Reevaluation of the South Asian MYBPC3Δ25bp Intronic Deletion in Hypertrophic Cardiomyopathy

Andrew R. Harper, MSc, MRCP; Michael Bowman, BSc; Jesse B.G. Hayesmoore, PhD; Helen Sage, MSc; Silvia Salatino, PhD; Edward Blair, BMSc, FRCP; Carolyn Campbell, FRCP; Bethany Currie, MSc; Anuj Goel, MBBS, MSc; Karen McGuire, BSc; Elizabeth Ormondroyd, PhD; Kate Sergeant, PhD; Adam Waring, BSc; Jessica Woodley, FRCP; Christopher M. Kramer, MD; Stefan Neubauer, MD; HCMR Investigators†; Martin Farrall, FRCP; Hugh Watkins, MD, PhD†; Kate L. Thomson, FRCPath, PhD*  

BACKGROUND: The common intronic deletion, MYBPC3Δ25, detected in 4% to 8% of South Asian populations, is reported to be associated with cardiomyopathy, with ≈7-fold increased risk of disease in variant carriers. Here, we examine the contribution of MYBPC3Δ25 to hypertrophic cardiomyopathy (HCM) in a large patient cohort.  

METHODS: Sequence data from 2 HCM cohorts (n=5393) was analyzed to determine MYBPC3Δ25 frequency and co-occurrence of pathogenic variants in HCM genes. Case-control and haplotype analyses were performed to compare variant frequencies and assess disease association. Analyses were also undertaken to investigate the pathogenicity of a candidate variant MYBPC3 c.1224-52G>A.  

RESULTS: Our data suggest that the risk of HCM, previously attributed to MYBPC3Δ25, can be explained by enrichment of a derived haplotype, MYBPC3Δ25/−52, whereby a small subset of individuals bear both MYBPC3Δ25 and a rare pathogenic variant, MYBPC3 c.1224-52G>A. The intronic MYBPC3 c.1224-52G>A variant, which is not routinely evaluated by gene panel or exome sequencing, was detected in ≈1% of our HCM cohort.  

CONCLUSIONS: The MYBPC3 c.1224-52G>A variant explains the disease risk previously associated with MYBPC3Δ25 in the South Asian population and is one of the most frequent pathogenic variants in HCM in all populations; genotyping services should ensure coverage of this deep intronic mutation. Individuals carrying MYBPC3Δ25 alone are not at increased risk of HCM, and this variant should not be tested in isolation; this is important for the large majority of the 100 million individuals of South Asian ancestry who carry MYBPC3Δ25 and would previously have been declared at increased risk of HCM.  

Key Words: exome ◼ genotype ◼ haplotypes ◼ humans ◼ introns  

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Hypertrophic cardiomyopathy (HCM) is the most common inherited cardiac condition, affecting at least ≈1:500 individuals.1 It is a genetically heterogeneous disorder, typically attributable to pathogenic variants in genes encoding cardiac sarcomere proteins, predominantly MYBPC3 and MYH7.2 Truncating variants in MYBPC3 are a well-recognized cause of HCM, and the majority are considered to cause autosomal dominant disease with high age-related penetrance; consequently, such variants are extremely rare in the wider nondisease population.2

Correspondence to: Kate L. Thomson, FRCP; Oxford Medical Genetics Laboratory, Oxford University Hospitals NHS Foundation Trust, Churchill Hospital, Oxford OX3 7LE, United Kingdom. Email kate.thomson@ouh.nhs.uk  

†Drs Watkins and Thomson contributed equally to this work as senior authors.  

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A 25 base pair deletion located within intron 32 of MYBPC3 (MYBPC3Δ25), the c.3628-41_3628-17del variant, is a notable exception. Detected in 4% to 8% of individuals of South Asian ancestry, and with an estimated 100 million carriers worldwide, this common variant is considered to be associated with cardiomyopathy, with an almost 7-fold increased risk of cardiomyopathy in heterozygous carriers. Although previous studies have considered the possibility that MYBPC3Δ25 lies in linkage disequilibrium with another MYBPC3 variant that causes or contributes to disease risk, comprehensive analyses in large patient cohorts have not been performed.

