



# Gene mutations resulting in the development of ARVC/D could affect cells of the cardiac conduction system

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In contrast to epithelial cells, cardiomyocytes are connected by complex hybrid-type adhering junctions, termed composite junctions (*areae compositae*). Composite junctions are found to be composed of typical desmosomal as well as adherens junction proteins. Therefore, in adult mammalian cardiomyocytes desmosomal proteins are not restricted to the relatively small desmosomes but are indirectly involved in anchoring the myofibrillar actin filaments. Subsequent investigations revealed that the formation of composite junctions is a rather late event during mammalian heart development and vertebrate heart evolution. Nascent, more round shaped cardiomyocytes of early developmental stages are connected by desmosomes and separate adherens junctions quite similar to cells of epithelial origin. During progression of development both types of adhering junctions seem to gradually fuse at the two poles of the mature mammalian cardiomyocytes to establish the hybrid-type composite junctions. Recently, we demonstrated that the specialized cardiomyocytes of the cardiac conduction system exhibit high amounts of desmosomes, not fully established composite junctions and adherens junctions. This underlines the fact that cells of the cardiac conduction system are known to resemble cardiomyocytes in their nascent state and do not undergo working myocardial differentiation. However, the astonishing high amount of desmosomal protein containing adhering junctions connecting, e.g., Purkinje fibers raises the possibility that pacemaker and conductive tissue may be affected by desmosomal gene mutations in ARVC/D patients.

**Keywords:** desmosome, area composita, heart, desmosomal gene mutation, conduction system, ARVC/D

## EFFECTS OF MUTATIONS IN GENES ENCODING FOR CARDIOMYOCYTE ADHERING JUNCTION COMPONENTS

Desmosomes and *fasciae adhaerentes* (sing., *fascia adhaerens*), the latter also termed adherens junctions are responsible for cell–cell adhesion and are often subsumed under the collective term adhering junctions. In various epithelia, like in the multistratified skin epithelium, desmosomes, and adherens junctions are distinct structures with only few shared components, such as, e.g., plakoglobin (Cowin et al., 1986). Desmosomes anchor the cytoskeletal intermediate filaments and *fasciae adhaerentes* the cytoskeletal actin microfilaments (Franke, 2009; Dubash and Green, 2011). In the heart things are quite different and more complex. Adult mammalian cardiomyocytes are for the most part connected by adhering junctions termed *areae compositae* (sing., *area composita*) or composite junctions to highlight their hybrid character (Franke et al., 2006, 2009; Pieperhoff et al., 2010a). Composite junctions consist of both, typical desmosomal and typical adherens junction proteins (Franke et al., 2006; Pieperhoff et al., 2010a). In composite junctions desmosomal proteins are therefore indirectly involved in supporting the myofibrillar actin anchorage in N-cadherin mediated cell–cell adhesion complexes (Goossens et al., 2007).

Today it is generally accepted that arrhythmogenic right ventricular cardiomyopathy/dysplasia (ARVC/D) is in most of the cases caused by mutations in desmosomal genes. Disease causing mutations have been found in genes encoding for the desmosomal plaque components plakophilin-2, desmoplakin, and plakoglobin

and the transmembrane desmosomal cadherins desmoglein-2 and desmocollin-2 (see, e.g., Rampazzo et al., 2002; Norman et al., 2005; Pilichou et al., 2006; Thiene et al., 2007; for further references please see Rickelt and Pieperhoff, 2012). Although rare, mutations in some non-desmosomal proteins such as, desmin (see **Figure 1**), transforming growth factor- $\beta$ 3 (TGFB3), transmembrane protein 43 (TMEM43), ryanodine receptor 2 (RYR2), lamins A and C, striatin and titin have also been associated with ARVC/D development (Rampazzo et al., 1995; Beffagna et al., 2005; Merner et al., 2008; Klauke et al., 2010; Meurs et al., 2010; Quarta et al., 2011; Taylor et al., 2011). ARVC/D is characterized by a progressive replacement of contractile heart muscle tissue by fibrotic and fat tissue (“fibrofatty replacement”) and severe arrhythmogenesis often followed by sudden cardiac mortality. Fibrofatty replacement was often but not exclusively found in the right ventricle (Bauce et al., 2005; Lindstrom et al., 2005; Thiene et al., 2007). Homozygous mutations in plakoglobin cause a syndromic disease form called “Naxos disease” involving skin and hair abnormalities in addition to the ARVC/D-type fibrofatty replacement of the myocardium (Protonotarios et al., 2001).

