**Title: Clinical Features and Natural History of Preadolescent Nonsyndromic Hypertrophic Cardiomyopathy**

**Brief Title: Preadolescent Nonsyndromic Hypertrophic Cardiomyopathy**

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|  | | | | **< 6 years (n= 242)** | | **Missing data** | | **6-12 years (n= 397)** | | **Missing data** | | **P value** | |
|  | | | |  | |  | |  | |  | |  | |
| Male sex | | | | 156 (64.5%) | | - | | 261 (65.7%) | | - | | 0.742 | |
| FHx HCM | | | | 111 (46.1%) | | 1 (0.00%) | | 228 (58.3%) | | 6 (1.5%) | | 0.010 | |
| FHx SCD | | | | 20 (8.3%) | | - | | 47 (11.8%) | | - | | 0.153 | |
| Unexplained syncope | | | | 13 (5.4%) | | - | | 26 (6.6%) | | - | | 0.547 | |
| NYHA/Ross>1 | | | | 35 (14.5%) | | 3 (0.01%) | | 97 (24.4%) | | 5 (1.3%) | | 0.003 | |
| B Blockers | | | | 87 (36.3%) | | 2 (0.01%) | | 151 (38.0%) | | - | | 0.757 | |
| NSVT | | | | 8 (4.2%) | | 61 (25.2%) | | 17 (5.0%) | | 66 (16.7%) | | 0.337 | |
| Z score LVMWT [median (IQR)] | | | | 8.3 (5.1, 13.7) | | 34 (14.0%) | | 8.9 (5.5, 14.9) | | 38 (9.6%) | | 0.2022 | |
| Z score LA [median (IQR)] | | | | 1.2 (-0.1-2.6) | | 109 (45.0%) | | 1.2 (0.2 – 3.0) | | 121 (30.5%) | | 0.0012 | |
| LVOT gradient [median (IQR)] | | | | 10 (5, 46) | | 45 (18.6%) | | 10 (6,25) | | 60 (15.1%) | | 0.4312 | |
| LVOT obstruction | | | | 63 (32.0%) | | 45 (18.6%) | | 82 (24.3%) | | 60 (15.1%) | | 0.055 | |
| Myectomy | | | | 35 (14.5%) | | - | | 32 (8.1%) | | 3 (0.01%) | | 0.011 | |
| ICD implantation | | | | 48 (19.8%) | | - | | 100 (25.5%) | | 4 (0.01%) | | 0.104 | |
|  | | Primary | | 34 (79.1%) | | - | | 87 (87.9%) | | - | | 0.174 | |
| Secondary | | 9 (20.9%) | | - | | 12 (12.1%) | | - | |
| Death or cardiac transplant | | | | 19 (7.9%) | | - | | 44 (11.1%) | | - | | 0.291 | |
|  | | SCD | | 10 (4.1%) | | - | | 21 (5.3%) | | - | |  | |
| Heart failure | | 4 (1.7%) | | - | | 1 (0.3%) | | - | |
| Other-CV | | 0 (0.0%) | | - | | 3 (0.7%) | | - | |
| Non- CV | | 1 (0.4%) | | - | | 0 (0.0%) | | - | |
| Unknown death | | 0 (0.0%) | | - | | 2 (0.5%) | | - | |
| Transplant | | 4 (1.7%) | | - | | 17 (4.3%) | | - | |
| Life threatening arrhythmic event | | | 23 (9.5%) | | - | | 46 (11.6%) | | - | | 0.411 | |
|  | SCD | | 10 (4.1%) | | - | | 21 (5.3%) | | - | |  | |
| Resuscitated arrest | | 9 (3.7%) | | - | | 8 (2.0%) | | - | |
| Appropriate ICD therapy | | 1 (0.4%) | | - | | 13 (3.3%) | | - | |
| Sustained VT | | 3 (1.2%) | | - | | 4 (1.0%) | | - | |

Supplementary table 1: Comparing the clinical characteristics and natural history of patients presenting under and over the age of 6 years.