Here, using genetic data from 2 large HCM cohorts, we present data suggesting that MYBPC3Δ25 is not a pathogenic risk factor in HCM. Rather, the increased frequency of this variant in South Asian cardiomyopathy cohorts reflects the enrichment of a derived haplotype, which bears both the common MYBPC3Δ25 variant and a rare pathogenic variant, MYBPC3 c.1224-52G>A. Additionally, we find that MYBPC3 c.1224-52G>A—an intronic variant that is not routinely detected on gene panel or exome sequencing—is the single most common pathogenic variant in individuals of South Asian ancestry in our cohort and the second most common in individuals of European ancestry.

METHODS
The complete methods are available in Materials in the Data Supplement. Due to the confidential nature of some of the research materials supporting this publication, not all of the data can be made accessible to other researchers. Please contact the corresponding author for more information. The study was approved by the local ethics committees, and all patients signed an informed consent.

RESULTS
Oxford Medical Genetics Laboratory Demographic and Clinical Details
Within the Oxford Medical Genetics Laboratory (OMGL) cohort, demographic information was available for 98.0% of individuals (2703/2757). The majority of referrals were provided by inherited cardiac condition centers within the United Kingdom (80.1%; 2166/2757). The average age was 54.5 years (±16.2), and 68.4% were men (n=1845; Table 1). No self-identified, or genetically derived, ancestry information was available.

HCMR Demographic and Clinical Details
Within the HCMR cohort, the average age was 49.5 years (±11.3), and 71.4% were men. Genetically derived ancestry predictions, determined through principal components analysis, demonstrated European ancestry in 78.3%, African ancestry in 9.0%, and South Asian ancestry in 5.1% of individuals (Table 1).

Population Frequency of MYBPC3Δ25
In the Genome Aggregation Database (gnomAD; v2.1.1), 6.2% of individuals ascribed South Asian ancestry were heterozygous for the MYBPC3Δ25 variant (943/15,296 [95% CI, 5.7%–6.5%]), 0.1% were homozygous (19). This is consistent with previous studies that have reported frequencies ranging from 2% to 8%. The MYBPC3Δ25 variant is highly specific to individuals of South Asian ancestry: 98.1% (95% CI, 97.0%–98.9%) of MYBPC3Δ25 variant carriers within gnomAD are derived from a South Asian population (Table 2).

Oxford Clinical Laboratory Cohort
In the OMGL HCM cohort, pathogenic variants were detected in 17.1% (471/2757), likely pathogenic variants in 6.9% (191/2757), and variants of uncertain significance in an additional 14.2% (392/2757) of individuals. A summary of the most frequently detected variants is presented in Table I in the Data Supplement.

Table 1. Demographic Summary for OMGL and HCMR Cohorts

|                  | OMGL        | HCMR        |
|------------------|-------------|-------------|
| Total, n         | 2757        | 2636        |
| Age, y (SD)      | 54.5 (16.3) | 49.5 (11.3) |
| Men              | 1845 (68.4%)| 1893 (71.4%)|
| Ancestry         |             |             |
| AFR              | NA          | 239 (9.0%)  |
| AMR              | NA          | 135 (5.1%)  |
| EAS              | NA          | 68 (2.6%)   |
| EUR              | NA          | 2074 (78.3%)|
| SAS              | NA          | 134 (5.1%)  |
| Variant carriers |             |             |
| P                | 471 (17.1%) | 572 (21.6%) |
| LP               | 191 (6.9%)  | 216 (8.2%)  |
| VUS              | 392 (14.2%) | 379 (14.3%) |
| Negative         | 1703 (61.8%)| 1483 (56.0%)|

Ancestry codes as per the International Genome Sample Resource: AFR indicates African; AMR, Ad Mixed American; EAS, East Asian; EUR, European; and SAS, South Asian. Counts for individuals with P, LP, or VUS included. HCMR indicates Hypertrophic Cardiomyopathy Registry; LP, likely pathogenic; NA, not available; OMGL, Oxford Medical Genetics Laboratory; P, pathogenic; and VUS, variant of uncertain significance.
## Table 2. Summary of Allele Frequency Differences Between Cases and Controls

