



# Founder mutations in hypertrophic cardiomyopathy patients in the Netherlands

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In this part of a series on cardiogenetic founder mutations in the Netherlands, we review the Dutch founder mutations in hypertrophic cardiomyopathy (HCM) patients.

HCM is a common autosomal dominant genetic disease affecting at least one in 500 persons in the general population. Worldwide, most mutations in HCM patients are identified in genes encoding sarcomeric proteins, mainly in the myosin-binding protein C gene (*MYBPC3*, OMIM #600958) and the beta myosin heavy

chain gene (*MYH7*, OMIM #160760). In the Netherlands, the great majority of mutations occur in the *MYBPC3*, involving mainly three Dutch founder mutations in the *MYBPC3* gene, the c.2373\_2374insG, the c.2864\_2865delCT and the c.2827C>T mutation. In this review, we describe the genetics of HCM, the genotype-phenotype relation of Dutch founder *MYBPC3* gene mutations, the prevalence and the geographic distribution of the Dutch founder mutations, and the consequences for genetic counselling and testing. (Neth Heart J 2010;18:248-54.)

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**H**ypertrophic cardiomyopathy (HCM) is a common genetic disease affecting at least one in 500 persons in the general population.<sup>1,2</sup> In 1958 Teare gave a description of HCM when he reported a series of eight young patients who died suddenly from a disorder of the heart muscle.<sup>3,4</sup> He was the first to describe the asymmetrical appearance of hypertrophy and its familial nature. He also described a disordered arrangement of muscle fibres at microscopic examination of the hearts of his cases, now known as myocyte disarray.

Nowadays, the diagnosis of HCM is most frequently made at two-dimensional echocardiography. The clinical diagnosis rests on the presence of a hypertrophied, non-dilated left ventricle on echocardiography (left ventricle wall thickness  $\geq 15$  mm or  $\geq 13$  mm in a patient's relative) in the absence of other cardiac or systemic diseases that may cause cardiac hypertrophy, such as aortic valve stenosis and hypertension.<sup>5-8</sup>

HCM has long been regarded as a disease that mainly affects young people. It was thought that penetrance, i.e. the presence of left ventricular hypertrophy, was complete at approximately 20 to 30 years of age.<sup>9</sup> It is more and more recognised that not only symptoms but also hypertrophy can develop at any age and that the clinical course of

the disease varies from person to person. Patients may remain asymptomatic throughout life, but the disease can also give rise to heart failure and other adverse events such as sudden cardiac death (SCD) and embolic stroke. Annual mortality rates from overt HCM in non-selected populations nowadays are 1 to 2% (SCD and end-stage heart failure).<sup>10-16</sup>

The treatment of patients with HCM is complex and requires understanding of the pathophysiology in each individual patient. Basically, management of the disease is based on relief of symptoms and on risk stratification to prevent SCD. Consensus documents are available to guide the treatment in HCM patients.<sup>17-19</sup>

### Genetics of HCM

HCM is inherited as an autosomal dominant trait. Currently, in more than half of the HCM patients a disease-causing mutation can be identified.<sup>20-27</sup> Mutations may occur in a large number of different genes, but are usually found in the genes encoding sarcomeric proteins (table 1). Most HCM patients carry one heterozygous mutation, but in 3 to 5% of cases, patients carry two mutations in the same gene: on both copies of the gene (compound heterozygote or homozygote) or in different genes (digenic). This is generally associated with a more severe phenotype with a younger age of onset (often <10 years) and more adverse events, such as sudden cardiac death (SCD).<sup>26,28-31</sup>

The two most frequently mutated genes worldwide are the *MYBPC3* gene (OMIM #600958) and the *MYH7* gene (OMIM #160760). These encode the sarcomeric proteins cardiac myosin-binding protein C and beta myosin heavy chain, respectively. The majority of the mutations worldwide, around 13 to 32%, are identified in the *MYBPC3* gene. Around 4 to 25% of the mutations are found in the *MYH7* gene.<sup>9,23-26,32</sup> Missense mutations (a point mutation in which a single nucleotide is changed, resulting in a codon that codes for a different amino acid) are the most frequent type of mutations in HCM patients. Missense mutations create a mutant protein that interferes with normal function and has a dominant negative effect on function (in which mutant protein adversely affects the normal, wild-type gene product). However, in the *MYBPC3* gene most mutations are nonsense or frameshift mutations that are presumed to result in truncated proteins,<sup>33,34</sup> suggesting haploinsufficiency (in which the total level of a particular protein produced by the cell is reduced and therefore not sufficient to permit the cell to function normally).

