CASE PRESENTATION

Fully penetrant genetic mutation results in wide familial variability: a cardiac magnetic resonance focused report

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Abstract: Dilated cardiomyopathy (DCM) is a myocardial disorder characterized by ventricular dilation (LV or biventricular) and systolic dysfunction, with a broad etiological spectrum, comprising numerous genetic and non-genetic causes. Cardiac magnetic resonance (CMR) has become an important tool in guiding the etiological diagnosis in DCM. We present the case of a 37-years old man admitted to our department in order to investigate the diagnosis of DCM using CMR. Cine imaging showed mild left ventricular (LV) dilatation and moderate systolic (LV ejection fraction = 42%) dysfunction, but also apical hypertrabeculation meeting the criteria for non-compaction and late gadolinium enhancement (LGE) images revealed mid-wall fibrosis in the basal and midventricular segments of the inferior interventricular septum (IVS) – typical of non-ischemic DCM. Complete family history revealed the diagnosis of DCM in the mother of the patient and in the maternal grandfather, who had died at 87. After genetic testing of the index patient showed a pathogenic mutation in the TTN (titin) gene (c.79273A>T), cascade genetic testing followed, for his mother, sister, uncle and two cousins who all came back positive for the same mutation. CMR examination of the mother done 6 years prior demonstrated severe LV dilatation and systolic dysfunction (LV ejection fraction = 23%), LV non-compaction and mid-wall IVS fibrosis. CMR examination was performed for the other members of the family and discovered pathological findings in the uncle (normal LV volume and function, but focal mid-wall fibrosis in the inferior IVS) and the male cousin (LV non- compaction), while the female cousin had a normal exam. Using CMR and genetic testing, this case report proves the phenotypic heterogenicity of a completely penetrant titin mutation in the same family. Moreover, CMR is shown to be essential in DCM evaluation, having the ability to guide etiologic diagnosis and to detect alterations such as fibrosis and non-compaction in the absence of LV dilation or dysfunction.
Keywords: cardiac magnetic resonance, dilated cardiomyopathy, genetics.

Rezumat: Cardiomiopatia dilatativă (CMD) este o boală a miocardului caracterizată prin dilatare ventriculară (stângă sau biventriculară) și disfuncție sistolică, cu un spectru etiologic larg, incluzând numeroase cauze genetice și non-genetice. Imagistica prin rezonanță magnetică cardiacă (RMC) a devenit un instrument important în ghidarea diagnosticului etiologic în CMD. Vă prezentăm cazul unui bărbat în vârstă de 37 de ani, admis în departamentul nostru pentru investigarea diagnosticului de CMD folosind RMC. Secvențele de tip Cine au arătat dilatarea ventriculului stâng (VS) cu disfuncție sistolică moderată (fracția de ejecție a VS=42%) dar și hipertrabeculare la nivel apical, îndeplinind criteriile de non-compactare. Secvențele tardive post-contrast (LGE) au pus in evidență fibroză medioparietală la nivelul segmentelor bazal și mijlociu ale septului interventricular (SIV) inferior - elemente tipice pentru CMD non-ischemică. Istoricul familial complet a pus în evidență prezența diagnosticului de CMD la mama pacientului și la bunicul matern (care decedase la 87 de ani). După testarea genetică a pacientului index care a evidențiat o mutație patogenă în gena TTN (titină) (c.79273A> T), a urmat o testare genetică în cascadă, pentru mama, sora, unchiul și doi veri, testare al carei rezultat fost pozitivă pentru toți cei testați. Examinarea RMC a mamei, făcută în urmă cu 6 ani, a demonstrat dilatarea VS și disfuncție sistolică severă (fracție de ejecție VS = 23%), non-compactare VS și fibroză medioparietală la nivelul SIV inferior. S-a efectuat RMC și pentru ceilalți membri ai familiei, relevând modificări patologice în cazul unchiului (volume și funcție normală a VS, dar cu prezența fibrozei focale medioparietale a segmentului mijlociu al SIV inferior) și al verișorului (non-compactare VS), în timp ce pentru verișoară examinarea a fost normală. Folosind RMC și testarea genetică, acest raport de caz dovedește heterogenitatea fenotipică a unei mutații în gena titinei cu penetranță completă în cadrul aceleiasi familii. Mai mult, RMC se dovedește a fi esențială în evaluarea CMD, având capacitatea de a ghida etiologic diagnosticul și de a detecta modificări precum fibroza și non-compactarea în absența dilatării sau disfuncției VS.
Cuvinte-cheie: rezonanță magnetică cardiacă, cardiomiopatie dilatativă, genetică.

