

Evolving phenotype of Marfan's syndrome

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Abstract

Aim—To examine evolution of the physical characteristics of Marfan's syndrome throughout childhood.

Methods—40 children were ascertained during the development of a regional register for Marfan's syndrome. Evolution of the clinical characteristics was determined by repeat evaluation of 10 patients with sporadic Marfan's syndrome and 30 with a family history of the condition. DNA marker studies were used to facilitate diagnosis in those with the familial condition.

Results—Musculoskeletal features predominated and evolved throughout childhood. Gene tracking enabled early diagnosis in children with familial Marfan's syndrome.

Conclusions—These observations may aid the clinical diagnosis of Marfan's syndrome in childhood, especially in those with the sporadic condition. Gene tracking has a role in the early diagnosis of familial Marfan's syndrome, allowing appropriate follow up and preventive care.

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Keywords: Marfan's syndrome; evolving phenotype; marker studies.

Marfan's syndrome is an autosomal dominant disorder of connective tissue characterised by musculoskeletal, ocular, and cardiovascular complications.¹ The underlying molecular defect is caused by mutations in the fibrillin gene on chromosome 15.^{2,3} Fibrillin, a large glycoprotein, is the principal structural component of the elastin associated connective tissue microfibrils. Microfibrils are particularly abundant in the aorta, periosteum, ciliary muscle zonules, and skin, tissues which are classically involved in Marfan's syndrome.⁴ The phenotype in adults is well documented and in the context of classical multisystem involvement the diagnosis of this condition is relatively straightforward.

Diagnosis of Marfan's syndrome in childhood can be problematic as many manifestations are age dependent and therefore the clinical criteria defined in the Berlin nosology⁵ cannot be strictly applied (table 1). This finding, combined with the extreme phenotypic heterogeneity both between different families and within individually affected family members and with the high incidence of sporadic cases (20-30%), contributes to the diagnostic difficulty.¹ Mutation analysis of the fibrillin gene on chromosome 15 is presently unhelpful as mutations have not been found in

Table 1 Diagnostic criteria for Marfan's syndrome according to the Berlin nosology 1986

Cardiovascular	Dilation of ascending aorta* Aortic dissection* Mitral regurgitation Mitral valve prolapse Abdominal aortic aneurysm
Ophthalmic	Ectopia lentis* Severe myopia Retinal detachment, flat cornea, and elongated globe
Neurological Respiratory/ integument	Dural ectasia* Pneumothorax
Skeletal	Striae Herniae Chest wall deformity Vertebral column deformity Arachnodactyly Narrow, high arched palate Tall stature Limb disproportion Abnormal joint mobility Protusio acetabuli

In the absence of a definitely affected first degree relative, there should be skeletal involvement plus involvement of two other systems, one with a major manifestation. *Two system involvement with one major manifestation is required when a first degree relative is affected.

most families, and where they have been defined each kindred seems to have a unique mutation. Gene tracking with a panel of highly informative intragenic microsatellite markers has been established as a useful tool in the presymptomatic diagnosis of familial Marfan's syndrome, allowing appropriate follow up and preventive care.⁶⁻⁸ Previous studies documenting the clinical characteristics of adults and children with severe cardiac abnormalities have given little appreciation of the extracardiac morbidity and the mode and age of presentation in childhood.⁹⁻¹⁶

We present the clinical features of 40 children under the age of 16 years in whom early diagnosis was made by clinical and molecular techniques. The evolution of the phenotypic features is described and may assist in the clinical diagnosis of Marfan's syndrome.

Patients and methods

Patients were ascertained during the development of a regional register for Marfan's syndrome, which was established with the aim of reducing premature death from cardiac complications of this condition. Probands were identified by reviewing case notes in the departments of genetics and cardiology. Diagnosis was confirmed in the proband, which in some cases was the child, and subsequently all first degree relatives at 50% risk of this autosomal dominant condition were screened by physical examination, echocardiography, and ophthalmological examination. Forty children under the age of 16 years were affected during the course of the study. Individuals

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Table 2 Patient characteristics