Since the discovery of the first genes for HCM, much has been speculated on specific genotype-phenotype correlations. At first specific mutations, predominantly in the *MYH7* gene, were described and were associated with a ‘malignant’ phenotype

(more SCD).<sup>35-37</sup> Whereas ‘benign’ mutations were reported in families with normal longevity as well.<sup>35,36,38-43</sup> The supposed ‘malignant’ and ‘benign’ effects of these mutations, however, have been contradicted in many subsequent studies. Nowadays it is believed that in general there are no clear genotype-phenotype relations with respect to magnitude of left ventricular hypertrophy and incidence of SCD.<sup>27,35,39,41,44-46</sup> These studies on genotype-phenotype correlations have also revealed that not all mutation carriers in a family have the same phenotype or are affected. This suggests the existence of modifier genes (genes that affect the expression of another gene), which modulate the phenotypic expression of the disease and incomplete penetrance of the disease (not all mutation carriers are clinically affected).

*De novo* mutations (newly arisen mutations) and germline mosaicism (mutation present in (part of) the germ cells) are rare in HCM.<sup>47-51</sup> Because most mutations are unique for a family, many of the identified mutations have therefore not been described before. In certain countries and populations, however, founder mutations have been identified, arising from a common ancestor many generations ago. These founder mutations often comprise a large part (10 to 25%) of the detected mutations in these countries. Founder mutations for HCM have been found in the Netherlands,<sup>52,53</sup> South Africa,<sup>54</sup> Finland,<sup>55</sup> Italy,<sup>56</sup> Japan,<sup>57</sup> South Asia<sup>58</sup> and in the Amish population of the United States.<sup>5</sup>

### Founder mutations in the Netherlands

DNA diagnostics for HCM have been available in the Netherlands since 1996. In about 50% of the index patients a disease-causing mutation is detected. The majority of mutations are located in the *MYBPC3* gene (20 to 35% of index patients). This can be explained by the occurrence of three Dutch founder mutations in the *MYBPC3* gene, the c.2373\_2374insG (p.Trp792fsX17) or alternatively

**Table 1.** Prevalence of sarcomeric genes associated with HCM.<sup>21,22,25,26,74-80</sup>

Gene	Name	Detection rate (%)
Sarcomeric		
<i>Myofilament</i>		
- MYBPC3	Myosin-binding protein C	13-32
- MYH7	Beta myosin heavy chain	4-25
- TNNT2	Troponin T2	0.5-7
- TNNI3	Cardiac troponin I	<5
- MYL2	Myosin light chain 2	<5
- MYL3	Myosin light chain 3	<1
- TPM1	Alpha tropomyosin	<1
- ACTC	Alpha actin	<1
- TNNC1	Troponin C	<1

