Muscle-Related Plectinopathies

Subjects: Others

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Plectin is a giant cytoskeletal crosslinker and intermediate filament stabilizing protein. Mutations in the human plectin gene (PLEC) cause several rare diseases that are grouped under the term plectinopathies. The most common disorder is autosomal recessive disease epidermolysis bullosa simplex with muscular dystrophy (EBS-MD), which is characterized by skin blistering and progressive muscle weakness. Besides EBS-MD, PLEC mutations lead to EBS with nail dystrophy, EBS-MD with a myasthenic syndrome, EBS with pyloric atresia, limb-girdle muscular dystrophy type R17, or EBS-Ogna.

plectin muscular dystrophy myopathology desmin intermediate filaments sarcomere structure

1. Introduction

Cardiac and skeletal striated muscles are elaborately organized machines designated for contraction. Sarcomeres, the smallest functional units of muscle contraction, comprise precisely organized filament systems including thin (actin) and thick (myosin) filaments, titin, and nebulin [1] and build up the myofibrillar apparatus. Desmin intermediate filaments (IFs), which are structurally organized by plectin in myoblasts (**Figure 1**A) and muscle fibers, constitute the principal component of the extrasarcomeric cytoskeleton. Plectin, a giant (>500 kDa) multi-modular cytolinker of the plakin protein family [2], may be considered as the universal cross-linking element of the cytoskeleton. Possessing binding sites for all types of IF subunit proteins, it networks and anchors them to sites of strategic importance for the organization and performance of cells, such as transmembrane junctional complexes, the nuclear envelope, and cytoplasmic organelles [3]. In addition, plectin harbors a functional actin-binding domain (ABD); binds to microtubule-associated proteins (MAPs); and interacts with transmembrane receptors, proteins of the subplasma membrane protein skeleton, components of the nuclear envelope, and several kinases with known roles in the migration, proliferation, and energy metabolism of cells (**Figure 1**B) [4][5]. Plectin's functional versatility is not only due to its multi-domain structure enabling a broad range of interactions, but it is also due to an unusual transcript diversity that is largely based on at least nine different, relatively short N-terminal sequences. Encoded by alternatively spliced first exons [6], individual plectin isoforms are differentially targeted to distinct cellular locations where they function as universal IF-docking sites, thus enabling them to fulfill distinct functions in different cell types and tissues [4][5]. In muscle tissue, the four most prominently isoforms expressed (plectin isoform 1d (P1d), P1f, P1b, and P1) are crucial for myofiber integrity by anchoring desmin IFs to Z-disks, costameres, mitochondria, and the nuclear/sarcoplasmic reticulum membrane system, respectively [7][8][9]. Thus, plectin acts as a multi-functional linker and signaling scaffold, centrally orchestrating the structural and functional organization of

filamentous cytoskeletal networks and thereby substantially contributing to the fundamental biomechanical properties of stress-bearing tissues such as muscle.

