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Prevalence and evolution of right ventricular dysfunction among different genetic backgrounds in dilated cardiomyopathy

Short title: RVD in genetically determined DCM

Paolo Manca, MD[1], Antonio Cannatà, MD[1-2], Vincenzo Nuzzi, MD[1], Daniel I. Bromage[2], Guerino Giuseppe Varrà, MD[1], Maddalena Rossi, MD[1], Matteo Dal Ferro, MD[1], Alessia Paldino, MD[1], Marta Gigli, MD[1], Giulia Barbati[3], Federica Ramani [1], Bruno Pinamonti, MD[1], Davide Stolfo, MD[1-4], Maurizio Porcu, MD,FESC[5], Luisa Mestroni, MD,FACC[6], Marco Merlo, MD[1], Gianfranco Sinagra, MD,FESC[1].

[1] Department of Cardiology, Azienda Sanitaria Universitaria Integrata Giuliano Isontina (ASUGI), University of Trieste, Trieste, Italy.

[2] Department of Cardiovascular Science, Faculty of Life Science and Medicine, King's College London, London, UK.

[3] Biostatistics Unit, University of Trieste, 34100 Trieste, Italy.

[4] Division of Cardiology, Department of Medicine, Karolinska Institutet, Stockholm, Sweden.

[5] Department of Cardiology, Azienda Ospedaliera Brotzu, Cagliari, Italy.

[6] Cardiovascular Institute, University of Colorado Anschutz Medical Campus, Aurora.

Corresponding Author:

Marco Merlo, MD, Division of Cardiology, Cardiovascular Department, Azienda Sanitaria Universitaria Integrata Giuliana Isontina (ASUGI), University of Trieste, Trieste, Italy Via Valdoni 7, 34149 - Trieste, Italy. Tel: +390403994477; fax: +390403994153. E-mail: marco.merlo79@gmail.com.

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Abstract (250/250 words)

Background: Titin (*TTN*) related dilated cardiomyopathy (DCM) has a higher likelihood of left ventricular reverse remodeling (LVRR) compared to other genetic etiologies. No data regarding the evolution of right ventricular dysfunction (RVD) according to genetic background is available.

Methods: Consecutive 104 DCM patients with confirmed pathogenic genetic variants (51 *TTN* related DCM; 53 other genetic DCM) and a control group of 139 patients with negative genetic testing and available follow-up data at 12-24 months were analyzed. RVD was defined as a right ventricular fractional area change (RVFAC) <35%. The main study end-point was the comparison of the evolution of RVD and the delta change of RVFAC throughout the follow-up according to etiology. A composite of [illegible]

Results: [illegible] genetic cohorts[illegible] related DCM cohort [illegible]

Conclusions: [illegible]

Keywords: [illegible]

Brief Summary

[illegible]

Introduction

Dilated cardiomyopathy (DCM) is a primary heart muscle disease defined by left- or bi-ventricular systolic dysfunction in the absence of abnormal loading conditions or significant coronary artery disease [1;2]. A specific genetic background is identified in up to 40% of DCM patients, with 40 to 60 causative genes involved in determining the clinical phenotype [3;4]. Among these, truncating variants in the titin (*TTN*) gene represent the most prevalent etiology, accounting for 11 to 25% of genetically determined DCM [4].

Recently, considerable efforts have been devoted to characterizing the clinical phenotype of *TTN* related DCM. Evidence suggests that *TTN* truncating variants are associated with milder forms of DCM and a higher likelihood left ventricular reverse remodeling (LVRR) with guideline-directed medical treatment (GMT) [5-7].

So far, no data are available about the prevalence and evolution of right ventricular (RV) involvement in patients affected by *TTN* related DCM. Right ventricular dysfunction (RVD) is identifiable in approximately 30% of DCM patients at the initial clinical presentation [8;9], with a

high rate of RVD recovery following 6-12 months of GMT [10]. However, differences in the prevalence and progression of RVD according to genetic background have not been explored.

The aim of this study was to assess the prevalence and evolution of RVD in patients with *TTN* related DCM compared to other pathogenic genetic variants and DCM patients with no genetic determinants.

Methods

Inclusion and exclusion criteria

All consecutive patients enrolled to the Trieste Heart Muscle Disease Registry, Italy [11], from January 1995 to December 2017, were screened for inclusion. Patients with an available genetic test documenting a pathogenic or likely pathogenic mutation and available follow-up data at 12-24 months were eligible. A control group of genetically tested DCM patients enrolled in the same time-frame, in which genetic testing was either negative or demonstrated a variant of uncertain significance, was also included. The enrolment was considered the first evaluation in our Center.

[illegible]

¢KŜ LJNŜăŜyŎŜ 2Ŧ Ŏ2N2yl·Nè l·NűŜNè ŘλăŜl·ăŜ ǿl·ă NdzfŜŘ 2dzű ōè Ŏ2N2yl·Nè l·NűŜNè l·yƎλ2ƎNl·LJKè 2N Ŏ2Y˙LJdzűŜŘ ű2Y˙2ƎNl·LJKè¢ 9yŘ2Y˙è2ŎI·NŘλl·f ōλ2LJăè ǿl·ă LJŜNŦ2NY˙ŜŘ λy˙LJl·űλŜyűă ǿλűK ădzăLJŜŎűŜŘ l·ŎűλØŜ Y˙è2ŎI·NŘλűλă¢

! ff LJl·űλŜyűă ǿŜNŜ 2y˙D a ¢Σ dzyfŜää Ŏ2yűNl·λyŘλŎl·ŭŜŘ 2N y2ű ű2fŜNl·ŭŜŘ ώмп6Σ l·yŘ NŜŎŜλØŜŘ λY˙LJfl·yűŜŘ Ŏl·NŘλ2ØŜNűŜN ŘŜŦλōNλffl·ű2Nă óL/5ăú l·yŘκ2N Ŏl·NŘλl·Ŏ NŜăèyŎKN2yλÎl·űλ2y˙űKŜNl·LJè ó/w¢ú l·ŎŎ2NŘλyƎ ű2 λyűŜNyl·űλ2yl·f ƎdzλŘŜfλySă ώмp6¢

Echocardiographic analysis

[± l·yŘ w± ŘλY˙Ŝyãλ2yã l·yŘ Ŧdzyŏűλ2y˙ǿŜNŜ l·ăăŜăăŜŘ l·ŎŎ2NŘλyƎ ű2 λyűŜNyl·űλ2yl·f ƎdzλŘŜfλySă ώмc6¢ [± Ø2fdzY˙Ŝă l·yŘ Řλl·Y˙ŜúŜNă ǿŜNŜ λyŘŜÈŜŘ l·ŎŎ2NŘλyƎ ű2 LJl·űλŜyűăΩ ō2Řè ădzNŦl·ŎŜ l·NŜl·¢ [±9C ǿl·ă Ŏl·fŎdzfl·ûŜŘ ōè {λY˙LJă2yΩă ōλLJfl·yŜ Y˙ŜűK2Ř¢

w±5 ǿl·ă Ŏ2yãλŘŜNŜŘ l·ă w± ŦNJl·Ŏűλ2yl·f l·NŜl· ŎKl·yƎŜ ów±C! /ú óώSyŘ-Řλl·ăű2fλŎ l·NŜl·çSyŘ-ăèăű2fλŎ l·NŜl·ßκSyŘ-Řλl·ăű2fλŎ l·NŜl· È мллú ғoρ̂:: ¢ /Kl·yƎŜă λy˙w± Ŧdzyŏűλ2y˙ŦN2Y˙ ōl·ăŜfλySŜ ű2 Ŧ2ff2ǿ-dzLJ ǿŜNŜ l·ăăŜăăŜŘ¢

[ŜŦű ØŜyűNλŎdzfl·N NŜØŜNăŜ NŜY˙2ŘŜfλyƎ ó[±wwú ǿl·ă ŘŜŦλySŘ ōè l·y˙l·ōă2fdzűŜ λyŎNŜl·ăŜ λy˙[±9C жмƒ̂:: ó2N l·ōă2fdzűŜ [±9C l·ű Ŧ2ff2ǿ-dzLJ жpƒ̂:: úΣ l·ăă2Ŏλl·ûŜŘ ǿλűK l· NŜfl·ŭλØŜ NŜŘdzŎűλ2y˙λy˙λyŘŜÈŜŘ fŜŦű ØŜyűNλŎdzfl·N ŜyŘ-Řλl·ăű2fλŎ ŘλI·Y˙ŜúŜN жмƒ̂:: ó2N l·ōă2fdzűŜ Ø1·fdzŜ l·ű Ŧ2ff2ǿ-dzLJ ЖooY˙Y˙κY˙H ú ώмт6¢

a λűNl·f NŜƎdzNƎλűl·ûλ2y˙ó a wú ǿl·ă Ŏ2yãλŘŜNŜŘ ăλƎyλŦλŎl·yű 2yfè λŦ Y˙2ŘŜNl·ûŜ ű2 ăŜØŜNŜ óƎNl·ŘŜ н ç пú¢

