Genetic Test for Dilated and Hypertrophic Cardiomyopathies: Useful or Less Than Useful for Patients?

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Abstract - Genetic testing for potentially heritable cardiomyopathies has advanced from basic scientific discovery to clinical application. Nowadays, genetic diagnostic tests for cardiomyopathies are clinically available. As a consequence it is fundamental the understanding of the clinical utility, in terms of diagnosis and prognosis, of genetic test results. In addition, the genetic counselling, regarding risks, benefits and options, is recommended for all patients and their relatives.

However the relation between genotype and phenotype remains often unclear, and there is frequently a variance of uncertain significance. Consequently, the genetic test should always be approached as one component of a comprehensive cardiac-gene evaluation.

This review aims to explore when genetic tests are indicated in patients with dilated and hypertrophic cardiomyopathy.

Keywords: Dilated Cardiomyopathy, Hypertrophic Cardiomyopathy, Genetic Testing

I. INTRODUCTION

The first gene-mutation causing cardiomyopathy was discovered more than thirty years ago. Nowadays the genetic mutations are at least 500 just for Hypertrophic Cardiomyopathy. However, the clinical beneficial of a genetic test result remains often unclear and questionable. Usually, the first approach to a patient with a cardiomyopathy is guided by the phenotype. Anamnesis and instrumental investigations, and above all electrocardiography and echocardiography, are extremely useful. Another diagnostic investigation, performed in specialized centres is magnetic resonance imaging (MRI).

It is very important to characterize the muscle tissue and the interstitial space. A detailed family history could guide the diagnosis of a familial genetic disease, although there is the possibility of a de novo mutation that should be suspected in the absence of a positive family history for disease. Different mutations in the same gene might cause different disease phenotype and different disease severity. For example laminin A/C mutations might cause isolated Dilated Cardiomyopathy (DCM), Emery-Dreifuss Muscular Dystrophy, or disorders without DCM.

Cardiologists should know the feasibility of a genetic diagnosis, its clinical relevance and its potential impact on prognosis. Another fundamental aspect is the genetic counselling, finalized to discuss the significance of the identification of the genetic mutation with the patient and its relevance in his/her life. Contrary to common misconception, genetic tests are probabilistic and not deterministic tests. Many positive tests are represented by DNA variants of uncertain clinical significance. The genetic testing for cardiomyopathies has some ethical problems: is it right to consider sick a patient with a mutation indicative of disease if he might never show the phenotype?

II. DILATATED CARDIOMYOPATHY

Dilated Cardiomyopathy is characterized by the systolic dysfunction and the left ventricular (LV) dilatation with the progressive LV failure. Although this disease has various etiopathogenesis, the term cardiomyopathy refers to genetic cardiomyopathy. Baig et al showed that the patient with DCM have a familiar DCM for 48% of cases, when asymptomatic LV dysfunction was considered the first sign on DCM [1-3]. The familiar screening is strongly recommended in familiar of patient with DCM [4]. However the role of genetic test is unclear.

Genetic test for dilated Cardiomyopathy. More than 30 genes have been identified as cause of DCM showing a marked locus heterogeneity. The genes implicated encode proteins involved in the structure of the cardiomyocyte as cytoskeletal proteins, myofilament proteins and ion channels. Mitochondrial defects have also been identified (Table 1) [5]. This heterogeneity highlights the various mechanisms involved in DCM. This disease is likely final phenotype of reduced contractile force of cardiomyocytes. Interestingly, some mutations of the genes causing DCM can cause also hypertrophic cardiomyopathy (HCM), clarifying the importance of secondary factors as modifiers genes and environment to determine the phenotype. Most genetic DCM inheritance follows an autosomal dominant pattern, although X-
linked, recessive, and mitochondrial patterns of inheritance occur. The sensitivity of genetic is estimated at 20% and none of genes appears to account for 5% of familial DCM. This low sensitivity is very important and it underlines the little diagnostic power of genetic testing in not-selected people. The sensitivity is higher in specific forms as the DCMs associated with conduction defects. Genetic DCM shows age-dependent penetrance and a variable expression. The same mutation can result in a different phenotype in members of the same family, underlying the importance of others factors [6]. Some mutations are more aggressive and they can often cause sudden death, e.g. mutations of laminin and desmin [7].