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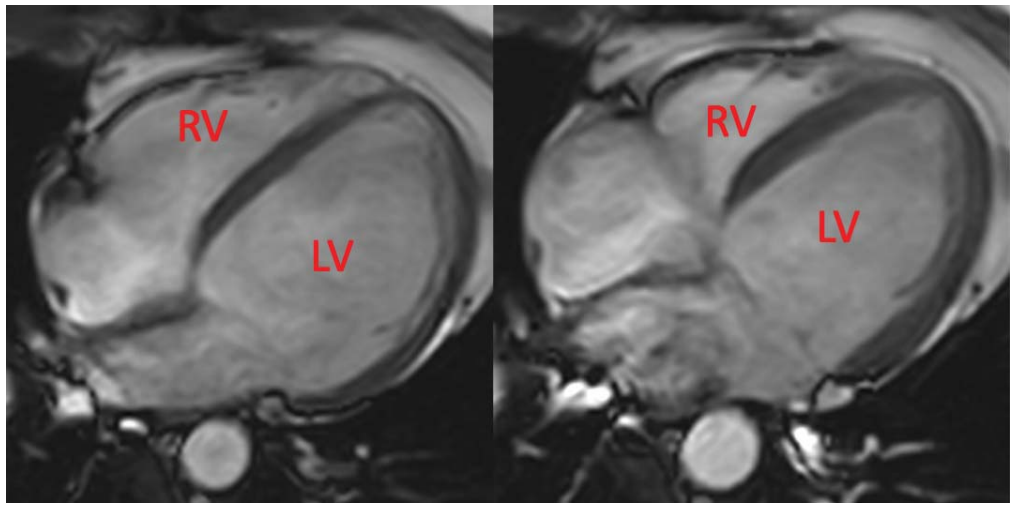

Figure 1. Long axis Cine SSFP imaging in the 4-chamber plane (left – end diastole; right – end systole) showing mild dilation of the left ventricle (LV) and non-compaction in the lateral wall and apex (non-compacted/compacted myocardium – NC/C = 2.5). Right ventricular (RV) dimensions and function were normal. LV = left ventricle; RV = right ventricle.

INTRODUCTION

Dilated cardiomyopathy (DCM) is a progressive and often irreversible disease of the myocardium characterized by left ventricular (LV) or biventricular dilation alongside systolic dysfunction. While non-genetic causes are numerous and of great importance, up to 35% of the patients diagnosed with DCM have genetic alterations which contribute to or cause the development of genetic DCM. The genes suffering mutations are encoding mainly for structural proteins of the cytoskeleton, the cardiomyocytic sarcomeres and nuclear envelope proteins. Although inheritance in an X-linked, autosomal recessive or mitochondrial pattern is possible, most of the genetic anomalies are inherited as an autosomal dominant trait. This report aims to highlight cardiac magnetic resonance imaging in a DCM family[1].