Genetic analysis and cluster Classification

¦ ăλyƎ bŜĚű-DŜySNl·ûλ2y˙{ŜljdzŜyŎλyƎ óbD{úΣ LJl·ûλŜyűăΩ ōf22Ř ăl·Y˙LJfŜă ǿŜNŜ ûŜăûŜŘ Ŧ2N ŎI·NŘλ2Y˙è2LJl·ûKè-NŜfl·ûŜŘ ƎŜySŜă¢ ¢KŜ ƎŜySŜűλŎ ûŜăűλyƎ Ŏ2ØŜNŜŘ Y˙2NŜ ûKl·y˙фpƒ̂:: 2Ŧ ˥y˙2ǿy˙5/a NŜfl·ûŜŘ ƎŜySăΣ ǿKλŎK Kl·ă ōŜŜy˙LJNŜØλ2dzăfè NŜLJ2NűŜŘ ώмн6¢ ! ff LJl·ûλŜyűă ǿŜNŜ ăŜljdzŜyŎŜŘ óăŜŜ ădzLJLJfŜY˙Ŝyűl·Nè Yl·ûŜNλl·f Ŧ2N Y˙2NŜ ŘŜűl·λfă 2y˙ûKŜ ƎŜySŜűλŎ LJl·ySf dzăŜŘú¢ ! ff Ø1·NλI·yűă ǿŜNŜ Ø1·fλRl·ûŜŘ ǿλűK ōλŘλNŜŎűλ2yl·f

{ l·yƎŜℕ ăŜljʤŜyŎλyƎ l·yŘ ǿŜℕŜ ŏfl·ăăλŦλŜŘ l·ŎŎ2ℕŘλyƎ ű2 ŎʤZℕℕŜyű ƎʤλŘŜfλySă ώмy6Φ ¢ĸŜ Yˇλy2ℕ l·ffŜfŜ ŦNŜljʤŜyŎè ó a ! Cú ǿl·ă ǾŜℕλŦλŜŘ λy˝űĸŜ Ǝy2Y ! 5 óĸűűLJăʏккƎy2Yˇl·Řфōℕ2l·Řλyãűλűdzű$Φ2ℕƎĸǾl·ℕλl·yűкнн-

псппфуфм-D- ! ú l·yŘ Ŏℕ2ăăŎĸŜŎ⟆ŜŘ ǿλűK űĸŜ /fλy±l·ℕ óĸűűLJʏккǿǿǿΦ yŎōλΦ yfYˇΦ yλKΦ Ǝ2Øк ŏfλyØl·ℕú l·yŘ

/ l·ℕŘλ2 / fl·ăăλŦλŜℕ óĸűűLJăʏккǿǿǿΦŎl·ℕŘλ2ŏfl·ăăλŦλŜℕΦ2ℕƎкú Řl·űl·ōl·ăŜăΦ

t l·űλŜyűă ǿλűK ℕJl·ℕŜ Ǿl·ℕλl·yűă λy˝ƎŜyŜă ōŜf2yƎλyƎ ű2 űĸŜ ăl·Yˇŝ ădzōŎŜftdzfl·ℕ Ŏ2YˇLJl·ℕűˇYˇŜyű 2ℕ ǿλűK ăλYˇλfl·ℕ

ŦdzyŎűλ2yã ǿŜℕŜ ŎfdzăűŜℕŜŘ λy˝ŘλŦŦŜℕŜyű Ǝℕ2dzLJăΣ l·ă LJℕŜǾλ2dzătè ŘŜăŎℕλōŜŘ ωт6Φ

. l·ăŜŘ 2y˝űĸŜ ƎŜyŜűλŎ űŜăű ℕŜădzfűăΣ LJl·űλŜyűă ǿŜℕŜ ŘλǾλŘŜŘ λyű2 ű ǿ2 Ǝℕ2dzLJăʏ ¢¢b ℕŜfl·ûŜŘ 5 / a l·yŘ

2űĸŜℕ ƎŜyŜűλŎ 5 / aΦ

Study endpoint and outcome measure

¢ĸŜ LJℕλYˇl·ℕè ŜyŘLJ2λyű ǿl·ă űĸŜ ŎKl·yƎŜ ûKℕ2dzƎK2dzű 2Ŧ w±C ! / l·yŘ űĸŜ ŘλŦŦŜℕŜyű LJℕŜǾl·fŜyŎŜ 2Ŧ w±5

ŦN2Yˇ ōl·ăŜfλyŜ ű2 Ŧ2ff2ǿ-dzLJ ℕŜǾl·fdzl·űλ2y˝ōŜűǿŜŜy˝¢¢b ℕŜfl·ûŜŘ 5 / a l·yŘ 2űĸŜℕ ƎŜyŜűλŎ 5 / a LJl·űλŜyűăΦ

! ădzōăŜljʤŜyű l·yl·fèăλă Ŏ2yŘdzŎűŜŘ λy˝ûĸŜ ƎŜyŜűλŎl·ffè ûŜăûŜŘ yŜƎl·ûλǾŜ 5 / a LJl·űλŜyűă ǿl·ă l·fă2 λyŎfdzŘŜŘ

l·yŘ Ŏ2YˇLJl·ℕŜŘ ű2 ûĸŜ ű ǿ2 Yˇl·λy˝Ŏ2K2ℕűăΦ

! Ŏ2YˇLJ2ăλûŜ 2Ŧ l·ft-Ŏl·dzăŜ Yˇ2ℕűl·fûûè l·yŘ ĸŜl·ℕűˇûℕl·yãLJfl·yűl·ûλ2y˝ó l ¢Èú ǿl·ă l·fă2 λyŎfdzŘŜŘ l·ă l·y˝

2dzűŎ2YˇŜ Yˇŝl·ădzℕŜΦ hdzûŎ2YˇŜ Řl·ûl· ǿl·ă 2ōûl·λyŜŘ Řλℕ$ŎûfèŦN2Yˇ ûĸŜ LJl·ûλŜyűΣ ûĸŜλℕ ƎŜyŜℕl·f LJKèăλŎλl·yΣ

2ℕ Ŧℕ2Yˇ ûĸŜ ℕŜƎλăûŜℕă 2Ŧ ŘŜl·ûK 2Ŧ ûĸŜ Yˇdzyλ$λLJl·fλûλŜă 2Ŧ ℕŜăλŘŜyŎŜΦ

¢ĸŜ ăűdzŘè ǿl·ă l·LJLJℕ2ǾŜŘ ōè ûĸŜ ŜűĸλŎă Ŏ2YˇYˇλûûŜŜ ó9ûĸλŎl·f l·LJLJℕ2Ǿl·f покнллфú l·yŘ LJŜℕŦ2ℕYˇŜŘ

l·ŎŎ2ℕŘλyƎ ű2 ûĸŜ l Ŝtăλy⟆λ ŘŜŎfl·ℕl·ûλ2yΦ ! ff LJl·ûλŜyűă Ǝl·ǾŜ ǿℕλûûŜyˇλyŦ2ℕYˇŜŘ Ŏ2yãŜyűΦ