|                     | Cases          |          | Controls       |          | OR (95% CI) | Fisher P Value‡ |
|---------------------|----------------|----------|----------------|----------|-------------|----------------|
|                     | OMGL HCMR Total Cases | P Value* | BRRD gnomAD exomes | gnomAD Genomes | Total gnomAD | TOPMED Total Controls† |
| **MYBPC3−52 minor allele frequency** |               |          |                |          |             |                |
| Global              | 0.00580 [0.00574 to 0.00587] (32/2757) | 0.00436 [0.00431 to 0.00442] (23/2636) | 0.00510 [0.00506 to 0.00514] (55/5393) | 0.359 [0.25 × 10⁻¹⁰ to 3.25 × 10⁻¹⁰] (6056) | ... (0/0) | 3.2 × 10⁻⁶ [9.56 × 10⁻⁷ to 3.40 × 10⁻⁶] (1/15667) | 3.2 × 10⁻⁶ [9.56 × 10⁻⁷ to 3.40 × 10⁻⁶] (1/15667) | ... [0 to 3.13 × 10⁻⁴] (0/62 784) | 6.57 × 10⁻⁶ [1.97 × 10⁻⁶ to 7.00 × 10⁻⁶] (1/76048) | 780 (135–16 384) | 6.77 × 10⁻⁹ |
| European (NFE)      | NA             | 0.00410 [0.00404 to 0.00416] (17/2074) | 0.00410 [0.00404 to 0.00416] (17/2074) | ... [0 to 5.45 × 10⁻⁵] (3/3606) | ... (0/0) | ... [0 to 2.55 × 10⁻⁵] (0/7696) | ... [0 to 2.55 × 10⁻⁵] (0/7696) | No ancestry data | ... [0 to 2.55 × 10⁻⁵] (0/7696) | (0/0) | 3.43 × 10⁻⁵ |
| South Asian         | NA             | 0.00224 [0.00218 to 0.00230] (6/134) | 0.00224 [0.00218 to 0.00230] (6/134) | ... [0 to 5.20 × 10⁻⁵] (0/378) | ... (0/0) | ... (0/0) | ... (0/0) | No ancestry data | ... (0/0) | ... |
| **MYBPC3Δ25 minor allele frequency** |               |          |                |          |             |                |
| Global              | 0.00383 [0.00359 to 0.00398] (20/2757) | 0.00338 [0.00336 to 0.00344] (19/2636) | 0.00365 [0.00363 to 0.00368] (36/5393) | 0.956 [9.56 × 10⁻⁶ to 3.40 × 10⁻⁶] (1/15667) | 9.56 × 10⁻⁶ [9.22 × 10⁻⁶ to 9.91 × 10⁻⁶] (9/139954) | 9.56 × 10⁻⁶ [9.22 × 10⁻⁶ to 9.91 × 10⁻⁶] (9/139954) | 3.39 × 10⁻⁶ [2.30 × 10⁻⁶ to 2.48 × 10⁻⁶] (3/62 784) | 2.39 × 10⁻⁶ [2.30 × 10⁻⁶ to 2.48 × 10⁻⁶] (3/62 784) | 0.00250 [0.00249 to 0.00251] (9/841/197114) | 1.41 (0.99–1.96) | 0.040 |
| European (NFE)      | NA             | ... [0 to 9.45 × 10⁻⁵] (0/2074) | ... [0 to 9.45 × 10⁻⁵] (0/2074) | ... [0 to 5.45 × 10⁻⁵] (0/3606) | ... (0/0) | ... (0/0) | ... (0/0) | No ancestry data | ... (0/0) | ... |
| South Asian         | NA             | 0.00634 [0.00625 to 0.00644] (17/134) | 0.00634 [0.00625 to 0.00644] (17/134) | ... [0 to 5.45 × 10⁻⁵] (0/3606) | ... (0/0) | ... (0/0) | ... (0/0) | No ancestry data | ... (0/0) | 1.98 (1.11–3.50) | 0.015 |

Minor allele frequency (95% binomial CI calculated using Wilson method) presented with variant carrier counts in parentheses beneath. BRRD indicates BioResource for Rare Disease cohort; gnomAD, genome aggregation database; HCMR, Hypertrophic Cardiomyopathy Registry; NA, not available; NFE, non-Finnish European; OMGL, Oxford Medical Genetics Laboratory; OR, odds ratio; and TOPMED, Trans-Omics for Precision Medicine. *OMGL and HCMR case proportions compared using 2-sample test for equality of proportions with continuity correction. †Total controls calculated from nonoverlapping samples provided by gnomAD and TOPMED. ‡Fisher P value relates to the hypothesis that cases, derived from the OMGL and HCMR cohorts, are enriched for either MYBPC3−52 or MYBPC3Δ25 when compared with nonoverlapping controls, provided by gnomAD and TOPMED.
0.7% (20/2757) of individuals were heterozygous for the MYBPC3Δ25 variant. In 50.0% (10/20) of individuals heterozygous for MYBPC3Δ25, a pathogenic or likely pathogenic sarcomeric gene variant was also detected; variants of uncertain clinical significance were detected in an additional 3 individuals (15.0%, 3/20; Table 3). Of these accompanying variants, MYBPC3 c.1224-52G>A was the most frequently observed, found in 30.0% (6/20) of individuals heterozygous for MYBPC3Δ25.

