

Cardiac β -myosin heavy chain defects in two families with non-compaction cardiomyopathy: linking non-compaction to hypertrophic, restrictive, and dilated cardiomyopathies

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Cardiomyopathies are classified according to distinct morphological characteristics. They occur relatively frequent and are an important cause of mortality and morbidity. Isolated ventricular non-compaction or non-compaction cardiomyopathy (NCCM) is characterized by an excessively thickened endocardial layer with deep intertrabecular recesses, reminiscent of the myocardium during early embryogenesis.

Aims Autosomal-dominant as well as X-linked inheritance for NCCM has been described and several loci have been associated with the disease. Nevertheless, a major genetic cause for familial NCCM remains to be identified.

Methods and Results We describe, in two separate autosomal-dominant NCCM families, the identification of mutations in the sarcomeric cardiac β -myosin heavy chain gene (*MYH7*), known to be associated with hypertrophic cardiomyopathy (HCM), restricted cardiomyopathy (RCM), and dilated cardiomyopathy (DCM).

Conclusion These results confirm the genetic heterogeneity of NCCM and suggest that the molecular classification of cardiomyopathies includes an *MYH7*-associated spectrum of NCCM with HCM, RCM, and DCM.

Introduction

Non-compaction cardiomyopathy (NCCM), also called isolated ventricular non-compaction (IVNC) or left ventricular non-compaction (LVNC), has recently been recognized as a novel cardiomyopathy.^{1–3} It is characterized by an excessively prominent trabecular meshwork and deep intertrabecular recesses, as seen early in human embryogenesis.^{4,5} The diagnosis is established by imaging the ventricular walls and cavities, by two-dimensional transthoracic echocardiography with colour Doppler flow, contrast echocardiography, left ventricular (LV) angiography, computed tomography, or magnetic resonance imaging.^{4,6–10} The diagnostic criteria, as proposed by Jenni *et al.*,⁴ are clinically most convenient and include abnormally thickened ventricular walls with a two-layered structure, consisting of thickened, non-compacted (NC)

endocardial myocardium and a thin compacted (C) epicardial myocardium (maximal end-systolic ratio NC/C ≥ 2 at parasternal short-axis view) with documentation of perfusion of the deep intertrabecular recesses with colour Doppler flow.

Clinical manifestations include the triad of heart failure, (potentially lethal) arrhythmias, and/or thrombo-embolism, mostly affecting patients at a relatively young age. NCCM is genetically heterogeneous and can be inherited as an autosomal-dominant or X-linked disorder. Thus far no common genetic determinants for NCCM have been identified.¹¹ A small proportion of familial autosomal-dominant NCCM can be explained by mutations in genes encoding cytoskeletal or cell junction proteins, *LMNA/C*, α -dystrobrevin, and *Cypher/ZASP*.^{12–15} In some families with X-linked NCCM, an association was found with mutations in the *TAZ* gene, which is allelic with Barth syndrome.¹⁶ Mutations in the alpha-cardiac actin (*ACTC*) gene are a rare cause for hypertrophic cardiomyopathy (HCM) or dilated cardiomyopathy (DCM). Recently, a mutation in this gene was

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identified in five families with HCM, LVNC, and atrial septal defects (ASDs), originating from the same region in Spain.¹⁷ Additional NCCM loci have been identified on chromosomes 1q43, 5q, and 11p15.^{18–20}

At the Cardiogenetics Centre of the Erasmus MC, molecular screening of sarcomeric genes in NCCM patients resulted in the identification of mutations in the sarcomeric cardiac β -myosin heavy chain gene (*MYH7*) in two separate families with autosomal dominantly inherited NCCM.

Methods

Diagnosis

In this study, the internationally acknowledged echocardiographic diagnostic criteria for NCCM were used, consisting of (i) segmental, excessive thickening of the LV wall with a two-layered structure: a thin, compacted epicardial layer and a much thicker, non-compacted endocardial layer with the characteristic appearance of numerous prominent trabeculations (meshwork) and deep intertrabecular recesses, (ii) colour Doppler evidence of deeply perfused intertrabecular recesses, (iii) predominant localization of thickening in the LV apical, mid-lateral, and mid-inferior walls, and (iv) the absence of co-existing cardiac anomalies.⁴ A clinical diagnosis of NCCM required compliance to all the four criteria.

