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Spectrum of desmosomal gene variations in patients with arrhythmogenic right ventricular cardiomyopathy

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Arrhythmogenic right ventricular cardiomyopathy (ARVC) is a hereditary myocardial disease with a high risk of sudden cardiac death. The most common genetic forms of the disease are associated with desmosomal gene mutations.
Aim. To study the prevalence of desmosomal forms of ARVC and to analyze variations in the *PKP2*, *DSG2*, *DSP*, *DSC2* and *JUP* genes in a sample of Russian patients with ARVC.
Material and methods. Included patients with ARVC underwent resting electrocardiography (ECG), 24-hour Holter ECG monitoring, echocardiography, chest x-ray, myocardial biopsy (if indicated), contrast-enhanced cardiac magnetic resonance imaging. All patients underwent medical genetic counseling. Mutations in the *PKP2*, *DSG2*, *DSP*, *DSC2*, and *JUP* genes was detected using high-throughput sequencing on the IonTorrent platform, followed by Sanger sequencing of uncovered gene regions. The pathogenicity of identified genetic variations was assessed according to modern guidelines.
Results. ARVC was established in 80 Russian unrelated patients. More than half of the probands (57%) in the study sample had definite diagnosis of ARVC, while 30% and 13% — borderline and possible ARVC, respectively. A positive family history of heart disease and/or SCD was noted in 30%. Genetic variants of pathogenicity class IV-V were detected in 15 (18,75%) probands in the *PKP2*, *DSG2*, *DSP* genes. The detection of genetic variants of pathogenicity class IV-V was different in the subgroups of patients with varying degrees of diagnosis reliability: 13 probands (28,3%) in the subgroup with definite ARVC and 2 probands (8,3%) in the subgroup with borderline ARVC. No genotype-positive probands were found in the subgroup with possible ARVC. Variations of unknown clinical significance were found in 13 (16,25%) probands.
Conclusion. The diagnostic yield of the desmosomal genes *PKP2*, *DSG2*, *DSP*, *DSC2*, and *JUP* was 19% with initial diagnosis of ARVC. The detection of mutations was significantly higher in patients with definite ARVC and severe disease manifestations.

Keywords: arrhythmogenic right ventricular cardiomyopathy, ARVC, medical genetic counseling, desmosomes.

Relationships and Activities: none.

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Arrhythmogenic right ventricular cardiomyopathy (ARVC) (OMIM #107970) — a genetically determined myocardial disease with a high risk of sudden cardiac death (SCD), characterized by fibrous and/or fatty replacement of cardiomyocytes mainly of the right ventricle, frequent ventricular arrhythmias leading to the heart failure development [1].

According to European and American studies, ARVC occurs in the population with a frequency from 1:2000 to 1:5000 people [2-4], but no large-scale epidemiological studies have been conducted in Russia. In different ethnic groups, ARVC causes 10-25% of SCD cases in young people aged 17-40 years [5-8]. ARVC is characterized by autosomal dominant type of inheritance with incomplete penetrance. Cases of autosomal recessive type of inheritance (Naxos syndrome, Carvajal syndrome) are known [9-11].

Historically, ARVC has been considered "desmosomal disease" because most cases of the disease are associated with potentially pathogenic variants in the genes encoding desmosomal proteins: transmembrane desmosomal cadherins (desmocollin, desmoglein) and adaptor proteins (desmoplakin, plakophilin, plakoglobin). However, potentially pathogenic variants have now been identified in the genes encoding area composita (cell adhesion proteins also associated with desmosomes) [12, 13].

Desmosomes are complex protein structures of the cell membrane that ensure structural and functional integrity of cells in various types of tissues, including in myocardium. Desmosomes are most represented in cells and tissues of organs that are exposed to frequent mechanical effects: skin, heart, salivary glands, thyroid gland, stomach, liver, pancreas, intestine, gallbladder, uterus, epithelial cells of nephrons [14].

It was hypothesized that disruption of desmosome assembly leads to the release and translocation of placoglobin protein into the nucleus, where it acts as a competitor of β-catenin and suppresses the canonical Wnt-signaling pathway. This leads to increased expression of adipogenesis and fibrogenesis genes and, thus, to the dominance of adipogenesis over myogenesis [15]. In addition, the role of glycogen synthase kinase 3 β (GSK3b), a suppressor of Wnt-signaling pathway, whose suppression led to prevention or delay of arrhythmogenic cardiomyopathy development in cellular and mouse models of the disease was shown [16].