HCM = hypertrophic cardiomyopathy, SCD = sudden cardiac death, NYHA = New York heart association, NSVT = non-sustained ventricular tachycardia, LVMWT = left ventricular maximal wall thickness, SD = standard deviation, IQR = interquartile range, LA = left atrial, LVOT = left ventricular outflow tract, ICD = implantable cardiac defibrillator, AV = atrioventricular, CV = cardiovascular, SCD = sudden cardiac death, VT = ventricular tachycardia

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|  | **Pre-adolescent** | | | **Adolescent** | | |
|  | Genetic testing (n=348) | No genetic testing (n=180) | P value | Genetic testing (n=287) | No genetic testing (n=178) | P value |
| Age at baseline | 6.5 (3.4) | 6.5 (3.5) | 0.9872 | 13.9 (1.3) | 13.9 (.2) | 0.7586 |
| Male sex | 226 (64.9) | 116 (64.4) | 0.715 | 200 (69.9) | 130 (73.0) | 0.473 |
| FHx HCM | 203 (59.0) | 88 (49.4) | 0.177 | 161 (56.9) | 86 (49.4) | 0.120 |
| FHx SCD | 38 (10.9) | 17 (9.4) | 0.515 | 48 (16.7) | 17 (9.6) | 0.030 |
| Unexplained syncope | 21 (6.0) | 12 (6.7) | 0.711 | 37 (12.9) | 22 (12.4) | 0.884 |
| NYHA/Ross>1 | 63 (18.3) | 49 (27.2) | 0.036 | 62 (21.6) | 42 (23.6) | 0.616 |
| NSVT | 14 (4.8) | 9 (5.8) | 0.918 | 13 (4.8) | 13 (7.9) | 0.349 |
| B Blockers | 126 (36.3) | 75 (41.7) | 0.440 | 123 (42.9) | 78 (43.8) | 0.124 |
| Z score LVMWT | 10.3 (7.2) | 10.4 (7.2) | 0.8546 | 11.7 (6.8) | 9.8 (7.3) | 0.0045 |
| Z score LA | -0.8 (4.6) | -0.9 (5.3) | 0.8440 | -0.5 (4.2) | 0.5 (4.6) | 0.0289 |
| LVOT gradient | 10 (5,30) | 10 (5.8,30) | 0.6240 | 9 (5,17) | 8 (5,15) | 0.2751 |
| Death | 9 (2.6%) | 23 (12.8) | <0.001 | 9 (3.1) | 8 (4.5) | 0.484 |
| Life threatening arrhythmic event | 39 (11.2) | 21 (11.7) | 0.555 | 29 (10.1) | 18 (10.1) | 0.998 |

Supplementary table 2: Comparing the clinical characteristics and natural history of patients with and without genetic testing

HCM = hypertrophic cardiomyopathy, SCD = sudden cardiac death, NYHA = New York heart association, NSVT = non-sustained ventricular tachycardia, LVMWT = left ventricular maximal wall thickness, SD = standard deviation, IQR = interquartile range, LA = left atrial, LVOT = left ventricular outflow tract,

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| --- | --- | --- | --- |
| Patient | Gene | Protein/nucleotide change | ACMG classification |
| 1 | MYH7 | p.Arg869His  c.2606G>A | Likely pathogenic |
| MYBPC3 | p.Lys1065Glnfs\*12  c.3192dup | Pathogenic |
| 2 | MYBPC3 | p.Trp1078\*  c.3234G>A | Pathogenic |
| TPM1 | p.Met281Val  c.841A>G | Pathogenic |
| 3 | MYBPC3 | p.Val219Leu  c.655G>C | Pathogenic |
| MYH7 | p.Val606Met  c.1816G>A | Pathogenic |
| 4 | MYH7 | p.Asp239Asn  c.715G>A | Likely pathogenic |
| TNNT2 | p.Arg285Cys  c.853C>T | Pathogenic |
| 5 | MYH7 | p.Ala 355Thr  c.1063G>A | Pathogenic |
| TNNT2 | p.Asn281Ile  c.842A>T | Likely Pathogenic |
| 6 | MYBPC3 | p.Arg502Trp  c.1504C>T | Pathogenic |
| MYBPC3 | c.1624+4A>T | Pathogenic |
| 7 | MYBPC3 | p.Arg845Cys  c.2533C>Y | Likely pathogenic |
| MYBPC3 | c.3330+5G>c | Pathogenic |
| 8 | MYBCP3 | p.Lys1065fsX1076  c.3191insC | Pathogenic |
| MYH7 | p.Glu930Gln  c.2788G>C | Likely pathogenic |
| 9 | MYBPC3 | c.2308+1G>A | Pathogenic |
| MYBPC3 | p.75D>N | Likely pathogenic |