**HCMR Cohort**

In the HCMR cohort, pathogenic variants were detected in 21.7% (572/2636), likely pathogenic variants in 8.2% (216/2636), and variants of uncertain significance in an additional 14.4% (379/2636) of individuals. A summary of the most frequently detected variants is presented in Table I in the Data Supplement. Overall, 0.7% (18/2636) of individuals were heterozygous for the MYBPC3Δ25 variant; no homozygous individuals were detected; 17 MYBPC3Δ25 variant carriers were ascribed as South Asian ancestry by genetic principal components analysis (94.4%, 17/18). The carrier frequency for MYBPC3Δ25 within the HCMR South Asian ancestry group was 12.7% ([95% CI, 8.1%–19.4%] 17/134).

In 58.8% (10/17) of South Asian individuals heterozygous for MYBPC3Δ25, a pathogenic variant in one of the sarcomeric genes was detected (Table 3). An additional 2 individuals were found to have variants of uncertain clinical significance (11.8%, 2/17). Replicating findings from our discovery cohort, the c.1224-52G>A variant was the most frequent, found in 29.4% (5/17) of South Asian individuals heterozygous for MYBPC3Δ25.

Overall, including the MYBPC3 c.1224-52G>A variant carriers between the HCMR (17/134) and gnomAD (943/15296) South Asian cohorts indicated a 2-fold enrichment within HCM cases (odds ratio [OR], 2.1 [95% CI, 1.2–3.4]; P=0.008). When HCMR probands with the MYBPC3Δ25/−52 haplotype were excluded, no difference was observed (OR, 0.96 [95% CI, 0.40–1.95]; P=1.0). Exact multivariate logistic regression, of individuals of South Asian ancestry from the HCMR and BioResource for Rare Disease cohorts (Table 4), provided evidence in support of disease association for the MYBPC3 c.1224-52G>A variant (OR, 15.90 [95% CI, 2.05–∞]; P=0.003) but not the MYBPC3Δ25 variant (OR, 1.76 [95% CI, 0.77–4.36]; P=0.15). The significance of the MYBPC3 c.1224-52G>A association adjusted for the MYBPC3Δ25 variant was confirmed using an exact Mantel-Haenszel test (P=0.003).

In individuals of South Asian ancestry in the HCMR cohort, the MYBPC3 c.1224-52G>A variant was found

### Table 3. Pathogenic, Likely Pathogenic, and Variants of Uncertain Significance Accompanying MYBPC3 in Individuals From Both the OMGL and HCMR Cohorts

| Gene   | Variant         | Variant Classification | Frequency in Individuals Heterozygous for MYBPC3Δ25 |
|--------|-----------------|------------------------|---------------------------------------------------|
| OMGL   |                 |                        |                                                   |
| MYBPC3 | c.1224-52G>A    | Pathogenic             | 6/20                                              |
| MYBPC3 | c.1227-13G>A    | Pathogenic             | 1/20                                              |
| MYBPC3 | c.2827C>T      p.(Arg943Ter) | Pathogenic             | 1/20                                              |
| MYH7   | c.2770G>A      p.(Glu924Lys) | Pathogenic             | 1/20                                              |
| MYBPC3 | c.2308G>A      p.(Asp770Asn) | Likely pathogenic      | 1/20                                              |
| MYBPC3 | c.2030C>T      p.(Pro677Leu) | VUS                   | 1/20                                              |
| MYH7   | c.3931C>G      p.(Gln1311Glu) | VUS                   | 1/20                                              |
| MYH7   | c.436A>G       p.(Lys146Glu) | VUS                   | 1/20                                              |
| HCMR   |                 |                        |                                                   |
| MYBPC3 | c.1224-52G>A    | Pathogenic             | 5/18                                              |
| MYBPC3 | c.1227-13G>A    | Pathogenic             | 1/18                                              |
| MYBPC3 | c.821+2T>C     | Pathogenic             | 1/18                                              |
| MYH7   | c.1988G>A      p.(Arg663His) | Pathogenic             | 1/18                                              |
| MYH7   | c.2221G>A      p.(Gly741Arg) | Pathogenic             | 1/18                                              |
| MYH7   | c.5065C>T      p.(Arg1689Cys) | VUS                   | 1/18                                              |
| MYH7   | c.170G>A       p.(Gly57Asp) | VUS                   | 1/18                                              |