Recent studies support the concept of a close functional relationship between the desmosome and the $Na_v1.5$ sodium channel protein. This is confirmed by experiments in which $Na_v1.5$ is co-deposited with protein N-cadherin [17], as well as the results of super-resolution microscopy demonstrating the presence of "adhesion/excitation" nodes formed by aggregates of $Na_v1.5$ and N-cadherin [18].

The goal of our study was to investigate the representation of desmosomal forms of the disease and analyze the spectrum of genetic variants in the genes *PKP2*, *DSG2*, *DSP*, *DSC2*, and *JUP* in a sample of Russian patients with ARVC.

Material and methods

The study included 80 probands with a referring diagnosis of ARVC, established on the basis of diagnostic criteria of ARVC 2010 in specialized cardiology and cardiosurgical institutions [19]. Voluntary written informed consent was obtained from all adult patients to participate in the study and further use of the data for scientific purposes. For minors, the consent was signed by a parent or legal guardian.

Clinical and instrumental examination was performed at the place of initial diagnosis and included resting electrocardiogram, 24-hour Holter electrocardiogram monitoring, transthoracic echocardiography, chest radiography, myocardial biopsy (when indicated), contrast-enhanced magnetic resonance imaging of heart. The diagnosis reliability was assessed using ARVC 2010 diagnostic criteria [19] prior to DNA diagnosis.

All patients underwent medical genetic counseling (primary and repeated consultations). The average period of dynamic observation was 73 months (minimum — 7 months, maximum — 11 years). The genetic study was performed in accordance with the protocol approved by the Local Ethics Committee of the FSBSI of the Russian Surgery Research Center n.a. academician B.V. Petrovsky (Protocol No. 135), and with the norms of the Helsinki Declaration (1964), and its subsequent revisions.

The search for mutations in the "desmosomal" genes *PKP2*, *DSG2*, *DSP*, *DSC2*, and *JUP* within the target gene panel (Appendix 1) was performed by high-throughput sequencing on the IonTorrent platform (device: Ion PGM™ System) (Thermo Fisher Scientific, USA) followed by direct capillary Sanger sequencing of uncovered gene regions. Verification of the genetic variants identified by the NGS method and cascade family screening for relatives of probands with genetic variants of pathogenicity classes IV-V were also performed by direct Sanger sequencing.

The pathogenicity of the identified genetic variants was evaluated *in silico* according to the guidelines for the interpretation of genetic variants [20-22]. Each identified genetic variant was assigned a pathogenicity class I to V according to the guidelines [20, 21]. Only genetic variants of classes V (pathogenic), IV (probably pathogenic), III (variant with unknown clinical significance) of pathogenicity

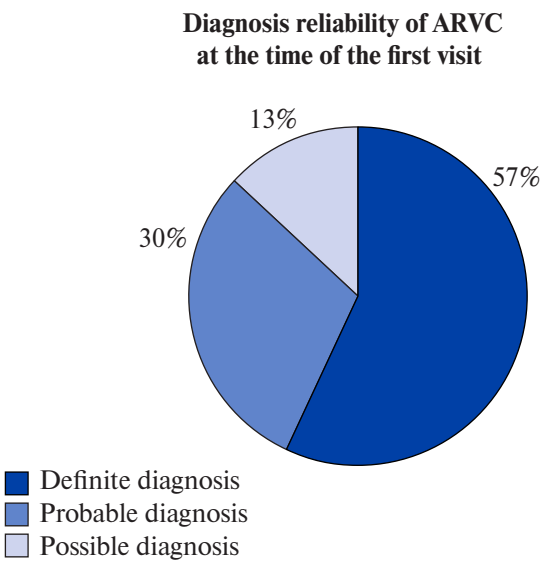

Figure 1. The severity of ARVC clinical signs and reliability of diagnoses in probands of the examined group.
Abbreviation: ARVC — arrhythmogenic right ventricular cardiomyopathy.

