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VIEWPOINT

Marfanoid–progeroid–lipodystrophy syndrome: a newly recognized fibrillinopathy

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We review six previous reports between 2000 and 2014 of seven unrelated patients with mutations in the *FBN1* gene affecting function. All mutations occurred in exon 64 of the *FBN1* gene. A distinctive phenotype consisting of partial manifestations of Marfan syndrome, a progeroid facial appearance, and clinical features of lipodystrophy was present in all individuals. We suggest that this previously unknown genotype/phenotype relationship constitutes a new fibrillinopathy for which the name marfanoid–progeroid–lipodystrophy syndrome would be appropriate.

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A wide range of phenotypes results from mutations affecting function of the fibrillin-1 gene *FBN1* (MIM 134797), collectively called the type 1 fibrillinopathies.[1,2] These include autosomal dominant Marfan syndrome (MFS; MIM 154700), isolated ectopia lentis-2 (MIM 129600), isolated ascending aortic aneurysm and dissections, neonatal MFS, Weill–Marchesani syndrome-2 (MIM 608328), AD (MIM 102370), stiff skin syndrome (MIM 184900), and GD dysplasia-2 (MIM 614185).

Many *FBN1* mutations overlap with classical MFS (MIM 154797), comprising ocular, cardiovascular, and skeletal manifestations as defined by the Ghent diagnostic criteria,[3] but others differ from MFS.[1] The UMD *FBN1* database (http://www.umd.be/FBN1/) as of 28 August 2014 (accessed 20 July, 2015) contains 3077 mutations.[4] That the Marfan phenotype evolves with age has been documented in 259 children with mutations affecting function of the *FBN1* gene.[5] A variable genotype/phenotype relationship has been observed between the type of mutation and Marfan phenotype.[6,7]

Six recent reports describe seven patients with a newly recognized syndrome, the clinical features of which overlap with those of congenital MFS, progeroid syndromes, and lipodystrophy.[8–13] All seven individuals harbor a disease-causing mutation in exon 64, the penultimate exon of the *FBN1* gene (Table 1).

In 2010 Graul-Neumann *et al* described a 27-year-old female patient with clinical features of congenital lipodystrophy, a progeroid facial appearance, and some signs of MFS.[8] Recognizable mutations in seven known lipodystrophy-associated genes (*APGAT2, BSCL2, CAV1, LMNA, PPARG, LMNB2*, and *PTRF-CAVIN*) and two progeroid-associated genes (*LMNA/C* and *ZMPSTE24*) were ruled out by extensive molecular analysis. Additional sequencing of the coding regions of the MFS-associated genes (*FBN1, TGFBR1*, and *TGFBR2*) revealed a *de novo* heterozygous 2-bp deletion c.8155_8156delAA in the coding exon 64 of the *FBN1* gene.[8] (The annotation of this and all the following *FBN1* variants is with respect to NM_000138.4.) This mutation was absent in both parents, the patient's unaffected sister, and in 150 unrelated controls. Multiplex ligation-dependent probe amplification excluded an additional deletion in the other allele. The deletion predicted a frame shift leading to a premature stop codon 17 codons downstream, p.(Lys2719Aspfs*18), resulting in a truncated fibrillin-1 protein. Clinical signs consistent with a MFS phenotype were severe myopia (−11 diopters), lens dislocation, dilatation of the aortic root (32 mm at the age of 16 years; 35 mm at the age of 27 years, both in the 97th percentile for body surface with otherwise normal aortic structures), and lumbosacral dural ectasia. Thus, three major criteria of the Ghent classification were fulfilled.[3] The predominant clinical signs in this patient were an extreme congenital lack of subcutaneous fat tissues and a consequent progeroid appearance of her face and body (Figure 1). Normal levels of fasting glucose, fasting insulin, C-peptide, and normal insulin receptors in cultured fibroblasts excluded diabetes mellitus, insulin resistance, and glucose intolerance. How the *FBN1* mutation may have contributed to the unusual phenotype remained an open question. One of us (EP) had previously followed this patient for 25 years without being able to establish a definitive diagnosis.

This first observation has been supported by five similar reports in six further unrelated individuals.[9–13]

In all seven patients, the mutation is located in exon 64 of the *FBN1* gene, as summarized in Table 1. All were *de novo*; two patients carried the same splice site mutation.[9,12] Garg and Xing[13] excluded other disease-causing genes in their two patients by whole-exome sequencing.