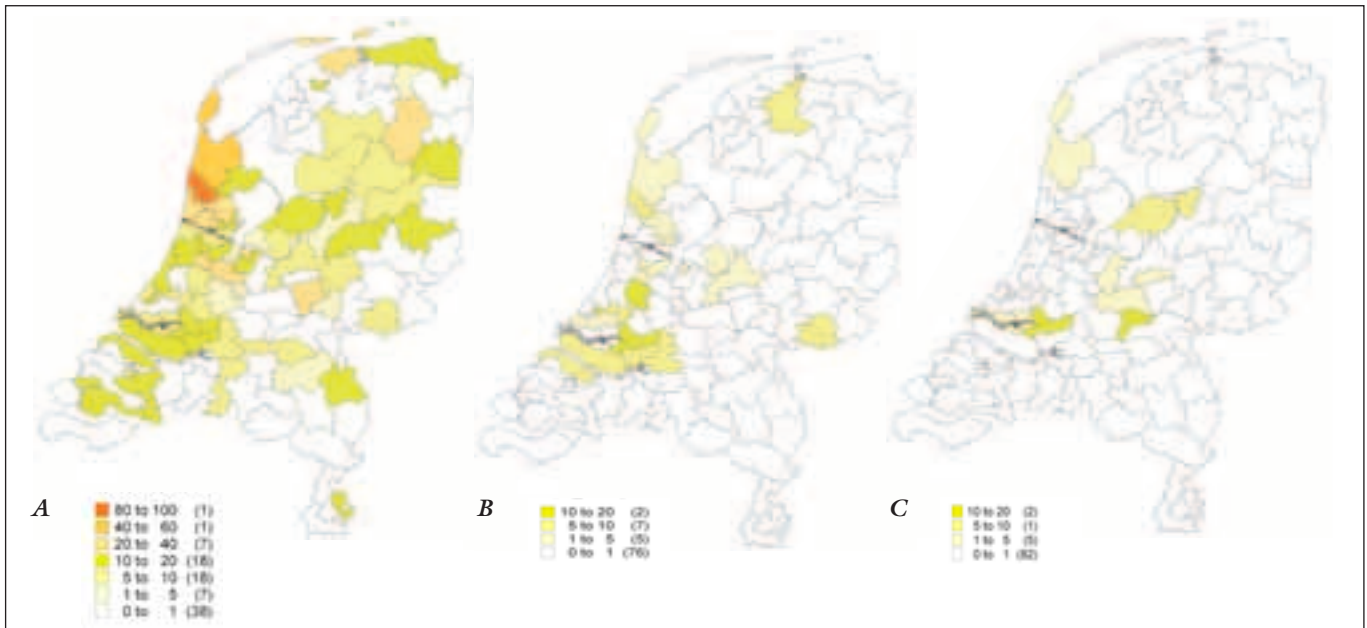


Figure 1. Distribution of the c.2373\_2374insG mutation (A), the c.2827C>T mutation (B) and the c.2864\_2865delCT mutation (C). Different colours refer to the number of patients with the mutation per 1,000,000 inhabitants in a specific postal code area. Between brackets the number of postal code areas.

c.2373dup, c.2864\_2865delCT (p.Pro955fsX95) and c.2827C>T (p.Arg943X).

In a previous survey the c.2373\_2374insG mutation was detected in almost a quarter of all HCM patients in the Netherlands, which is unique for cardiogenetic diseases. The mutation was described to be predominantly present in the north-western part of the country. The recombination frequency of the haplotype associated with this founder mutation suggested a common ancestor of at least 25 generations ago.<sup>52</sup> The other two founder mutations were each detected in about 5% of the Dutch HCM patients.<sup>60</sup>

More recently the combined data on DNA diagnostics from all Dutch DNA laboratories screening HCM genes (Academic Medical Centre Amsterdam, Erasmus Medical Centre Rotterdam, Academic Hospital Maastricht) showed that between 1996 and 2006 one of the three prevalent founder mutations was detected in 157 out of 735 HCM index patients (21%). In 126 patients the c.2373\_2374insG mutation was detected (17%). The c.2827C>T mutation and the c.2864\_2865delCT in the *MYBPC3* gene were less prevalent with 19 (2.6%) and 12 (1.6%) patients carrying this mutation, respectively.

Figure 1 shows the distribution of the three founder mutations in the Netherlands (per 1,000,000 inhabitants). We obtained these data by adjusting the different number of index patients carrying a founder mutation per postal code for the number of inhabitants per postal code available at the National Institute Statistics Netherlands (Cen-

traal Bureau voor de Statistiek, CBS). In the Netherlands there are approximately 430,000 postal codes. The analysis was based on the PC2 code (the first two numbers of the postal code), which comprises 90 postal codes. Data were visualised with MapInfo Professional (MapInfo, Toronto, Canada).

The c.2373\_2374insG mutation was predominantly present in the north and north-western part of the Netherlands (as described previously), the c.2827C>T mutation predominantly in the south and south-western part of the Netherlands and patients with the c.2864\_2865delCT mutation were located in the south-west and middle of the country. This region-specific distribution of patients can explain the higher frequency of specific Dutch founder mutations in literature by DNA laboratories from that region.<sup>52,60</sup>

Although the relative distribution of the founder mutations in HCM is presented here, the frequency of founder mutations may be biased in those areas where no or very few patients were referred for DNA diagnostics. A study on referral for long-QT syndrome showed regional differences in referral of patients for DNA diagnostics.<sup>61</sup> This can also be the case for HCM. However, less than one patient was referred in only four of 90 postal areas (mean number of referrals per region was 8.2), possibly interfering with reliable estimations of the frequency of founder mutations in these specific postal areas.