Patient No	FH/SP	Age at diagnosis (years)	Presenting feature	Height centile	Weight centile	Pal	AR	Sco	PD	PP	ST	FF	Dis	EL	MY	MVP	MR	AD
1	FH	16	MS, cardiac	90th	50th	+	+	+	+	-	-	+	+	-	-	-	-	+
2	FH	14	MS	97th	50th	+	+	+	-	+	-	+	+	-	-	-	-	-
3	SP	7	MS	> 97th	50th	+	+	+	+	+	+	+	+	-	-	-	-	+
4	FH	2.5	MS	> 97th	50th	+	+	+	+	+	-	+	+	-	-	-	-	-
5	SP	16	MS	> 97th	75th	-	+	-	+	+	+	+	+	-	-	+	+	-
6	FH	11	MS	> 97th	50th	+	+	+	+	+	+	+	+	-	-	-	-	+
7	FH	9	MS, cardiac	> 97th	50th	+	+	-	+	+	-	+	+	-	-	-	-	+
8	FH	0.5	MS	> 97th	50th	+	+	-	+	+	-	+	+	-	-	-	-	+
9	SP	14	MS, cardiac	> 97th	75th	+	+	+	+	-	-	+	+	-	-	-	-	+
10	FH	2	MS	> 97th	97th	+	+	-	+	+	-	+	+	-	+	-	-	-
11	FH	3	MS	> 97th	97th	+	+	-	+	+	-	+	+	-	-	-	-	-
12	SP	3	MS, ocular	> 97th	97th	+	+	+	-	+	+	+	+	+	+	-	+	+
13	FH	15.5	MS	> 97th	50th	+	+	+	+	-	+	+	+	-	-	-	-	+
14	FH	13.5	MS	> 97th	75th	+	-	-	-	-	+	+	+	-	-	-	-	-
15	FH	13.5	MS	> 97th	50th	+	+	-	+	-	+	+	+	-	-	-	-	-
16	FH	10	MS	> 97th	25th	+	-	+	+	+	-	+	+	-	-	+	+	-
17	FH	12.5	MS	> 97th	75th	+	+	+	+	+	+	-	+	-	-	-	-	-
18	FH	11	MS	> 97th	75th	+	-	+	-	-	-	-	+	-	-	+	+	-
19	SP	14	MS	> 97th	50th	+	+	+	+	+	+	+	+	-	+	-	-	-
20	FH	10	MS	75th	50th	-	+	+	+	+	+	-	+	-	-	-	-	-
21	SP	14	MS	> 97th	75th	+	+	+	+	+	+	+	+	-	-	-	-	-
22	SP	11	MS, cardiac	> 97th	75th	-	+	+	+	+	+	+	+	-	-	-	-	+
23	SP	11	MS	25th	3rd	+	+	+	+	+	+	+	+	-	+	-	-	-
24	FH	1.5	Ocular	90th	25th	+	+	+	-	-	+	+	+	+	+	-	-	+
25	FH	4	MS	97th	75th	+	+	+	+	+	-	-	+	-	-	-	-	+
26	FH	2.5	MS	75th	10th	+	+	-	+	+	+	+	+	-	-	-	-	-
27	FH	7	MS	97th	50th	+	+	-	-	+	-	+	+	-	-	-	-	+
28	FH	5	MS	75th	50th	+	+	+	+	+	-	+	+	-	-	-	-	-
29	FH	12	MS, cardiac	90th	50th	+	+	-	-	+	-	+	+	-	-	-	-	+
30	FH	4	MS	> 97th	50th	+	+	+	+	+	+	+	+	-	+	-	-	+
31	FH	4	MS	> 97th	25th	+	+	+	+	+	+	+	+	-	-	-	-	+
32	FH	3	MS, ocular	> 97th	50th	+	+	-	+	+	-	+	+	+	+	-	-	-
33	FH	4	MS, ocular	97th	75th	+	+	-	+	+	+	+	+	+	-	-	-	-
34	FH	0.25	MS	> 97th	97th	-	+	+	-	+	-	-	-	-	-	-	-	-
35	FH	14	Ocular	90th	25th	+	+	+	-	+	+	+	+	+	+	-	-	+
36	FH	2	MS, ocular	> 97th	50th	+	+	+	+	+	-	+	+	+	+	+	+	+
37	FH	12	MS	> 97th	50th	+	+	+	+	+	+	+	+	-	-	+	+	-
38	SP	10	MS	> 97th	50th	+	+	+	+	+	+	+	+	-	+	+	-	-
39	SP	14	MS, cardiac	> 97th	50th	+	+	+	+	-	+	+	+	-	+	+	+	-
40	FH	0.25	MS	> 97th	50th	+	+	-	+	-	-	-	+	-	-	-	-	-

FH, family history; SP, sporadic case; MS, musculoskeletal; Pal, high arched palate; AR, arachnodactyly; Sco, scoliosis; PD, pectus deformity; PP, pes planus; ST, striae; FF, facial features; Dis, limb disproportion; EL, ectopia lentis; MY, severe myopia; MVP, mitral valve prolapse; MR, mitral regurgitation; AD, aortic dilatation; +, present; -, absent.

reported here were examined on a minimum of two occasions by the authors and many were seen annually for up to 10 years. Neonates with Marfan's syndrome were not included as they have a different prognosis and clinical picture.^{17,18} All were evaluated by detailed physical examination, ophthalmological examination, and echocardiography. A full family pedigree was obtained and DNA marker studies carried out where appropriate.

