Introduction: ALPK3 null variants (ALPK3nv) in simple heterozygosis represent an established and emerging genetic cause for hypertrophic cardiomyopathy. Some studies have indicated that this genetic substrate would be associated with a disease of late-onset disease and incomplete penetrance.

Purpose: To perform an extended genotype-phenotype correlation analysis with respect to simple heterozygous ALPK3nv carriers, focusing on age at diagnosis, maximum wall thickness and survival analysis, performed on the largest available released cohort to date.

Methods: ALPK3 gene was included in an extended NGS panel in 16,780 probands from a reference multicentric genetic laboratory, of whom 6,505 were referred with a HCM phenotype. We collected a composite cohort of ALPK3nv (considering frameshift, nonsense and splice-site predicted frameshift variants), including index and familial cases referred to this laboratory, but also cases reported in the literature. Phenotypic behavior was analyzed, mainly considering age at diagnosis, maximum LV wall thickness, and a composite of events (heart failure and arrhythmia-related endpoints).

Results: A heterozygous ALPK3 null variant was identified in 110 probands out of 6,505 index cases diagnosed with HCM in our center (1.7% of HCM cases). For genotype-phenotype analysis, in total 189 heterozygous carriers were included, considering relatives and cases from the literature; 21 carriers had biallelic involvement (were homozygous or compound heterozygous for two ALPK3Knv).

Among ALPK3nv heterozygous carriers, mean age at diagnosis was 53.4 (±15.2) years; mean left ventricular thickness was 17.7 (±4.9) mm, and morphological profile was mainly apical (42%) and/or concentric (26%). Males tended to be diagnosed at an earlier age than females (median age of diagnosis was 56 vs 71 years, respectively, p <0.01). Five events were observed in this group (four males and one female) all of them related to heart failure, and occur in carriers older than 45 years. The clinical profile was drastically different in cases with biallelic involvement, with a mean age at diagnosis of 22.2±9.3, mean LV wall thickness of 24 mm (±8.6), with LV dysfunction observed in 25%. Nine events were observed in this group, also mostly associated with HF (70%).

Conclusions: ALPK3 null variants in simple heterozygosis can explain 1.7% of HCM. They were associated with late-onset disease, especially in females, predominance of apical and/or concentric forms, and a phenotype that was not particularly severe, both morphologically and in terms of survival.