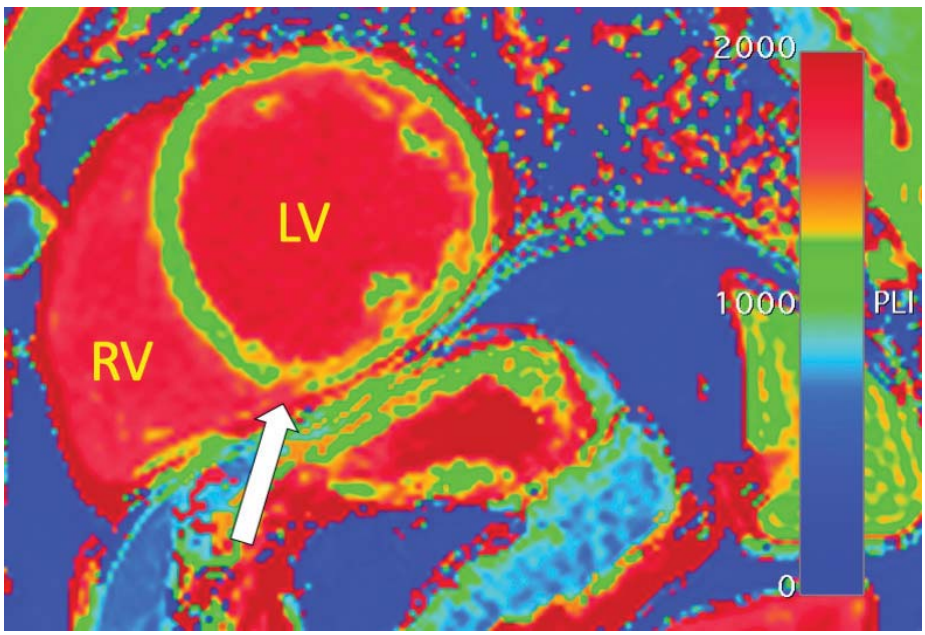

Figure 2. T1 mapping image in the short axis mid-ventricular plane showing high T1 in the inferior septum (white arrow). The color green represents normal T1, while yellow means high T1 (>1300 ms). LV = left ventricle; RV = right ventricle.

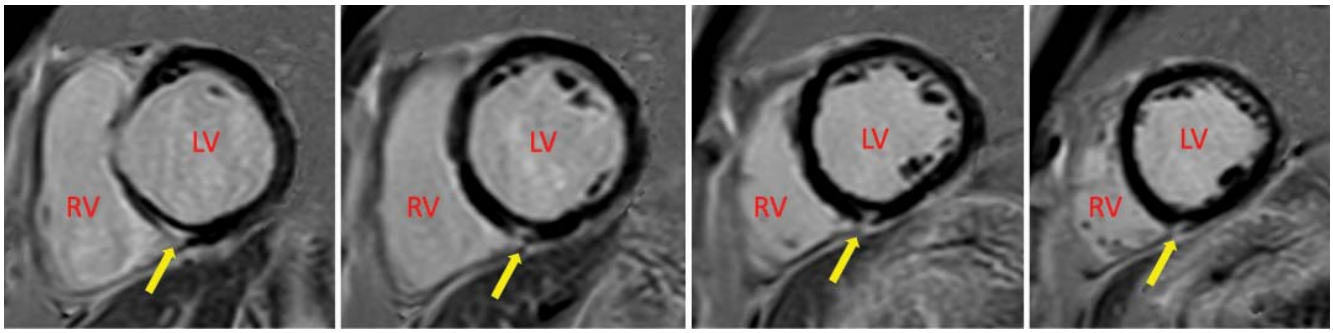

Figure 3. Serial short axis late gadolinium enhancement PSIR images showing mid-wall left ventricular (LV) basal and midventricular fibrosis (yellow arrows) in the inferior interventricular septum with incomplete extension towards the anterior IVS – incomplete „septal stripe". LV = left ventricle; RV = right ventricle.

CASE PRESENTATION

A 37-year-old man, who had presented dyspnea and had undergone a cardiological check-up, was sent to our department in order to evaluate the diagnosis of dilated cardiomyopathy through cardiac magnetic resonance (CMR), which was performed on a 3.0 Tesla machine. Long axis SSFP Cine imaging showed dilation of the left ventricle, while also demonstrating apical hypertrabeculation meeting the criteria for non-compaction (Figure 1; Video file 1).

Using short axis SSFP Cine imaging, ventricular volumes and function were computed showing mild LV dilation, with a left ventricular end-diastolic volume (LVEDV) of 222 ml (117 ml/m^2) and moderate systolic dysfunction (left ventricular ejection fraction – LVEF of 42%) due to generalized hypokinesia. Right ventri-

