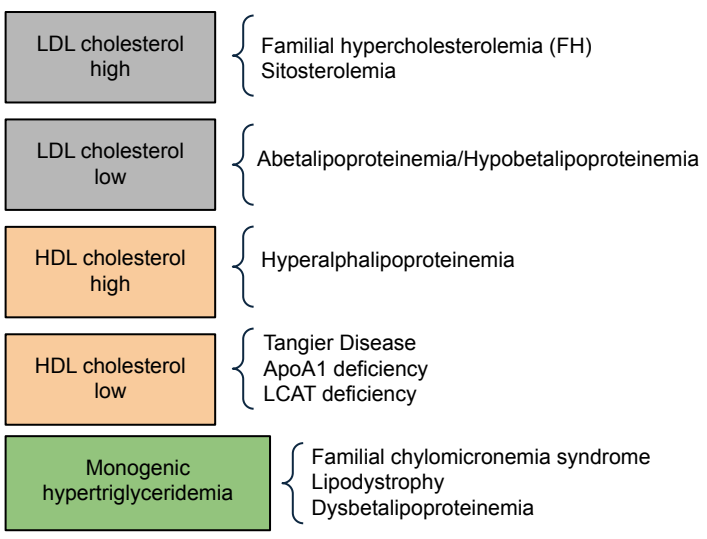
RESULTS AND DISCUSSION

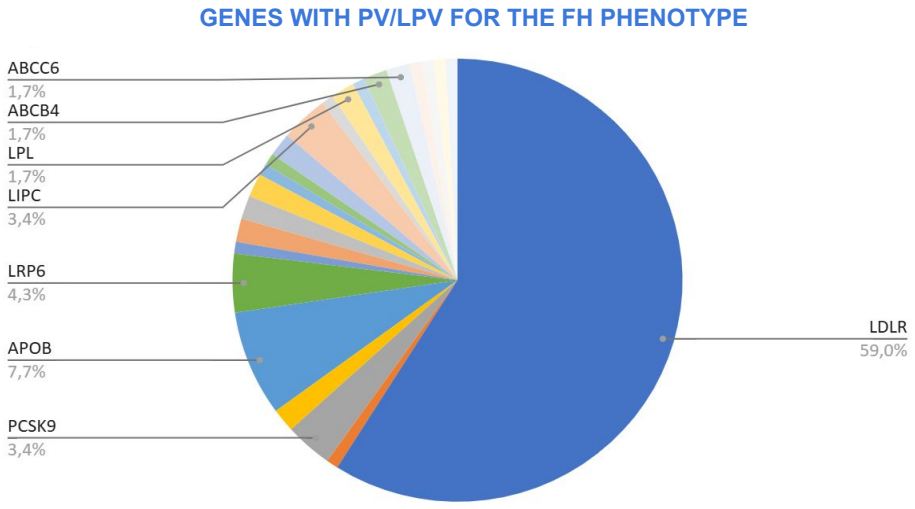
Between January 2022 and December 2024, 344 individuals (mean age 50 years; range 2–85; female-to-male ratio 6:4) underwent WES. A total of 354 variants were identified. No pathogenic or likely pathogenic variants were found in 63% of patients (n=224). In 130 individuals (37%), a rare germline variant was identified: 61% were classified as pathogenic or likely pathogenic, while 39% were variants of uncertain significance (VUS).

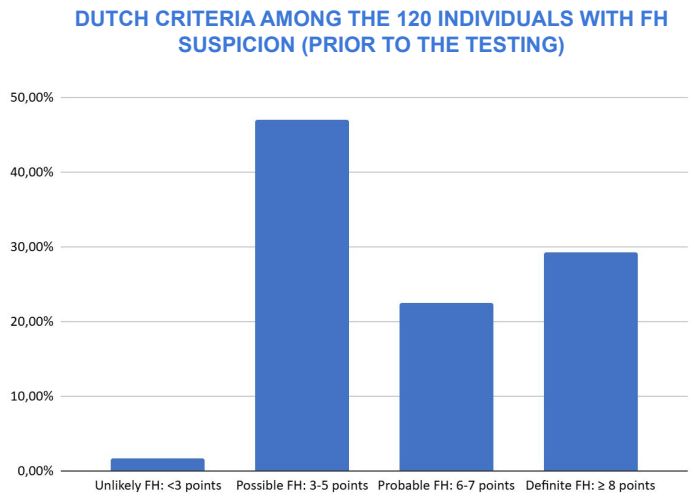
Clinical diagnoses included familial hypercholesterolemia (FH) (n=323; 93.8%), familial chylomicronemia syndrome (n=13; 3.7%), sitosterolemia (n=4; 1.1%), hypoalphalipoproteinemia (n=2; 0.56%), and lipodystrophy (n=1; 0.2%). In FH-suspected cases, the diagnostic yield was 76% (91/120), consistent with literature-reported yields of 30–80%, depending on the criteria used (e.g., Dutch Lipid Clinic Network score).

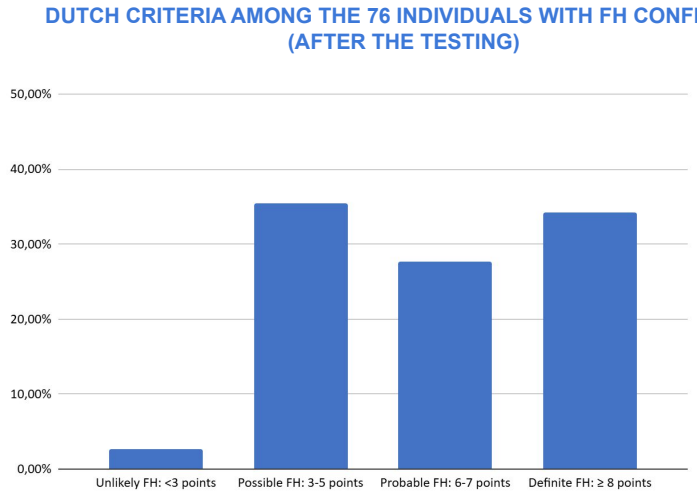
To enhance analysis, patients were stratified into three subgroups based on lipid profile or clinical presentation: (1) LDL Disorders: 105 variants were identified in genes including LDLR (n=71; 68%), APOB (n=9; 8.6%), PCSK9 (n=5), LRP6 (n=5), APOE, ABCB4, ABCC6, ABCG8, ALB (each n=2), and single variants in ABCG5, ABCC8, LDLRAP1, LPA, NPC1L1. (2) HDL Disorders: 4 variants in CELA2A (n=2), ABCA1 (n=1), and APOA2 (n=1).

(3) Hypertriglyceridemia/Lipodystrophy: 16 variants in LIPC (n=7; 43.8%), LPL (n=2), PPARG (n=2), AGPAT2 (n=2), and single variants in GPIHBP1, LMNB2, and SLC25A13.









CONCLUSION

Genetic testing is essential for identifying individuals with inherited dyslipidemias who may benefit from early diagnosis, personalized treatment, and cascade family screening. The MAPA Genoma Brazil cohort contributes significantly to understanding the genetic landscape of dyslipidemias in an admixed population and provides a foundation for precision lipidology in Brazil.

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