Statistical analysis

/ fλyλÖl·f l·yŘ fl·ō2₪l·ű2₪è Øl·₪λl·ōfŜă ǿŜ₪Ŝ ŜÈLJ₪ŜăăŜŘ l·ă YˇŜl·yˇ l·yŘ {5Σ YˇŜŘλl·yˇ l·yŘ λyűŜ₪ljdzl·₪ŰλfŜ ₪l·yƎŜă óLvwúΣ 2₪ l·ă Ö2dzyűă l·yŘ LJŜ₪ÖŜyűl·ƎŜăΣ l·ă l·LJLJ₪2LJ₪λl·ûŜΦ /₪2ää-ăŜÖűλ2yλf Ö2YˇLJl·₪λă2yã ōŜűǿŜŜyˇƎ₪2dzLJă ǿŜ₪Ŝ Yˇl·ŘŜ ōè űKŜ l·yλf·tèăλă 2Ŧ Øl·₪λl·yÖŜ ûŜăű 2yˇÖ2yűλydz2dză Øl·₪λl·ōfŜăΣ dzăλyƎ űKŜ .₪2ǿyˇ-C2₪ăèűKŜ ăűl·ûλăűλÖ ǿKŜyˇűKŜ l·ăădzYˇLJűλ2yˇ2Ŧ Ŝljdzl·f Øl·₪λl·yÖŜă ŘλŘ y2ű K2fŘΣ 2₪ űKŜ y2y-LJl·₪l·YˇŜű₪λÖ YˇŜŘλl·yˇűŜăű ǿKŜyˇyŜÖŜăăl·₪è /Kλ-ăljdzl·₪Ŝ 2₪ CλăKŜ₪ ŜÈl·Öű ûŜăûă ǿŜ₪Ŝ Öl·fÖdzfl·ûŜŘ Ŧ2₪ Öl·ûŜƎ2₪λÖl·f Øl·₪λl·ōfŜăΦ C2₪ ōλyλl·₪è Øl·₪λl·ōfŜăΣ űKŜ aÖbŜYˇl·₪ ûŜăű ǿl·ă Öl·fÖdzfl·ûŜŘΦ tl·λ₪ŜŘ ăl·YˇLJfŜ ¢-ûŜăûă ǿŜ₪Ŝ LJŜ₪Ŧ2₪YˇŜŘ ű2 l·ăăŜăă űKŜ ŜØ2fdzűλ2yˇ2Ŧ w±C! / λyˇűKŜ ŘλŦŦŜ₪Ŝyű Ö2K2₪ûăΦ ¦yλØl·₪λl·ōfŜ f2ƎλăűλÖ ₪ŜƎ₪Ŝăăλ2yˇǿl·ă LJŜ₪Ŧ2₪YˇŜŘ ű2 l·ăăŜăă űKŜ ōl·ăŜfλyŜ LJl·₪l·YˇŜűŜ₪ă l·ăă2ÖλI·ûŜŘ ǿλűK ûKŜ Yˇl·λyűŜyl·yÖŜ 2₪ λyÖλŘŜyÖŜ 2Ŧ w± Řèă Ŧdzyűλ2yˇl·ű Ŧ2ff2ǿ-dzLJΦ ! Ydzfűλl·₪λl·ōfŜ Y2ŘŜf λyÖfdzŘλyƎ ûKŜ Øl·₪λl·ōfŜă ǿλűK LJ-Øl·fdzŜ ғлΦм l·ű ûKŜ dzyλØl·₪λl·ōfŜ l·yl·fèăλă ώмфϐ ǿl·ă LJŜ₪Ŧ2₪YˇŜŘΦ 5dzŜ ű2 ûKŜ f2ǿ ydzYˇōŜ₪ 2Ŧ ŜØŜyűăΣ 2ûKŜ₪ ûǿ2 Ydzfűλl·₪λl·ōfŜ Y2ŘŜfă ǿŜ₪Ŝ ōdzλfű l·yŘ ûKŜ ! ¦ / 2Ŧ ûKŜ Y2ŘŜfă ǿl·ă Ö2YˇLJl·₪ŜŘ ǿλűK l· wh / ÖdzNJØŜΦ ! Yl·LJfl·yˇ-aŜλŜ₪ ÖdzNJØŜ Ŧ2₪ l·ft-Öl·dzăŜ Y2₪ûl·fλûè l·yŘ l¢È ǿl·ă dzăŜŘ ű2 Ö2YˇLJl·₪Ŝ LJl·ûλŜyűă l·ÖÖ2₪ŘλyƎ ű2 ûKŜλ₪ ƎŜyŜűλÖ ōl·ÖlƎ₪2dzyŘ l·yŘ w±5 l·ű Ŧ2ff2ǿ-dzLJ λyˇŘŜűŜ₪YˇλyλyƎ ûKŜ 2dzûÖ2YˇŜ YˇŜl·ădz₪ŜΦ LyˇűKŜ Yˇl·λyˇl·yl·fèăλă Ŧl·YˇλfλI·f Öl·ăŜă ǿŜ₪Ŝ λyÖfdzŘŜŘΦ ! ăŜyăλûλØλûè l·yl·fèăλă Ö2yăλŘŜ₪λyƎ 2yfè LJ₪2ōl·yŘă ǿl·ă LJŜ₪Ŧ2₪YˇŜŘΦ LyűŜ₪-2ōăŜ₪ØŜ₪ l·yŘ λyű₪l·-2ōăŜ₪ØŜ₪ Øl·₪λl·ōλfλûè λyˇw±C! / YˇŜl·ădz₪ŜYˇŜyű ǿl·ă l·ăÖŜ₪ûl·λyŜŘ ōè ₪l·yŘ2Yˇfè ăŜfŜÖűλyƎ l· ăl·YˇLJfŜ 2Ŧ пл LJl·ûλŜyűă ǿλűK 5 / aΦ ¢ǿ2 ŘλŦŦŜ₪ŜyűΣ 2LJŜ₪l·ű2₪ă ótΦ aΦ l·yŘ ±ΦbΦú LJŜ₪Ŧ2₪YˇŜŘ l· Ř2dzōfŜ ŜØl·fdzl·ûλ2yˇű2 l·ÖKλŜØŜ ϕ£ţ̂ LJ2ǿŜ₪ l·yŘΣ ûKdzăΣ ű2 ŘŜűŜÖű l·yˇλyűNJl·Öfl·ăă Ö2₪₪Ŝfl·ûλ2yˇóL / /ú 2Ŧ лΦy dzyŘŜ₪ ûKŜ yűzff KèLJ2ûKŜăλă 2Ŧ L / / Γ лΦcΣ ōè dzăλyƎ l·yˇC-ûŜăű ǿλűK l· ăλƎyλŦλÖl·yÖŜ fŜØŜf 2Ŧ лΦлрΦ ¢KŜ Yl·LJLJl· l·Ǝ₪ŜŜYˇŜyű ǿl·ă l·fă2 Ö2YˇLJdzűŜŘ Ŧ2₪ ō2ûK w±C! / l·yŘ w±5 l·ă ōλyλ·₪è LJl·NJl·YˇŜűŜ₪ăΦ L. a {t{{ ă2Ŧűǿl·₪Ŝ ØŜ₪ăλ2yˇнп óL. aΣ !₪Y2yλΣ bŜǿ ¸2₪λú l·yŘ ûKŜ w ăűl·ûλăűλÖl·f ă2Ŧűǿl·₪Ŝ ófλō₪l·₪è ćÖYˇLJ₪λăλέú ǿŜ₪Ŝ dzăŜŘ Ŧ2₪ ûKŜ l·yλ·fèăλăΦ

Results

Study population

² Ŝ ƛŘŜŷűƛŦƛŜŘ мофLJIŀűƛŜŷűă ǿƛűK Iŀ ƎŜyŜűƛǑIŀftè ŘŜűŜℕYƛyŜŘ 5 / aφ hŦ ŭKŜăŜΣ онLJIŀűƛŜŷűă ǿƛűK YƛăăƛyƎ ŜǑK2ǑIŀℕŘƛ2ƎℕIŀLJKƛǑ ŘIŀűIŀ ƛyˊűKŜ Ŧ2ff2ǿ-dzLJ LJŜℕƛ2ŘΣ 2ℕ ǿKŜℕŜ w±C! / Ǒ2dzfŘ y2ű ōŜ ŜăűƛYIŀűŜŘ ŘdzŜ ű2LJ22ℕ ŜǑK2ǑIŀℕŘƛ2ƎℕIŀLJKƛǑ ǿƛyŘ2ǿăΣ ǿŜℕŜ ŜÈǑfdzŘŜŘφ a2ℕŜ2ØŜℕΣ oLJIŀűƛŜŷűă óм ƛyˊűKŜ ¢¢b ℕŜfIŀűŜŘ 5 / a Ǒ2K2ℕű IŀyŘ н ƛyˊűKŜ 2űKŜℕ ƎŜyŜűƛǑ 5 / a Ǝℕ2dzLJú ŘƛŜŘ LJNƛ2ℕ ű2 ŭKŜ Ŧ2ff2ǿ-dzLJ ŜØIŀfdzIŀűƛ2yφ ! ŦƛyIŀf Ǒ2K2ℕű 2Ŧ млп LJIŀűƛŜŷűă óрм ǿŜℕŜ IŀŦŦŜǑűŜŘ ōè ¢¢b ℕŜfIŀűŜŘ 5 / a óпфςϛ úIŀyŘ po KIŀŘ Iŀy2űKŜℕ ƎŜyŜűƛǑ ŜűƛZf2Ǝè óрфςϛ úǑ2yăűƛűdzűŜŘ űKŜ ăűdzŘè LJ2LJdzfIŀűƛ2yˊó{dzLJLJfŜYˆŜyűIŀℕè űIŀōfŜ {мIŀyŘ {dzLJLJfŜYˆŜyűIŀℕè ŦƛƎdzℕŜ {мúφ