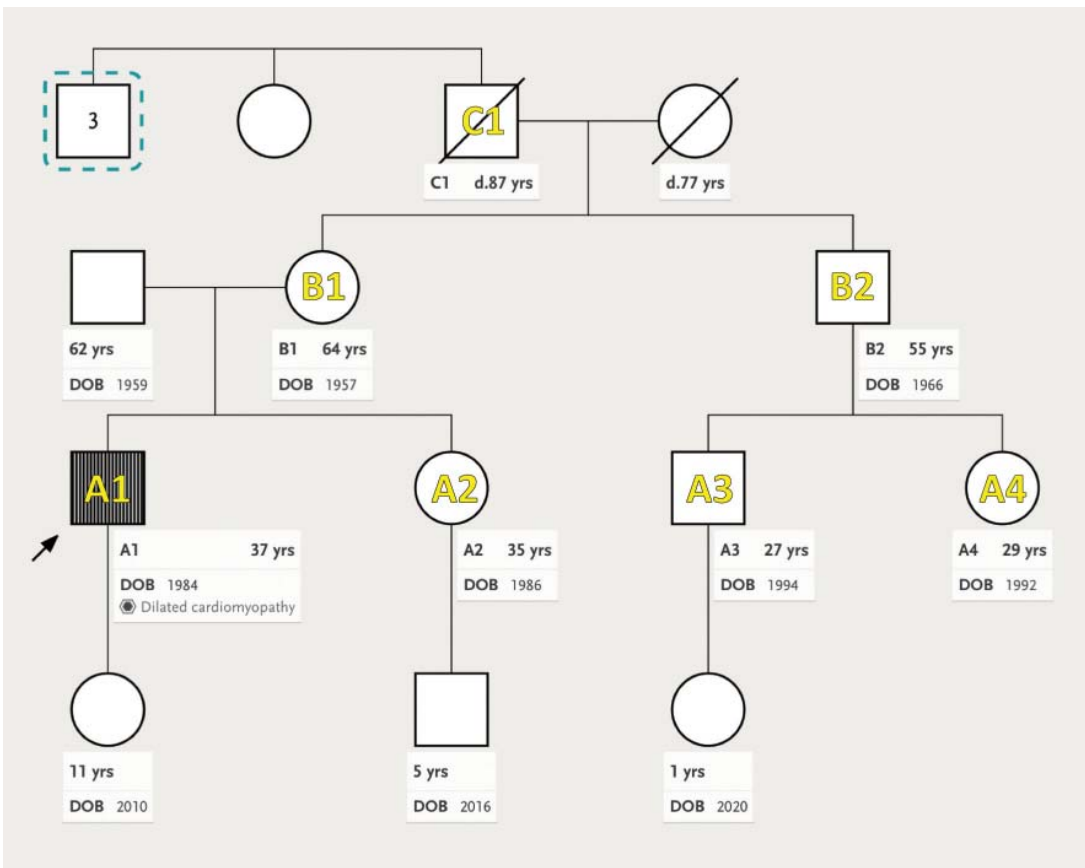

Figure 4. Initial pedigree: index patient (A1) is indicated by black arrowhead. Family members encoded for reference in the following text and images.