Functional alterations in ARVC/D most likely include alterations in gap junctions and sodium channels as a result from adhering junction defects (Kaplan et al., 2004; Sato et al., 2009, 2011). Furthermore, suppressed Wnt-signaling by nuclear plakoglobin may be involved in fibrofatty replacement and ARVC/D phenotype development (Garcia-Gras et al., 2006; MacRae et al.,

2006; Hirschy et al., 2010; Lombardi et al., 2011). In earlier investigations, cell contacts have been found to be an independent factor for cardiomyocyte survival *in vitro* (Clark et al., 1998) showing the general importance of these structures beside their important role in cell–cell adhesion.

Overexpression of mutant desmosomal genes or introduction of mutant desmosomal genes in mice (Pilichou et al., 2009) and other animal model systems (zebrafish) will help further to understand ARVC/D disease development and treatment (Macrae, 2010; Fabritz et al., 2011).

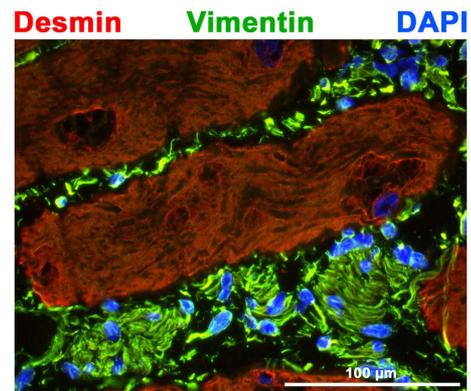
Recently, screening for novel candidates of ARVC/D causing genes have been for the first time extended to typical *fascia adhaerens* components, yet without striking results (Christensen et al., 2011). However, many other candidate genes, localized in the composite junctions within the intercalated disk may be included in future screenings (e.g., Kargacin et al., 2006; Otten et al., 2010; Seeger et al., 2010). Hopefully, this will improve molecular diagnostics, genetic testing, and genetic management of this disease (Fressart et al., 2010).

### POSSIBLE EFFECTS OF ARVC/D CAUSING GENE MUTATIONS ON CELLS OF THE CARDIAC CONDUCTION SYSTEM

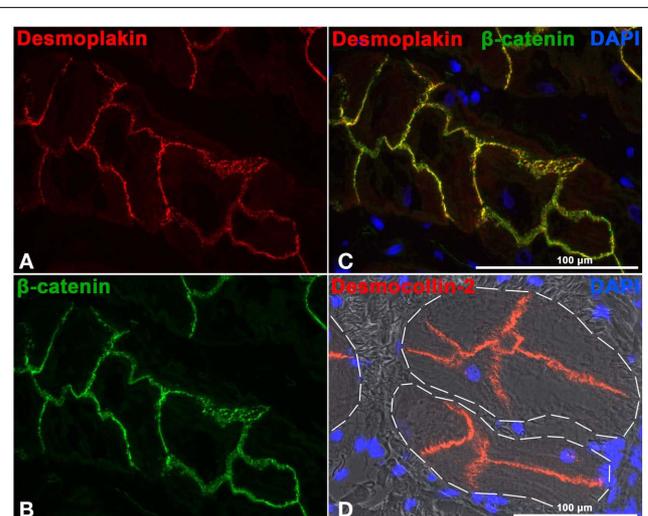
In the higher vertebrate heart muscle the rhythmic contraction of single cardiomyocytes is secured by a hierarchical system which includes the cardiac conduction system composed of pacemaker and conductive tissue. Pacemaker and conductive tissue consists of specialized cardiomyocytes which did not undergo working myocardial differentiation (Christoffels et al., 2010). Cells of the cardiac conduction system are insulated by connective tissue from the working myocardium in some areas of the heart (see **Figure 1**; see also, Anderson et al., 2009; Pieperhoff et al., 2010b). Electrical impulses are generated by cells of the sinoatrial (SA) node and travel to the atrioventricular (AV) node (Bakker et al., 2010). The conduction velocity is greatly reduced in the AV node to allow the atrium to contract before the ventricle (Mamlin and Fisch, 1965). The fast conduction system within the ventricle includes the bundles of His (1893), the right and left bundle branches (RBB, LBB) on either side of the ventricular septum and the meshwork of Purkinje fibers (Purkyne, 1845; Tawara, 1906; Shimada et al., 2004; Miquerol et al., 2011).

