Genotype-phenotype correlation and allele dating analysis of a novel variant in hypertrophic cardiomyopathy: p.Arg652Lys in MYH7

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Background/Introduction: Hypertrophic cardiomyopathy (HCM) is a genetic disease characterised by increased left ventricle (LV) wall thickness caused by mutations in sarcomeric genes. Finding a causal mutation can help to better assess the proband's risk, as it allows the presence of the mutation to be evaluated in relatives and the follow-up to be focused on carriers.

Purpose: The objectives of the present study are to assess the genotype-phenotype correlation of a novel variant found in patients with HCM and explore the possibility of a founder effect in the Balearic Islands, Spain.

Methods: We performed an observational study with phenotype description and genotype correlation of patients with HCM in whom we found a novel variant in the MYH7 gene (NM_000257.4:c.1955G>A) which putatively causes a p.Arg652Lys missense protein change.

We did IBD/coalescent-based allele dating analysis of this novel variant.

Results: This previously non-described variant was found in twelve families with HCM. Out of those, 59 patients corresponding to 8 families were clinically characterized with a median follow-up of 63 months. Among them, 39 (66%) carry the variant. Twenty-five (64%) of carriers developed HCM. A median maximum LV wall thickness of 16.5 mm was described. The LV hypertrophy was asymmetric septal in 75% of cases, with LV outflow tract obstruction in 28%. The incidence of a composite of serious adverse cardiovascular events (sudden death, aborted sudden death, appropriate implantable cardiac defibrillator dis-charge, an embolic event, or admission for heart failure) was observed in five (20%) patients.

This p.Arg652Lys variant was classified as likely pathogenic (LP) and associated with the development of HCM for the following reasons: 1) It is found in patients with HCM, but not in controls, 2) There is evident segregation with HCM on the 8 families described, and 3) It is located in an active site of the protein where a variant in the same amino acid has already been clearly established as pathogenic (p.Arg652Gly).

Interestingly, the exclusive presence of the variant in our region could correspond to a founder effect in the Balearic Islands, Spain, which we have further investigated. IBD/coalescent-based allele dating analysis reveals that the origin of this allele is 96 generations away which would correspond to 1900–2400 years ago, when the Balearic Islands were already populated.

Conclusions: We can define the p.Arg652Lys variant in MYH7 as LP in HCM and a founder effect is in the Balearic Islands is highly probable due to the exclusive presence at the region and the dating analysis of it.

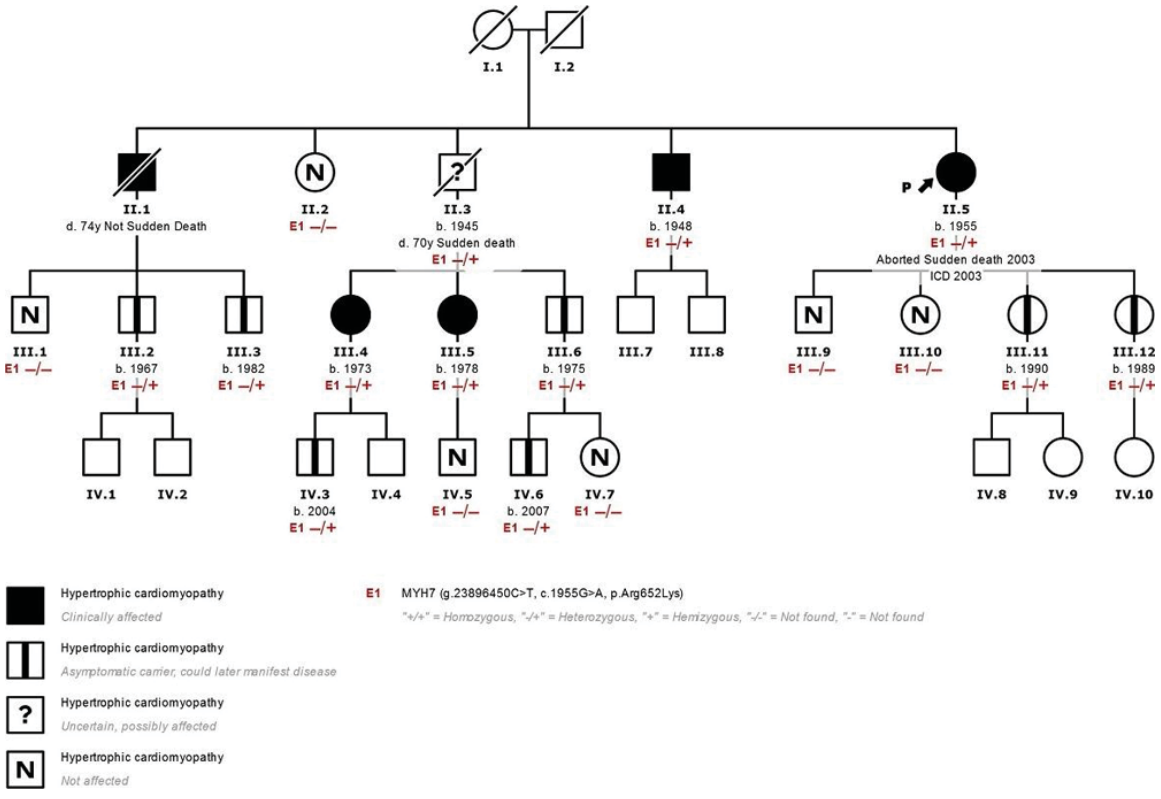

Figure 1. Family tree of a typical family with HCM