

Survival analysis in hypertrophic cardiomyopathy caused by the three most common pathogenic TPM1 variants

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Purpose: To evaluate survival free of cardiovascular events in carriers of the three most frequent TPM1 pathogenic hypertrophic cardiomyopathy (HCM) variants.

Methods: Clinical and genetic data on families carrying TPM1 variants in the literature and identified in our center were systematically revised and collected in a database. Classification of variant's pathogenicity was in accordance with ACMG criteria. We evaluated available follow-up data and constructed Kaplan-Meier survival curves to cardiovascular death (sudden death, appropriate cardiodefibrillator shock, heart failure death, and stroke-related death) or heart transplant. Long-rank test was used to compare event-free survival time.

Results: 562 carriers (343 HCM-probands and 219 relatives; 51.3% male carriers) were identified carrying 73 missense variants considered disease causing. TPM1 p.Asp175Asn (87 probands, 109 relatives, 6 unaffected), p.Arg21Leu (52 probands, 25 relatives, 16 unaffected), and p.Met281Val

(37 probands, 8 relatives, 9 unaffected) were the most prevalent HCM-variants. Among these three variants, survival data was reported for 508 individuals. Eight-nine carriers had suffered events: 74 sudden deaths (55% males), nine heart failure deaths (44% males), two transplants (50% males), and five stroke-related death (25% males). Incidence of cardiovascular death or transplant was similar between TPM1 p.Arg21Leu and p.Met281Val ($p=0.75$) and different than p.Asp175Asn ($p=0.03$ and $p=0.06$, respectively) and all TPM1 variants ($p=0.004$ and $p=0.04$). Analysis by sex showed TPM1 p.Arg21Leu female carriers had better prognosis than p.Asp175Asn male carriers ($p=0.048$) and all TPM1 male and female carriers ($p=0.02$ and $p=0.04$) (curves not showed in the graph).

Conclusion: TPM1 p.Arg21Leu and p.Met281Val could have a better prognosis than p.Asp175Asn and all other TPM1 missense variants in HCM. No marked difference was observed between male and female carriers. More than 80% of the events were arrhythmic deaths.