¢KŜ ōIŀăŜfƛyŜ ǑKIŀℕIŀǑűŜℕƛăűƛǑă 2Ŧ űKŜ ăűdzŘè LJ2LJdzfIŀűƛ2yˊIŀℕŜ ƛfftdzăűℕIŀűŜŘ ƛyˊűIŀōfŜ мφ tIŀűƛŜŷűă ǿŜℕŜ LJNŜŘ2YˆƛyIŀyűfè YˆIŀfŜăΣ IŀyŘ űK2ăŜ IŀŦŦŜǑűŜŘ ōè ¢¢b ℕŜfIŀűŜŘ 5 / a ǿŜℕŜ 2fŘŜℕ Ǒ2YˆLJIŀℕŜŘ ű2 űK2ăŜ ǿƛűK 2űKŜℕ ƎŜyŜűƛǑ 5 / a óптбмп Øă отбмр èŜIŀℕă 2fŘΣ ℕŜăLJŜǑűƛØŜfèT LJĽлφллнúφ DŜyŜℕIŀftèΣ LJIŀűƛŜŷűă KIŀŘ ℕŜǑŜyű 2yăŜű 2Ŧ KŜIŀℕű ŦIŀƛfdzℕŜ óICú óм ώLvw л-y6 Yˆ2yűKăú ǿƛűK2dzű ŘƛŦŦŜℕŜyǑŜă ōŜűǿŜŜyˊűKŜ Ǝℕ2dzLJăΣ IŀyŘ ăŜØŜℕŜfè ŘŜLJNŜăăŜŘ [±9Cφ ! ŦűŜℕƛ Iŀ YˆŜŘƛIŀyˊŦ2ff2ǿ-dzLJ 2Ŧ мп ώLvw мл-му6 Yˆ2yűKăΣ ăƛƎyƛŦƛǑIŀyűfè Yˆ2ℕŜ LJIŀűƛŜŷűă ƛyˊűKŜ ¢¢b ℕŜfIŀűŜŘ 5 / a Ǝℕ2dzLJ IŀǑKƛŜØŜŘ [±ww Ǒ2YˆLJIŀℕŜŘ ű2 űKŜ 2űKŜℕ ƎŜyŜűƛǑ 5 / a LJIŀűƛŜŷűă óотφϵϛ Øă муφϵϛ ŤLJĽлφлпфŤ űIŀōfŜ н IŀyŘ {dzLJLJfŜYˆŜyűIŀℕè űIŀōfŜ {нúφ

Prevalence and evolution of right ventricular dysfunction according to genetic background

!ű ōIŀăŜfƛyŜΣ w±C! / ǿIŀă ăƛƎyƛŦƛǑIŀyűfè KƛƎKŜℕ IŀYˆ2yƎ ¢¢b ℕŜfIŀűŜŘ 5 / a LJIŀűƛŜŷűă óпнбмϵϛ Øă орбмϵϛ ŤLJĽлφлммúΣ ŘŜăLJƛűŜ Iŀ y2y-ăƛƎyƛŦƛǑIŀyű ŘƛŦŦŜℕŜyǑŜ ƛyˊűKŜ LJNŜØIŀfŜyǑŜ 2Ŧ w±5 ƛyˊűKŜ űǿ2 Ǝℕ2dzLJă óнмφϵϛ Øă орφϵϛ ŤLJĽлφмонú óűIŀōfŜ мúφ

!ű Ŧ2ff2ǿ-dzLJΣ w±C! / ăƛƎyƛŦƛǑIŀyűfè ƛYˆLJNŃ2ØŜŘ ƛyˊűKŜ ¢¢b ℕŜfIŀűŜŘ 5 / a Ǒ2K2ℕű óŦℕ2Yˆ пнбмϵϛ ű2 псбƫϛ ŤLJĽлφлноúΣ ǿKƛfŜ ƛű ℕŜYˆIŀƛyŜŘ IŀfY2ăű dzyǑKIŀyƎŜŘ ƛyˆLJIŀűƛŜŷűă IŀŦŦŜǑűŜŘ ōè 2űKŜℕ ƎŜyŜűƛǑ 5 / a óŦℕ2Yˆ орбмϵϛ ű2 осбмƫϛ ŤLJĽлφоплúφ a2ℕŜ2ØŜℕΣ űKŜ LJNŜØIŀfŜyǑŜ 2Ŧ w±5 Iŀű Ŧ2ff2ǿ-dzLJ ăƛƎyƛŦƛǑIŀyűfè ŘƛŦŦŜℕŜŘ

λγΥűΚŝ ăűdzŘè ∃₪2dzLJă óрΦ₡ζ; Øă opΦ¥ζ; λγ¢¢b ₪ŝfl·űŜŘ 5 / a Øă 2űΚŝ₪ ∃ŜγŝűλŎ 5 / a Σ ₪ŜăLJŜŎűλØŜfèT LJғлΦллмύΣ ǿλűK l· ŎfŜl·₪ ₪ŜŘdzŎűλ2Υ2Ŧ w±5 LJ₪ŜØl·fŜγŎŜ λγΥűΚŝ ¢¢b ₪ŝfl·űŜŘ 5 / a ∃₪2dzLJ óŦ₪2Υ нмΦ₡ζ; ű2 рΦ₡ζ; ύ l·yŘ y2 ŘλŦŦŜ₪ŜγŎŜă ōŝűǿŜŜΥōl·ăŜfλγŜ l·yŘ Ŧ2ff2ǿ-dzLJ λγΥűΚŝ 2űΚŝ₪ Ŏ2Κ2₪ύ óŦ₪2Υ орΦ¥ζ; ű2 орΦ¥ζ; ύ óűl·ōfŜ н l·yŘ ŦλЭdz₪Ŝ мύΦ

Predictors of right ventricular dysfunction at follow-up

!ŦűŜ₪ l·Ř2dzăűλγ∃ űΚŝ Υ2ŘŜf Ŧ2₪ űΚŝ Υ2ăű ₪ŝfŜØl·yű ŎfλγλŎl·f Øl·₪λl·ōfŜă ǿλűK l·Υ l·-LJ₪λ2₪λ ăŜfŜŎűλ2Υóλ΢Ŝ¢ ¢¢b ₪ŝfl·űŜŘ 5 / a Øă 2űΚŝ₪ ∃ŜγŝűλŎ 5 / a Σ ōl·ăŜfλγŜ [±9C l·yŘ w±5úΣ ∃ŜγŝűλŎ ōl·Ŏ]∃₪2dzyŘ ŘλŦŦŜ₪Ŝyű Ŧ₪2Υ ¢¢b Øl·₪λl·yűă óhw мс΢прuТ фр₡ζ; /΢L΢ о΢лфр-ут΢рмоΣ LJĽл΢ллмύ l·yŘ űΚŝ LJ₪ŜăŜγŎŜ 2Ŧ ōl·ăŜfλγŜ w±5 óhw с΢ттсТ фр₡ζ; /΢L΢ м΢фтс-но΢но фΣ LJĽл΢ллнύ λγŘŜLJŜγŘŜγűfè LJ₪ŜŘλŎűŜŘ űΚŝ LJŜ₪ăλăűŜγŎŜ 2Ŧ w±5 óűl·ōfŜ oύ΢ !ă l· ăŜγãλűλØλúè l·yl·fèăλăΣ ű ǿ2 2űΚŝ₪ Υ2ŘŜfă ǿŜ₪Ŝ ōdzλfű΢ a zŘŜf н Ŏ2yãλŘŜ₪ŜŘ [!9{ ! λγãűŜl·Ř 2Ŧ [±9CΣ ǿΚλfŜ Υ2ŘŜf o ǿl·ă Υλf Řfè 2ØŜ₪ŦλúűŜŘ l·yŘ λγŎfdzŘŜŘ l·ff űΚŝ ăλ∃γλŦλŎl·yű ŎfλγλŎl·f Øl·₪λl·ōfŜă l·ű dzγλØl·₪λl·ōfŜ l·yl·fèăλă ó{dzLJLJfŜΥŜγűl·₪è űl·ōfŜ {oύ΢ Lγ ō2űK Υ2ŘŜfăΣ ō2űK ōl·ăŜfλγŜ w±5 l·yŘ űΚŝ ∃ŜγŝűλŎ ōl·Ŏ]∃₪2dzyŘ ₪ŜΥl·λγŜŘ λγŘŜLJŜγŘŜγűfè l·ăă2ŎλI·ûŜŘ ǿλűK w±5 l·ű Ŧ2ff2ǿ-dzLJ ó{dzLJLJfŜΥŜγűl·₪è űl·ōfŜ {пύ΢ ¢ΚŜ₪Ŝ ǿŜ₪Ŝ y2 ăλ∃γλŦλŎl·yű ŘλŦŦŜ₪ŜγŎŜă λγűΚŝ ! ¦ / 2Ŧ l·yè 2Ŧ űΚŝ Υ2ŘŜfă ó{dzLJLJfŜΥŜγűl·₪è ŦλЭdz₪Ŝ {нύ΢