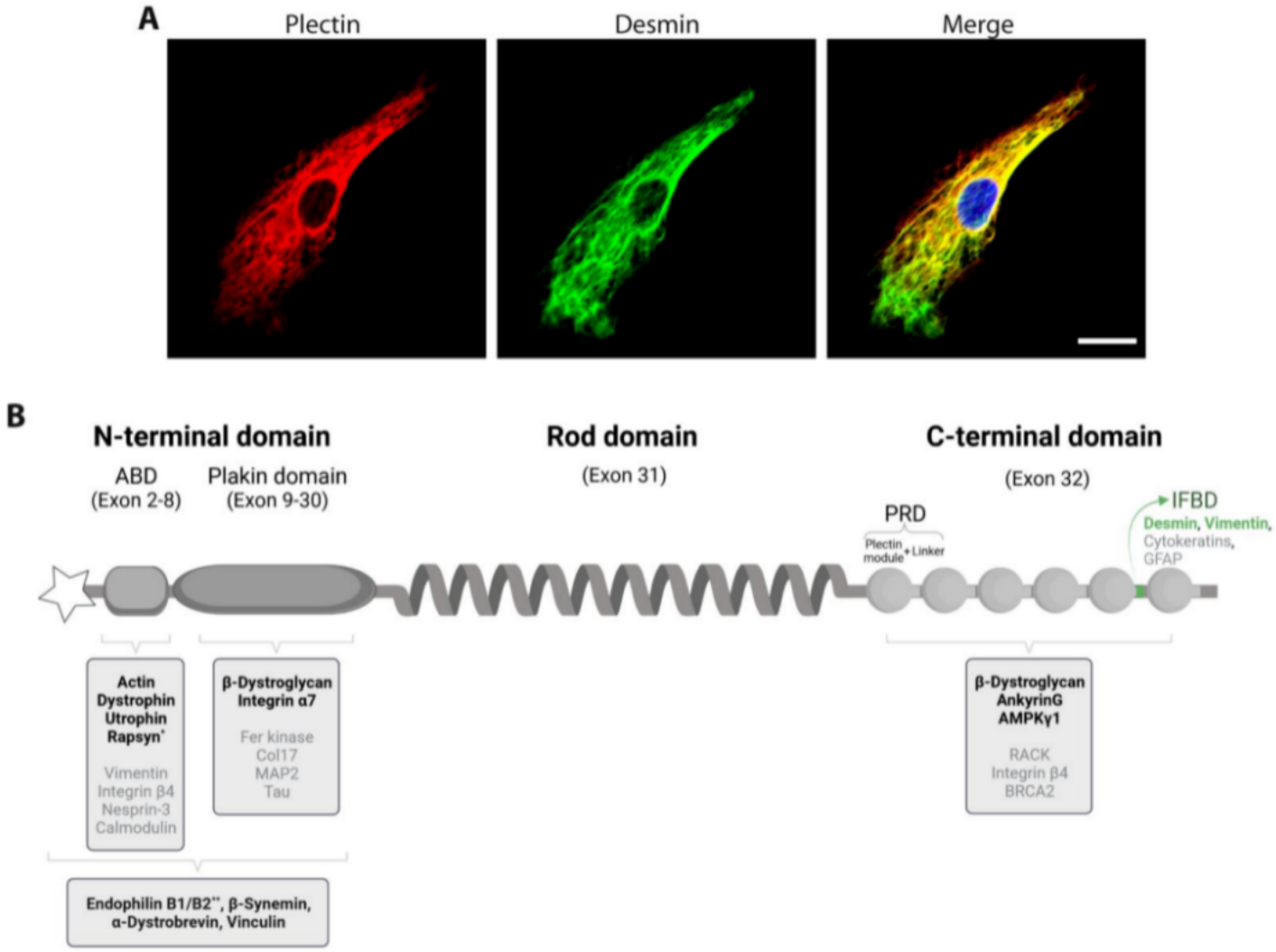

Figure 1. Subcellular localization of plectin in a myoblast and schematic representation of plectin and its binding partners, with a special focus on direct interaction partners identified in myoblasts and/or skeletal muscle. (**A**) Immunofluorescence microscopy of a human primary myoblast using antibodies to plectin (in red) and desmin (in green). The nucleus was visualized using DAPI (blue in the merged image). Note the co-localization of plectin and desmin. Scale bar: 15 µm. (**B**) Schematic domain map of the protein. The tripartite structure of plectin comprises a central rod domain (encoded by exon 31) flanked by N- and C-terminal domains. The N terminus harbors differentially spliced first exons (star), an actin-binding domain (ABD, exons 2–8), and a plakin domain (exons 9–30), while the C terminus comprises six plectin repeat domains (PRD), each containing a conserved core (plectin module) and a linker region. An intermediate filament binding domain (IFBD) is located between modules 5 and 6 (green). Binding partners are indicated below the scheme; binding partners which were experimentally found in myoblasts/skeletal muscle are highlighted in bold. * Interaction was shown for isoform P1f. ** Interaction was shown for isoform P1.