Molecular analysis

Genomic DNA from index patients in autosomal-dominant NCCM families A and B was extracted from peripheral blood cells using standard techniques. Using a candidate gene approach, mutation analysis of the *MYH7*, *TAZ*, *LMNA/C*, *MYBPC3*, *TNNC1*, *TNNT2*, *TNNI3*, *MYL2*, *MYL3*, *CSRP3*, *TCAP*, *ACTC*, and *TPM1* genes was performed using direct sequence analysis of all coding regions and intron-exon boundaries. Sequence analysis of M13-tagged PCR products was carried out on an ABI3730xl capillary sequencer using Big Dye Terminator v 3.1 chemistry (Applied Biosystems). (Details of the method and primer sequences are available on request.) Analysis of sequence data was performed using SeqScape analysis software (V2.5, Applied Biosystems).

Family A

In 2003, a 27-year-old woman presented with symptoms of severe congestive heart failure with progressive dyspnoea, fatigue, and oedema. Echocardiographically she had a moderately dilated LV with severe systolic dysfunction. The apical, lateral, and inferior walls were excessively thickened with prominent hypertrabeculation ('meshwork') with NC/C ratio >2. Her ECG showed sinus rhythm with left bundle branch pattern (QRS width 142 ms). Treatment with diuretics, ACE-inhibitors, β -blockers, and anticoagulants resulted in good clinical improvement. After 4 years of follow-up, she remains asymptomatic with NYHA functional class I. Her LV function also significantly improved with current LV end-diastolic and -systolic dimensions of 60/41 mm and fractional shortening of 32%. The familial history revealed a probably affected 27-year-old sister, who died 6 days after giving birth to her third child; LV function was severely impaired, with substantially dilated LA and LV. She developed clinical features of severe congestive heart failure with ventricular tachycardia and ventricular fibrillation, which could not be resuscitated. Her 73-year-old father was also known with congestive heart failure, but also with coronary heart disease and diabetes. Echocardiography showed typical morphological features of NCCM, with excessively thickened myocardium of the apical, lateral, and anterior LV walls.

Cardiological screening of seven asymptomatic siblings showed typical echocardiographic NCCM features in two sisters, aged 35 and 30, respectively, and two brothers, aged 34 and 49, respectively (Figure 1). The asymptomatic daughter of the eldest brother was

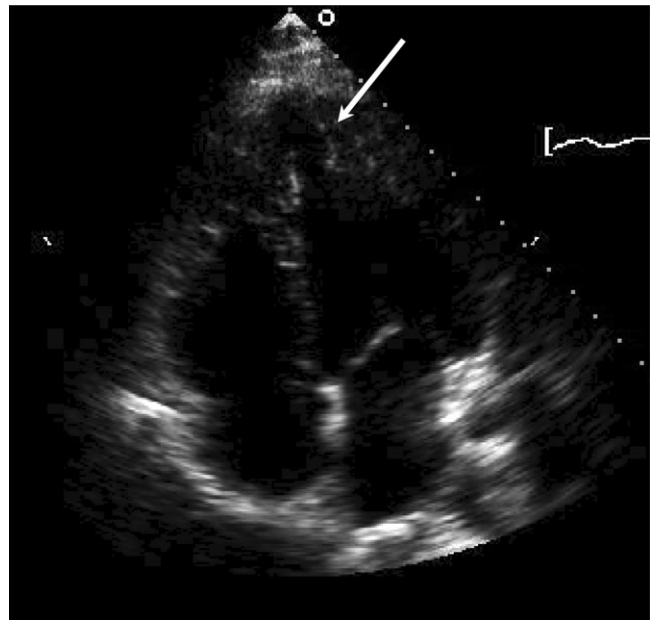


Figure 1 Two-dimensional echocardiographic four-chamber view of the 35-year-old asymptomatic sister of the proband of family A, showing excessive trabeculations of the apical (arrow) and mid-lateral left ventricular walls and mild left ventricular systolic dysfunction. The right ventricle was also excessively trabeculated.

also diagnosed with NCCM at age 24. Three brothers were free of cardiological features of NCCM.