Until a few years ago, the phenotype of *MYBPC3* mutation carriers was considered to be

mild and accompanied by a late onset of symptoms,<sup>62</sup> but recent studies and also our own observations show that caution must be exercised with assigning prognostic significance to a particular mutation or mutations in a particular gene, since previous studies are performed in small cohorts involving larger families with variable disease penetrance and expression.<sup>23,27,67</sup> Data from the Academic Medical Centre Amsterdam on disease penetrance in 88 probands and 213 relatives show that the age of clinical diagnosis is not different for various types of *MYBPC3* gene mutations (figure 2). This also holds for the three Dutch founder mutations. Unpublished data on Dutch mutation carriers suggest that there is no association between the phenotype and the mutated gene. All HCM mutations show age dependent and incomplete disease penetrance.<sup>68,69</sup> Many founder mutation carriers only show hypertrophy from adulthood, and some are still without significant hypertrophy in their eighties (figure 2).

*Screening of relatives: genetic counselling and testing*

Consensus guidelines for HCM encourage screening of relatives, because of the risk of HCM-associated sudden cardiac death in these relatives and the availability of effective preventive options.<sup>7</sup> Recently a multidisciplinary consensus on genetic testing and counselling in HCM has been developed by different scientific associations (Multidiscipline guideline: Genetic diagnostics and genetic counselling in Hypertrophic Cardiomyopathy (HCM); www.nvvc.nl).<sup>70</sup> Identification of a disease-causing mutation in an HCM patient (the index) provides the opportunity to accurately identify the asymptomatic adult relatives who are at risk by means of predictive DNA testing. In the Netherlands diagnostic and predictive DNA testing is covered by standard health insurance, and DNA testing for

HCM has increased since 1996. Specialised multidisciplinary cardiogenetics outpatient clinics are now present in all eight university hospitals and in some local hospitals. To detect mutation carriers, systematic screening of relatives in families with a disease-causing mutation, so called cascade screening, is performed in these centres.<sup>71</sup> Cascade screening is performed in all HCM families with a detected disease causing mutation in one of the genes associated with HCM, including the Dutch founder mutations. Relatives without the familial HCM mutation can be reassured and discharged from cardiological follow-up. Relatives who carry the familial HCM mutation are, according to international guidelines, like affected HCM patients (with or without mutation), advised to have periodic cardiological screening for left ventricular hypertrophy and risk factors for SCD.<sup>18</sup> If no mutation can be detected in an HCM index patient, a genetic form of HCM cannot be excluded and first-degree relatives are still at risk to develop HCM. Therefore they are advised to have periodic cardiological evaluations (annually between 12 and 18 years and once every five years >18 years) directed at diagnosing hypertrophy or ECG abnormalities associated with HCM.<sup>18</sup>

Predictive genetic testing for hereditary diseases in healthy relatives of index patients is known to be associated with psychosocial distress.<sup>72</sup> Relatives tested for a mutation predisposing them to HCM have to deal with the risk of disease and its progression, the threat of SCD, and the possibility of having transmitted the disease to their offspring. In addition, advised lifestyle adjustments and the sudden death of relatives may cause anxiety. Literature shows that psychosocial distress for hereditary heart diseases is mostly concentrated around the period the testing is performed and returns to baseline levels after 18 months, comparable with the general population.<sup>72,73</sup> Therefore it is recommended that predictive testing is performed only after genetic counselling, where these issues are discussed with the relatives. We recommend offering psychological support on a voluntary basis to all relatives before predictive genetic testing for HCM. ■

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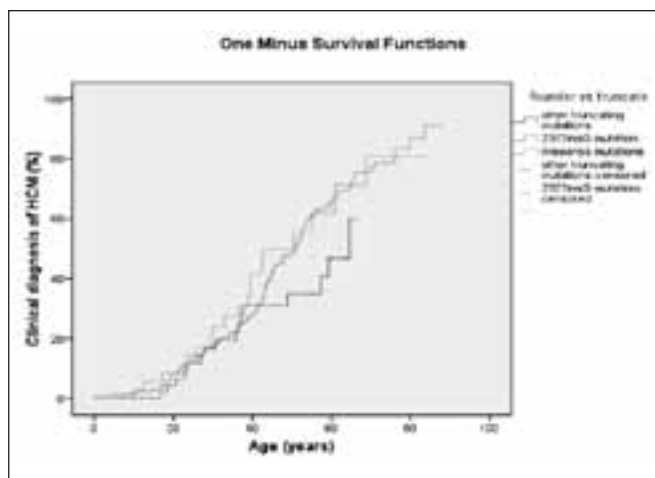


Figure 2. Disease penetrance in 301 HCM mutation carriers with different types of mutations in the *MYBPC3* gene.



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