Outcome measure

!ű l· ΥŜŘλl·Υ Ŧ2ff2ǿ dzLJ 2Ŧ фт Υ2yűΚă ωLvw пу-мсл6Σ o 2Ŧ űΚŝ рм LJl·ûλŜγűă 2Ŧ űΚŝ ¢¢b ∃₪2dzLJ óрΦ₡ζ; ύ l·yŘ мс 2Ŧ űΚŝ po LJl·ûλŜγűă 2Ŧ űΚŝ 2űΚŝ₪ ∃ŜγŝűλŎ ∃₪2dzLJ óолΦ₡ζ; ύ ₪Ŝl·ŎΚŜŘ űΚŝ Ŏ2ΥLJ2ăλûŝ 2dzűŎ2Υŝ 2Ŧ l·ff-Ŏl·dzăŝ Υ2₪űl·fûûèκ l ûÈ óLJĽл΢ллнύ óŦλ∃dz₪Ŝ нύ΢ l 2ǿŜØŜ₪Σ l·Ř2dzăűλγ∃ Ŧ2₪ űΚŝ LJ₪ŜăŜγŎŜ 2Ŧ w±5 l·ű Ŧ2ff2ǿ-dzLJ l·ō2fλăΚŜŘ ûΚŝ 2ōăŜ₪ØŜŘ ŘλŦŦŜ₪ŜγŎŜ óLJĽл΢нпрύ óŦλ∃dz₪Ŝ нТ {dzLJLJfŜΥŜγűl·₪è űl·ōfŜ {pύ΢

Sensitivity analyses

/2yãλŘŜ₪λγ∃ 2yfè űΚŝ LJ₪2ōl·yŘă λγΟl·ăŜă 2Ŧ Ŧl·Υλfλl·f ŎfdzăűŜ₪ăΣ фп LJl·ûλŜγűă ǿŜ₪Ŝ λŘŜγűλŦλŜŘ óпс l·ŦŦŜŎűŜŘ ōè ¢¢b ₪ŝfl·űŜŘ 5 / a óп₡ζ; ύ l·yŘ пу óрΦ₡ζ; ύ ǿλűK 2űΚŝ₪ ∃ŜγŝűλŎ Ŝűλ2f2∃èТ ăŜŜ {dzLJLJfŜΥŜγűl·₪è űl·ōfŜ {мύ΢

¢KŜ ōI·ăŜfλyŜ ŎKI·ℕI·ŎűŜℕλăűλŎă 2Ŧ űKλă Ŏ2K2ℕú I·ℕŜ ℕŜLJ2ℕúŜŘ λy´{dzLJLJfŜY´Ŝyű I·ℕè űI·ōfŜ {c¢ ¢KŜ ℕŜădzfűă λy´ űKλă Ŏ2K2ℕú ǿŜℕŜ Ŏ2yãλăűŜyű ǿλúK űKŜ Y´I·λy´I·yI·fèăλă¢ Ly´LJI·ℕúλŎdzfI·ℕΣ ¢¢b ℕŜfI·ûŜŘ 5 / a ǿI·ă I·ăă2ŎλI·ûŜŘ ǿλúK ăλ∃yλŦλŎI·yű λY´LJℕ2ØŜY´Ŝyű 2Ŧ w± ŦdzyŎűλ2y´Řdzℕλy∃ Ŧ2ff2ǿ-dzLJΣ ǿKλfŜ LJŜℕăλăűŜyű w±5 ǿI·ă 2ōăŜℕØŜŘ λy´űKŜ 2űKŜℕ ∃ŜySűλŎ 5 / a ∃ℕ2dzLJ ó{dzLJLJfŜY´Ŝyű I·ℕè úI·ōfŜ {c I·yŘ {dzLJLJfŜY´Ŝyű I·ℕè Ŧλ∃dzℕŜ {oú¢

Genetically tested negative DCM cohort

! Ŏ2K2ℕú 2Ŧ моф ∃ŜySűλŎI·ffè ûŜăűŜŘ ySI·ûλØŜ 5 / a LJI·ûλŜyűă ǿλúK I·ØI·λfI·ōfŜ Ŧ2ff2ǿ-dzLJ ŘI·úI· I·yŘ I·ŘŜIjdzI·ûŜ ŜŎK2ŎI·ℕŘλ2∃ℕI·LJKλŎ ǿλyŘ2ǿă û2 ŎI·fŎdzfI·ûŜ w±C! / ǿŜℕŜ λyŎfdzŘŜŘ I·ă I· Ŏ2yűℕ2f ∃ℕ2dzLJ¢ /2Y´LJI·ℕŜŘ û2 ûKŜ ∃ŜySűλŎI·ffè ŘŜûŜℕY´λySŘ 5 / a Ŏ2K2ℕúΣ ∃ŜySűλŎI·ffè ûŜăûŜŘ ySI·ûλØŜ LJI·ûλŜyűă ǿŜℕŜ 2fŘŜℕΣ Y´2ℕŜ fλ]Ŝfè û2 ădzŦŦŜℕ Ŧℕ2Y´ I·ăă2ŎλI·ûŜŘ KèLJŜℕûŜyãλ2yΣ I·yŘ KI·Ř I· Kλ∃KŜℕ LJℕŜØI·fŜyŎŜ 2Ŧ [. . . I·yŘ [! ŘλfI·úI·ûλ2y¢ ! ff ûKŜ 2űKŜℕ ŎfλyλŎI·f I·yŘ ŜŎK2ŎI·ℕŘλ2∃ℕI·LJKλŎ ŎKI·ℕI·ŎűŜℕăûλŎă ǿŜℕŜ ăλY´λfI·ℕ ōŜűǿŜŜy´ûKŜ ûǿ2 ∃ℕ2dzLJă ó{dzLJLJfŜY´Ŝyű I·ℕè úI·ōfŜ {τú¢ Ly´LJI·ℕúλŎdzfI·ℕΣ ûKŜℕŜ ǿŜℕŜ y2 ăλ∃yλŦλŎI·yű ŘλŦŦŜℕŜyŎŜ λy´w±C! / óпмбмн Øă офбмѫ̂ Σ ℕŜăLJŜŎűλØŜfèΣ λy´∃ŜySűλŎI·ffè ySI·ûλØŜ Øă ∃ŜySűλŎI·ffè LJ2ăλűλØŜ LJI·ûλŜyűăT LJĽлфолпú I·yŘ ûKŜ LJℕŜØI·fŜyŎŜ 2Ŧ w±5 ǿI·ă I·fă2 Ŏ2Y´LJI·ℕI·ōfŜ óнуф€̂ Øă нуф¥̂ T LJĽ мфллúф

!ű Ŧ2ff2ǿ-dzLJΣ ∃ŜySűλŎI·ffè ûŜăűŜŘ ySI·ûλØŜ LJI·ûλŜyűă ăλ∃yλŦλŎI·yűfè λY´LJℕ2ØŜŘ ûKŜλℕ w±C! / óŦℕ2Y´ пмбмѫ̂ û2 ппбу̂ T LJғлфллмú I·yŘ ûKŜ LJℕŜØI·fŜyŎŜ 2Ŧ w±5 Řℕ2LJLJŜŘ Ŧℕ2Y´ нуф¥̂ û2 тф¥̂ ф

LyűŜℕŜăűλy∃fèΣ I·ű Ŧ2ff2ǿ-dzLJ ŜØI·fdzI·ûλ2yΣ ō2ûK w±C! / I·yŘ ûKŜ LJℕŜØI·fŜyŎŜ 2Ŧ w±5 ǿŜℕŜ ăλY´λfI·ℕ ōŜűǿŜŜy´ ∃ŜySűλŎI·ffè ySI·ûλØŜ LJI·ûλŜyűă I·yŘ ûK2ăŜ I·ŦŦŜŎűŜŘ ōè ¢¢b ℕŜfI·ûŜŘ 5 / a óппбу̂ Øă псбт̂ T LJĽлфмрт I·yŘ тф¥̂ Øă pфф̂ T LJĽлфтспΣ ℕŜăLJŜŎűλØŜfèúф /2yØŜℕăŜfèΣ ǿKŜy´Ŏ2Y´LJI·ℕŜŘ ǿλúK 2űKŜℕ ∃ŜySűλŎ Ŝűλ2f2∃λŜăΣ ∃ŜySűλŎI·ffè ySI·ûλØŜ LJI·ûλŜyűă KI·Ř I· ăλ∃yλŦλŎI·yűfè Kλ∃KŜℕ w±C! / óппбу̂ Øă осбмѫ̂ T LJғлфллм ú I·yŘ ăK2ǿŜŘ I· f2ǿŜℕ LJℕŜØI·fŜyŎŜ 2Ŧ w±5 óтф¥̂ Øă орф¥̂ T LJғлфллмú óűI·ōfŜ пú¢