The main clinical features of this newly recognized disorder, summarized in Table 2, include intrauterine growth retardation, birth before 40 weeks gestation, and generalized lack of subcutaneous fat except in the breast and iliac region leading to a senile appearance of the face at birth in all patients (Figure 1). Mental and motor development are within normal limits. Associated clinical signs of MFS are variable. Whereas hyperextensible joints, arachnodactyly, and severe myopia have been observed in 6/7 individuals, other important signs of MFS are not present in all: aortic root dilatation in 3/7, mitral valve prolapse in 3/7, lumbosacral dural ectasia in 2 (in 5 not recorded), pectus excavatus in 3/7, and lens dislocation in 3/7. Scoliosis was reported in two patients aged 23 and 17 years, but not in the others. In view of the differences in ages ranging from 3.5 to 27 years, the clinical findings in these five patients are difficult to interpret and compare. The three manifestations of this disorder, (i) incomplete signs of MFS; (ii) progeroid appearance not associated with other manifestations of early aging; and

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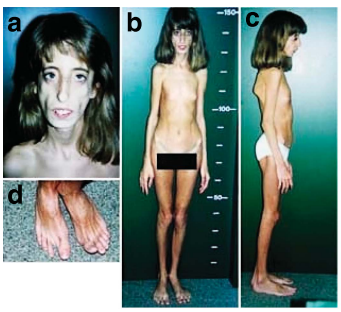
(iii) lipodystrophy not associated with metabolic disturbances, appear to be limited to mutations affecting function of the *FBN1* gene in exon 64 (Figure 2).

Currently, no clear genotype/phenotype relationship has been established with the exception of the so-called neonatal region in *FBN1* exons 24–32 where a subset of mutations is associated with extremely severe manifestations with onset at birth (PMID: 10189088). In addition, all *FBN1* mutations associated with geleophysic (GD) and acromicric dysplasia (AD) are located in exons 41 and 42 (PMID: 21683322), and mutations found in a subset of individuals with stiff skin syndrome are all located within exon 37 (PMID: 20375004). The clustering of *FBN1* mutations found in individuals with the progeroid form suggest the existence of a fourth substantial genotype/phenotype relationship for some *FBN1* mutations.

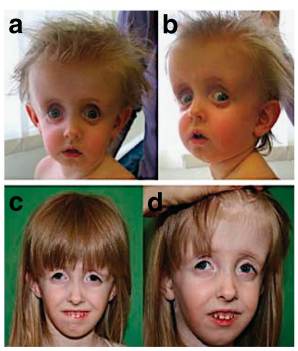
The relationship between genotype and phenotype in the condition considered here raises an interesting question: How can mutations in only one exon lead to such a remarkable pleiotropic phenotype with some variable MFS signs, but otherwise different from classical MFS? The mutations reported to date in the progeroid form of MFS lead to frame shifts and premature truncation codons that are predicted not to be subjected to NMD, the mutations being either small insertions or deletions in coding exon 64 or alter the donor splice site of intron 64. Fibrillin-1 consists of 2871 amino acids and contains multiple epidermal growth factor (EGF)-like domains with both calcium-binding (cbEGF) and non-calcium-binding (EGF) properties that interact with other proteins.[14] It results from proteolytic cleavage of profibrillin-1 at a cleavage site between amino acids arginine 2731 and serine 2732 in exon 64, corresponding to codons 2685–2742 (nt 8052–8226), at the end of the carboxy-terminal domain.[15] Three groups of fibrillins, as 350-kDa extracellular matrix proteins together with transforming growth factor β-binding proteins, are important components of the extracellular matrix.[2,15–17] Jacquinet *et al*[12] noted that exon 64 of profibrillin-1 harbors a highly conserved recognition sequence R-G-R-K-R-R for propeptidase convertases of furin.[17] Defective microfibril function will affect the formation and organization of fibrillin monomers within microfibrils, and interfere with the structure and function of the extracellular matrix in general. As the C-terminal globular domain of fibrillin-1 is structurally similar to other extracellular matrix proteins, fibulin-3 and fibulin4,[18,19] the functional loss of this segment might be critical for the pathogenesis of

Table 1 Marfanoid–progeroid–lipodystrophy syndrome—*de novo* mutations in exon 64 of the *FBN1* gene