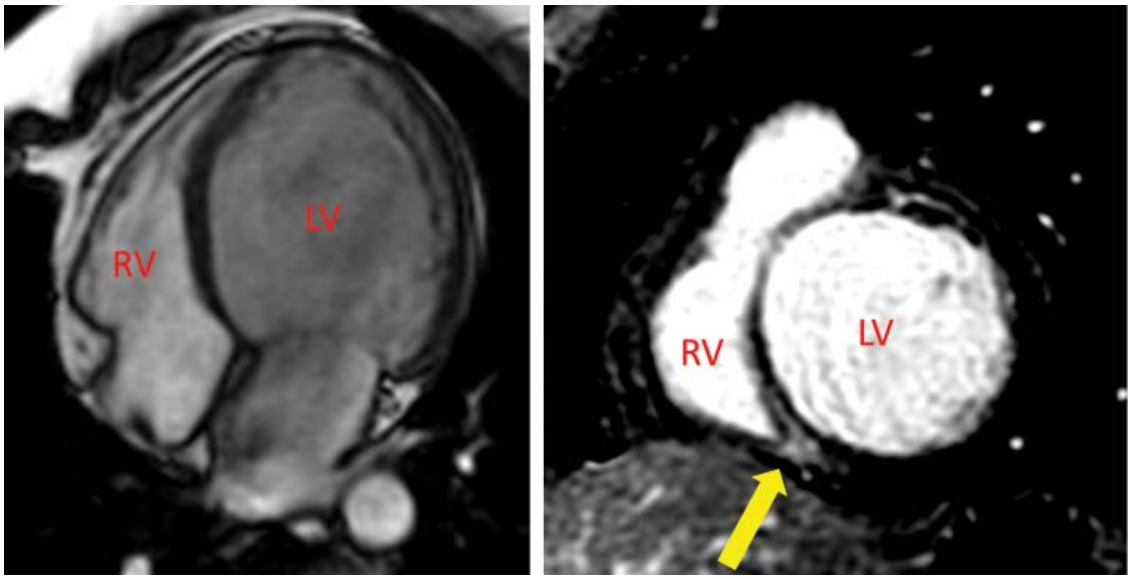

Figure 5. CMR images of the index patient's mother, 6 years prior. Left – SSFP Cine long axis 4-chamber image in end-diastole showing severe LV dilation and lateral wall non-compaction. Right – Short axis late gadolinium enhancement imaging showing mid-wall fibrosis in the basal inferior IVS. LV = left ventricle; RV = right ventricle.

cular (RV) dimension and function were normal. While, T2-weighted imaging showed no sign of myocardial edema, T1 mapping sequences revealed high T1 in the basal and mid inferior part of the interventricular septum (T1 = 1350 ms) (Figure 2).

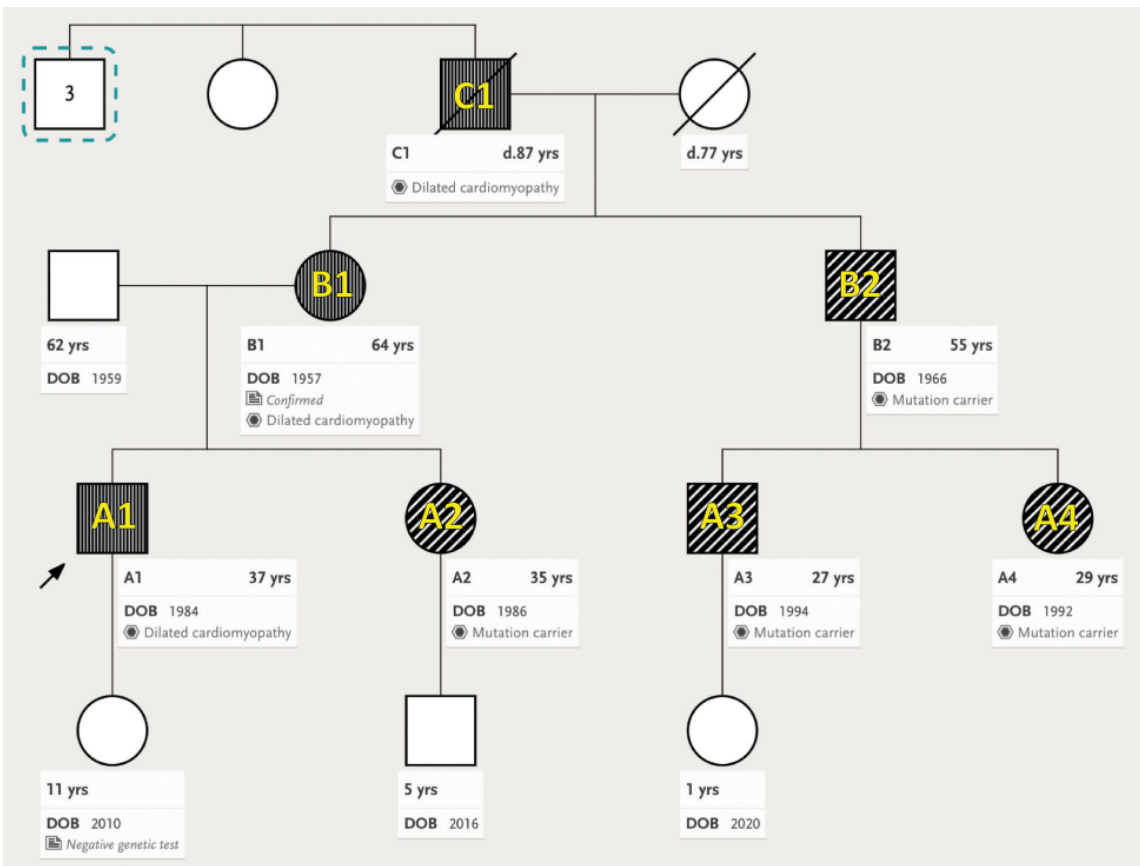

Figure 6. Updated family pedigree after complete genetic testing showing almost full penetrance.

Late gadolinium enhancement PSIR images reveal myocardial mid-wall fibrosis in the inferior IVS the partially extends towards the anterior IVS – incomplete „septal stripe" (Figure 3).