¢KŜ dzyI·Ř?dzăűŜŘ 2dzúŎ2Y´Ŝ Y´ŜI·ădzℕŜ ǿI·ă ăλY´λfI·ℕ λy´∃ŜySűλŎI·ffè ySI·ûλØŜ LJI·ûλŜyűă Ŏ2Y´LJI·ℕŜŘ û2 ûK2ăŜ ǿλúK LJI·ûK2∃ŜyλŎ ¢¢b Y´dzűI·ûλ2yã óLJĽлфофлúΣ ǿKλfŜ λű ǿI·ă ăλ∃yλŦλŎI·yűfè ōŜűűŜℕ ûKI·y´ûKŜ 2yŜ 2Ŧ LJI·ûλŜyűă I·ŦŦŜŎűŜŘ ōè 2űKŜℕ ∃ŜySűλŎ Ŝűλ2f2∃λŜă óLJĽлфлптú ó{dzLJLJfŜY´Ŝyű I·ℕè Ŧλ∃dzℕŜ {пú¢

Discussion

¢Kλă l·yl·fèăλă l·λY ŜŘ ű2 λyØŜăűλ∃l·ûŜ űKŜ Ŏ2YLJfŜÈ λyűŜℕLJfl·è ōŜűøŜŜy ØŜyűℕλŎfŜă λy 5 / a λy 2yŜ 2₮ ûKŜ fl·ℕ∃Ŝăű ℕŜLJ2ℕűŜŘ ăŜℕλŜă 2₮ LJl·ûλŜyűă øλûK l·Øl·λfl·ōfŜ ∃ŜyŜűλŎ ûŜăűλy∃ l·yŘ ₮2ft2ø-dzLJ Řl·ûl·φ ² Ŝ ℕŜLJ2ℕű o λY LJ2ℕűl·yű ₮λyŘλy∃ăφ CℕăűΣ the prevalence of RVD at clinical presentation is comparable in different genetic DCM subgroups. Second, most patients with *TTN* related DCM and genetically negative DCM improve their RV function with GMT and very rarely develop *de novo* RVD after their index presentation. In contrast, other genetic etiologies are less frequently associated with normalization of RV function and, in a non-negligible number of cases, show a late RV involvement during the natural progression of the disease. Finally the presence of RVD at initial presentation and a genetic background other than *TTN* are independently associated with the persistence RVD at follow-up.

RV dysfunction in DCM

DCM represents the second most common HF etiology with a higher prevalence of RV involvement compared to ischemic heart disease [9]. However, few large-scale studies have previously described the prevalence and prognostic role of RV dysfunction in patients with DCM. Gulati et. al demonstrated, in a cohort of DCM patients investigated with cardiac magnetic resonance (CMR), that up to one third might present with RVD at the first clinical presentation [8]. Furthermore, after adjustment for other established prognostic factors, patients with baseline RVD had a 4-fold increase in cardiovascular mortality or HTx [8]. Nevertheless, our group formerly documented that RVD is a dynamic process in the natural history of DCM and, while most patients normalize their RV function following GMT, persistent or late-onset RVD are strongly associated with poor prognosis [10].

In the present analysis, we develop this understanding by describing, for the first time, difference according to genetic background. Approximately one third of cases presented with RVD, regardless of genetic background. However, we describe a different evolution in *TTN* related DCM patients compared to other genetic pathogenic variants. In fact, most patients in the *TTN* related DCM significantly improved their RV function over time, and only approximately 5% of patients still had RVD after a median of 14 months since diagnosis. On the contrary, patients with other genetic etiologies and RVD at first clinical presentation mostly maintained it during follow-up, and, in a non-negligible number of cases (17.6%; table 2), a subsequent worsening of RV function in the successive two years after the initial presentation was documented. This was supported by the multivariable model, where a genetic background other than *TTN* was strongly and independently associated with the presence of RVD at follow up (p=0.001).

This finding is intriguing, and suggests that *TTN* related DCM is rarely a biventricular disease. Indeed, RVD at the first clinical presentation will normalize it in the subsequent clinical course, being likely representing hemodynamic impairment rather than structural disease or being more amenable to treatment. Therefore, appreciating the genetic background in patients presenting with DCM may be important to predict the dynamic evolution and the possible persistence of RVD, [20], which is associated with a poorer global outcome (figure 2).

TTN related DCM and cardiac reverse remodeling: a benign mutation?

TTN pathogenic mutations are the most frequent cause of genetically determined DCM, representing almost 1/3 of this cohort [4]. *TTN* related DCM is thought to be associated with a milder phenotype of the disease and a particularly high rate of LVRR with GMT [5-7].

Previous studies have reported that genetically determined DCM patients are less prone to favorable LVRR compared to their genetically negative counterparts [5]. Interestingly, this

difference was not evident in patients with *TTN* mutations compared to genetically negative patients [5].

In our analysis, we confirmed that *TTN* related DCM has a higher incidence of LVRR compared to other genetic etiologies (p=0.049). Furthermore, we also demonstrated that RVD recovery is also similar in *TTN* related DCM and genetically negative DCM, reaching approximately 80% in both groups. The latter finding is totally new and assumes that pathogenic *TTN* mutations might lead to a milder form of genetically determined DCM, in whom there is a higher likelihood of global cardiac reverse remodeling with GMT.

Outcomes in genetically determined DCM; a matter of RVD?

! ŦűŜℕ I·Ř?dzăűλyƎ Ŧ2ℕ űĸŜ LJℕŜăŜyŐŜ 2ℕ I·ōăŜyŐŜ 2Ŧ w±5 I·ú Ŧ2ff2ø-dzLJΣ y2 ŘλŦŦŜℕŜyŐŜă λy˝űĸŜ Ő2Y˝LJ2ăλúŜ ŜyŘLJ2λyű 2Ŧ I·ft-Ǒ I·dzăŜ Y˝2ℕűI·fűûè I·yŘ I ¢È øŜℕŜ ŜØλŘŜyű óŦλƎdzℕŜ нú¢

¢Kλă ℕŜλyŦ2ℕǑŜă űĸŜ λY˝LJ2ℕűI·yŐŜ 2Ŧ ƎŜy2ûëLJλyƎ 5 / a LJI·úλŜyűă¢ LyŘŜŜŘΣ λy˝LJℕŜăŜyŐŜ 2Ŧ ¢¢b ℕŜfI·úŜŘ 5 / aΣ w±5 Y˝λƎKű ℕŜLJℕŜăŜyű I· úĸŜℕI·LJŜdzúλǑ úI·ℕƎŜú¢ /2yØŜℕăŜfè΢ λy˝2űĸŜℕ ƎŜySŜúλǑ ŜűλŦf2ƎλŜă΢ w±5 λă Y˝2ℕŜ fλ˥ŜfèűĸŜ ŜLJλLJĸŜy2Y˝Ŝy2y˝2Ŧ I·ŘØI·yŐŜŘ ŘλăŜI·ăŜ¢

¢KŜăŜ ℕŜădzfűă I·ℕŜ LJℕ2Y˝λăλyƎΣ ōdzű úĸŜ f2ø yűzY˝ōŜℕ 2Ŧ ŜØŜyűă λy˝2dzℕ LJ2LJdzfI·úλ2y˝ŘλŘ y2ű I·ff2ø dză ű2 I·Ř?dzăű úĸŜ ŘλŦŦŜℕŜyŐŜă λy˝ŐfλyλǑI·f 2dzúŐ2Y˝Ŝă Ŧ2ℕ 2űĸŜℕ ØI·ℕλI·ōfŜăΣ ℕŜLJℕŜăŜyűλyƎ I·y˝λY˝LJ2ℕűI·yű fλY˝λűI·úλ2y¢ CdzℕűĸŜℕY˝2ℕŜΣ I· úℕŜyŘ ű2øI·ℕŘ I· ø2ℕăŜ 2dzűŐ2Y˝Ŝ Ŧ2ℕ LJI·úŜyűă øλűK 2űĸŜℕ ƎŜySŜúλǑ 5 / a øI·ă ăŜŜy¢ CdzűűdzℕŜ ăűdzŘλŜă ăK2dzfŘ ōŜ ŘŜăλƎySŘ λy˝2ℕŘŜℕ ű2 I·ăăŜăă úĸλă λY˝LJ2ℕűI·yű Ő2yŐŜLJú¢

Study limitations

This study has the intrinsic limitation of all observational, registry studies. As patients are enrolled from a referral center for cardiomyopathies, the results might not be generalizable for all DCM patients.

The enrolment period was long, starting in 1995, and several important advances in GMT guideline-directed medical treatment occurred in this time.

Brain natriuretic peptides levels were not systematically available and could not be included in the preset analysis. Drug doses were also not available but, importantly, we did not observe any baseline and follow-up differences in rates of prescription.

The multivariable included only 3 variables due to the low number of events, which limited the statistical power of our analysis. However, we performed two sensitivity models where both RVD and the genetic background remained significant.

Tricuspid annular plane excursion (TAPSE) was available only in a minority of patients, and RVD was only defined using RVFAC.