| Gene      | Protein                        | Function                                                                 |
|-----------|--------------------------------|--------------------------------------------------------------------------|
| ACTC      | cardiac actin                  | Sarcomeric protein; muscle contraction                                   |
| DES       | desmin                         | DAGC; transduces contractile forces                                       |
| SGCD      | δ-sarcoglycan                  | DAGC; transduces contractile forces                                       |
| MYH7      | β-myosin heavy chain           | Sarcomeric protein; muscle contraction                                   |
| TNN2      | cardiac troponin T             | Sarcomeric protein; muscle contraction                                   |
| TPM1      | α-tropomyosin                  | Sarcomeric protein; muscle contraction                                   |
| TTN       | titin                          | Sarcomere structure/extensible scaffold for proteins                     |
| VCL       | metavinculin                   | Sarcomere structure; intercalated discs                                  |
| MYBP3     | myosin-binding protein C       | Sarcomeric protein; muscle contraction                                   |
| MLP/CSRP3 | muscle LIM protein             | Sarcomere stretch sensor/ Z discs                                        |
| ACTN2     | α-actinin-2                    | Sarcomere structure; anchor for myofibrillar actin                       |
| PLN       | phospholamban                  | Sarcoplastic reticulum Ca++ regulator; inhibits SERCA2 pump             |
| ZASP/LDB3 | Cypher                         | Cytoskeletal assembly; targeting/clustering of membrane proteins         |
| MYH6      | α-myosin heavy chain           | Sarcomeric protein; muscle contraction                                   |
| ABCC9     | SUR2A                          | Kir 6.2 regulatory subunit, inwardly rectifying cardiac KATP channel    |
| TNN1C     | cardiac troponin C             | Sarcomeric protein; muscle contraction                                   |
| Titin-cap TCAP | titin-cap or telethonin  | Z-disc protein that associates with titin; aids sarcomere assembly |
| TNN1S     | cardiac troponin 1             | Sarcomeric protein; muscle contraction; also seen as recessive          |
| EYA4      | eyes-absent 4                  | Transcriptional coactivators (Six and Dach)                             |
| TMPO      | thymopoietin                   | Also LAP2; a lamin-associated nuclear protein                            |
| PSEN1/2   | presenilin 1 / 2               | Transmembrane proteins, gamma secretase activity                         |
| CRYAB     | alpha B crystallin             | Cytoskeletal protein                                                     |
| PDLIM3    | PDZ LIM domain protein 3       | Cytoskeletal protein                                                     |
| MYPN      | myopalladin                    | Sarcomeric protein, z-disc                                              |
| LMNA      | laminin a-4                    | Extracellular matrix protein                                             |
| ILK       | integrin-linked kinase         | Intracellular ser-threo kinase; interacts with integrins                |
| RBM20     | RNA binding protein 20         | RNA binding protein of the spliceosome                                   |
| LMNA      | lamin A/C                      | Structure/stability of inner nuclear membrane                           |
| SCN5A     | sodium channel                 | Controls sodium ion flux                                                |
| DMD       | dystrophin                     | DAGC; transduces contractile force                                       |

Table 1. Dilated Cardiomyopathy (DCM): genes mutated in DCM.
The most common genes mutated in DCM and the proteins that they codified for. Modified from: Hershberger RE, Morales A, Siegfried JD. Clinical and Genetic Issues in Dilated Cardiomyopathy: a Review for Genetics Professionals. Genet Med 2010; 12(11): 655-67.
III. HYPTERTROPHIC CARDIOMYOPATHY