Gene tracking was carried out with DNA extracted from peripheral blood. Amplification of polymorphic intragenic markers for the fibrillin gene on chromosome 15 was performed using a polymerase chain reaction. Gene tracking was used only where two or more unequivocally affected individuals were identified within a family.

Results

A diagnosis of Marfan's syndrome was established in 40 children (26 boys and 14 girls) from 29 kindreds. Ten children had sporadic Marfan's syndrome and 30 a clear family history of the condition. The mean (SD) age at diagnosis in patients with a sporadic syndrome (11.4 (3.95) years) was greater than for those with a familial condition (7.31 (5.23) years). In the absence of an unequivocally affected first degree relative, the requirements for diagnosis according to the Berlin criteria are stricter and therefore children with sporadic Marfan's syn-

drome will tend to be more severely affected and inevitably age at diagnosis will be greater than for those with a familial condition. Table 2 summarises the details.

MUSCULOSKELETAL CHARACTERISTICS

The most notable feature at the time of presentation was height equal to or greater than the 97th centile. One child with sporadic Marfan's syndrome did not fulfil this finding having a height on the 25th centile. In this child height was in excess of that predicted by parental heights and therefore still fulfilled the criteria of being tall compared with that of first degree relatives. Two children have received treatment to limit eventual height. Treatment with testosterone was initiated at the age of 14 years in a boy who had attained a height of 197 cm (>97th centile) with no radiological evidence of epiphyseal fusion. An 11 year old girl having reached a height of 178 cm (>97th centile) was treated with ethinyl oestradiol for four years and subsequently attained a height of 189 cm (>97th centile). Interpretation of the upper segment to lower segment ratio to assess limb disproportion in childhood is difficult as the ratio tends to decrease with age,¹⁹ however, fig 1 shows that the ratio declined within the abnormally low range in most patients. Thirty seven individuals had an exaggerated arm span exceeding height by at least 5 cm. Throughout childhood and adolescence, in contrast to

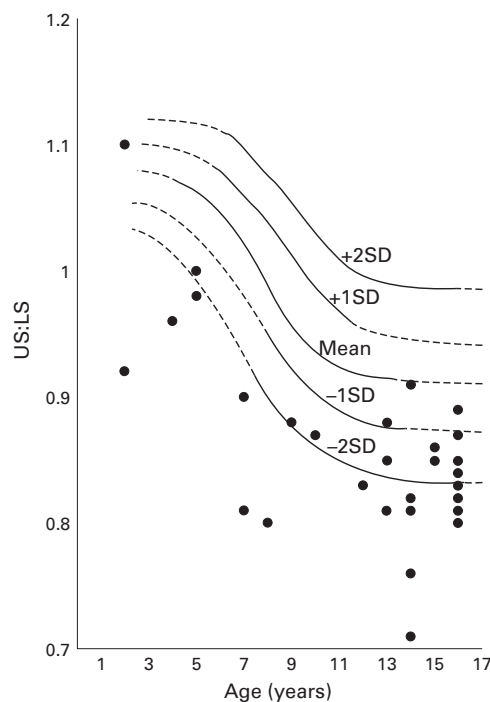


Figure 1 Upper segment : lower segment ratio in Marfan's syndrome.

height, the median weight at the time of diagnosis and on subsequent assessment was about the 50th centile.

Thirty one children had a chest deformity and the youngest age at which this was detected was 18 months. A pectus carinatum deformity was documented in 17 patients and in eight of these there was marked asymmetry, while the excavatum deformity noted in 14 individuals tended to be symmetrical. Abnormality of chest shape was noted before the age of 10 years in all individuals but the deformity often worsened during adolescence. Only two had surgical correction of an excavatum deformity which had progressed rapidly before the age of 10 years.

A scoliosis was present in 27 children. The youngest age at which this was noted was 14 months. The affected parent of this child had severe scoliosis in childhood and underwent spinal fixation with Harrington rods. Twenty three individuals with mild scolioses remain under observation. Four children have been treated successfully with physiotherapy, none has required bracing or Harrington rod insertion. Only two had symptomatic back pain. Back pain in adults with Marfan's syndrome is a common complaint, which suggests that although the scolioses were mild in most individuals, they account for considerable morbidity in later life.