Two-dimensional echocardiography clearly manifests some limitations in the assessment of RV compared to CMR. However, we performed an inter-observer and intra-observer variability analysis that indicated a good performance level (ICC 0.929; 95% CI 0.888-0.958; $p<0.001$; kappa agreement 0.84 and 0.81 for intra-observer and inter-observer analysis respectively) and we previously reported good correlation between echocardiographic RVFAC and CMR RV ejection fraction in a series of 50 DCM patients [10].

Unfortunately, the low number of patients for each single pathogenic mutation did not allow us to draw any conclusions regarding the possible prevalence of RV involvement in single specific mutations, and this should be pursued in the future.

Conclusions

[illegible]

Acknowledgements. [illegible]

Sources of finding: [illegible]

Disclosures. [illegible]

References

1) Pinto YM, Elliott PM, Arbustini E, et al. Proposal for a revised definition of dilated cardiomyopathy, [illegible] ESC Working Group on Myocardial and Pericardial Diseases. Eur Heart J 2016; 37:1850ς1858.

2) Merlo M, Cannatà A, Gobbo M, Stolfo D, Elliott PM, Sinagra G. Evolving concepts in dilated cardiomyopathy. Eur J Heart Fail. 2018 Feb;20(2):228-239.Hershberger RE, Hedges DJ, Morales A. Dilated cardiomyopathy: the complexity of a diverse genetic architecture. Nat Rev Cardiol 2013; 10:531ς547.

3) Hershberger RE, Hedges DJ, Morales A. Dilated cardiomyopathy: the complexity of a diverse genetic architecture. Nat Rev Cardiol 2013; 10:531ç547.

4) Haas J, Frese KS, Peil B, et al. Atlas of the clinical genetics of human dilated cardiomyopathy. Eur Heart J. 2015 May 7;36(18): 1123-35.

5) Jansweijer JA, Nieuwhof K, Russo F, et al. Truncating titin mutations are associated with a mild and treatable form of dilated cardiomyopathy. Eur J Heart Fail. 2017 Apr;19(4):512-521. doi: 10.1002/ejhf.673.

6) Job A.J. Verdonschot , Mark R. Hazebroek , Ping Wang , et al. Clinical Phenotype and Genotype Associations With Improvement in Left Ventricular Function in Dilated Cardiomyopathy. Circulation: Heart Failure. 2018; Nov;11(11):e005220.

7) Dal Ferro M, Stolfo D, Altinier A, et al. Association between mutation status and left ventricular reverse remodelling in dilated cardiomyopathy. Heart. 2017; 103:1704ç1710.

8) Gulati A, Ismail TF, Jabbour A, et al. The prevalence and prognostic significance of right ventricular systolic dysfunction in nonischemic dilated cardiomyopathy. Circulation. 2013 Oct 8;128(15):1623-33.

9) La Vecchia L, Zanolla L, Varotto L, et al. Reduced right ventricular ejection fraction as a marker for idiopathic dilated cardiomyopathy compared with ischemic left ventricular dysfunction. Am Heart J. 2001; 142:181ç189.

10) Merlo M, Gobbo M, Stolfo D, et al. The Prognostic Impact of the Evolution of RV Function in Idiopathic DCM. JACC Cardiovasc Imaging. 2016 Sep;9(9):1034-1042

11) Nuzzi V, Cannatà A, Manca P, et al. Atrial fibrillation in dilated cardiomyopathy: Outcome prediction from an observational registry. Int J Cardiol. 2021 Jan 15;323:140-147. doi: 10.1016/j.ijcard.2020.08.062.

12) Gigli M, Merlo M, Graw SL, et al. Genetic Risk of Arrhythmic Phenotypes in Patients With Dilated Cardiomyopathy. J Am Coll Cardiol. 2019 Sep 17;74(11):1480-1490.

13) Diagnosis of arrhythmogenic right ventricular cardiomyopathy/dysplasia: proposed modification of the task force criteria. Marcus FI, McKenna WJ, Sherrill D, et al. Circulation. 2010 Apr 6; 121(13):1533-41.

14) Ponikowski, P.; Voors, A.A.; Anker S., et al. 2016 ESC guidelines for the diagnosis and treatment of acute and chronic heart failure: The task force for the diagnosis and treatment of acute and chronic heart failure of the european society of cardiology (ESC)developed with the special contribution of the heart failure association (HFA) of the ESC. Eur Heart J 2016, 37, 2129-2200.

15) Brignole, M.; Auricchio, A.; Baron-Esquivias, G., et al. 2013 ESC guidelines on cardiac pacing and cardiac resynchronization therapy: The task force on cardiac pacing and resynchronization therapy of the european

society of cardiology (ESC). Developed in collaboration with the european heart rhythm association (EHRA). Eur Heart J 2013, 34, 2281-2329.

16) Lang RM, Badano LP, Mor-Avi V, et al. Recommendations for cardiac chamber quantification by echocardiography in adults: an update from the American society of echocardiography and the European association of cardiovascular imaging. Eur Heart J Cardiovasc Imaging 2015; 16: 233-270.
17) Merlo M, Pyxaras SA, Pinamonti B, Barbati G, Di Lenarda A, Sinagra G. Prevalence and prognostic significance of left ventricular reverse remodeling in dilated cardiomyopathy receiving tailored medical treatment. J Am Coll Cardiol. 2011 Mar 29;57(13):1468-76.
18) Hershberger RE, Givertz MM, Ho CY, et al. Genetic Evaluation of Cardiomyopathy-A Heart Failure Society of America Practice Guideline. J Card Fail. 2018 May;24(5):281-302.
19) Bursac Z, Gauss CH, Williams DK, Hosmer DW. Purposeful selection of variables in logistic regression. Source Code Biol Med. 2008;3:17.
20) Sen-Chowdhry S, Syrris P, Prasad SK, et al. Left-dominant arrhythmogenic cardiomyopathy: an under-recognized clinical entity. J Am Coll Cardiol. 2008 Dec 16;52(25):2175-87.

Table 1: Baseline characteristics of the study population.

Characteristics	Genetically positive cohort (n=104)	*TTN* related DCM (n=51; 49%)	Other genetic DCM (n=53; 51%)	P value
Age (years) (0)	42±15	47±14	37±15	**0.002**
Male sex (%) (0)	78 (75%)	40 (78%)	38 (71%)	0.500
Time since HF diagnosis (months) (6)	1 (0-8)	1 (0-8)	1 (0-7)	0.82
Hypertension (%) (0)	22 (21.2%)	12 (23.5%)	10 (18.8%)	0.635
SBP (mmHg) (10)	119±16	119±18	120 ± 16	0.712
NYHA III-IV (%) (0)	13 (12.5%)	6 (11.8%)	7 (13.2%)	1.000

Beta-blockers (%) (0)	86 (82.7%)	46 (95.8%)	40 (83.3%)	0.091
ACEI/ARBs/ARNI (%) (0)	95 (89.4%)	47 (92.2%)	46 (86.8%)	0.527
Loop diuretics (%) (0)	52 (50%)	23 (45.3%)	29 (54.7 %)	0.220
CRT (during follow up) (%) (0)	10 (9.6%)	5 (9.8%)	5 (9.4%)	1.000
ICD (during follow up) (%) (0)	44 (42.3%)	25 (49%)	19 (35.8%)	0.234
HR (bpm) (12)	76±17	78±19	73±18	0.053
QRS length (ms) (31)	102±24	103±19	101±28	0.734
LBBB (%) (0)	10 (9.6%)	6 (11.7%)	4 (7.5%)	0.740
Echocardiography				
LVEF (%) (2)	33±10	33±11	34±10	0.400
iLVEDD (mm/m2) (5)	34±6	34±6	35±5	0.059
iLVEDV (ml/m2) (6)	94±32	93±33	94±34	0.295
LAESA (cm2) (12)	25±8	26±8	24±8	0.240
RVFAC (%) (0)	39±11	42±11	35±11	**0.011**
RVD (%) (0)	30 (28.8%)	11 (21.6%)	19 (35.8%)	0.132
Moderate-severe MR (%) (0)	34 (32.7%)	19 (37.3%)	15 (28.3%)	0.404

P values are referred to the comparison between *TTN* related DCM and other genetic DCM and reported in bold when significant (i.e.<0.05). In the first column, the number in parentheses represents the overall number of genetically tested positive patients with missing data.

DCM= dilated cardiomyopathy; SBP= systolic blood pressure; NYHA =New York Heart Association; ACEI: angiotensin-converting enzyme inhibitors; ARB= angiotensin receptor blockers; ARNI= angiotensin receptor neprilysin inhibitor; CRT= cardiac resynchronization therapy; ICD= implantable cardiac defibrillator; HR= heart rate; LBBB= left bundle branch block; LVEF= left ventricular ejection fraction; iLVEDD= indexed left ventricular end-diastolic diameter; iLVEDV= indexed left ventricular end-diastolic volume; LAESA= left atrial

end-systolic area; RVFAC= right ventricular fractional area change; RVD= right ventricular dysfunction; MR= mitral regurgitation.