Hypertrophic cardiomyopathy (HCM) is a common disease, that affects 1 in 500 people [8]. Usually it is inherited as an autosomal dominant trait, instead de novo mutations are rare [9]. The phenotype of a patient with HCM is characterized by asymmetrical cardiac hypertrophy, that doesn’t have any evident cause, myocyte disarray, and fibrosis. Patients show a marked phenotypic variability, even within the same family, and an incomplete penetrance [8]. HCM is one of the most frequently identified causes of sudden cardiac death caused by the high prevalence of malignant arrhythmias. Although many patients with HCM are asymptomatic and sudden death may be unpredictable, genetic screening in families is essential for prevention. Mutations in MYH7 and MYBPC3 genes, that encode for the beta-myosin heavy chain and the cardiac myosin binding protein-C, are present in about 80% of HCM cases [10,11]. Mutations in other genes, such as TNNT2, TNNI3, and TPM1, encode for proteins of the troponin complex and occur in 10% to 15% of HCM patients [12]. 9 genes are used for genetic testing. Considering all genetic testing these 9 genes, a mutation is identified in 40% to 60% of sporadic and familial cases[10]. Anyway, the relation between genotype and phenotype remains elusive, because of extreme genetic heterogeneity, variation in penetrance and expressivity, even considering individuals carrying identical mutations. Cases with a negative HCM genetic test might have HCM-causing mutations in unexplored regions within the known HCM genes or in undiscovered genes.

Rarely the phenotype is related to underlying HCM disease gene, and so it might bepoorlyuseful for managing patients. Mutations in MYH7 alleles usually are associated with an important clinical disease expression. Instead, mutations in MYBPC3 alleles have been associated with later onset disease [13]. Patients with TNNT2 mutations usually show a lower severity of LV hypertrophy but a higher arrhythmia risk [14]. Only few specific mutations might carry a prognostic implication. That is the reason why a genetic test result in isolation will not constitute an indication for an ICD for primary prevention.

In conclusion, genetic testing is recommended for patients with a clinical diagnosis of HCM when the genetic testing benefit family members and potentially other relatives (table 3). It is recommended in families with a history of sudden death, in families in which numerous relatives are at risk and that need periodic clinical evaluation without the genetic testing, and when the clinical diagnosis is difficult. It might be recommended even the genetic analysis of post mortem samples if there is a case of sudden deathin a family where HCM was not previously known. Family screening is recommended for all first-degree relatives and it is important also for cost-effectiveness reasons. Indeed, when a family member has an negative genetic testing.

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**Table 2. Recommendations to genetic testing in Dilated Cardiomyopathy.**

*Modified from HRS/EHRA Expert Consensus Statement on the State of Genetic Testing for the Channelopathies and Cardiomyopathies [16]*

When the mutation of the proband is known, the family genetic screening is very helpful to diagnose eventual early DCM. However clinicians should always keep in mind that, considered the heterogeneity of expression, some carriers would never develop the disease. The family screening is mandatory for the aggressive gene-mutations as mutations of laminin. Indeed the gene testing changes prognosis only for laminin mutations. In conclusion, clinically the genetic testing is recommended only for family screening and especially for aggressive mutations (table 2). However, it is very important to evaluate the mutations for research purposes, especially for possible gene therapy in future.

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**STATE OF GENETIC TESTING FOR DILATED CARDIOMYOPATHY (DCM)**

Class I

- Patients with a clinical diagnosis of DCM and significant cardiac conduction disease and/or a family history of premature unexpected sudden death have been recommended for a comprehensive or targeted (LMNA and SCN5A) DCM genetic testing.
- Family members and appropriate relatives of an index case have been recommended for a mutation-specific genetic testing.

Class IIa

- Patients with familial DCM have been recommended for genetic testing to confirm the diagnosis, to recognize those who are at highest risk of arrhythmia and syndromic features, to facilitate cascade screening within the family, and to help with family planning.

**STATE OF GENETIC TESTING FOR HYPTERTROPHIC CARDIOMYOPATHY (HCM)**

Class I

- Patients with a clinical diagnosis of HCM based on examination of the patient’s clinical history, family history, and electrocardiographic echocardiographic phenotype have been recommended for a comprehensive or targeted (MYBPC3, MYH7, TNNI3, TNNT2, TPM1) HCM genetic testing.
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result, he/she can be discharged and there is no reason for clinical investigations or long-term follow-up [15]. Long-term studies are required to accumulate reliable evidence on genotype–phenotype relations.