A candidate gene approach, to identify a genetic defect in this family, included screening of known genes associated with DCM and HCM and revealed a missense mutation in the p.Leu301Gln in exon 11 (nucleotide change c.902T>A) of the *MYH7* gene in four NCCM patients of this family (Figure 2).²¹

The p.Leu301Gln mutation segregated with the clinical features of NCCM in this family (Figure 3). The p.Leu301Gln mutation was not observed on 400 control chromosomes or in 300 HCM patients. p.Leu301Gln is in the functionally important globular head region (subfragment S1; the 'motor domain') of β -myosin heavy chain, a region in which multiple pathogenic mutations have been described. Moreover, this mutation is pathogenic according to a prediction algorithm.²² No mutations were found in the *TAZ*, *LMNA/C*, *MYBPC3*, *TNNC1*, *TNNT2*, *TNNI3*, *MYL2*, *MYL3*, *CSRP3*, *TCAP*, *ACTC*, and *TPM1* genes.

Family B

In 2003, a 35-year-old man was hospitalized with severe symptoms of congestive heart failure. At the age of 3 years, he was treated for lymphoblastic leukaemia with chemo- and radiotherapy (cytosine, arabinoside, methotrexate, and prednisone). Two months prior to hospitalization, he experienced progressive dyspnoea, orthopnoea, palpitations, fatigue, coughing, nausea, and vomiting. ECG showed sinus tachycardia with 123 b.p.m., a left bundle branch block (QRS width 154 ms), and biphasic P in V1. Echocardiographic examination revealed NCCM with severe systolic LV dysfunction (Figures 4A and B). Furthermore, a substantial thrombus was seen in the LV. Treatment with intravenous heparin and coumarine resulted in complete resolution of the LV thrombus after a few weeks (not shown). With diuretics, an ACE-inhibitor, and β -blocker therapy, an excellent clinical response was observed. After 2.5-year follow-up, he remains asymptomatic with moderate LV impairment.

Although chemotherapy-induced cardiomyopathy was primarily considered, the typical echocardiographic features of NCCM warranted screening of first-degree relatives, including both children

