Genetic basis of hypertrophic cardiomyopathy
Bos, J.M.

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The Growing Field of Genetic Contributors to the Pathogenesis of Hypertrophic Cardiomyopathy or About ‘lumpers’ and ‘splitters’: McKusick revisited
In 1969, Victor McKusick, a medical geneticist, wrote a paper entitled ‘On lumpers and splitters, or the nosology of genetic disease’[1]. In this paper, McKusick disclosed the two leading principles in genetic nosology (study of classification of disease): ‘pleiotropism’ (multiple effects of a single etiologic factor) and ‘genetic heterogeneity’ (existence of two or more fundamentally distinct entities with essentially one and the same phenotype). And, already in 1969, McKusick articulated that against man’s naturally tendency to ‘lumping’ (recognize similarities and lump a disease under one umbrella), geneticist are forced to be ‘splitters’ instead[1]. This 40-year old paper seems prophetic for the current state of genetics of hypertrophic cardiomyopathy (HCM). Characterized by not only profound genetic heterogeneity, but also vast phenotypic and pathological diversity, for years the field of HCM tried to fit this disease in one, two or more diagnostic corners and continuing genetic discoveries still raise the question whether we should still be ‘lumpers’ or ‘splitters’.

Clinically, since Teare and Brock first described HCM as ‘asymmetrical hypertrophy of the heart in young adults’[2, 3], this disease has been known by many names, such as idiopathic hypertrophic subaortic stenosis[4], muscular subaortic stenosis[5] and hypertrophic obstructive cardiomyopathy[6]. It wasn’t until 1995 that it was agreed upon to ‘lump’ all these syndromes under one name[7]. Accordingly, HCM is now described as left and/or right ventricular hypertrophy, usually asymmetric and involving the interventricular septum with predominant autosomal dominant inheritance involving sarcomeric contractile proteins[7]. Pathologically, HCM has been characterized by microscopic features of cardiomyocyte hypertrophy, myofibrillar disarray and interstitial fibrosis, although recent research has shown an emerging role of myocardial ischemia, coronary microvascular dysfunction and myocardial bridging[8, 9]. And genetically, over 24 HCM-susceptibility genes have been elucidated with mutations found in genes encoding proteins of the cardiac myofilament, Z-disc and calcium-handling pathways as well as multiple genes involving syndromes mimicking the HCM phenotype [10]. Also, numerous HCM modifier genes have been identified [11, 12, 13].
And lastly, based on previous studies and observations described in this thesis, we have seen a strong genotype-morphology correlation between reverse-curve HCM and the presence of a myofilament mutation[14] and subsequently observed that Z-disc HCM is predominantly sigmoidal[15], suggesting a strong link between ventricular septal morphology and HCM-substrate. With all these different observations and possible clinical, pathological, genetic or morphological groupings, we can ask ourselves whether we should start ‘splitting’ HCM into for example morphologic and genetic subgroups of HCM, or keep ‘lumping’ and focus our research back onto understanding a proposed ‘final common pathway’ for HCM[16, 17].

This thesis has uncovered some new insights in this disease with the discovery of novel HCM-associated genes located to the cardiac Z-disc (Chapter 2 and 3) [18, 19], a morphologic predilection for sigmoidal morphology and relationships between sex, shape, and genetic substrate (Chapters 4 and 5) [15, 20] as well as the discovery of a novel HCM-susceptibility gene (TIEG1) and possible biomarker (PTTG1) for HCM (Chapter 6). However, multiple challenges and research questions remain, whose answers will help us further understand the pathogenesis of this disease, the role of modifiers, epigenetic factors and environmental influences, and novel therapeutic strategies.

First of all, with 30-50% of HCM genetically unexplained, the number of HCM-associated genes is expected to rise either by candidate gene selection, linkage analysis of large families with unexplained HCM, or large genome wide association studies. It remains to be seen whether a gene explaining a large portion of HCM (like MYH7-HCM and MYBPC3-HCM) will be found, but it is a certainty that novel disease-associated genes will be discovered. However, with the mutations expected to be found at a low frequency, it will raise the question whether the variants are really pathogenic or just rare, innocuous amino-acid alterations. Before such variants are published as disease causing/contributing, it will call for increasingly stringent clinical, familial, functional and bioinformatics studies.
With the 1000-genome project in its final stages cataloguing the full genetic code and its interpersonal variations of 1000 ostensibly healthy volunteers, a lot more knowledge on normal genetic variation will enter the public databases to help answer an important part of this question. But, especially in a fairly common disease like HCM, one still has to wonder: what is normal? Expressing sometimes at a later age, it can be envisioned that some people participating in the 1000-genome project were considered healthy upon entry in the study, but still develop hypertrophy and HCM later on in life. More than ever, especially in the current age of clinical genetic testing for HCM, it is important to separate the real from the rare. Research programs should be performing appropriate functional assays into possible pathogenic variants and genetic testing companies should be performing their due diligence determining the possible disease associated role of a finding (pathogenic or innocuous?) before reporting back to the clinician and patient.

