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Geographical distribution of plakophilin-2 mutation prevalence in patients with arrhythmogenic cardiomyopathy

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Abstract Arrhythmogenic cardiomyopathy (AC) is characterised by myocardial fibrofatty tissue infiltration and presents with palpitations, ventricular arrhythmias, syncope and sudden cardiac death. AC is associated with mutations in genes encoding the desmosomal proteins plakophilin-2 (*PKP2*), desmoplakin (*DSP*), desmoglein-2 (*DSG2*), desmocollin-2 (*DSC2*) and junctional plakoglobin (*JUP*). In the present study we compared 28 studies (2004–2011) on the prevalence of mutations in desmosomal protein encoding genes in relation to geographic distribution of the study population. In most populations, mutations in *PKP2* showed the highest prevalence. Mutation prevalence in *DSP*, *DSG2* and *DSC2* varied among the different geographic regions. Mutations in *JUP* were rarely found, except in Denmark and the Greece/Cyprus region.

Keywords Cardiomyopathy · Plakophilin-2 · Mutation · Desmosome · Prevalence · Geography

Introduction

Arrhythmogenic cardiomyopathy (AC), previously known as arrhythmogenic right ventricular cardiomyopathy or dysplasia (ARVC/D), is a myocardial disease usually with autosomal dominant inheritance and an estimated prevalence of 1:2000 to 1:5000 in the Western world [1, 2]. Based on clinical symptomology, the disease affects men more commonly than women (3:1) and usually becomes manifest between the second and the fourth decade of life. In clinical practice, patients with AC generally manifest with ventricular arrhythmias, palpitations, syncope related to physical exertion, and in a late-stage congestive heart failure. Unfortunately, sudden cardiac death during various daily life activities is the first presentation in 7–23% of affected patients [3]. Histopathologically, the heart of patients with AC shows myocardial cell death and progressive fibrofatty tissue substitution primarily of the right ventricular myocardium, preceding ventricular dilatation.

Cardiac tissue has to withstand high pressures to enable ejection and therefore individual cardiomyocytes are interconnected robustly by desmosomes in the intercalated disks (IDs). IDs, which consist of three multiprotein complexes, *i.e.* adherens junctions, desmosomes and gap junctions, provide mechanical and electrical coupling between cells, and serve as an anchoring site for ion channels [4, 5]. Loss-of-function mutations in five different desmosomal protein encoding genes, plakophilin-2 (*PKP2*), desmoplakin (*DSP*), desmoglein-2 (*DSG2*), desmocollin-2 (*DSC2*) and junctional plakoglobin (*JUP*), have been identified in AC [6]. The prevalence of these mutations might be related to ethnicity, founder mutations or founder populations [7–9] and therefore may be different in geographically distinct populations. For example, as shown by Van der Zwaag et al. [9] 12 index patients carrying the same *PKP2* mutation shared the same haplotype, indicative for a common founder. Geographical distribution of the index patients suggested that

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Table 1 Number of mutations in five desmosomal genes in genetic studies on AC patients of different geographical regions