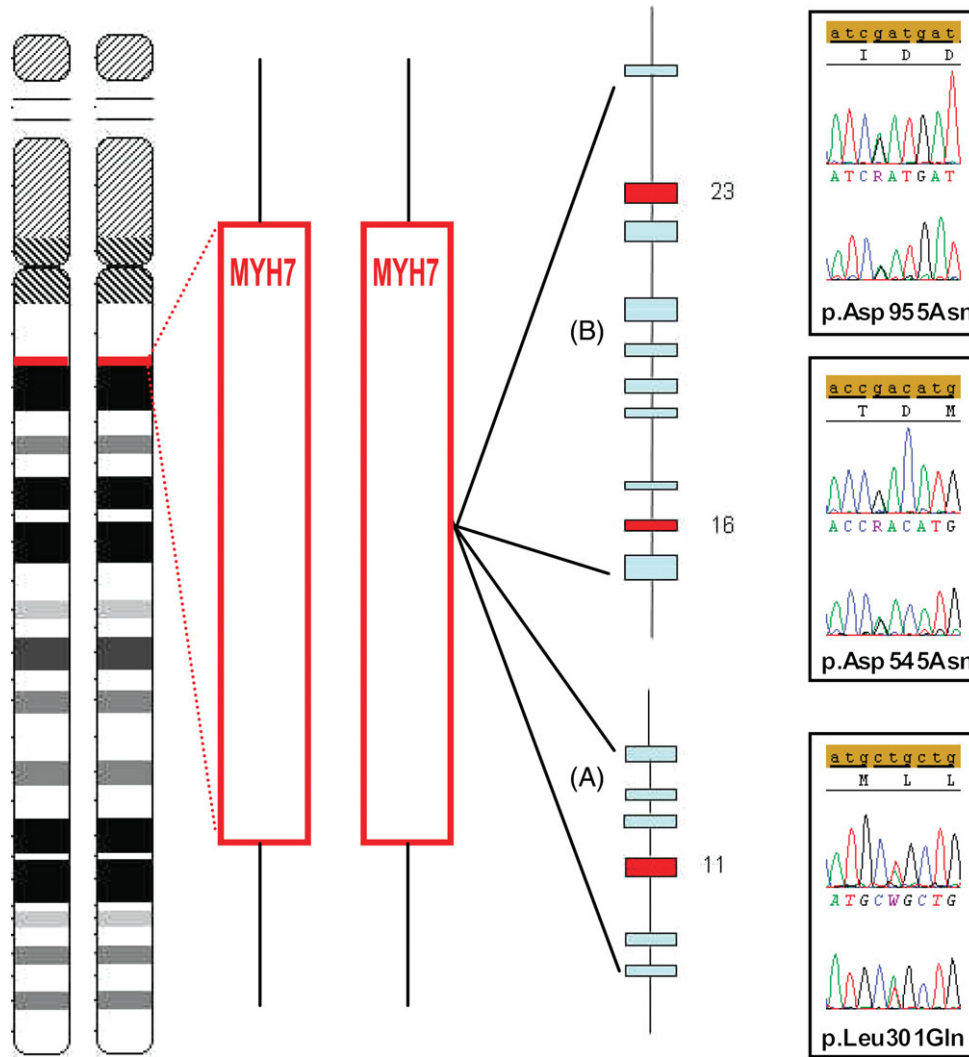


Figure 2 Schematic diagram showing chromosome 14 with the location of the *MYH7* gene (14q12). Mutations were identified on one allele of the *MYH7* gene in exon 11 in family A and in exons 16 and 23 in family B. Sequence traces show the mutations identified in families A and B.

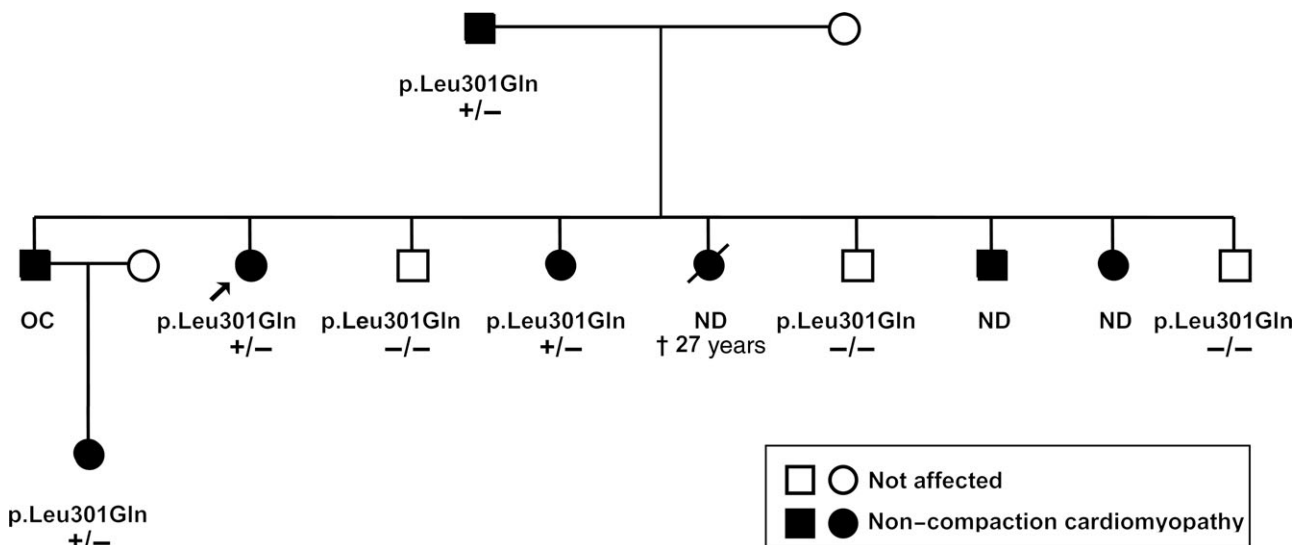


Figure 3 Pedigree of family A. The proband is indicated by the arrow. ND, not determined; OC, obligate carrier; +/-, heterozygous for the p.Leu301Gln *MYH7* mutation; -/-, p.Leu301Gln absent.