Supplementary table 3: Genetic variants of patients with compound heterozygous or homozygous sarcomeric variants.

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|  | **1-<12 years** | | | **>=12 years** | | |
|  | Disease causing variant (P/LP)  (n=186) | No disease causing variant  (n=162) | P value | Disease causing variant (P/LP)  (n=134) | No disease causing variant  (n=152) | P value |
| Age at baseline | 6.5 (3.4) | 6.5 (3.3) | 0.4465 | 13.9 (1.4) | 13.9 (1.2) | 0.4662 |
| Male sex | 114 (61.3) | 112 (69.1) | 0.126 | 101(66.5) | 99 (73.9) | 0.171 |
| FHx HCM | 131 (71.2) | 72 (45.0) | <0.001 | 105 (70.0) | 56 (42.11) | <0.001 |
| FHx SCD | 21 (11.3) | 17 (10.5) | 0.812 | 31 (20.4) | 17 (12.6) | 0.077 |
| Unexplained syncope | 12 (6.5) | 9 (5.6) | 0.726 | 19 (12.5) | 18 (13.3) | 0.833 |
| NYHA/Ross>1 | 29 (15.6) | 34 (21.0) | 0.192 | 29 (19.1) | 33 (24.4) | 0.270 |
| NSVT | 7 (4.6) | 7 (5.1) | 0.863 | 6 (4.2) | 7 (5.6) | 0.682 |
| B Blockers | 62 (33.5) | 64 (39.5) | 0.263 | 60 (39.5) | 63 (46.7) | 0.249 |
| Z score LVMWT | 10.6 (7.5) | 9.9 (6.7) | 0.8139 | 12.6 (7.0) | 10.7 (6.6) | 0.9897 |
| Z score LA | -0.4 (4.3) | -1.3 (4.9) | 0.9560 | -0.2 (4.0) | -0.7 (4.4) | 0.8131 |
| LVOT gradient | 9 (6,20) | 10 (5,35) | 0.2768 | 8 (5,15) | 10 (5, 21) | 0.1526 |
| LVOT obstruction | 32 (20.9) | 42 (30.4) | 0.063 | 24 (17.0) | 25 (21.0) | 0.413 |
| Death | 4 (2.2) | 5 (3.1) | 0.583 | 3 (2.0) | 6 (4.4) | 0.231 |
| Life threatening arrhythmic event | 21 (11.3) | 18 (11.1) | 0.958 | 13 (8.6) | 16 (11.9( | 0.355 |

Supplementary table 4: Comparing the clinical characteristics and natural history of patients with and without a disease-causing variant in sarcomeric or non-sarcomeric gene identified on genetic testing

HCM = hypertrophic cardiomyopathy, SCD = sudden cardiac death, NYHA = New York heart association, NSVT = non-sustained ventricular tachycardia, LVMWT = left ventricular maximal wall thickness, SD = standard deviation, IQR = interquartile range, LA = left atrial, LVOT = left ventricular outflow tract, SCD = sudden cardiac death