Geographical region Author/year [ref.#]	Total patients	*PKP2* (%)	*DSP* (%)	*DSG2* (%)	*DSC2* (%)	*JUP* (%)	Patients with mutation (%)
USA							
Dalal et al/2006 [28]	58	25 (43)	n.d.	n.d.	n.d.	n.d.	25 (43)
Awad et al/2006 [21]	33[a]	0 (0)	0 (0)	4 (12)	n.d.	n.d.	4 (12)
Yang et al/2006 [29]	66	n.d.	4 (6)	n.d.	n.d.	n.d.	4 (6)
Den Haan et al/2009 [22]	**82**	**37 (45)**	**1 (1)**	**7 (9)**	**0 (0)**	**1 (1)**	**43 (52)**
USA/Netherlands							
Kapplinger et al. 2011 [12]	175	88(50)	2(1)	16(9)	4(2)	1(1)	102 (58)
USA/Canada							
Marcus et al/2009 [30]	100[b]	22 (22)					22 (22)
Canada							
Barahona-Dussault et al/2010 [23]	**23[c]**	**7 (30)**	**1 (4)**	**1 (4)**	**3 (13)**	**0 (0)**	**10 (43)**
Germany/USA							
Gerull et al/2004 [6]	120	32 (27)	n.d.	n.d.	n.d.	n.d.	32 (27)
Heuser et al/2006 [31]	88[d]	0 (0)	n.d.	0 (0)	1 (1)	n.d.	1 (1)
United Kingdom							
Syrris et al/2006 [32]	77[e]	0 (0)	0 (0)	0 (0)	4 (5)	0 (0)	4 (5)
Syrris et al/2006 [33]	100[f]	11 (11)	0 (0)	n.d.	n.d.	0 (0)	11 (11)
Sen-Chowdhry et al/2007 [19]	156	10 (6)	17 (11)	10 (6)	2 (1)	0 (0)	39 (25)
Sen Chowdhry et al/2007 [24]	**69**	**6 (9)**	**7 (10)**	**5 (7)**	**2 (3)**	**0 (0)**	**20 (30)**
Syrris et al/2007 [34]	86[g]	0 (0)	0 (0)	9 (10)	n.d.	0 (0)	9 (10)
the Netherlands							
Van Tintelen et al/2006 [35]	56	24 (43)	n.d.	n.d.	n.d.	n.d.	24 (43)
Bhuiyan et al/2009 [36]	57	23 (40)	n.d.	5 (9)	2 (4)	n.d.	30 (53)
Cox et al/2011 [25]	**149**	**78 (52)**	**2 (1)**	**5 (3)**	**4 (3)**	**0 (0)**	**87 (58)**
Italy/Poland							
Basso et al/2006 [37]	21	3 (14)	3 (14)	4 (19)	n.d.	n.d.	10 (48)
Italy							
Pilichou et al/2006 [20]	80[h]	11 (14)	13 (16)	8 (10)	n.d.	n.d.	32 (40)
Bauce et al/2010 [26]	**42**	**7 (17)**	**5 (12)**	**4 (10)**	**2 (5)**	**0 (0)**	**18 (43)**
France/Switzerland							
Fressart et al/2010 [17]	**135**	**42 (31)**	**6 (5)**	**14 (10)**	**2 (2)**	**0 (0)**	**62 (46)**
Greece/Cyprus							
Antoniades et al/2006 [38]	187	16 (9)	n.d.	n.d.	n.d.	26 (14)	42 (22)
Denmark							
Christensen et al/2010 [39]	53	7 (13)	n.d.	n.d.	n.d.	n.d.	7 (13)
Christensen et al/2010 [27]	**55**	**7 (13)**	**2 (4)**	**2 (4)**	**4 (7)**	**4 (7)**	**18 (33)**
Finland							
Lahtinen et al/2008/2011 [8, 40]	29	3 (10)	1 (3)	1 (3)	0 (0)	n.d.	5 (17)
China							
Qiu et al/2009 [41]	18	7 (39)	n.d.	n.d.	n.d.	n.d.	7 (39)
South Africa							
Watkins et al/2009 [7]	36	9 (25)	n.d.	n.d.	n.d.	n.d.	9 (25)

[a] The population was first tested negative for mutations in PKP2 or DSP and then screened for mutations in DSG2. [b] Other desmosomal genes were screened for but not reported. [c] JUP was only tested in patients negative for PKP2, DSP, DSG2 and DSC2 mutations. [d] DSG2 and DSC2 was only tested in patients negative for PKP2 mutations. [e] DSC2 was only tested in patients negative for PKP2, DSP, DSG2 and JUP mutations. [f] PKP2 was only tested in patients negative for DSP and JUP mutations. [g] DSG2 was only tested in patients negative for PKP2, DSP and JUP mutations. [h] DSG2 was only tested in patients negative for PKP2 and DSP mutations. n.d., not determined. Studies in bold analysed mutations in all five desmosomal genes and data are displayed graphically in Fig. 2