NCBI transcript IDs: MYBPC3 NM_000256.3 and MYH7 NM_000257.2. HCMR indicates Hypertrophic Cardiomyopathy Registry; OMGL, Oxford Medical Genetics Laboratory; and VUS, variant of uncertain significance.
to occur on the second most commonly observed MYBPC3Δ25 haplotype (Figure 1). Hence, there is evidence of strong linkage disequilibrium between MYBPC3Δ25 and MYBPC3 c.1224-52G>A (D′=0.81 and r²=0.22; Figure I in the Data Supplement; Table II in the Data Supplement). In South Asian individuals, the MYBPC3 c.1224-52G>A variant also occurred on a haplotype that did not include the MYBPC3Δ25 variant.

Investigating the Pathogenicity of MYBPC3 c.1224-52G>A

The MYBPC3 c.1224-52G>A variant (Chr11[GRCh37]:g.47364865C>T, NM_000256.3) was detected in 32 of 2757 (1.2% [95% CI, 0.8%–1.6%]) probands in the OMGL cohort and in 23 of 2636 (0.9% [95% CI, 0.6%–1.2%]) probands in the HCMR cohort. A 2-sample test for equality of proportions, with continuity correction, suggests the minor allele frequencies derived from OMGL and HCMR are equivalent (P=0.98).

No other pathogenic or likely pathogenic sarcomere gene variants were detected in these cases. Within the OMGL cohort, MYBPC3 c.1224-52G>A was confirmed to cosegregate with HCM in 4 families (Figure II in the Data Supplement); in 3, it was detected in the proband and 2 other affected relatives. Within the wider HCMR and OMGL populations, MYBPC3 c.1224-52G>A was found to occur on 2 additional haplotypes, distinct from the 2 South Asian haplotypes, which argues against a unique founder mutation.

The c.1224-52G>A variant occurs once within 76048 nonoverlapping individuals, present within gnomAD (v.2.1.1) and NHLBI Trans-Omics for Precision Medicine (https://bravo.sph.umich.edu/freeze5/hg38/), indicating a global minor allele frequency, incorporating all available ancestral groups, of 6.57×10⁻⁶. A comparison of the proportion of individuals heterozygous for this variant in the combined OMGL and HCMR cohorts (55/5393), against these reference populations, generates an extreme effect size (OR, 780 [95% CI, 135–16 384]; P=9.74×10⁻⁶⁴).

In silico splice site tools predict that c.1224-52G>A introduces a cryptic splice acceptor site in intron 13 (NM_000256.3), 50 nucleotides upstream (5′) of the native site. Polymerase chain reaction of cDNA reverse transcribed from RNA from 2

| Table 4. South Asian Cases vs Controls |
|----------------------------------------|
| MYBPC3Δ25 Carrier | MYBPC3Δ25 Noncarrier | MYBPC3Δ25 Carrier | MYBPC3Δ25 Noncarrier |
|-------------------|---------------------|-------------------|---------------------|
| MYBPC3 c.1224-52G>A Carrier | 5 | 12 | 1 | 116 |
| MYBPC3 c.1224-52G>A Noncarrier | 0 | 21 | 0 | 357 |

A 2-by-2-by-2 contingency table reporting counts of genotypes for cases vs controls by indel carriers vs noncarriers by −52 carriers vs noncarriers for individuals of South Asian ancestry. Case data derived from HCMR and control data derived from BRRD. BRRD indicates BioResource for Rare Disease cohort; and HCMR, Hypertrophic Cardiomyopathy Registry.
individuals with the c.1224-52G>A variant generated an aberrant product. Sequencing of this product confirmed in silico predictions and showed inclusion of 50 intronic nucleotides in the transcript (Figure 2). Inclusion of these nucleotides is predicted to lead to a frameshift in the amino acid sequence and insertion of a premature termination codon at position 438 (p.Ser408fs*31).