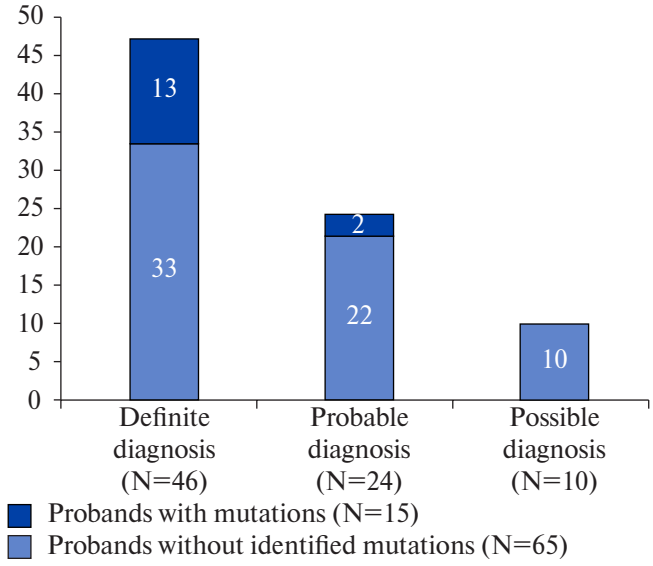

Figure 2. Detectability of genetic variants of pathogenicity classes IV-V in desmosomal genes in samples of patients with reliable, probable, and possible diagnoses of ARVC.

Appendix 1

Reference sequence numbers (NCBI) of genes cDNA *PKP2*, *DSG2*, *DSP*, *DSC2*, *JUP*, *TMEM43*, *LMNA*, *DES*, *TGFB3*, *PLN*, *SCN5A*, *CTNNA3*, *EMD*, *CRYAB*, *LDB3*, *FLNC* included in the studied panel of genes

No.	Gene	cDNA Isoform (NCBI RefSeq)
1	*PKP2*	NM_004572.3
2	*DSG2*	NM_001943.5
3	*DSP*	NM_004415.4
4	*DSC2*	NM_024422.6
5	*JUP*	NM_001352773.1
6	*TMEM43*	NM_024334.3
7	*LMNA*	NM_170707.4
8	*DES*	NM_001927.4
9	*TGFB3*	NM_003239.4
10	*PLN*	NM_002667.5
11	*SCN5A*	NM_198056.2
12	*CTNNA3*	NM_013266.4
13	*EMD*	NM_000117.3
14	*CRYAB*	NM_001289807.1
15	*LDB3*	NM_007078.3
16	*FLNC*	NM_001458.4

were included in the final DNA diagnostic report given to patients and subsequent analysis.

For pathogenic (V) and probably pathogenic (IV) genetic variants, we used the historical term "mutations" later in the paper.

Quantitative indicators are presented as an average ± SD.

Results

Medical genetic counseling and genetic screening were performed in 80 probands (men 36) with a referring diagnosis of ARVC, which was established in specialized cardiology and cardiac surgery centers. The average age of patients at the time of applying for DNA diagnostics was 38,7±14,4 years.

The reliability of clinical diagnosis of ARVC, established before DNA diagnosis, was assessed on the basis of diagnostic criteria of ARVC 2010 [19]. Most of all in the study sample were patients with a reliable diagnosis (N=46; average age 40,7±15,1 years; 24 M). Probands with probable (N=24; average age 35,0±12,5 years; 11 M) and possible (N=10; average age 37,8±14,4 years; 1 M) diagnoses of ARVC were 30% and 13% of the sample, respectively (Figure 1).

A family history of a demonstrably aggravated primary heart disease and/or SCD was noted in 24 (30%) families. In 20 probands, cardiomyopathies were detected in first-degree relatives, and in 4 families — also in relatives of the second or more degree of relationship. In two families, the sudden death of a relative of a young age (up to 40 years old) was noted. In addition, in two families with a burdened family history, the death of a relative in infancy (up to 1 year) was noted by unknown cause. According to 21 probands, they were the only patients among known relatives; therefore, we estimate the frequency of sporadic cases of ARVC in

Table 1

Spectrum of class IV-V pathogenicity genetic variants detected in patients with ARVC in genes encoding desmosome proteins