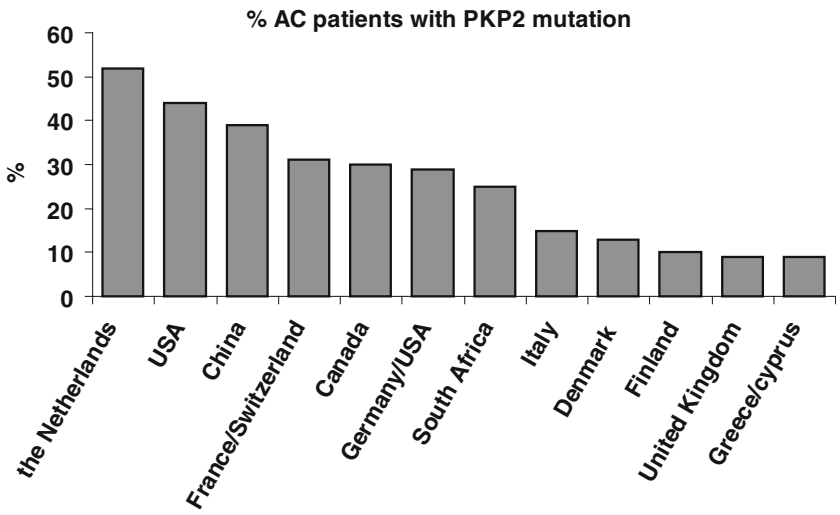

Fig. 1 Ranked prevalence of *PKP2* mutations associated with AC in different geographical regions

the mutation originated in the northern part of the Netherlands [9]. In the present study we describe results from literature on the geographical distribution of mutation prevalence of diagnosed AC patients. Our analysis demonstrates that approximately 46% of AC cases can be correlated with mutations in one or more desmosomal genes. Furthermore, mutations within the *PKP2* gene have the strongest prevalence within the AC population. Finally, some large differences between populations of distinct geographical locations exist.

Methods

Search methods and selection criteria

PubMed and the Cochrane Library databases were examined using combinations of the following search terms and abbreviations: arrhythmogenic right ventricular dysplasia/cardiomyopathy, prevalence, genetic mutations, mutational analysis, desmosomes, plakophilin-2 (PKP2), desmoplakin (DSP), desmoglein-2 (DSG2), desmocollin-2 (DSC2), and plakoglobin (JUP). We considered only full-length articles in English, published in the 2004–2011 period, which contained a sample size of more than 15 confirmed AC patients, according to the 1994 or 2010 Task Force Criteria (TFC) [10, 11].

Results

Table 1 summarises the relevant data from 28 studies, ordered according to the country/region from which the study population was derived. In most studies, potential mutations in *PKP2* were screened for, and in a subset of the studies

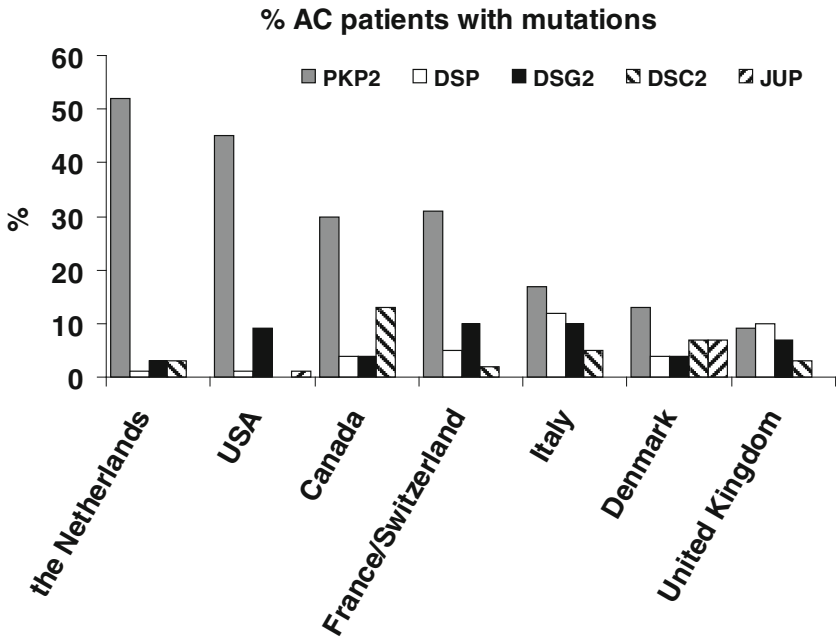

Fig. 2 Prevalence of plakophilin-2 (*PKP2*), desmoplakin (*DSP*), desmoglein-2 (*DSG2*), desmocollin-2 (*DSC2*) and junctional plakoglobin (*JUP*) mutations in seven geographic regions