REFERENCES

[1] Michels VV, Moll PP, Miller FA, Tajik AJ, Chu JS, Driscoll DJ, et al. The Frequency of Familial Dilated Cardiomyopathy in a Series of Patients with Idiopathic Dilated Cardiomyopathy. N Engl J Med 1992;326(2):77-82.
[2] Baig MK, Goldman JH, Caforio AP, Coonar AS, Keeling PJ, McKenna WJ. Familial Dilated Cardiomyopathy: Cardiac Abnormalities Are Common in Asymptomatic Relatives and May Represent Early Disease. J Am Coll Cardiol 1998;31(1):186-94.
[3] Grunig E, Tasman JA, Kucherer H, Franz W, Kubler W, Katus HA. Frequency and Phenotypes of Familial Dilated Cardiomyopathy. J Am Coll Cardiol 1998;31(1):186-94.
[4] Hershberger RE, Lindenfeld J, Mestroni L, Seidman CE, Taylor MR, Towbin JA, et al. Genetic Evaluation of Cardiomyopathy a Heart Failure Society of America Practice Guideline. J Card Fail 2009;15(2):83-97.
[5] Judge DP, Johnson NM. Genetic Evaluation of Familial Cardiomyopathy. J Cardiovasc Transl Res 2008;1(2):144-54.
[6] Jefferies JL, Towbin JA. Dilated Cardiomyopathy. Lancet 2010;375(9716):752-62.
[7] Van Spaendonck-Zwarts K, van Hessem L, Jongbloed JD, de Walle HE, Capetanaki Y, van der Kooi AJ, et al. Desmin-Related Myopathy: a Review and Meta-Analysis. Clin Genet 2010;Jul 21, “forthcoming”.
[8] Maron BJ, McKenna WJ, Danielson GK, Kappenberger LJ, Kuhn HJ, Seidman CE, et al. American College of Cardiology/European Society of Cardiology Clinical Expert Consensus Document on Hypertrophic Cardiomyopathy. A Report of the American College of Cardiology Foundation Task Force on Clinical Expert Consensus Documents and the European Society of Cardiology Committee for Practice Guidelines. J Am Coll Cardiol 2003;42(9):1687-713.
[9] Watkins H, Thierfelder L, Hwang DS, McKenna W, Seidman JG, Seidman CE. Sporadic Hypertrophic Cardiomyopathy Due to de novo Myosin Mutations. J Clin Invest 1992;90(5):1666-71.
[10] Richard P, Charron P, Carrier L, Ledeuil C, Cheav T, Pichereau C, et al. Hypertrophic Cardiomyopathy: Distribution of Disease Genes, Spectrum of Mutations, and Implications for a Molecular Diagnosis Strategy. Circulation 2003;107(17):2227-32.
[11] Van Driest SL, Ommen SR, Tajik AJ, Gersh BJ, Ackerman MJ. Yield of Genetic Testing in Hypertrophic Cardiomyopathy. Mayo Clin Proc 2005;80(6):739-44.
[12] Marian AJ. Genetic Determinants of Cardiac Hypertrophy. Curr Opin Cardiol 2008;23(3):199-205.
[13] Niimura H, Bachinski LL, Sangwatanaroj S, Watkins H, Chudley AE, McKenna W, et al. Mutations in the Gene for Cardiac Myosin-Binding Protein C and Late-Onset Familial Hypertrophic Cardiomyopathy. N Engl J Med 1998;338(18):1248-57.
[14] Watkins H, McKenna WJ, Thierfelder L, Suk HJ, Anan R, O’Donoghue A, et al. Mutations in the Genes for Cardiac Troponin T and Alpha-Tropomyosin in Hypertrophic Cardiomyopathy. N Engl J Med 1995;332(16):1058-64.
[15] Wordsworth S, Leal J, Blair E, Legood R, Thomson K, Seller A, et al. DNA Testing for Hypertrophic Cardiomyopathy: a Cost-Effectiveness Model. Eur Heart J 2010;31(8):926-35.
[16] Ackerman MJ, Priori SG, Willems S, Berul C, Brugada R, Calkins H, et al. HRS/EHRA Expert Consensus Statement on the State of Genetic Testing for the Channelopathies and Cardiomyopathies: This Document Was Developed as a Partnership Between the Heart Rhythm Society (HRS) and the European Heart Rhythm Association (EHRA). Europace 2011;13(8):1077-109.