Gene	Nucleotide replacement	Protein change	Frequency (gnomAD)	Pathogenicity class	Number of probands
PKP2	c.336+1G>T		n/a	V	1
PKP2	c.962_965del	p.Val321Alafs*30	n/a	IV	1
PKP2	c.1523_1538del	p.Asn508Thrfs*7	n/a	IV	2
PKP2	c.1613G>A	p.W538*	0,00001591	IV	1
DSG2	c.146G>A	p.R49H	0,000004008	IV	1
DSG2	c.523+1G>A		0,000004201	V	1
DSG2	c.581C>T > (in homozygous state)	p.S194L (in homozygous state)	0,00002807	IV	2
DSP	c.1141-2A>G		0,000003981	V	1
DSP	c.1542dupT	p.Pro515Serfs*13	n/a	IV	1
DSP	c.1846C>T	p.Gln616*	n/a	IV	1
DSP	c.2130+1G>A		n/a	V	1
DSP	c.2672dup	p.Y891*	n/a	IV	1
DSP	c.3583delinsAATATAGT	p.Val1195Asnfs*8	n/a	IV	1

Abbreviation: n/a — no data.

Table 2

Spectrum of class III pathogenicity genetic variants detected in patients with ARVC in genes encoding desmosome proteins

No.	Gene	Nucleotide replacement	Protein change	Frequency (gnomAD)	Pathogenicity class	Number of probands
1	*PKP2*	c.1576A>G	p.T526A	0,0001202	III	1
2	*PKP2*	c.1745T>C	p.L582P	n/a	III	1
3	*DSG2*	c.733A>C	p.N245H	0,00003183	III	1
4	*DSP*	c.273+5G>A		0,00028	III	1
5	*DSP*	c.1349C>T	p.P450L	0,00001769	III	1
6	*DSP*	c.2622C>G	p.I874M	0,00004248	III	1
7	*DSP*	c.3600T>G	p.N1200K	0,00007083	III	1
8	*DSP*	c.4018C>T	p.R1340C	0,00004389	III	1
9	*DSP*	c.7856T>C	p.I2619T	n/a	III	1
10	*DSC2*	c.601G>A	p.V201I	0,00001193	III	1
11	*DSC2*	c.1436G>A	p.R479H	0,000007077	III	1
12	*JUP*	c.884_886del	p.Leu295_Ala296delinsPro	n/a	III	1
13	*JUP*	c.1916A>G	p.E639G	n/a	III	1

Abbreviation: n/a — no data.

Russian patients to be at least 26%. In the remaining families (35 probands, 44%), there was insufficient information on the health status of relatives (including one of the parents) to conclude that the disease was familial or sporadic.

We analyzed the spectrum of detected genetic variants in the desmosomal genes *PKP2*, *DSG2*, *DSP*, *DSC2*, and *JUP* in the examined group of patients (n=80) (Table 1). Variants with high pathogenicity classes (IV-V) were detected in 15 probands, which amounted to 18,75% of the whole examined group of patients (Table 1). Half of the identified genetic variants were identified for the first time.

Most of the mutations were detected in the heterozygous state, connected to autosomal dominant type of inheritance. The largest number of mutations (n=6) was detected in the gene *DSP*. 4 mutations in 5 probands were detected in the gene *PKP2*, 3 mutations in 4 probands — in the gene *DSG2*. Deletion of C.1523_1538del in the gene *PKP2* was detected by us in two unrelated probands. The missense mutation p.S194L in the homozygous state

in the gene *DSG2* was also detected in two unrelated probands.

No variants with high pathogenicity class were detected in the genes *DSC2* and *JUP*, which allows to consider these genetic forms of ARVC quite rare in the group of Russian patients.

We also analyzed the detection of genetic variants of pathogenicity classes IV-V in desmosomal genes separately in subgroups of patients with different degrees of confidence in the diagnosis of ARVC, assessed only on the basis of clinical manifestations of the disease, before DNA diagnosis (Figure 2).

Pathogenic and probably pathogenic genetic variants in desmosomal genes predominated in the subgroup of probands with a reliable diagnosis of ARVC, including probands carrying >1 potentially pathogenic genetic variant (13 probands; 28,3% in the subgroup) (Figure 2). In the subgroup of probable probands, mutations were detected in 2 probands (8,3% in the subgroup). No genotype-positive patients were detected among probands with a minimal set of diagnostic features (diagnosis of ARVC is possible) (Figure 2).