2. Human Plectinopathies

The proposed concept that plectin contributes to the stability and coherence of cells was confirmed by showing that mutations in the human plectin gene (*PLEC*, NM_000445) on chromosome 8q24 cause a variety of human disorders referred to as “plectinopathies”. Plectinopathies belong to the group of rare diseases with an incidence of less than 5 affected individuals for every 10,000 people. As of today, almost 100 disease-causing *PLEC* gene alterations comprising missense, frame-shift, and splice site mutations as well as small in-frame deletions have been reported. Most *PLEC* mutations cause epidermolysis bullosa simplex with muscular dystrophy (EBS-MD, MIM #226670), an autosomal recessive skin blistering disorder associated with progressive muscle weakness [4]. A plethora of additional symptoms has been described for EBS-MD patients in recent years, including cardiac pathology, nail deformation, tooth decay, erosive lesions on the oral or laryngeal mucosa, hoarseness, respiratory complications during infant life, and urethral strictures. In addition to EBS-MD, *PLEC* mutations have been shown to lead to EBS-MD with a myasthenic syndrome (EBS-MD-MyS) or EBS with pyloric atresia (EBS-PA, MIM #612138) [4]. Autosomal dominant *PLEC* mutations (c.5998C > T, p.R2000W; c.8668A > T, p.T2890S; and c.10579C > T, p.R3527C) cause EBS-Ogna (MIM #131950), where the patients suffer from generalized skin blistering or fragile skin without showing any muscular symptoms [10][11][12]. Recently, the first mutations in alternative first exons have been described. A homozygous 9 bp deletion (c.1_9del1f) containing the initiation codon of exon 1f (and therefore resulting in the loss of isoform P1f) was identified in several patients suffering from limb-girdle muscular dystrophy (LGMDR17, previously denoted as LGMD2Q [13], MIM #613723); however, these patients did not show any overt signs of an epidermolytic skin disease [14][15]. Since then, another exon 1f-specific mutation (c.58G > T, p.E20X) has been reported, where three siblings suffered from MD and respiratory problems but who did not present with any skin involvement [16]. Likewise, a homozygous nonsense mutation in exon 1a (c.46C > T), leading to a premature termination codon p.R16X and therefore to the disruption of P1a, an isoform that is hardly expressed in muscle, resulted in a skin-only EBS phenotype without muscle involvement (EBS with nail dystrophy, EBSND, MIM #616487) [17]. Taken together, plectinopathies emerge as complex multi-systemic disorders, primarily affecting tissues exposed to great mechanical stress such as skin and muscle but including more and more additional symptoms and disease manifestations.

3. Clinical Phenotypes and Muscle-Related Disease Manifestations of Human Plectinopathies

3.1. EBS-MD, the Most Common Muscle-Related Plectinopathy

While EBS-MD patients usually suffer from skin blistering early in life, muscle-specific symptoms can occur between early infancy up to the fourth decade of life, with first signs such as gross developmental motor delays (e.g., delayed independent walking), fatigability, muscle weakness, predominantly affecting proximal upper and lower muscle groups, and ptosis. Disease progression is relatively slow; most affected individuals noted the first signs of distal or proximal muscle weakness in the second decade of life. Loss of ambulation was reported for EBS-MD patients between 14 and 47 years of age. Out of 53 EBS-MD cases with genetically determined *PLEC* mutations (see **Table 1**), muscular symptoms have been described for 37 patients (~70%) at the

time of publication. No muscular symptoms were reported for the remaining 16 cases at the time of publication, but one might anticipate that these patients will likely also develop muscular weakness later in life. Blood serum creatine kinase (CK) levels have been reported for five EBS-MD cases, with two patients showing normal and three showing increased values [18][19][20][21][22]. Electromyography (EMG) in EBS-MD patients revealed a myopathic pattern with short duration, polyphasic, and low-amplitude motor unit potentials [19][23][24][25]. Furthermore, fibrillation potentials, positive sharp waves, and pseudomyotonic/myotonic discharges have been reported, whereas nerve conduction and neuromuscular transmission appeared to be normal [19].

Table 1. Patients with genetically determined *PLEC* mutations associated with muscle-related disease manifestations.