Pathological alterations in the cardiac conduction system have been described to cause sudden cardiac death before (e.g., Thiene et al., 1983) but never been found nor described in cases of ARVC/D. However, risk stratification of ARVC/D patients using ECG analyses revealed that “prolonged PR interval, prolonged QRS in lead VI, and presence of bundle branch block were predictors for adverse outcome” (Lemola et al., 2005).

Conductive cells have been found to be connected by a relatively high density of desmosomal protein containing desmosomes and composite junctions (Pieperhoff et al., 2010b). Cell contacts of conductive cells resemble adhering junctions of nascent cardiomyocytes (Pieperhoff and Franke, 2007; Pieperhoff et al., 2010b). Desmocollin-2 and desmoplakin (see **Figure 2**) and all other desmosomal as well as adherens junction components involved in connecting cardiomyocytes can be found in adhering junctions of Purkinje fiber cells (Pieperhoff et al., 2010b). This is why, mutations in desmosomal (and non-desmosomal) genes resulting



**FIGURE 1 |** Shown is a cryostat cross-section through ovine Purkinje fibers. Double label immunofluorescence microscopy was performed with antibodies to desmin (red) and vimentin (green) in addition to nuclear DAPI staining (blue). Note that the insulating connective tissue is strongly positive for vimentin, whereas Purkinje fibers are positive for desmin similar to cardiomyocytes of the working myocardium. For experimental details please see Pieperhoff et al. (2010b).



**FIGURE 2 |** Cryostat sections through ovine (A–C) and bovine (D) Purkinje fibers. (A–C) Double label immunofluorescence microscopy with antibodies to desmoplakin [red (A)] and  $\beta$ -catenin green (B)]. The overlay of (A) and (B) is shown in (C) in addition to nuclear DAPI staining (blue). Note the often dotted staining pattern but high abundance of the desmosomal plaque component desmoplakin in conductive cells of the Purkinje fibers. (D) Desmocollin-2 antibody labeling (red) and DAPI staining (blue) merged with the phase contrast image. The white dashed lines demarcate the border between conductive tissue and insulating connective tissue. See also Pieperhoff et al. (2010b).

in the described defects in the myocardium could affect cells of the cardiac conduction system similarly. This could then contribute to severe arrhythmogenesis in ARVC/D patients and may explain why the presence of left bundle branch blocks in ECG analyses has been found to be a predictor for the adverse outcome of the disease (Lemola et al., 2005). Possible disease mechanisms could

include cell adhesion defects, alterations in gap junction localization and function, resulting conduction disturbance and fibrofatty replacement of cardiomyocytes of the conduction system as similarly described in cardiomyocytes of the working myocardium (Norgett et al., 2000; Norman et al., 2005; MacRae et al., 2006; Herren et al., 2009; Sato et al., 2011).

## SUMMARY AND CONCLUSION

Cardiomyocytes of the working myocardium and of the cardiac conduction system share many similarities. The high abundance of desmosomal protein containing adhering junctions connecting cardiomyocytes of the conduction system raises the possibility that conductive and pacemaker tissue might be affected by desmosomal gene mutations in cases of ARVC/D. Even minor alterations in

cells of the cardiac conduction system could contribute to severe arrhythmogenesis in ARVC/D patients.

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