Clinical phenotypes associated with Desmosome gene mutations


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Background

• Defects of genes coding desmosome proteins are known to be typically associated with Arrhythmogenic Right Ventricular Cardiomyopathy/Dysplasia (ARVC).
• Genetic variations have been found in the desmosomes, intercellular junctions that are responsible for cell-to-cell binding, and recur in about 40% of patients with ARVC.
• The most investigated genes for ARVC are:
  – JUP (Junctional Plakoglobin, 17q21)
  – PKP2 (Plakophilin-2, 12p11)
  – DSC2 (Desmocollin 2, 18q12.1)
  – DSG2 (Desmoglein 2, 18q12.1-q12.2)
  – DSP (Desmoplakin, 6p24)

Sen-Chowdhry S et al., J Cardiovasc Electrophysiol 2005
ARVC features and genes:

A “desmosomal” defect:
- PKG
- DSC2
- PKP2
- DSG2
- JUP

Plus additional:
- Cardiac ryanodine receptor 2 (RyR2 ARVD2)
- TGFβ3 (ARVD1)
- TMEM43

Pilichou et al., *Circulation* 2006
Pathophysiological mechanisms

Desmosome mutations exert pathogenic effects at different levels:

Desmosome composition and function (haploinsufficiency; absence of essential protein-protein interaction; incorrect incorporation of the mutated protein into the desmosome)

Intercalated disk (loss of the protection from mechanical stress)

Wnt/b-catenin signalling (desmosome dysfunction results into inhibition of Wnt/b-catenin signalling resulting in shift of the myocyte fate towards an adipocyte)
Background

We actually know that ARVC can overlap with DCM:

1. Many patients with ARVC may present biventricular involvement, with left ventricular enlargement and/or dysfunction, also in early stages of the disease

2. Many patients with idiopathic DCM can show diffuse or regional right ventricular involvement (dilatation and/or dysfunction) even in early stages and/or a hypertrabeculation of the right ventricular apex

ARVC have been recently subgrouped as classical, biventricular and left dominant forms.

Marcus FI et al. Circulation 2010
Background

3. also the presence of ventricular arrhythmias in DCM may simulate an ARVC with left ventricular involvement.

4. clinical overlapping of the two diseases → they may have a common genetic origin.

Sen-Chowdhry S. et al. J Am Coll Cardiol 2008
Purpose

1. Characterisation of the clinical phenotypes of patients addressed to our attention with the diagnosis of suspected ARVC and dilated cardiomyopathy (DCM)

2. Screening of desmosome genes
Methods

• Population:
  – **181 probands** (unrelated);
  – mean age 42.3 ± 11.3 y
    • addressed to our attention with the diagnosis of suspected ARVC (n=124, including 5 cases of cardiac arrest followed by death in 4, coma lasting two years in 1 patient)
    • idiopathic dilated cardiomyopathy (DCM) (n=57)
Methods

• **Clinical and instrumental evaluation of probands:**
  – Physical examination
  – ECG
  – Echo
  – Holter ECG monitoring
  – Signal averaged ECG
  – Laboratory tests including sCPK
  – Cardiac Magnetic Resonance
  – Endomyocardial biopsy
  – electrophysiology study
  – genetic counselling (pre- and post-test) and genetic testing

→ Informed and consenting *relatives*: clinical screening and genetic testing.
Methods

Diagnostic criteria

• ARVC:
  – McKenna’s major/minor criteria
    \[Mckenna\ WJ\ et\ al.\ Br\ Heart\ J.\ 1994;\ 71(3):215-8\]
  – Modified ARVC diagnostic criteria
    \[Marcus\ Fl\ et\ al.\ Circulation\ 2010;\ 121(13):1533-41\]

• DCM: WHO criteria
We analysed:

– PKP2 (Plakophillin-2, 12p11)
– DSC2 (Desmocollin 2, 18q12.1)
– DSG2 (Desmoglein 2, 18q12.1-q12.2)
– DSP (Desmoplakin, 6p24)
– JUP (Junctional Plakoglobin, 17q21)
– TGF-B3 (Transforming Growth Factor Beta3)
– TMEM 43 (Transmembrane Protein 43, 3p25)

Parallel analysis of LMNA and LDB3 genes was performed in ARVC probands with relatives affected by DCM with conduction disease, sudden death (SD) and diagnosis of left ventricular non compaction (LVNC).
Methods

Genotyping methods

• The coding and flanking regions of the 5 genes were analysed either by DHPLC and direct automated sequencing of the heteroduplex amplicons or by direct sequencing of coding and flanking regions.