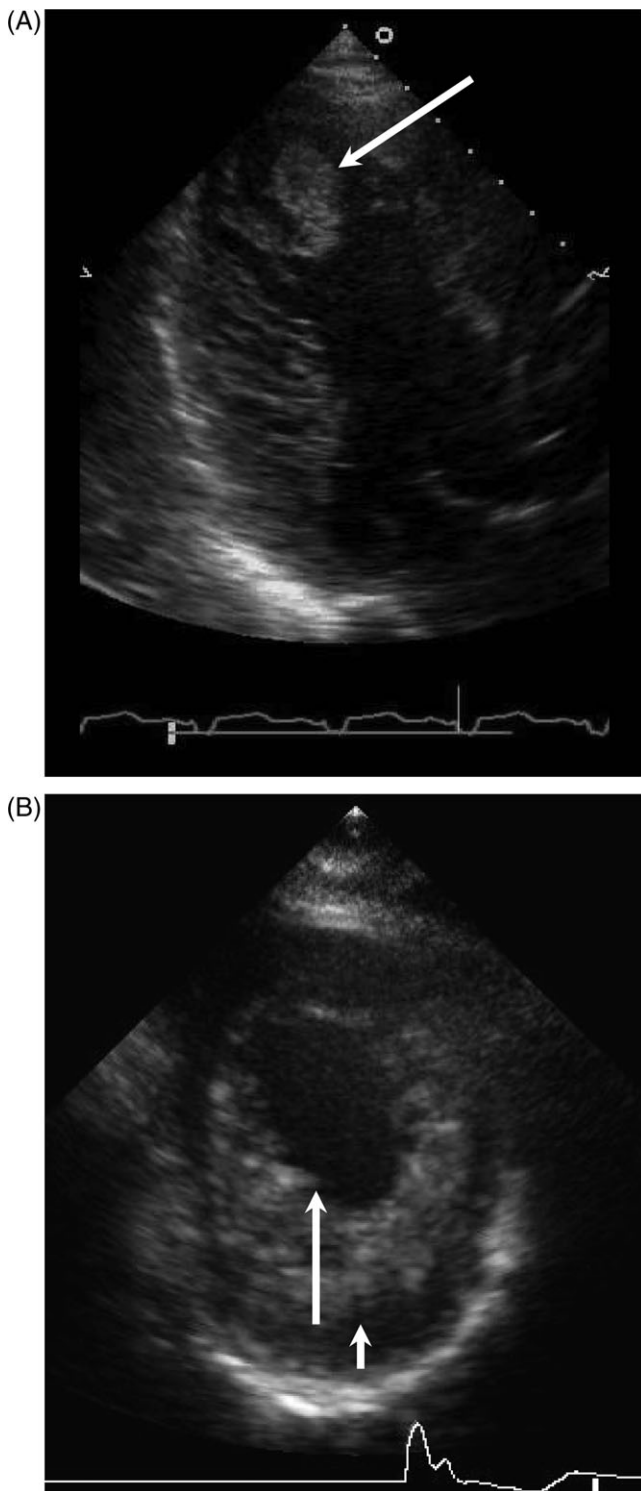


Figure 4 (A) Apical three-chamber and parasternal short-axis view of the index showing prominent thickened apical, lateral, and posterior walls of the left ventricle with loose meshwork of trabeculations; the arrow indicates the left ventricular thrombus; (B) arrows show the non-compacted to compacted ratio in systole is >2 .

of the proband. In the asymptomatic 11-year-old son, echocardiographic examination revealed mild apical LVNC. No cardiac features of NCCM were found in the 14-year-old daughter. In the proband's asymptomatic 32-year-old brother, echocardiography showed moderately impaired systolic LV function with global hypokinesia (ejection fraction 30%) and typical features of non-compaction.

Treatment with ACE-inhibitors, anticoagulants, and β -blockers was started. At follow-up, the ejection fraction improved and he remains free of symptoms. Neurological evaluation did not show features of limb girdle or progressive distal myopathy in this family.

Cardiological evaluation of the father, suffering from Alzheimer's disease, similarly revealed NCCM at the apex of the LV. His ejection fraction was 45% at presentation. His ECG showed sinus bradycardia. He is receiving treatment with ACE-inhibitors and anticoagulants. The asymptomatic 72-year-old sister of the father, with a history of diabetes mellitus type II and a coronary bypass, showed hypertrabeculation of the apical, inferior, and posterolateral LV walls, consistent with NCCM. A brother of the father died 2 years after being diagnosed with NCCM, at age 69. Neither of the parents of the father was known to have a heart condition; they both suffered a cerebro-vascular accident; the father died at age 78, the mother at age 75.