Pathogenicity Classification for MYBPC3 c.1224-52G>A

Using the American College of Medical Genetics framework,6 the MYBPC3 c.1224-52G>A variant was classified as pathogenic based on the following criteria: PS3: RNA studies have provided evidence of an aberrant effect on splicing (our analyses and published data7); PS4: the variant is significantly more frequent in probands with HCM than in population controls; PM2: the variant is very rare in the wider population; and PP1: there is evidence of cosegregation with HCM in multiple families (4 in our cohort and published data7).

DISCUSSION

When the MYBPC3Δ25 variant was first reported to be associated with cardiomyopathy in the South Asian population, it was thought likely to have a direct role in disease pathogenesis; since the initial report, it has come to be considered as one of the most compelling examples of a common, low-penetrance variant contributing to the genetic architecture of HCM.3,8–12 Genetic analyses undertaken in this study challenge these previous assertions and show that the MYBPC3Δ25 variant does not directly confer an increased risk of cardiomyopathy but instead acts as a proxy marker for a rare, large effect size, intronic pathogenic variant, MYBPC3 c.1224-52G>A (Figure 3). Consequently, we conclude that heterozygosity for the MYBPC3Δ25 common variant is not pathogenic for HCM.

Through RNA studies and segregation analyses, we provide robust evidence to support the pathogenicity of the MYBPC3 c.1224-52G>A variant. This variant has previously been described in the literature as a pathogenic variant;7 however, neither its high prevalence nor its relationship with MYBPC3Δ25 has been reported. Our analyses reveal MYBPC3 c.1224-52G>A to be a recurrent variant, and one of the most frequent pathogenic variants across all known HCM genes in both European and South Asian populations, comparable to other well-established recurrent and founder pathogenic variants (eg, MYBPC3 c.2373dup13 and MYBPC3 p.Glu258Lys9), and exceeded only by the MYBPC3 p.Arg502Trp variant, the most common pathogenic variant in HCM.2,5,14 Further, the MYBPC3 c.1224-52G>A variant has a strikingly
high OR for disease ($\approx 700$), suggesting that it is a high penetrance allele.

Haplotype analyses indicate that an ancestral $\text{MYBPC3}^{c.1224-52G>A}$ variant arose on a haplotype bearing the common $\text{MYBPC3}^{\Delta25}$ variant and that the reported association between $\text{MYBPC3}^{\Delta25}$ and HCM in the South Asian population was due to the increased frequency of the derived $\text{MYBPC3}^{\Delta25/-52}$ haplotype, which had not previously been differentiated from the common $\text{MYBPC3}^{\Delta25}$ haplotype. In our cohort, after accounting for the $\text{MYBPC3}^{\Delta25/-52}$ haplotype, the frequency of the $\text{MYBPC3}^{c.1224-52G>A}$ allele appears equivalent between HCM cases and reference controls, which casts doubt upon previous pathogenic inferences from risk associations and suggests that it is not clinically appropriate to type the $\text{MYBPC3}^{\Delta25}$ in isolation. Indeed, the ability to detect the $\text{MYBPC3}^{\Delta25/-52}$ haplotype is critical not only for individuals with a clinical diagnosis of HCM but for the vast majority of the 100 million individuals of South Asian ancestry heterozygous for the $\text{MYBPC3}^{\Delta25}$ alone, who would previously have been declared at increased risk of HCM.

**Limitations**

Our conclusions rely on the observed $\text{MYBPC3}^{\Delta25}$ and $\text{MYBPC3}^{\Delta25/-52}$ haplotype frequencies being representative of the wider South Asian population. Here, direct evaluation of $\text{MYBPC3}^{\Delta25}$ and $\text{MYBPC3}^{\Delta25/-52}$ and HCM disease risk has relied on analysis performed using individuals ascribed South Asian ancestry based on genetic principal components analysis from 2 independent, but relatively small, cohorts. Large reference cohorts, specifically gnomAD and Trans-Omics for Precision Medicine, were useful in quantifying the allele frequencies of both $\text{MYBPC3}^{\Delta25}$ and $\text{MYBPC3}^{c.1224-52G>A}$ but were not suitable for the direct evaluation of the $\text{MYBPC3}^{\Delta25/-52}$ haplotype, given the lack of individual-level data.