Thus, we concluded that the CMR aspect is that of typical non-ischemic DCM and followed-up with complete family history (including drawing a 2-generation pedigree – Figure 4).

Family history revealed that the patient's mother (B1) was actually herself diagnosed with DCM 7 years before and had a cardiac defibrillator implanted for primary prevention of sudden cardiac death due to reduced LVEF. She also had a CMR exam 6 years prior which demonstrated severe LV dilation (LVEDV = 202 ml; 121 ml/m^2) and reduced LVEF (23%), lateral LV non-compaction and mid-wall IVS fibrosis (Figure 5; Video file 2).

Moreover, the maternal grandfather (C1) had also been diagnosed with DCM, however he had very mild symptoms and had died at 87. Positive family history made it very likely that a genetic test would reveal a causing mutation for DCM and, indeed, the index patient's test revealed a pathogenic mutation in the TTN (titin) gene (c.79273A>T). Cascade genetic testing followed, firstly for the mother (B1), sister (A2) and uncle (B2), which all came back positive for the same mutation, followed by testing of the 2 cousins (A3, A4) which also came back positive. (Updated pedigree in Figure 6).

The uncle and two cousins underwent CMR examinations, while the sister (A2) is scheduled to have a CMR in the following months. The uncle (B2) had normal LV volume and function, no LV non-compaction, but had focal mid-wall fibrosis in the inferior IVS. The male cousin (A3), had normal LV volume and function, no myocardial fibrosis, but had LV non-compaction, while the female cousin (A4) had a completely normal exam. The different CMR findings of all the family members are summarized in Figure 7 – the central illustration of this report.

DISCUSSION

This case report underlines the fact that the effects of mutations on the mechanisms of disease expression are still an unresolved issue of research. In this family, there was substantial difference in phenotypic expression of the disease, even though the mutation they carried was the same. On one hand, we have the paternal grandfather of the proband who had a mild form of DCM, with a normal lifespan, no major cardiovascular events or repeated hospitalizations for heart failure. On the other hand, the mother of the proband suffers from a severe form of DCM, diagnosed at the age of 54, and underwent an ICD implantation procedure for primary prevention of sudden cardiac death, while the index patient, at the age of 37, already has moderate systolic dysfunction. Moreover, on the other side of the family, the uncle, at the age of 55, has no dilation or dysfunction of the LV, only presenting focal myocardial fibrosis, while his son has LV non-compaction as a sign of cardiomyopathy. Whether genetic modulators or non-genetic triggers had contributed to the development of DCM is an issue that still needs to be addressed[2]. Another particularity of this family is that, despite and autosomal genetic inheritance pattern (50% chance of transmission to any child), the penetrance was complete.

TTN mutations are the most frequent cause of genetic DCM. Titin is the largest protein in the human body, encoded by 364 exons in the TTN gene, and represents an essential component of the sarcomere. The impact of titin mutations in the development of cardiac disease highlights our only partial understanding of its properties and function. Initially, titin was thought to be related mostly to sarcomeric integrity and passive stiffness, but recent evidence suggests that titin may contribute significantly to the length-dependent activation through structural rearrangements of both thin- and thick-filament proteins[3]. These complex findings partially explain how the heterogeneity of pathogenicity of TTN influences cardiac phenotypes[4].

Finally, our findings are in accordance with an excellent recent CMR study on the specific fibrosis patterns of different DCM-causing gene mutations[5]. Indeed, basal inferior IVS fibrosis is reported to be found in TTN mutations, among others. This confirms that CMR plays an important role in guiding the etiologic diagnosis in DCM.

CONCLUSION

Through extended CMR and genetic evaluation, this report illustrates the phenotypic heterogenicity of a completely penetrant TTN mutation within one family, suggesting a possible influence of other genetic or non-genetic factors and potential compensatory mechanisms. Moreover, we highlight the importance of CMR evaluation in DCM, showing that alterations such as myocardial fibrosis or LV non-compaction can be present in cases without LV dilation or dysfunction.

Conflict of interest: none declared.