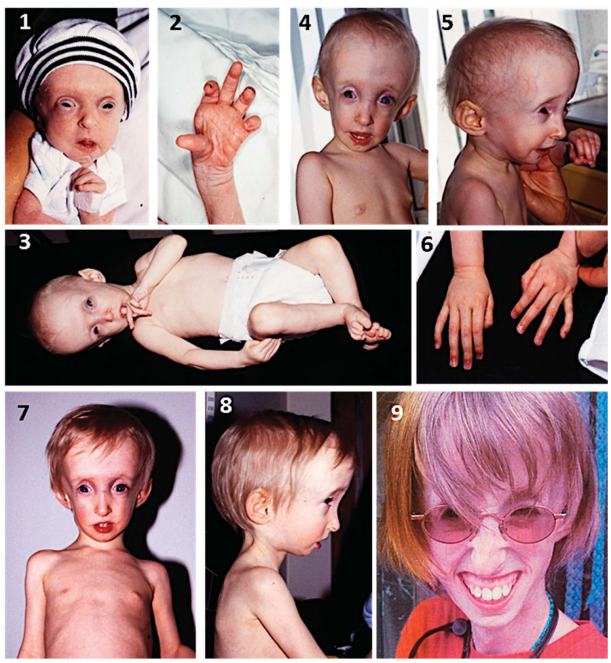
Authors	*Type of mutations and functional consequences*	
Graul-Neumann *et al*[8]	c.8155_8156delAA	p.(Lys2719Aspfs*18)
Horn and Robinson[9]	c.8226+1G>T	Splice mutation, exon 64 skipping
Goldblatt *et al*[10]	c.8156_8175del	p.(Lys2719Thrfs*12)
Takenouchi *et al*[11]	c.8175_8182del8bp	p.(Arg2726Glufs*9)
Jacquinet *et al*[12]	c.8226+1G>A	splice mutation, exon 64 skipping
Garg and Xing[13]	c.8206_8026insA	p.(Thr2736Asnfs*1) (patient 1)
	c.8222T>C	p.(Ile2741Thr) (patient 2)
	c.8226+1G>T	p.(Glu2742Glufs*43)



(Graul-Neumann et al, 2010[8])



(Horn & Robinson, 2011[9])



(Jacquinet et al, 2014[12])

Figure 1 Clinical phenotype of marfanoid–progeroid–lipodystrophy syndrome in three unrelated individuals (from Graul-Neumann *et al*, 2010,[8] Horn & Robinson, 2011,[9] and Jacqinet *et al*, 2014[12]).

Table 2 Main clinical features of Marfanoid–progeroid–lipodystrophy syndrome

Phenotype	*Graul-Neumann et al*[8]	*Horn and Robinson*[9]	*Goldblatt et al*[10]	*Takenouchi et al*[11]	*Jacquinet et al*[12]	*Garg and Xing*[13]	
Age (years)	27	3.5	20	10	16	23	17
Gender	Female	Female	Male	Female	Female	Female	Female
Birth weight (g)	1780	1185	1040	1427	1720	1190	1172
Length (cm)	41.5	40	Not recorded	40	45	40	40
Gestation	36 weeks	32 weeks	28 weeks	34 weeks	39 weeks	32 weeks	32 weeks
OFC (cm)	32	29	Not recorded	30.6	32	29	28.5
Marfanoid signs							
Lens dislocation	Yes (13 years)	No	Yes (16 years)	No	No	Left eye	No
Myopia	Severe	No	Severe	Severe	Severe	Yes	Yes
Aortic root dilat	Yes	No	No	No	Yes	No	Yes
Mitral valve prolapse	Yes	Yes	No	No	No	No	Yes
Dural ectasia	Yes	Not recorded	Not recorded	Yes	Not recorded	Not recorded	
Arachnodactyly	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Pectus excavatum	No	Not recorded	Yes	Yes	No	No	Yes
Hyperextensible joints	Yes	Not recorded	Yes	Not recorded	Yes	Yes	Yes
Scoliosis	No	Not recorded	No	No	No	Yes	Yes
Progeroid facial signs	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Lipodystrophy congenital	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Glucose, insulin	Normal	Not recorded	Normal	Not recorded	Normal	Not recorded	

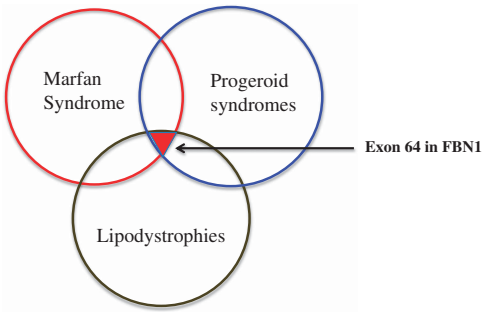


Figure 2 Overlapping clinical features in marfanoid–progeroid–lipodystrophy syndrome, resulting from mutations in exon 64 of the *FBN1* gene.

the progeroid form of MFS. As not all mutations in exon 64 nor all premature truncation or splice site mutations in the 3′ exons of *FBN1* are associated with the progeroid phenotype,[7] the frameshift mutations described in the progeroid form of MFS must alter the function of fibrillin-1 in some specific way.

Further functional studies exploring the quantity and size of the fibrillins produced in this particular clinical context, as well as studies of the extracellular matrix composition are needed to better characterize the pathogenesis of this particular syndrome compared with other fibrillinopathies.

In summary, as specific mutations in the penultimate exon of the *FBN1* gene result in similar clinical manifestations that overlap with those of MFS, progeroid syndromes, and lipodystrophies the designation marfanoid–progeroid–lipodystrophy syndrome appears to be appropriate for this newly defined genetic disorder.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

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