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Genetic characterization and genotype-phenotype associations in a large cohort of patients with hypertrophic cardiomyopathy – An ancillary study of the Portuguese registry of hypertrophic cardiomyopathy☆

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Introduction

- Hypertrophic cardiomyopathy (HCM) genotype-phenotype associations described in the literature are almost exclusively based in single-centre data
- Published national and international registries of HCM do not describe genotype findings in detail and do not analyse genotype-phenotype associations
- Portuguese Registry of Hypertrophic Cardiomyopathy (PRo-HCM) registry provides a detailed contemporary assessment of the clinical profile, management strategies and outcomes of HCM
- Overall results recently published - main article focused on a description of the clinical and outcome characteristics of the cohort

Aims

- Ancillary study of the genotype data of PRo-HCM

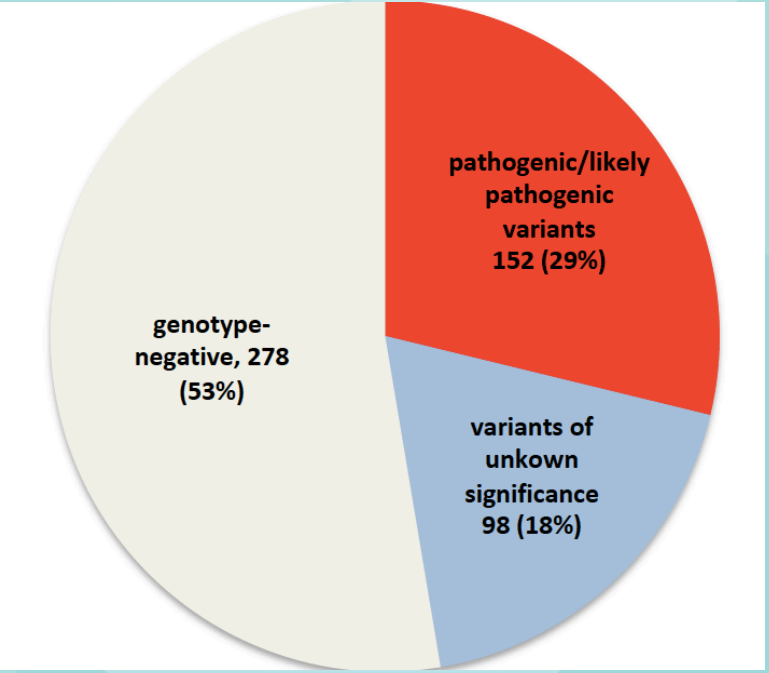
- Characterize the status of the clinical use of genetic testing in HCM patients
- Thorough revision of the variants
- Describe the main genetic findings regarding sarcomere genes and explore genotype-phenotype associations in this large registry population
- Largest genetics study on Portuguese Hypertrophic Cardiomyopathy (HCM) patients to date and one of the largest HCM genetics study based on a registry

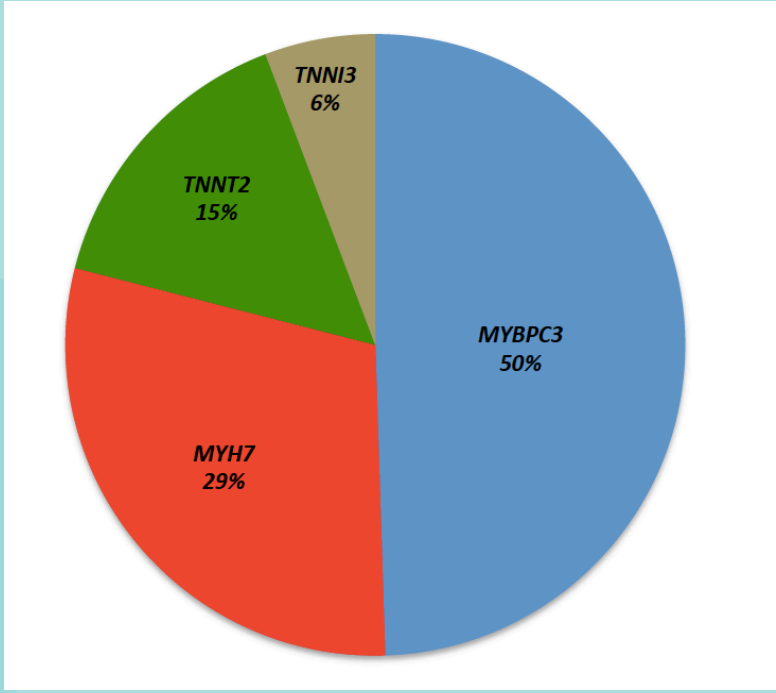
Results (demographics)

