A novel mutation in desmocollin-2 reveals a functional link between desmosomes and gap junctions

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ESC: Arrhythmogenic mechanisms in inherited cardiomyopathies (abstract 86183 )
30 Aug 2010
ARVC: High risk of Sudden Cardiac Death

Antonio Puerta, 25/08/2007, 22 years old

Arrhythmogenic Right Ventricular Cardiomyopathy (ARVC)

Taken from: http://archivo.marca.com

Taken from: Thiene at al. Orphanet J. Rare Dis. 2007 2:45
Desmosomes

Desmoglein-2
Desmocollin-2
(Desmosomal Cadherins)

Desmoplakin

Plakoglobin

Plakophilin-2

Taken from: Stokes Curr Opin Cell Biol. 2008
Desmosomal disease

Arrhythmogenic Right Ventricular Cardiomyopathy (ARVC)

Skin and hair disorders

Syndromic forms (e.g. Naxos disease)

Taken from: Protonotarios & Tsatsopoulou Orphanet J. Rare Dis. 2006 1:4

Taken from: Thiene et al. Orphanet J. Rare Dis. 2007 2:45
Arrhythmias and Gap junctions

Gap junctions (Connexin43):

Desmosomal mutations cause Gap junction remodelling

Gehmlich/Asimaki unpublished

Taken from: http://cellbiology.med.unsw.edu.au/units/images
Case

52 year old female presented with palpitations and family history of sudden cardiac death (daughter)

Normal cardiac structure and function (echo)

ECG: sinus rhythm with first degree AV block
(PR interval 261 msec)
normal QRS duration
Depolarisation abnormalities = minor criterion

Electrophysiological study (EP)
Conduction slowing:

- moderately prolonged total RV endocardial activation times (82 vs. < 65 msec)

- Reduced max. endocardial activation gradient 0.22 mm/ms (controls: 0.51 ± 0.15 mm/ms)


- Fractionated and low amplitude electrograms
Desmosomal mutation screening

Missense mutation in Desmoglein-2:
DSG2 A517V, most likely benign

Truncation mutation in Desmocollin-2:
DSC2 Q851fsX855
Truncation of intracellular cadherin segment of DSC2a isoform
Molecular Changes

Histology: Fibrosis

Loss of plakoglobin signal
(diagnostic feature of ARVC: Asimaki NEJM 2009)

Cardiac biopsy (RV septum)
Molecular Changes – Western blotting

Changes in Connexin43 expression & phosphorylation

NF: non-failing control
P: patient
Connexin43 localisation unchanged

Cardiac biopsy (RV septum)
Functional studies: Localisation

Incorporation into intercalated discs

Neonatal rat cardiomyocytes
### Binding to desmosomal proteins

**GST-pulldown assays**

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<th>Dsc2b</th>
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**Impaired binding to plakoglobin**

*Dr. Katja Gehmlich*  
*ESC 2010*
Novel interaction between DSC2a and Connexin43
Impaired binding to Connexin43

Mutation disrupts DSC2a – Connexin43 interaction

GST-pulldown assays
Impaired binding to Connexin43

Mutation disrupts DSC2a – Connexin43 interaction
Conduction abnormalities in a patient with a borderline ARVC diagnosis
Summary

- Conduction abnormalities in a patient with a borderline ARVC diagnosis
- DSC2a truncation mutation identified, protein dominant negative mode of action
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- Impaired binding to plakoglobin ➔ loss of plakoglobin signal from intercalated discs
Conduction abnormalities in a patient with a borderline ARVC diagnosis

DSC2a truncation mutation identified, protein dominant negative mode of action

Impaired binding to plakoglobin ➔ loss of plakoglobin signal from intercalated discs

Novel interaction DSC2a – Connexin43 mutant defective:
  ➔ changes in Cx43 expression and phosphorylation
Conclusions

- Changes in gap junction protein Connexin43 precede overt ARVC phenotype
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- Novel functions of the DSC2a isoform: Interaction with cytoplasmic tail of Connexin43
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- Changes in gap junction protein Connexin43 precede overt ARVC phenotype

- Novel functions of the DSC2a isoform: Interaction with cytoplasmic tail of Connexin43

- Changes in Cx43 phosphorylation before loss of protein from the intercalated discs
Acknowledgements

Collaborators

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