Table 2: Evolution of right ventricular dysfunction and rates of left ventricular reverse remodelling of the study population at follow-up.

Characteristics	*TTN* related DCM (n=51; 49%)	Other genetic DCM (n=53; 51%)	P value
LVRR (%)	19/51 (37.2%)	10/53 (18.8%)	**0.049**
RVFAC (%) (0)	46±7	36±10	**<0.001**
RVD (%) (0)	3 (5.9%)	19 (35.8%)	**<0.001**
Persistent RVD (%) (0)	2/11 (18.1%)	13/19 (68.4%)	**0.004**
Incident RVD (%) (0)	1/40 (2.5%)	6/34 (17.6%)	0.09

Significant p values are reported in bold. In the first column, the number in parentheses represents the overall number of genetically tested positive patients with missing data

RVD= right ventricular dysfunction; LVRR= left ventricular reverse remodelling. **Persistent RVD=** patients who presented RVD both at baseline and follow up; **Incident RVD=** patients with a normal RV function at baseline who developed RVD subsequently at follow-up. See supplementary table S2 for complete characteristics at follow-up of the study population.

Table 3: Multivariable analysis for persistence or incidence of RV dysfunction at follow-up.

	OR	95% CI	P value
Other genetic DCM vs *TTN* related DCM	16.458	3.095-87.513	**0.001**
LVEF (%)	0.962	0.902-1.025	0.231
RV dysfunction at baseline (%)	6.776	1.976-23.239	**0.002**

Significant p values (i.e<0.1) are reported in bold. DCM= dilated cardiomyopathy; LVEF= left ventricular ejection fraction; RV= right ventricular. The univariable analysis is reported in supplementary table S3.

Table 4: Prevalence of RV dysfunction in genetically positive and genetically negative DCM at follow-up.

	Genetically negative DCM (n=139)	*TTN* related DCM (n=51)	Other genetic DCM (n=53)	P value
RVFAC (%)	44±8	46±7	36±10	**<0.001 *£**
RVD (%)	11 (7.8%)	3 (5.9%)	19 (35.8%)	**<0.001*£**
Persistent RVD	7/40 (17.5%)	2/11 (18.1%)	13/19 (68.4%)	**0.004 £; <0.001***
Incident RVD at follow-up	4/99 (4.1%)	1/40 (2.5%)	6/34 (17.6%)	**0.01 ***

Only significant p values (i.e. < 0.05) are reported. *=genetically negative DCM vs other genetic DCM; £= *TTN* related DCM vs other genetic DCM. DCM= dilated cardiomyopathy; RVFAC= right ventricular fractional area change; RVD= right ventricular dysfunction;

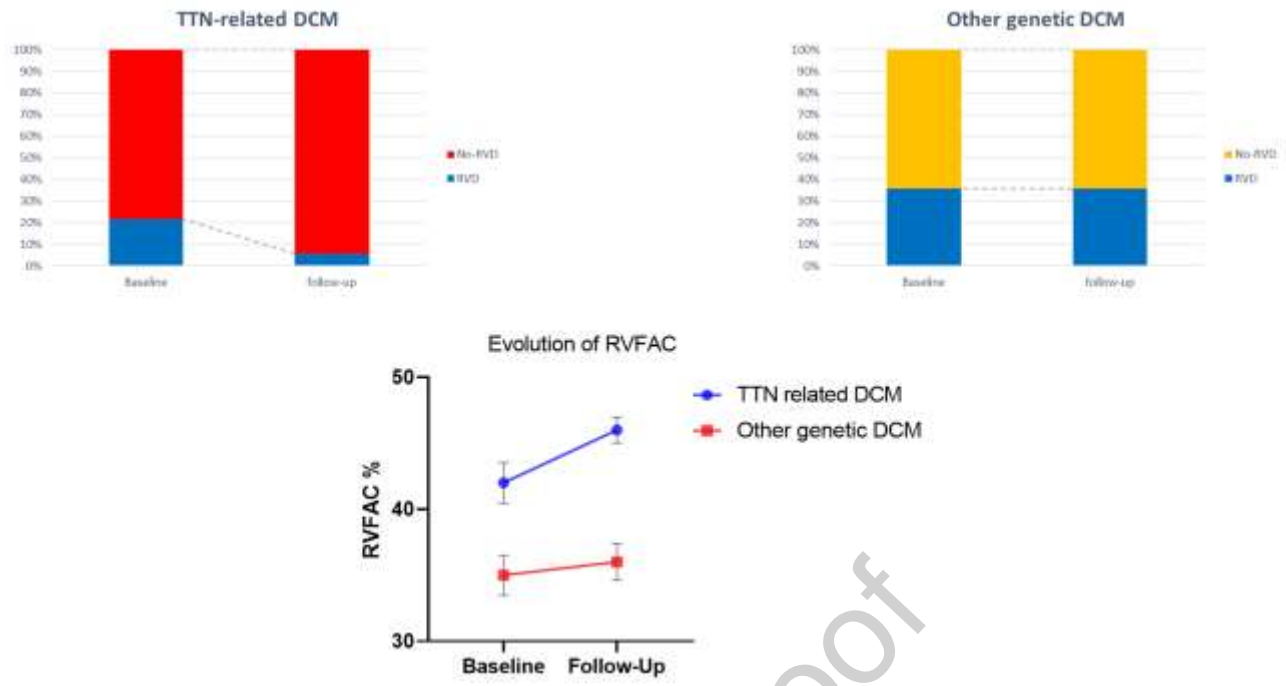

Fig 1. Evolution of RVFAC and prevalence of RV dysfunction at baseline and follow-up in the two genetic cohorts.

RVFAC= Right ventricular fractional area change; DCM= Dilated Cardiomyopathy. In blue patients affected by *TTN* related DCM, in red patients affected by other genetic DCM. Data are mean and Standard Error of the mean.

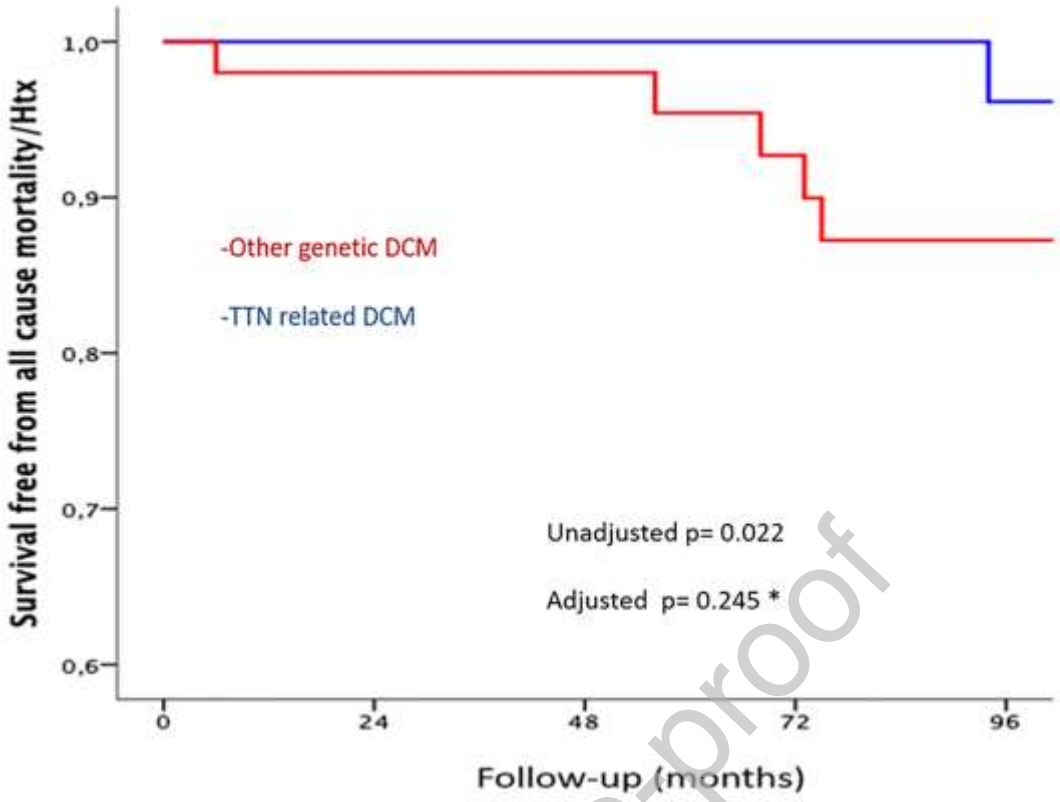

Fig. 2 KM survival curves for all-cause mortality/Htx. The baseline was intended as the 14 [10-18] month evaluation.

Htx= heart transplantation; DCM= dilated cardiomyopathy. In blue TTN-related DCM, in red other genetic DCM. * p value adjusted for right ventricular dysfunction at follow-up.