- 1042 pts recruited to the registry
- 528 (51%) had genetic testing
- 51±16 years-old, 59% males
- Birthplace: 31% North, 28% Centre and 41% South
- 436 (83%) probands and 92 (17%) relatives
- 69% of the relatives had genetic testing vs 48% of the probands

- Age: 46±17y G+ vs 53±15y G-, p<0.001

Results (overall genetic results)





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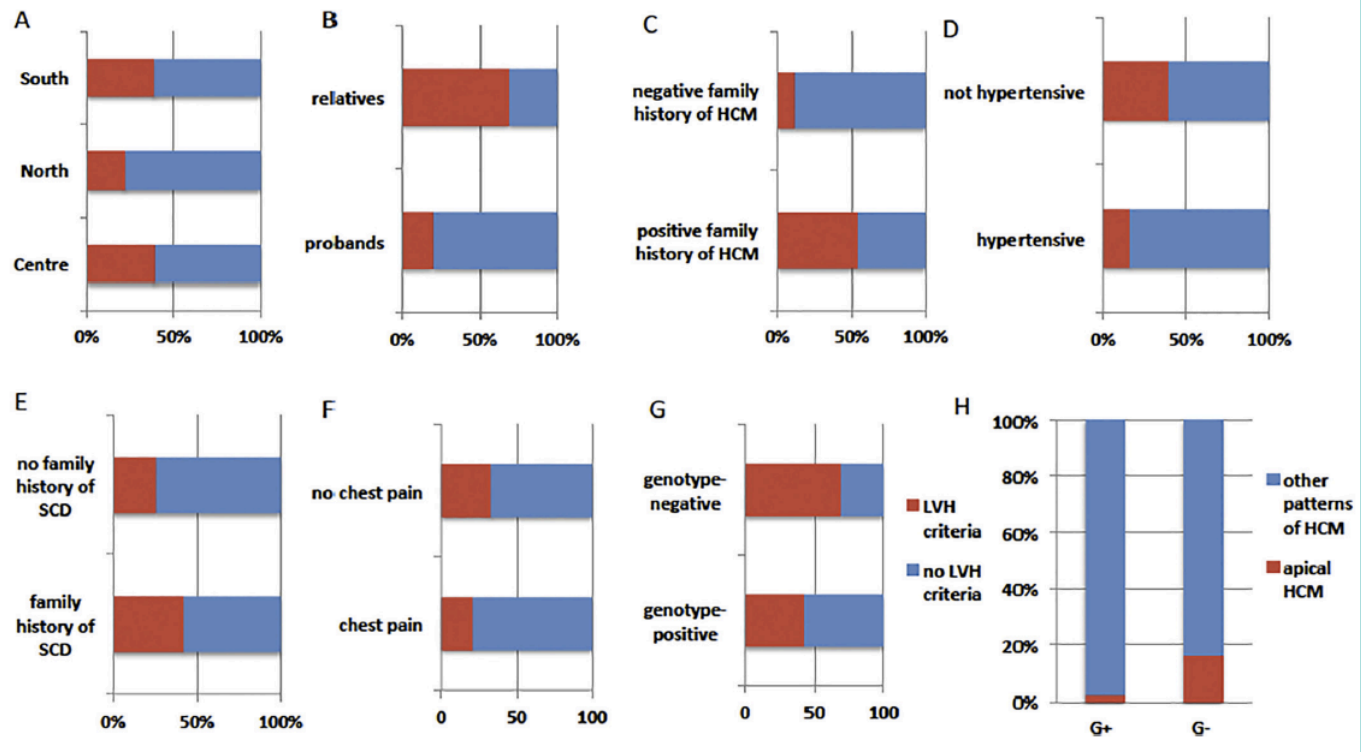
Results (genotype-phenotype associations)



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Results (sudden death risk)

Genotype-positive patients more frequently had:

- > 1 "classic" risk factor for sudden cardiac death (SCD):
  42 vs 26%, p=0.033
- higher median ESC-SCD risk score:
  4.6 vs 2.7%/5 years, p=0.003
- lower prevalence of a low-risk score:
  39% vs 69% in G-, p=0.002