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|  | **Pre-adolescent** | | | **Adolescent** | | |
| **Disease causing sarcomeric variant (P/LP) (n=175)** | **No disease causing sarcomeric variant**  **(n=162)** | **P value** | **Disease causing sarcomeric variant (P/LP) (n=148)** | **No disease causing sarcomeric variant**  **(n=134)** | **P value** |
| Age at baseline | 6.5 (3.4) | 6.4 (3.4) | 0.8722 | 13.9 (1.4) | 13.7 (1.2) | 0.304 |
| Male sex | 108 (61.7) | 112 (69.1) | 0.153 | 99 (66.9) | 99 (73.9) | 0.200 |
| FHx HCM | 125 (72.3) | 72 (45.0) | <0.001 | 104 (71.2) | 56 (42.1) | <0.001 |
| FHx SCD | 20 (11.4) | 17 (10.5) | 0.784 | 31 (21.0) | 17 (12.6) | 0.061 |
| Unexplained syncope | 10 (5.7) | 9 (5.6) | 0.950 | 18 (12.2) | 18 (13.3) | 0.768 |
| NYHA/Ross>1 | 27 (15.6) | 34 (21.4) | 0.405 | 29 (20.3) | 33 (25.0) | 0.551 |
| NSVT | 6 (4.2) | 7 (5.1) | 0.866 | 6 (4.3) | 7 (5.6) | 0.713 |
| B Blockers | 56 (32.2) | 64 (39.5) | 0.209 | 59 (39.9) | 63 (46.7) | 0.277 |
| Z score MWT | 10.8 (7.7) | 9.9 (6.7) | 0.8567 | 12.5 (7.0) | 10.7 (6.6) | 0.986 |
| Z score LA | -0.5 (4.3) | -1.3 (4.9) | 0.940 | -0.1 (4.0) | -0.7 (4.4) | 0.880 |
| LVOT gradient | 9 (6,20) | 10 (5, 35)) | 0.1407 | 8 (5,15) | 10 (5, 21) | 0.2362 |
| LVOTO | 31 (21.5) | 42 (30.4) | 0.088 | 23 (16.8) | 25 (21.0) | 0.388 |
| Death | 4 (2.3) | 5 (3.1) | 0.649 | 3 (2.0) | 6 (4.4) | 0.247 |
| Life threatening arrhythmic event | 21 (12.0) | 18 (11.1) | 0.799 | 12 (8.1) | 16 (11.9) | 0.292 |

Supplementary table 5: Comparing the clinical characteristics and natural history of patients with and without a disease-causing sarcomeric variant in identified on genetic testing

HCM = hypertrophic cardiomyopathy, SCD = sudden cardiac death, NYHA = New York heart association, NSVT = non-sustained ventricular tachycardia, LVMWT = left ventricular maximal wall thickness, SD = standard deviation, IQR = interquartile range, LA = left atrial, LVOT = left ventricular outflow tract, SCD = sudden cardiac death

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|  | Univariable Cox regression analysis | | | Multivariable Cox regression analysis |  |  |
|  | Hazard ratio | 95% CI | P value | Hazard ratio | 95% CI | P value |
| Increasing age | 1.09 | 1.01 – 1.18 | 0.022 |  |  |  |
| FHx HCM | 1.04 | 0.63 – 1.72 | 0.865 |  |  |  |
| NYHA >1 | 4.28 | 2.60 – 7.06 | <0.001 | 2.20 | 0.90 – 5.44 | 0.085 |
| LVOT gradient | 1.002 | 0.99 – 1.01 | 0.589 |  |  |  |
| LA z score | 1.15 | 1.09 – 1.22 | <0.001 | 1.21 | 1.07 – 1.36 | 0.020 |
| LVMWT z score | 1.003 | 0.97 – 1.04 | 0.859 |  |  |  |
| Disease causing variant | 0.40 | 0.16 – 0.99 | 0.048 | 0.37 | 0.15 – 0.90 | 0.029 |
| B-blocker therapy | 1.16 | 0.70 – 1.93 | 0.562 |  |  |  |

Supplementary table 6: Cox regression analysis of baseline clinical features associated with mortality of cardiac transplant

Supplementary figure 1: Participation recruitment and retention in the International Paediatric Hypertrophic Cardiomyopathy Consortium

Supplementary figure 2: Flow sheet showing genetic testing strategy

\*Nucleic acid or amino acid change not provided by participating centres