Secondly, since most research thus far has been focused on translated portions of the genome, a huge part of our genetic code remains poorly understood from the standpoint of HCM pathogenesis. Promoter regions, splice sites, enhancers and other intronic functional and non-functional domains might end up playing an important role in the pathogenesis of many diseases including HCM. Next-generation sequencing techniques will make it easier to read much larger portions of the genome with the possibility to identify novel, disease associated variants located to potentially functional domains of the intronic genome (‘introme’). Although putatively pathogenic, novel assays to prove its pathogenicity will have to be developed to add the satisfactory level of clinical significance to these variants. Also on the level of translation, post-translational processes and epigenetics (DNA methylation, chromatin remodeling, RNA transcription etc), a lot remains to be discovered. Not only just amino-acid altering variations or insertions/deletions might contribute to disease development, but also translational and posttranslational modifications that take place in the human cell.
Steps in this direction have for example already been taken by the discovery and description of the role of microRNA’s (miR’s) in hypertrophic heart disease and their role as negative regulators of gene expression. MiR’s are small, non-coding RNA-molecules that inhibit translation or promote degradation of target mRNAs. Previous studies on two mouse models of pathological hypertrophy – transverse aortic constriction (TAC) and calcineurin transgenic mice – demonstrated 6 miR’s were up-regulated, which in vitro, were sufficient to induce hypertrophic growth of cardiomyocytes[21]. A transgenic mouse model over-expressing miR-195 showed that even a single miR could induce pathological hypertrophy and heart failure[21]. Multiple studies in vivo and in vitro, have since been published with miR expression profiles in different settings of cardiac hypertrophy demonstrating the potential role of miR’s and possible therapeutic target in (hypertrophic) heart disease and HCM [21, 22, 23, 24, 25, 26]. Comprehensive genetic analyses of the genes encoding these miRs or their respective target sites have yet to be performed in a large collection of patients with HCM. Also, no studies have yet demonstrated expression profiles of miRs in human HCM samples.

Thus far, no therapeutic option exists to treat, prevent or reverse cardiac hypertrophy in patients with genotype positive HCM or HCM in general, although animal studies do suggest that disease prevention/regression is a possibility. In a randomized trial, diltiazem (a L-type calcium channel blocker) treated MYH7-HCM transgenic mice showed significant improvement of cardiac systolic function, significantly less hypertrophy at 30 and 39 weeks as well as less fibrosis and myocyte disarray compared to untreated, transgenic mice [27]. These findings were replicated in a troponin T-HCM transgenic mouse model also [28]. Currently, human clinical trials are near completion of their first stages evaluating treatment with diltiazem and the progression of hypertrophy in genotype positive patients without signs of hypertrophy. Similar animal studies have been published showing that other drugs like ace-inhibitors, aldosterone receptor blockers, angiotensin-II blockers or statins might attenuate progression of hypertrophy, fibrosis and myofibrillar disarray in transgenic mouse models, but small human trials have been inconclusive or have yet to be finalized[29, 30, 31, 32, 33, 34, 35]. Prevention of hypertrophy or at least slowing its progression should change its natural history although it remains to be seen whether these or other drugs could also prevent the incidence of sudden cardiac death.
Even with novel techniques, identification of novel putative pathogenic variants in unexplored regions or discovery of novel pathways, it’s possible that a subset of patients will remain without a genetic explanation of their disease. Furthermore, as HCM is characterized by profound heterogeneity, even within patients of families with the same genetic background, the genetic, epigenetic, environmental basis for incomplete penetrance and variable expressivity remains poorly understood. Already demonstrated by previous modifier and gender studies, one can envision that certain intrinsic or environmental factors such as gender, (low-grade) hypertension, race or smoking amongst others, trigger one of the pro-hypertrophic pathways leading to a disease diagnosed by clinicians as HCM, but studies have yet to study and identify specific environmental factors that influence the disease.

Lastly, research can be focused on understanding the pathogenic pathways of cardiomyopathies as allelic diseases. Particularly when one looks at the HCM-associated genes encoding Z-disc proteins, it is striking that most are also associated in the pathogenesis of DCM with both cardiomyopathic phenotypes sometimes seen in the same family [36, 37, 38, 39, 40, 41, 42, 43, 44]. This poses the question how mutations in one gene can lead to two divergent compensatory responses and whether these pathways are induced by the underlying genotype or that exogenous factors determine whether one develops HCM or DCM. Looking at the role of Z-disc genes in the heart and functional capacities in the stretch-sensor and mechanoreceptor function of the heart, one can see where pathways of possible stretch-induced hypertrophy and dilatation of these diseases overlap, but studies are still needed to dissect the exact pathways whereby these divergent diseases develop. Not only are similar genotypic background seen between HCM and DCM; recently for example sarcomeric genes have been associated in the pathogenesis of left ventricular non-compaction (LVNC) [45] and restrictive cardiomyopathy (RCM)[45, 46]. Presently, the McKusick ‘pleiotropism’ encompasses 4 distinct cardiomyopathies capable of emanating from sarcomeric perturbations.

Thus, in a time where we have gained more and more knowledge on the extent and breadth of clinical, pathological, genetic and morphological heterogeneity of HCM and have witnessed the expansion of cardiomyopathic pleiotropism, perhaps we should heed McKusick’s 40-year old admonition to resist the urge to lump and be a ‘splitter’ instead.
References


168