Ref	Mutation 1 DNA	Protein	Mutation 2 DNA	Protein	Geno-Type	MD (Onset)	Sex	MB
EBS-MD								
[25]	906 + 19_40del *	V303_P313ins11	906 + 19_40del *	V303_P313ins11	hom.	adolescence	F	no
[26]	954_956dupGCT	L319dup	4222C > T	Q1408X	c.het.	MD not dev. at 4 years; but histological changes	M	yes
[26]	954_956dupGCT	L319dup	4222C > T	Q1408X	c.het.	N/A	M	no
[27]	956T > C	L319P	2807G > A	W936X	c.het.	MD not dev. at 18 years	M	no
[27]	956T > C	L319P	6955C > T	R2319X	c.het.	MD not dev. at 31 years	F	no
[28]	968G > A	R323Q	4840G > T	E1614X	c.het.	twenties	M	yes
[28]	968G > A	R323Q	4840G > T	E1614X	c.het.	MD not dev. at 9 years	F	no
[29]	1530_1531ins36	A510_I511ins12	2677_2685del	Q893_A895del	c.het.	42 years	F	N/A
[30]	1648C > G	R500G	1648C > G	R500G	hom.	MD not dev. at 2 years	M	no
[21]	2264_2266del	F755del	2264_2266del	F755del	hom.	twenties	F	n.s.
[24]	2264_2266del	F755del	3119_3210del	K1040RfsX	c.het.	27 years	M	yes
[31]	2264_2266del	F755del	9194dup	S3066EfsX55	c.het.	MD not dev. at 3 years	M	no

Ref	Mutation 1 DNA	Protein	Mutation 2 DNA	Protein	Geno-Type	MD (Onset)	Sex	MB
[32] [33]	2677_2685del	Q893_A895del	2677_2685del	Q893_A895del	hom.	early thirties	F	no
[32] [33]	2677_2685del	Q893_A895del	2677_2685del	Q893_A895del	hom.	early thirties	F	no
[19]	2677_2685del	Q893_A895del	4930C > T	Q1644X	c.het.	28 years	M	yes
[34]	2694−9_2705del	N/A	5032delG	V1678WfsX65	c.het.	MD not dev. at 5 months	F	no
[33] [35] [36]	3157C > T	Q1053X	5806C > T	Q1936X	c.het.	infancy	M	no
[37]	3341 + 1G > T	N/A	6955C > T	R2319X	c.het.	MD not dev. at 1.5 years	-	no
[37]	4126−4A > G	N/A	7804C > T	Q2602X	c.het.	18 years	-	no
[37]	4216C > T	Q1421X	4216C > T	Q1421X	hom.	teens	-	no
[38]	4294_4306dup	V1436GfsX40	4365delC	S1456RfsX93	c.het.	20 years	M	N/A
[36] [39]	4348C > T	Q1450X	4348C > T	Q1450X	hom.	19 years	F	no
[40]	4549C > T	R1517X	4549C > T	R1517X	hom.	MD not dev. at 24 years	M	no
[36]	4643_4667dup	K1558GfsX89	7120C > T	Q2374X	c.het.	MD not dev. at 7 years	M	no
[41]	4840G > T	E1614X	4840G > T	E1614X	hom.	teens	-	no
[24] [42]	5018_5036del	L1673RfsX64	5018_5036del	L1673RfsX64	hom.	MD not dev. at 5 years	F	yes
[43]	5105_5112del	R1702QfsX14	5105_5112del	R1702QfsX14	hom.	10 years	M	n.s.
[44]	5137C > T	Q1713X	7051C > T	R2351X	c.het.	MD not dev. at 4 years	M	no
[45]	5254C > T	Q1752X	7285C > T	R2429X	c.het.	adolescence	F	n.s.
[18]	5257dupG	E1753GfsX17	5257dupG	E1753GfsX17	hom.	MD not dev. at 3 years	F	no
[46]	5410G > T	E1804X	5410G > T	E1804X	hom.	17 years	M	no