DNA analysis of five patients revealed the mutations p.Asp545Asn in exon 16 (nucleotide change c.1633G $>$ A) and p.Asp955Asn in exon 23 (nucleotide change c.2863G $>$ A) of the *MYH7* gene (Figure 2).²¹ Segregation analysis in this family subsequently demonstrated that these two *MYH7* mutations were on the same allele (Figure 5). The p.Asp545Asn and p.Asp955Asn missense mutations were not observed on 400 control chromosomes or in 300 HCM patients. p.Asp545Asn is in the functionally important globular head region (subfragment S1; the 'motor domain') of the myosin heavy chain, a region in which multiple pathogenic mutations have been described. p.Asp955Asn is in the head-rod junction region (subfragment S2), a functionally important region for the interaction with the regulatory domain of myosin-binding protein C (*MYBPC3*).²³ Moreover, each of these mutations is pathogenic according to a prediction algorithm.²² No mutations were identified in the *TAZ*, *LMNA/C*, *MYBPC3*, *TNNC1*, *TNNT2*, *TNNI3*, *MYL2*, *MYL3*, *CSRP3*, *TCAP*, *ACTC*, and *TPM1* genes.

Discussion

Clinically, familial cardiomyopathies are classified as HCM, DCM, restrictive cardiomyopathy (RCM), and NCCM, also called isolated non-compaction of the left ventricle (IVNC) or left ventricular non-compaction (LVNC) cardiomyopathy. The refinement of cardiac imaging techniques and more awareness among clinicians result increasingly in the recognition of the distinct features of NCCM, where in the past, misclassification may have occurred, particularly when sub-optimal (i.e. older) imaging methods were used. Cardiological screening of relatives indicating familial recurrence of NCCM showed that genetic factors are important in the aetiology of this disease. In HCM, sarcomeric gene mutations are the predominant underlying genetic cause. Familial DCM is mainly associated with mutations in cytoskeleton and extracellular matrix genes, in addition to mutations in sarcomeric genes. Rare mutations, mostly in non-HCM/DCM genes, have been identified in a small proportion of familial NCCM. However, so far, no major genetic defect for NCCM has been identified. The identification of mutations in the *MYH7* gene in two separate, large NCCM families suggests that *MYH7* defects may be an important genetic cause for this form of cardiomyopathy. Defects in the *MYH7* gene are a major cause of familial HCM and DCM, and, in addition, *MYH7* mutations were recently shown to be associated with HCM with a restrictive phenotype (RCM).²⁴ This article is the first to link *MYH7* gene defects to familial NCCM. In family A, we found the single p.Leu301Gln mutation segregating with NCCM. In family B, we identified the missense double-mutation p.Asp545Asn/p.Asp955Asn on the same *MYH7* allele segregating with the disease.