• The same genes were analysed in 400 DNA controls, in which the mutations were not present.
Results

• Mutations of the desmosome genes were found in 57 probands out of 181 consecutive unrelated ARVC and DCM patients (31.5%)

M (72%), F (28%)

• 70% *Autosomal Dominant Familial* disease
  – 42% proven (≥ 2 affected individuals)
  – 28% likely familial disease (suspected)

• 30% *de novo* disease
Results

Genetic analysis

Desmosome genes mutations

- PKP2: 44.4%
- DSG2: 16.7%
- DSP: 5.6%
- JUP: 2.7%
- DSC2: 1.9%
- TMEM 43: 27.9%
Results

• Excluding known missense polymorphisms, we identified 54 variants in the desmosome genes, 2 in LMNA and 1 in LDB3:
  – 12 out of frame ins/del/dupl (3 + 1 missense) (22.2%)
  – 2 stop (3.7%)
  – 1 intronic variant (1.9%)
  – 1 in frame del + 1 missense (1.9%)
  – 14 double/compound missense (26%)
  – 4 double mutation (7.4%) in 5 families:
    • 3 missense on desmosome genes + LMNA
    • 1 missense on desmosome genes + LDB3
  – 21 single missense mutations (39%).

• Of the 38 missense mutations of desmosome genes, 15 are considered as provisional (GVUS).

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Results

Out of the **57** unrelated mutated probands, the **conclusive clinical diagnosis** was the following:

- **28** pts (28 out of 33 with original diagnosis of ARVC) were confirmed with diagnosis of ARVC:
  - 19 typical classic (right dominant) ARVC (33%)
    » 13 fulfilling the Task Force criteria, 6 not fulfilling
  - 3 biventricular ARVC (5.2%) (out of 11 originally diagnosed)
  - 3 left dominant ARVC (5.2%) (out of 4 originally diagnosed)
  - 3 with uncomplete diagnostic criteria for ARVC (5.2%)

- **29** pts (instead of original 17) were confirmed/changed diagnosis of DCM:
  - 10 DCM with right ventricular involvement (17.5%)
  - 19 DCM without right ventricular involvement (33%)
57 probands with positive genetic test: final diagnosis

• The reason for which in few cases the original diagnosis of DCM was changed into ARVC or viceversa, could be:

1. Modification of ARVC diagnostic criteria, with improved sensitivity on familial and early ARVC forms
2. Family clinical and genetic study on proband’s relatives, that gave suggestions on proband’s diagnosis
3. Genetic results (sometimes helpful, sometimes confounding)
PKP2 Exo1 + Exo9 (trans) p.Asp26Asn p.Arg651Gln

Change of DCM into ARVC diagnosis

Genetic and revised clinical criteria

DCM with RV dilation  Biventricular ARVC
Confirmation of ARVC diagnosis

CASE 2

PKP2  Ex 10
p. Pro671FsX12
Comparing clinical findings of the 3 mutated brothers...

Confirmed classical ARVC diagnosis

Confirmation of co-segregation of genetic mutation
Z.M., idiopathic DCM, 50 y.

Cardiac MRI: mild LV hypertrabeculation

Ergometric test and ecg monitoring: no arrhythmias

Coronary angiography and endomyocardial biopsy: neg
CONFOUNDING GENETIC DATA

WOULD YOU CHANGE DIAGNOSIS DCM INTO ARVC ONLY ON THE BASIS OF GENETIC RESULTS?

*DSC2 Ex 16 p.Glu896fsX4

DESMOCOLLIN
Conclusions

1. Desmosome gene mutations occur in both ARVC and DCM. The two forms may show overlapping phenotypes.

2. Actual diagnostic criteria for ARVC, even if recently modified, are often insufficient (low sensitivity, high specificity) to make a diagnosis.

3. Family screening may help
Conclusions

4. Forcing clinical diagnosis under the genetic diagnosis (desmosome genes = ARVC) will generate nosology problems, especially considering the three ARVC variants (classical, biventricular and left dominant) and the possible overlapping with DCM with right ventricular involvement.

5. Given that to date the DCM and ARVC diagnoses are done on clinical ground, the identification of desmosome gene mutations in DCM does not influence the clinical diagnosis.

6. If and when classification will be based on genetic ground, then the diagnosis could be “desmosomalopathy with DCM phenotype”.
The end

Thank you!