Ref	Mutation 1 DNA	Protein	Mutation 2 DNA	Protein	Geno-Type	MD (Onset)	Sex	MB
[46]	5410G > T	E1804X	5410G > T	E1804X	hom.	15 years	M	n.s.
[47] [48]	5728C > T	Q1910X	5728C > T	Q1910X	hom.	infancy	F	yes
[47] [48]	5728C > T	Q1910X	5728C > T	Q1910X	hom.	infancy	F	n.s.
[37]	5770C > T	Q1924X	N/A	N/A	N/A	30 years	-	no
[32] [33] [36] [49]	5815delC	L1939WfsX6	5815delC	L1939WfsX6	hom.	late twenties	F	yes
[50]	5849_5856dup	E1953WfsX8	5849_5856dup	E1953WfsX8	hom.	infancy	M	n.s.
[42] [49]	5854_5855del	E1952GfsX60	5854_5855del	E1952GfsX60	hom.	MD not dev. at 3 years	F	yes
[22]	5902_5093del	K1968GfsX44	9109_9125del	V3037CfsX78	c.het.	8 years	M	n.s.
[34]	6013G > T	E2005X	13378A > T	K4460X	c.het.	MD not dev. at 6 months	M	no
[51]	6622C > T	Q2208X	8119C > T	Q2707X	c.het.	6 years	M	no
[36]	6549_6582del	L2184RfsX21	13040dupG	I4348HfsX8	c.het.	10 years	F	no
[37]	6682C > T	Q2228X	10456C > T	Q3486X	c.het.	5 years	-	no
[52]	6955C > T	R2319X	6955C > T	R2319X	hom.	25 years	F	no
[20]	7100C > T	R2351X	7100C > T	R2351X	hom.	teens	M	no
[53]	7159G < T	E2387X	7159G < T	E2387X	hom.	adolescence	F	no
[33] [35] [36]	7261C > T	R2421X	12578_12581dup	Y4195DfsX41	c.het.	5 years	M	no
[41]	7261C > T	R2421X	N/A	N/A	N/A	childhood	-	no
[41] [49] [50]	7393C > T	R2465X	7393C > T	R2465X	hom.	early childhood	M	yes
[54]	7468C > T	Q2490X	7468C > T	Q2490X	hom.	MD not dev. at 4 years	M	no

Ref	Mutation 1 DNA	Protein	Mutation 2 DNA	Protein	Geno-Type	MD (Onset)	Sex	MB
[55]	10909C > T	R3637C	10909C > T	R3637C	hom.	yes (onset N/A)	M	no
[55]	10909C > T	R3637C	10909C > T	R3637C	hom.	yes (onset N/A)	M	no
[23] [24]	13459_13474dup	E4492GfsX48	13459_13474dup	E4492GfsX48	hom.	4 years	F	yes
EBS-MD-MyS								
[56]	IVS11 + 2T > G	N/A	10187_10190del	K3395GfsX11	c.het.	birth	M	yes
[57]	1500_1501ins36	R500_V501ins12	1500_1501ins36	R500_V501ins12	hom.	childhood	F	yes
[57]	1500_1501ins36	R500_V501ins12	1500_1501ins36	R500_V501ins12	hom.	childhood	M	no
[58]	2539−2A > G	N/A	11737delC	R3913VfsX30	c.het.	25 years	M	yes
[59]	3086G > A	R1029H	9679_9766del	D3229VfsX21	c.het.	N/A	F	no
[59]	3086G > A	R1029H	9679_9766del	D3229VfsX21	c.het.	N/A	M	no
[59]	3086G > A	R1029H	9679_9766del	D3229VfsX21	c.het.	N/A	M	no
[60] [61]	6169C > T	Q2057X	12043dupG	E4015GfsX69	c.het.	9 years	F	yes
[61]	6955C > T	R2319X	12043dupG	E4015GfsX69	c.het.	3 years	M	yes
EBS-PA								
[62]	913C > T	Q305X	913C > T	Q305X	hom.	N/A	M	no
[63]	913C > T	Q305X	1344G > A	N/A	c.het.	N/A	M	no
[62]	1563_1567del	G522WfsX11	1563_1567del	G522WfsX11	hom.	N/A	F	no
[64]	2680_2693del	E894AfsX84	2680_2693del	E894AfsX84	hom.	N/A	F	no
[62]	2769_2788del	W923CfsX53	2769_2788del	W923CfsX53	hom.	N/A	M	no
[40]	2888dupT	F963PfsX19	N/A	Q2367X	c.het.	MD not dev. at 6 years	F	no
[37]	3342−2A > G	N/A	3902_3903del	Q1301LfsX8	c.het.	N/A	-	no
[63]	3565C > T	R1189X	3565C > T7612C > T	R1189XQ2538X	hom.& c.het	N/A	F	no