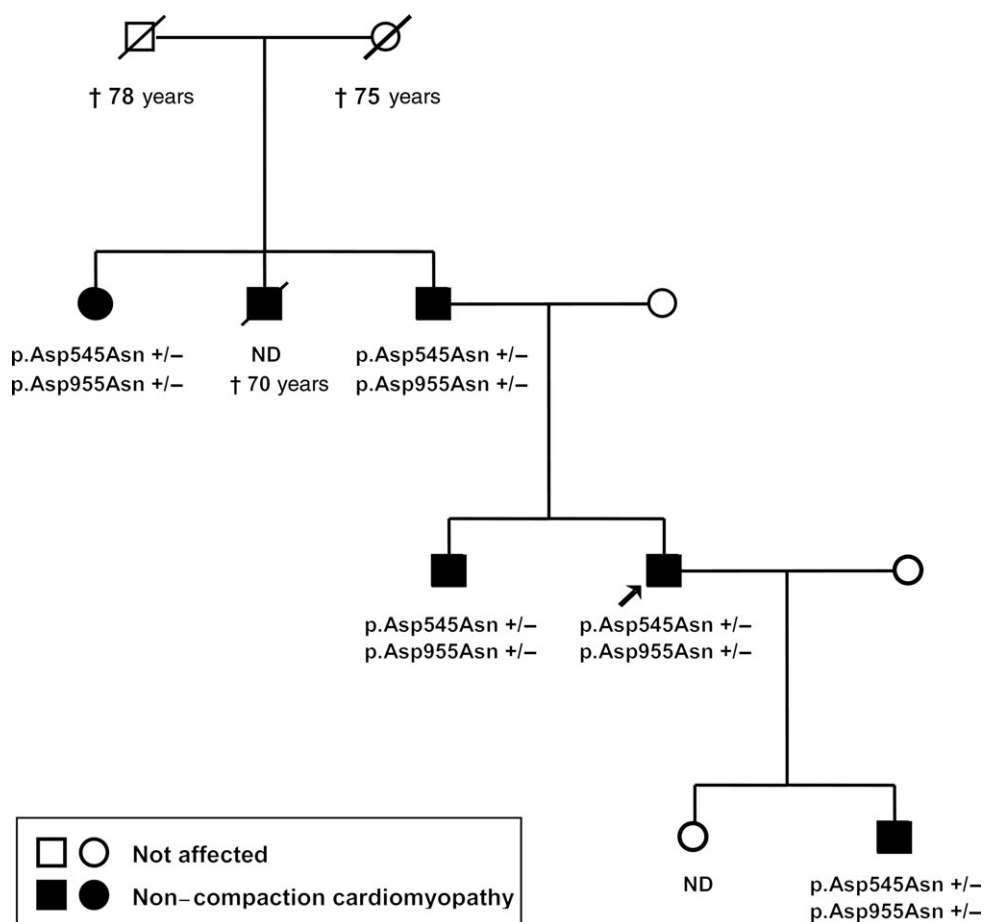


Figure 5 Pedigree of family B. The arrow indicates the proband. ND, not determined; +/-, heterozygous for the p.Asp 545Asn and p.Asp 955Asn MYH7 mutations. † indicates deceased (death at this age).

The majority of mutations in the *MYH7* gene are missense mutations. Truncating mutations in *MYH7*, causing loss of function of one allele, are rarely observed. It is therefore unlikely that haploinsufficiency, i.e. the presence of only one intact allele of the gene, is the main underlying pathophysiological mechanism of *MYH7*-associated disease. This implies that the mutated *MYH7* gene product acts as a 'dominant-negative' protein, perturbing the function of the protein formed by the normal *MYH7* allele.^{25,26} This, so-called poison-polypeptide theory, easily accommodates the presence of double mutations on the same *MYH7* allele, in which the second mutation further modifies the function of the mutated protein.²⁷ Our findings show that a single mutated *MYH7* allele, either carrying one missense mutation or a double missense mutation in *cis*, may result in dominantly inherited NCCM with a variable phenotype.

The major cardiomyopathies are genetically heterogeneous diseases for which the causative genes are partially overlapping. The phenotypic variability of sarcomeric mutations is illustrated by *MYH7* mutations, known to be involved in HCM, DCM, RCM, and NCCM (this study). Whether this means that these are different diseases or rather different manifestations (phenotypes) of the same pathological mechanism is presently not clear. The molecular basis of the phenotypic plasticity of *MYH7* mutations remains unknown but it is likely to be multifactorial. It can be partially explained by the effect of different

mutations on structural and regulatory components of the force generation and relaxation complex. Alternatively, effects of mutant proteins on energy homeostasis of the cardiomyocyte may influence disease outcome. The resulting phenotype is likely determined not only by the causal sarcomeric mutation but also by modifier genes, epigenetic factors, and environmental factors.

Thus far it is thought that an intrauterine arrest of myocardial development with lack of compaction of the loose myocardial meshwork is the pathophysiological mechanism behind NCCM.²⁸ *MYH7* and other sarcomeric gene mutations are well known causes for late onset forms of HCM and DCM, presenting clinical features mostly at adult age. The identification of *MYH7* mutations in familial NCCM and an *ACTC* mutation in HCM with NCCM and ASD,¹⁷ together with the observation of late onset NCCM in a Duchenne patient,²⁹ suggests that the aetiology of NCCM extends beyond an arrest in embryonic cardiac development (i.e. the possibility of late onset NCCM).

The current findings expand the genetic heterogeneity of NCCM, and the identification of *MYH7* defects in familial NCCM suggests that NCCM may be part of a cardiomyopathy spectrum including HCM, RCM, and DCM.

Regular cardiac follow-up of at-risk relatives is recommended in familial cardiomyopathies associated with sarcomeric defects. Similarly, periodic cardiological screening of unaffected at-risk relatives in familial NCCM could be necessary. Our observation also warrants

molecular screening for *MYH7* and possibly other sarcomeric defects in NCCM patients and has implications for cardiac screening for NCCM features in familial HCM, RCM, and DCM.

Conflict of interest: none declared.

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