Parameters	Pathogenic/likely pathogenic variant - any main sarcomere gene		
	No	Yes	p[a]
SCD risk factors according to ESC 2003 guidelines and			
Syncope[b]	39 (13,1)	18 (14,9)	0,628
Family history of SCD[b]	75 (26,0)	49 (41,5)	**0,002** *
NSVT[b]	64 (23,6)	31 (28,2)	0,351
MLVWT ≥ 30 mm[b]	20 (6,7)	9 (7,5)	0,761
ABPRE[b]	15 (9,3)	4 (7,3)	0,787
Number of risk factors[b]			
0	151 (50,0)	41 (33,6)	**0,033**
1	103 (34,1)	58 (47,5)	
2	35 (11,6)	17 (13,9)	
3	12 (4,0)	5 (4,1)	
4	1 (0,3)	1 (0,8)	
Other potential risk modifiers			
LAD bridging[b]	7 (5,3)	3 (9,7)	0,405
Apical aneurysm[b]	12 (4,2)	2 (1,7)	0,254
LV systolic dysfunction[b]	16 (5,4)	6 (5,0)	0,875
LVOTO[b]	112 (38,8)	26 (22,6)	**0,002** *
ESC SCD risk score 2014			
SCD score (value)[c]	4,3 ± 3,9	6,6 ± 6,7	**0,003** *
SCD score (risk category)[b]			
≤4%	59 (69,4)	12 (38,7)	**0,002** *
4%–6%	9 (10,6)	11 (35,5)	
≥6%	17 (20)	8 (25,8)	

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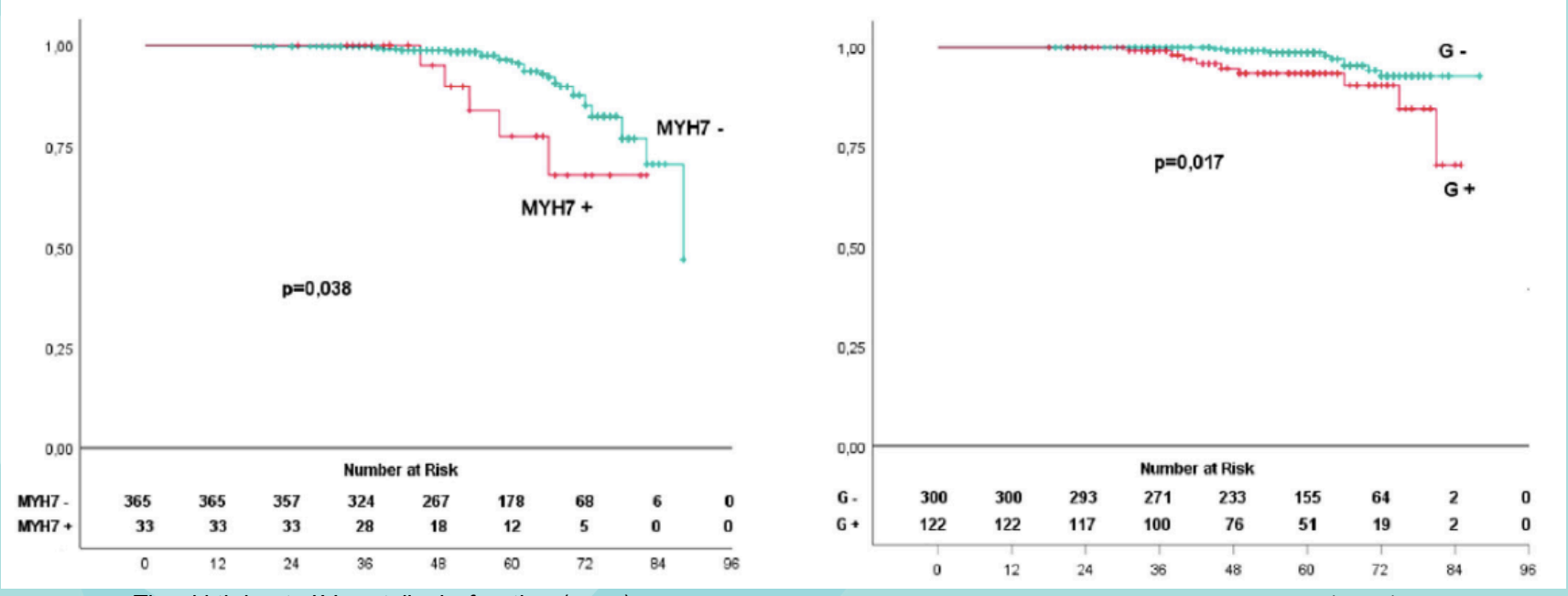
Results (genotype-outcome)



Time birthday to LV systolic dysfunction (years)

Time birthday to sudden death (years)

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Conclusions

- Half of the registry patients had genetic testing
- Yield of positive results relatively low (<30%) using current strict criteria for pathogenicity
- Distribution among causal genes similar to published populations
- G+ pts had distinct demographics, imaging characteristics and family history and increased risk of SCD
- *MYH7* was associated with LV dysfunction during follow-up

Ackowledgements

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- **All the investigators from the participating centres**