Ref	Mutation 1 DNA	Protein	Mutation 2 DNA	Protein	Geno-Type	MD (Onset)	Sex	MB
[37]	4119_4120del	N/A	12499C > T	R4167X	c.het.	MD not dev. at 12 years	-	no
[39]	7396C > T	Q2466X	7633C > T	Q2545X	c.het.	N/A	M	no
[62]	9085C > T	R3029X	9085C > T	R3029X	hom.	N/A	F	no
[65]	11912del	K3971Ter	12499C > T	R4167X	c.het.	birth	M	no
[66]	10984C > T	E3662X	11453_11462del	I3818RfsX90	c.het.	birth	M	no
LGMDR17 (P1f mutation)								
[14]	1_9del **	-	1_9del **	-	hom.	3 years	M	yes
[14]	1_9del **	-	1_9del **	-	hom.	early childhood	M	no
[14]	1_9del **	-	1_9del **	-	hom.	early childhood	F	no
[14]	1_9del **	-	1_9del **	-	hom.	early childhood	F	no
[14]	1_9del **	-	1_9del **	-	hom.	2 years	M	yes
[14]	1_9del **	-	1_9del **	-	hom.	early childhood	M	n.s.
[15]	1_9del **	-	1_9del **	-	hom.	6 years	F	n.s.
[15]	1_9del **	-	1_9del **	-	hom.	26 years	F	n.s.
[15]	1_9del **	-	1_9del **	-	hom.	early childhood	F	n.s.
[15]	1_9del **	-	1_9del **	-	hom.	early childhood	F	yes
[16]	58G > T **	E20X	58G > T **	E20X	hom.	early childhood	M	yes
[16]	58G > T **	E20X	58G > T **	E20X	hom.	N/A	M	no
[16]	58G > T **	E20X	58G > T **	E20X	hom.	N/A	F	no
Other MD-related plectinopathy reports								
[67]	3064C > T	Q1022Ter	11503G > A	G3835S	c.het.	4 years	F	no

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very early age and before the onset of muscular symptoms, it would be advisable to also perform the corresponding measurements in plectinopathy patients at early time points.

Up until now, 13 cases with LGMDR17 due to mutations in exon 1f have been published [14][15][16]. In general, most LGMDR17 patients suffered from early onset limb-girdle syndrome followed by several years of plateau. They presented with delayed motor milestones, difficulties in walking and climbing stairs, easy fatigability, and muscle cramps. A routine EMG examination, performed on the index patient in the initial study, was clearly myopathic [14].

Ref	Mutation 1 DNA	Protein	Mutation 2 DNA	Protein	Geno-Type	MD (Onset)	Sex	MB
[67]	3064C > T	Q1022Ter	11503G > A	G3835S [15]	c.het.	16 years	F	no
[68]	6118C > T	R2040W	10063T > A	F3355I	c.het.	2 years	M	yes

By mutation in exon 1f, one patient suffering from severe MD with EBS-obvious skin disorder was diagnosed with LGMDR17 due to a compound heterozygous *PLEC* mutations in exon 31 and 32 (c.5995C > T, p.R1999W; c.9940T > A, p.F3314I), comparable to "classical" EBS-MD-causing *PLEC* mutations and not restricted to skeletal muscle-specific isoforms [68]. The patient developed the first signs of muscle weakness at 2 years of age (R17 defined as age at the common reference sequence, P1c (also referred to as transcript variant 1 in the databases, GenBank accession number NM_000445) [68]. Two more patients were diagnosed with LGMDR17 and myasthenic symptoms without any skin involvement carried by compound heterozygous *PLEC* mutations in exon 25 and 32 (c.3064C > T, p.Q1022Ter; c.11503G > A, p.G3835S), showing progressive limb and ocular muscle weakness with ptosis and dysphagia [67]. In these patients, serum CK levels were reported to be elevated, evaluation for anti-AChR antibody was negative, and EMG examinations showed a myopathic pattern, but nerve conduction studies revealed normal results [67].