We also detected 13 rare genetic variants that were assigned to class III of pathogenicity (variants of unknown clinical significance (hereinafter — VUS) based on the ACMG2015 and ROMG criteria [20, 21] (Table 2). These variants were detected in 13 probands (16,25%). Three of these probands also had detected pathogenic/probably pathogenic genetic variants and 10 (12,5%) probands had only variants of unknown clinical significance. The largest number of variants with unknown clinical significance was detected in the gene *DSP*, which also dominated by the number of identified mutations. Unfortunately, the finding status of class III of pathogenicity does not allow any convincing comparative analysis of the clinical picture in patients who are carriers of these variants.

Discussion

Initially, ARVC was considered a "desmosis disease", however, taking into account the new diagnostic capabilities of DNA diagnostics, descriptions of mutations in other genes showed the genetic heterogeneity of the disease. It can be assumed that desmosomal genetic variants cause a more frequent pronounced ARVC phenotype, while mutations in other genes lead to a spectrum of diseases, including other types of cardiomyopathies and ARVC phenocopies.

The phenotype of "desmosomal" ARVC is associated with damage to both the right and left ventricle, in some cases skin manifestations of the disease are possible, for example, with Naxos syndrome [13].

To date, NGS sequencing of target gene panels and full-exome sequencing are the main approaches to DNA diagnosis of ARVC [2]. Despite increasing opportunities for genetic testing, the molecular cause of the disease remains undetectable in approximately 50% of patients, and some of the findings represent genetic variants of unknown clinical significance [2]. Whole-genome sequencing is considered, but it does not lead to a significant increase in the detectability of mutations, so the cost/efficiency ratio of this approach remains suboptimal.

According to current guidelines [19, 23], identification of a pathogenic/probably pathogenic genetic variant associated with ARVC and/or arrhythmogenic left ventricular cardiomyopathy phenotypes is a great diagnostic criterion for the disease. Therefore, one of the main purposes of this study is to clarify the ARVC diagnosis in proband. But only in 2 (2,5% of the examined cohort) probands with a probable diagnosis of ARVC, we detected variants of pathogenicity classes IV-V by DNA diagnosis, and managed to raise the diagnosis status to a reliable one. The data from our study show that the highest detectability of mutations is observed in probands with an extensive clinical picture of the disease, for which the appearance of an additional large criterion does not change the level of diagnosis reliability. This may give the impression of a decrease in the relevance of DNA diagnostics for patients with a reliable ARVC diagnosis. However, the importance of positive genetic test results remains high for family members of proband (1st and 2nd degree relatives as well as more distant relatives) and for the health care system as a whole. All current recommendations emphasize the need for regular dynamic monitoring and instrumental examination for first- and second-degree relatives if there is already a patient diagnosed with ARVC in the family. The start date of dynamic monitoring of relatives coincides with the diagnosis of proband. However, stipulated timeframe for leaving dynamic observation is not specified. Given the incomplete penetrance of mutations and different timing of manifestation, dynamic monitoring is assumed to be lifelong. This means that even in the absence of manifestations of the disease, relatives must be examined regularly, which is a time-consuming, psychological, and often financial burden on the family as well as on the health care system. In a number of European countries, such as Sweden, the role of cascade family screening and the identification of *genotype-negative* relatives who do not need a program of dynamic surveillance is considered a priority goal, more important for the

health care system than confirming the diagnosis in the proband himself [24].

In our group of patients, mutations were found in the genes *PKP2*, *DSG2* and *DSP*. The types of ARVC caused by mutations in these genes are among the most frequent in all ethnic groups except the inhabitants of Naxos Island (Greece) [9]. Usually, the greatest number of mutations are detected in the plakophilin gene (*PKP2*) — 20-46% [2]. In European countries, carriers of mutations in the *PKP2* gene account for up to 70% of carriers of mutations in desmosome genes [25]. In the desmoglein gene (*DSG2*), 3-20% of mutations are detected in European patients [2]. In Asian countries, the frequency of mutations in the gene *DSG2* is higher than in European countries: 15,8% in Japan [26] vs 4% in the Netherlands [25].

Mutation frequencies have also been determined for the desmoplakin (*DSP*) genes at 3-20% and desmocollin (*DSC2*) at 1-15% [2]. In our study, the most mutations were detected in the gene *DSP* rather than in *PKP2*, which distinguishes our sample of patients from the European samples.

