Population Sampling and in vitro Modeling of a 25bp Deletion in MYBPC3 Associated With Hypertrophic Cardiomyopathy

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Introduction

Hypertrophic cardiomyopathy (HCM) is a heart condition that results in left ventricular hypertrophy (muscle thickening) (Figure 1), difficulties with pumping blood, arrhythmias, and is the leading cause of sudden cardiac death (SCD) in young adults and athletes. The prevalence of HCM has been estimated to be as high as 1 in 500 within the general population [1]. However, due to cost and sensitivity problems, it is not routinely screened for in the United States.

The majority of mutations leading to HCM have been identified in sarcomeric proteins, mainly the cardiac isoform of myosin-binding protein C (MYBPC3). Of particular interest is a 25bp deletion (rs36212066) in intron 32 of MYBPC3 (MYBPC3Δ25), which has been associated with left ventricle dysfunction and the development of HCM. This 25bp intronic deletion results in a mis-splicing event and exclusion of exon 33 during translation (Figure 3). MYBPC3Δ25 is known to have a high carrier frequency in South Asians (up to 6%) [2], but was previously unobserved in Europeans.

While in vitro models of HCM have been created in human induced pluripotent stem (iPS) cells, none have been made so far for MYBPC3. Such models can be used in conjunction with population genotyping to help explain the pathology and incompletely penetrant rs36212066 and may provide targets for pharmaceutical therapy.

Results

Out of the 23andMe customer database, we detected 165 heterozygote carriers and 5 homozygotes. As expected, the carriers were predominantly individuals of South Asian ancestry and our observed allele frequency was consistent with previous studies conducted in India. Worldwide genotyping had previously observed the deletion in South and East Asia but not in Europe or Africa. Our data suggests that the deletion is present in Europeans as well, though at a low frequency that would have made it undetectable in earlier work.

Methods

23andMe developed a custom probe to assay rs36212066 on the latest iteration of its genotyping chip (V3).

A total of 110,751 customers were genotyped on the V3 chip containing these probes. The accuracy of our genotyping was validated through bi-directional Sanger sequencing; all homozygotes, 60 heterozygote carriers, and 60 controls were validated. All samples were concordant.

Discussion

Using the 23andMe database, we were able to detect rs36212066 in Europeans, a population in which it had not been previously observed. We also returned results to participants using an HCM report on the 23andMe genome service [4].

It is possible that the European carriers acquired it through recent South Asian admixture. To rule this mechanism out, we are in the process of phasing and haplotype analysis using 23andMe's ancestry painting algorithm.

Due to the lack of widespread screening for HCM, self-reported status for the condition is unlikely to be an effective proxy for phenotyping the carriers in the 23andMe customer database. Follow-up echocardiograms in consultation with physicians may be an effective way to replicate this association in a cohort of South Asians living in the United States.

The HCM status of the homozygotes is of particular interest, as they are hypothesized to have a more severe phenotype. To date, the cardiomyopathy status of living homozygotes for rs36212066 has not been studied.

Acknowledgments

We thank 23andMe’s customers who consented to participate in research for enabling this study. We also thank the employees of 23andMe who contributed to the development of the infrastructure that made this research possible. We would also like to thank CIRM and NIH for funding and the Gladstone Core Facilities, Roddenberry Stem Cell Core Facility.

References and Resources

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