(from the Netherlands, USA, Canada, United Kingdom, Denmark, Italy and France/Switzerland), patients were screened for all five desmosomal protein encoding genes. After removing double counted patients, necessary since some larger studies used a subset of previous study populations (e.g. Kapplinger et al.[12]) and some studies searched for additional mutations in patients scoring negative for *PKP2* mutation, we observed that of 931 individual patients (probands) screened for, 210 (22.6%) were found to carry a mutation in *PKP2*. When prevalence is ordered based on geographical distribution (Fig. 1), relatively most *PKP2* mutations were found in the Netherlands, USA and China (39–52%), while rates below 10% were found in the UK and Greece/Cyprus.

When considering the subset of studies that screened for mutations in all AC associated desmosomal genes, i.e. *PKP2*, *DSP*, *DSG2*, *DSC2* and *JUP*, it was found that 46% of the AC patients carried a mutation in one or more of these genes. Figure 2 shows the results of mutation prevalence per country/region, again indicating a high prevalence of *PKP2* mutations in USA and the Netherlands while, especially in Italy, Denmark and UK, mutations in other desmosomal protein encoding genes are associated more frequently with the AC phenotype. Mutation in the desmosomal gene *JUP* is associated with AC rarely, with the exception of Denmark and Greece/Cyprus (Table 1).

Discussion

Our analysis indicates that approximately 46% of the AC cases can be linked to mutations in genes encoding desmosomal proteins. Mutations in 'non-desmosomal' genes coding for transforming growth factor β3 [13] and ryanodine receptor [14], transmembrane protein 43 [15], and the recently identified phospholamban mutation [16] may account in addition for cases of AC. However, the causal effects of transforming growth factor β3 and ryanodine receptor mutations in AC are currently disputed. Screening genes for other structural proteins in the ID, *i.e.* β-catenin, a-T-catenin and PERP, in a Danish population of 55 confirmed AC patients revealed no mutations [17].

Some regions in our analysis have a large area size (USA, Canada) and/or contain populations from geographically distinct areas (e.g. Germany/USA), although in the latter the USA population is of West-European descent. In other studies, the population was derived from a relatively small region (Padua region, Italy). Therefore, data as presented here may not completely reflect the prevalence of the entire country as regional differences within one country are likely to be found in future. Furthermore, the patient population often included individuals from different origins. For example, Fressart et al. [18] included AC patients from Hispanic, Maghreb and Caribbean origin. Interesting in this respect are the findings of a recent study by Kapplinger et al. [12], where it was shown that in the control population in the absence of heart disease manifestation, DNA variant prevalence in desmosomal protein encoding genes was approximately threefold lower in Caucasians than in non-Caucasians. However, so-called 'radical mutations' which are most likely associated with an AC phenotype showed a very low prevalence in both Caucasian (0%) and non-Caucasian (0.6%) controls. Finally, radical mutations, defined by the authors as insertions, deletions, splice junction or nonsense mutations, constitute the majority of genetic alterations in so-called mutation-positive AC patients, while many of the missense mutations found in controls and patients most likely have no causal effect with AC [12].

Another complicating factor in comparing different studies is the use of new criteria in the revised TFC to include patients. For example, Sen-Chowdhry et al. [19] included probands with left ventricular or biventricular cardiomyopathy, which may explain the high prevalence of *DSP* mutations in this study population. However, patients with predominantly left ventricular involvement were often excluded by other authors, due to strict adherence to the TFC defined in 1994 [11]. Previous studies applied different criteria for mutational analysis. For example, Pilichou et al. [20] and Awad et al. [21] sequenced the *DSG2* gene only in patients who did not have *PKP2* or *DSP* mutations. In most new studies, all desmosomal protein encoding genes are screened [18, 22–27].

When genetic screening is indicated, all desmosomal protein encoding genes should be included. *JUP* is only rarely associated with AC, except in Denmark and the Greece/Cyprus region. In the latter region the high incidence of *JUP* mutations may be due to Naxos disease, a specific condition of AC combined with woolly hair and cutaneous hyperkeratosis.

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