Phenotype of patients with mutation in the gene *DSP* has its own peculiarities: these patients significantly more often have biventricular ARVC, develop LV systolic dysfunction (40%) and chronic heart failure (13%), as compared to patients with mutation in the gene *PKP2* [27, 28]. In addition, there is evidence that mutations in the gene *DSP* are associated with myocarditis accession [29], which is confirmed by our own data [30, 31].

Mutations in the gene *JUP* are rare in all ethnic groups, and their detection rate is not reliably known. In our study, we also failed to identify any variant in this gene that is reliably associated with the disease.

"Founder effect" is known for some mutations in ARVC, for example, for the mutation p.C796R in the gene *PKP2* found in 9 unrelated patients, all of Dutch origin [32]. None of the "European" mutations with the founder effect were found in Russian patients. The vast majority of mutations occurred only once and were unique to the family. Only 2 mutations occurred more than once: the mutation p.S194L in the homozygous state in the gene *DSG2* was found in two families of Caucasian origin, and the mutation s.1523_1538del in the heterozygous state in the gene *PKP2* was also found in two unrelated probands. To date, there is no information on relationship of the two probands carrying the same mutation, but it cannot be ruled out that both probands may have a common ancestor.

In our study, 15 mutations and 10 variants with unknown clinical significance were detected in the desmosome genes. The ratio "mutation:VUS" was 1:0,86. Thus, about 1/3 of the patients had at least one identified rare desmosomal variant. However, the *diagnostic* efficacy of the genetic study performed was only 19%, because only variants of pathogenicity class IV-V have a reasonable contribution to the diagnosis. Interestingly, in our sample of patients, probands carrying desmosomal variants of pathogenicity classes III-V were twice as numerous in the subgroup with a reliable diagnosis of ARVC (41,3%) compared with the subgroups with probable (16,6%) and possible (20,0%) diagnoses. In our opinion, this is an indirect confirmation that many variants qualified as VUS have pathogenetic significance, but insufficient study of molecular pathogenesis does not allow using these data correctly for diagnostic purposes.

In our laboratory, there is a rule to put class III pathogenicity variants in genes reliably associated with ARVC in the final report. Therefore, much attention is paid to correct medical-genetic counseling of families where such variants have been detected. In the medical consultation protocol, the phrase "The detection of pathogenicity class III variants cannot be used to confirm or exclude any diagnosis, or to justify the prescription, modification or cancellation of previously prescribed treatment or examinations" is routinely entered into the medical consultation protocol. Direct indication of this avoids undesirable iatrogenic influences on the family and relatives, and avoids the appointment of unwarranted instrumental examinations. However, putting these options in the conclusion has an important aspect — it opens to the family an opportunity to reinterpret the identified options. Genetic and basic studies are actively developing; data on the genetic nature of diseases and the functional significance of individual genetic variants are accumulating and being updated very rapidly. The need for periodic re-analysis and repeated contact with patients when new data are obtained regarding the genetic variants identified in them has been repeatedly emphasized [33, 34]. The optimal frequency of re-contacts and re-interpretation of such options is still a matter of discussion, but most experts recommend re-evaluating the value of the options 1-2 years after initial conclusion issuance. Therefore, proper medical genetic counseling of such families includes discussion of the significance, possibility, frequency, and procedure for re-interpretation of variants with unknown clinical significance.

Conclusion

In the molecular genetic study of desmosomal genes *PKP2*, *DSG2*, *DSP*, *DSC2* and *JUP* in patients with a guiding diagnosis of ARVC, the diagnostic

yield was 19%. At the same time, the detectability of mutations depended on severity of clinical signs of the disease, and was greatest among patients with the highest reliability of diagnosis. The detectability of variants with unknown clinical significance was also high, the ratio "mutation:VUS" was almost 1:1. Although these genetic variants are currently *not clinically used* and do not allow any actions to be taken, we consider it possible to make them into conclusions on the DNA diagnostics results. However, this tactic is justified only if patients receive appropriate medical-genetic counseling and they can seek reinterpretation of these variants after 1-2 years.

Given the central role of desmosomes in the process of cell adhesion, further functional studies of mutant proteins can shed light not only on clarification of molecular pathogenesis of the disease, but also contribute to the correct reinterpretation of genetic variants.

Relationships and Activities: none.

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