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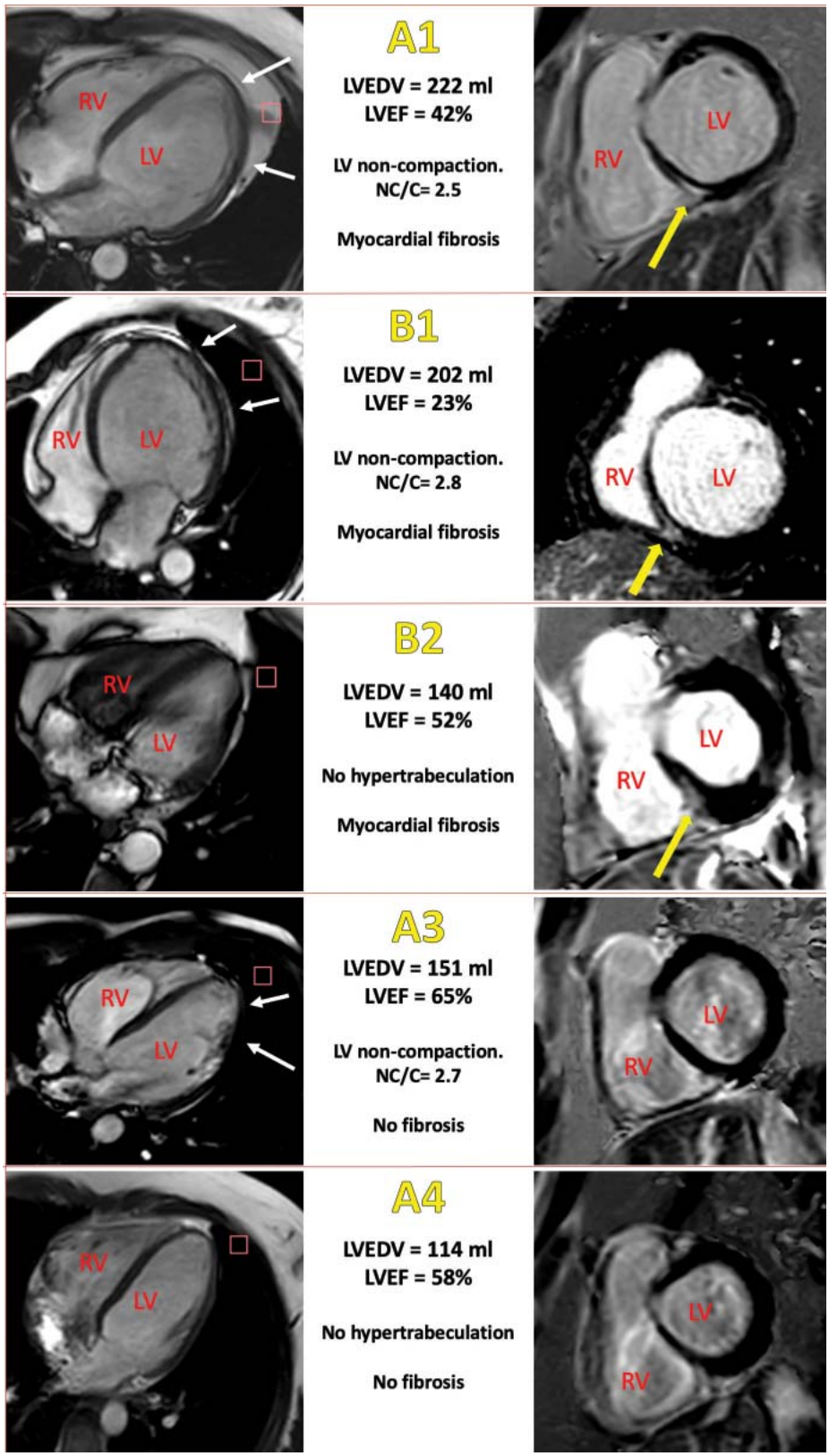

Figure 7. Central illustration. Comparison of CMR findings in all family members, showing high phenotypic variability. Family members are listed from top to bottom according to the codes given in the pedigree. For each patient, on the left there is a long-axis 4 chamber plane at end-diastole with white arrows pointing towards non-compacted zones and a 1 cm^2 red square for reference. On the right there is a basal short axis late enhancement image with yellow arrows pointing towards fibrosis.
LV = left ventricle; RV = right ventricle; LVEDV = left ventricular end-diastolic volume; LVEF = left ventricular ejection fraction; NC/C = ratio of non-compacted over compacted myocardium.