Our case series comprised 2 large HCM cohorts with a combined total of 5394 HCM probands (OMGL, $n=2757$; HCMR, $n=2636$), representing the largest published HCM cohort to date. $\text{MYBPC3}^{\Delta25}$ and $\text{MYBPC3}^{\Delta25/-52}$ haplotype frequencies were equivalent within these mixed ancestry HCM cohorts. Ancestry data were only available from the HCMR cohort, in which 134 cases were defined as South Asian; additional analyses in other South Asian cohorts will refine $\text{MYBPC3}^{\Delta25/-52}$ haplotype frequency estimates and allow more accurate quantification of the strength of the association of this haplotype to HCM in this population.

The findings in this study relate specifically to HCM. In the original case-control study by Dhandapany et al., 3 composite case groups were assembled that included individuals diagnosed with HCM ($n=357$), dilated cardiomyopathy ($n=395$), and restrictive cardiomyopathy ($n=395$), and restrictive cardiomyopathy ($n=15$). While our findings refute a pathogenic role for the $\text{MYBPC3}^{\Delta25}$ variant in HCM, at present, our conclusions do not extend to these other cardiomyopathies or to homozygosity for this variant. However, given current understanding of the diametrically opposing molecular mechanisms that underpin sarcomeric HCM and...
understanding of the genetic architecture of HCM and, conversely, these findings have significant implications for our understanding of other cardiomyopathy genes where truncating variants have only been associated with HCM and not primary dilated cardiomyopathy.

Conclusions

The results of this study provide strong evidence to refute a direct pathogenic link between the MYBPC3 Δ25 variant and HCM risk; this is important for the very large number of South Asian individuals who will be found to have this variant when undergoing either targeted or genome-wide genetic analysis. Additionally, they highlight MYBPC3 c.1224-52G>A as an important HCM variant. They also reiterate the importance of sequencing deeper intronic regions in the MYBPC3 gene, and, indeed, other cardiomyopathy genes where truncating variants are believed to cause the disease. Collectively, these findings have significant implications for our understanding of the genetic architecture of HCM and for the clinical management of patients with HCM.

ARTICLE INFORMATION

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Affiliations

Radcliffe Department of Medicine, University of Oxford, Oxford, United Kingdom (A.R.H., AG, EO, SN, MF, HW, KLT). Division of Cardiologie Medicine, John Radcliffe Hospital, Oxford, United Kingdom (A.R.H., AG, EO, SN, MF, HW, KLT). Wellcome Centre for Human Genetics, Oxford, United Kingdom (A.R.H., SS, AG, AW, MF, HW, KLT). Oxford Medical Genetics Laboratories, Churchill Hospital, Oxford, United Kingdom (MB, JBGH, HS, CC, BCM, K.S., KLT). Oxford Centre for Genomic Medicine, Oxford University Hospitals NHS Foundation Trust, Oxford, United Kingdom (EB). West Midlands Regional Genetics Laboratory, Birmingham Woman's and Children's NHS Foundation Trust, Birmingham, United Kingdom (JW). University of Virginia Health System, Charlottesville, VA (CMK).