Ref = Reference, MD = muscular dystrophy, MB = muscle biopsy, EBS = epidermolysis bullosa simplex, dup = duplication, del = deletion, hom = homozygous, c.het = compound heterozygous, dev = developed, f = female, M = male, N/A = not available, n.s. = biopsy performed, but data not shown in the respective publication, MyS = myasthenic syndrome, PA = pyloric atresia, LGMDR17 = limb girdle muscular dystrophy type R17. Plectin mutations are listed according to the respective plectinopathy phenotype and position within the gene. Mutations are assigned to the common reference sequence, P1c (also referred to as transcript variant 1 in the databases, GenBank accession number NM_000445) [68]. Two more patients were diagnosed with LGMDR17 and myasthenic symptoms without any skin involvement carried by compound heterozygous *PLEC* mutations in exon 25 and 32 (c.3064C > T, p.Q1022Ter; c.11503G > A, p.G3835S), showing progressive limb and ocular muscle weakness with ptosis and dysphagia [67]. In these patients, serum CK levels were reported to be elevated, evaluation for anti-AChR antibody was negative, and EMG examinations showed a myopathic pattern, but nerve conduction studies revealed normal results [67].

3.3. Emerging Cardiac Pathologies in Plectinopathy Patients

The clinical phenotypes of human plectinopathies with the predominant involvement of skin and skeletal muscle highlight the notion that plectin centrally contributes to the fundamental biomechanical properties of stress-bearing tissues. Accordingly, plectin-related disease manifestations affecting the heart, a striated muscle organ with a high mechanical workload, are indeed plausible. The concept of an importance of plectin in cardiac tissue was further substantiated by several EBS-MD case studies, which reported on cardiac disease manifestations including left ventricular hypertrophy of the heart [23], atrial fibrillation in conjunction with reduced ejection fraction and hypokinetic left ventricular cardiac walls [69], biventricular dilated cardiomyopathy [28], and left ventricular non-compaction cardiomyopathy [20]. In another EBS-MD patient, a postoperative paroxysmal atrial fibrillation after a surgery was noted [19]. In 2016, an EBS-MD patient was reported, who, in addition to the typical skin and skeletal muscle involvement, developed a dilated cardiomyopathy and life-threatening episodes of cardiac arrhythmias necessitating the implantation of a single-chamber cardioverter defibrillator [24]. This work was the first report indicating that life-threatening cardiac disease manifestations may occur before the onset of skeletal muscle symptoms, underscoring the importance of routine cardiological evaluation including electrophysiological and cardiac imaging studies that should be part of the diagnostic work-up of all EBS-MD and EBS-MD-MyS patients. This is also in line with another study, in which a family with several cases of fatal cardiomyopathy was reported, and *PLEC* mutations were finally identified for the index patient [25]. Recently, out of a family with three siblings suffering from LGMDR17 due to a mutation in exon 1f, one patient died from sudden cardiac death after spontaneous pneumothorax [16]. Finally, the role of a *PLEC* missense variant as a risk factor for atrial fibrillation has been controversially discussed [70][71]. Despite its clear clinical relevance, data on plectin in normal and diseased human hearts is very scarce. Up until now, only a single publication exists in which the pathological consequences of *PLEC* mutations on human cardiac tissue have been described [28]. In the reported EBS-MD patient with

progressive biventricular cardiomyopathy due to compound heterozygous *PLEC* mutations, an aberrant plectin staining with the loss of the normal plectin-desmin colocalization at intercalated disks and Z-disks as well as a sarcoplasmic protein aggregation pathology were found.

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