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APPENDIX

HCMR Investigators: Theodore Abraham, MD, Hypertrophic Cardiomyopathy Center of Excellence, Johns Hopkins University, Baltimore, MD; Lisa Anderson, MD, St George's University Hospitals NHS Trust, London, United Kingdom; Evan Appelbaum, MD, Departments of Medicine, Cardiovascular Division & Radiology, Beth Israel Deaconess Medical Center, Harvard Medical School, Boston, MA; Camillo Autore, MD, Division of Cardiology, Department of Clinical & Molecular Medicine, St. Andrea Hospital, Sapienza University, Rome, Italy; Colin Berry, MD, British Heart Foundation Glasgow Cardiovascular Research Center, Institute of Cardiovascular & Medical Sciences, University of Glasgow, UK; Elena Biagini, MD, Cardio-Thoracic-Vascular Department; University Hospital of Bologna, Policlinico S. Orsola-Malpighi, Bologna, Italy; William Bradlow, MD, Department of Cardiology, New Queen Elizabeth Hospital Birmingham, UK; Chiara Bucciarelli-Ducci, MD, Bristol Heart Institute, Bristol National Institute of Health Research (NIHR) Biomedical Research Center, University Hospitals Bristol NHS Trust & University of Bristol, UK; Amedeo Chiribiri, MD, PhD, Cardiovascular Division, King's College London British Heart Foundation Centre of Excellence, The Rayne Institute, St. Thomas' Hospital Campus, London, UK; Lubna Choudhury, MD, Division of Cardiology, Department of Medicine, Bluhm Cardiovascular Institute, Northwestern University Feinberg School of Medicine, Chicago, IL; Andrew Crean, MD, Division of Cardiology, Peter Munk Cardiac Center, University Health Network, University of Toronto, Ontario, Canada; Dana Dawson, MD, Aberdeen Cardiovascular & Diabetes Center, University of Aberdeen, UK; Milind Y. Desai, MD, Department of Cardiovascular Medicine, Center for Radiation Heart Disease, Heart & Vascular Institute, Cleveland Clinic, Cleveland, OH; Eleanor Einsteins, MD, Division of Cardiology, Department of Medicine, McGill University, Royal Victoria Hospital, Montreal, Quebec, Canada; Andrew Flett, MD, Department of Cardiology, University Hospital Southampton NHS Foundation Trust, Southampton, UK; Matthias Friedrich, MD, Department of Medicine, Heidelberg University, Heidelberg, Germany; Stephen Heitner, MD, Oregon Health & Sciences University (OHSU), Division of Cardiovascular Medicine, Knight Cardiovascular Institute, Portland, OR; Adam Helms, MD, Department of Internal Medicine, University of Michigan, Ann Arbor, MI; Carolyn Ho, MD, Cardiovascular Division, Brigham and Women's Hospital, Boston, MA; Daniel L. Jacoby, MD, Section of Cardiovascular Medicine, Department of Internal Medicine, Yale School of Medicine, New Haven, CT; Han Kim, MD, Duke Cardiovascular Magnetic Resonance Center & Division of Cardiology, Duke University Medical Center, Durham, NC; Bette Kim, MD, Mount Sinai West, Icahn School of Medicine at Mount Sinai, New York City, NY; Eric Larose, MD, Quebec Heart & Lung Institute, Laval University, Quebec, Canada; Mahzad Mahmood, MD, Division of Cardiovascular Medicine, Erasmus Medical Centre, Rotterdam, Netherlands; Saidi Mohiddin, MD, Barts Heart Center, The Cardiovascular Magnetic Resonance Imaging Unit, St Bartholomew's Hospital, London, UK; Sherif Nagueh, MD, Methodist DeBakey Heart & Vascular Center, Houston, TX; David Newby, MD, Center for Cardiovascular Science, University of Edinburgh, UK; laco- po Olivotto, MD, Cardiomyopathy Unit & Genetic Unit, Careggi University Hospital, Florence, Italy; Anjali Owens, MD, Center for Inherited Cardiovascular Disease, Division of Cardiovascular Medicine, Perelman School of Medicine, University of Pennsylvania, Philadelphia, PA; F. Pierre-Mongeons, MD, Montreál Heart Institute, Canada; Sanjay Prasad, MD, National Heart & Lung Institute, Imperial College London, Royal Brompton Hospital, London, UK; Omero Rimoldi, MD, Vita Salute University & San Raffaele Hospital, Milan, Italy; Michael Salerno, MD, Department of Medicine, University of Virginia, Charlottesville, VA; Jeanette Schulz-Menger, MD, Charité, Medical Faculty of the Humboldt University, Experimental & Clinical Research Center and Helios Clinics, Cardiology, Berlin, Germany; Mark Sherrid, MD, Hypertrophic Cardiomyopathy Program, Leon Charney Division of Cardiology, Department of Medicine, New York University School of Medicine, New York.

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NY; Peter Swoboda, MD, Department of Cardiovascular Imaging Science, Leeds Institute of Cardiovascular & Metabolic Medicine, University of Leeds, UK; Albert van Rossum, MD, Department of Radiology, Amsterdam AMC, HZ Amsterdam, the Netherlands; Jonathan Weinsaft, MD, Departments of Medicine & Radiology, Weill Cornell Medical College, New York, NY; James White, MD, Calgary Foothills Medical Center, University of Calgary, Alberta, Canada; Eric Williamson, MD, Department of Radiology, Mayo Clinic, Rochester, MN.