The presence of arachnodactyly was defined clinically by a positive Steinberg sign when the thumb protrudes from the ulnar border of the hand when apposed across the palm²⁰ and a positive Walker-Murdoch sign when a combination of slim wrists and long digits results in noticeable overlap of the thumb and little finger when the wrist is grasped.²¹ This was

found in all except three children and was identifiable from birth in five.

Thirty one children had pes planus which in most was associated with joint hypermobility with a Beighton score of greater than 5/9.²² The most common symptom of joint hypermobility, in addition to finger flexibility, was a tendency for the ankle to turn over easily. This may have contributed to delayed age at walking (greater than 18 months) in eight patients who responded to ankle support boots. Joint dislocation was seen in only three children and involved dislocation of the patella.

A narrow, high arched palate was seen in 36 of 40 individuals. This usually became evident around the age of three to four years. Dental crowding necessitating extraction and dental bracing was a frequent feature in adolescents, the timing of intervention being dependent on the age of the patient and eruption of secondary dentition.

The classical facial features of Marfan's syndrome with mid-face hypoplasia, micrognathia, and down sloping palpebral fissures were noted in 33 children.

The presence of multiple (more than six) red striae distensae unrelated to weight gain over the lumbar region and shoulders is a feature common in many adults with Marfan's syndrome. Although striae were found in 88% of children in the study who were followed up to the age of 16 years, they were noted in only one child before the age of 11 years. This feature may manifest about the time of puberty as rapid growth spurts earlier in childhood do not seem to be associated with development of stretch marks.

Pneumothorax did not occur in any individual in our study. Three children are asthmatic which is not significantly different from the incidence of asthma in the general population.

OCULAR MANIFESTATIONS

Ectopia lentis was found in only six children (15%). This percentage corresponds to the incidence of ectopia lentis in adults with Marfan's syndrome in our study. No patient had lens dislocation before the age of 18 months. Five children with ectopia lentis represent four families in which some, but not all, other affected individuals have lens dislocation. Eleven individuals had severe myopia (greater than 5 dioptres), all diagnosed before the age of 10 years. Two are registered as partially sighted and receive educational support for visual disability. No child experienced retinal detachment.

CARDIOVASCULAR MANIFESTATIONS

Twenty two patients had echocardiographic evidence of cardiovascular abnormality. All were asymptomatic. Aortic root dilatation, defined in relation to body surface area by standard graphs,²³ was shown echocardiographically in 17 patients. This was associated with mild aortic incompetence in one patient. The widest aortic root diameter recorded was 4.5 cm in a 15 year old girl. No individual less than 16 years of age had an aortic dissection.

Major aortic involvement, defined as aortic dissection or need for elective aortic surgery, was documented in 14 of 19 families represented by the 30 children with familial Marfan's syndrome in this study group. Mitral valve prolapse was documented in seven patients, six of whom had associated mitral regurgitation.

EVOLUTION OF THE PHENOTYPE

Neonatal period

No major problems were encountered in the neonatal period. Birth weights were all within two 2 SDs of the mean and did not cluster in the lower range of normal. Birth length was not recorded in most patients. Arachnodactyly was noted in five patients at birth.

Psychomotor development

Age of walking was delayed in eight children who had profound joint hypermobility and ankle laxity. No delay in speech development was reported. Three children have mild learning disability, which may be due to visual impairment in one. This does not differ significantly from the incidence of learning deficit in the general population.

Natural history

The most common presenting feature was musculoskeletal abnormality in the form of tall stature. This represented a marked deviation from the height of unaffected siblings. Height in excess of the 97th centile was apparent in most affected children by the age of 2 years and thereafter the increase in height paralleled normal velocity curves but remained above the 97th centile. A scoliosis became apparent in most patients between the ages of 10 and 14 years (mean (SD) 10.3 (4.4)), although it was evident before the age of 6 years in six patients. The mean (SD) age at which chest wall deformity was manifest was 6.9 (3.3) years. Classical facial features together with a narrow, high arched palate was usually evident about the age of 3 to 4 years. Two of 18 children followed to the age of 16 years did not develop striae distensae. The mean (SD) age at which striae were first noted was 13.9 (1.9) years. The presence of pes planus occurred in most patients from about the age of 2–3 years.

Ocular abnormality in the form of ectopia lentis was the presenting feature in six children and was noted between the ages of 18 months and 14 years. No child presented with lens dislocation above this age. Significant myopia was detected in 11 children between the ages of 4 and 10 years.

The mean (SD) age at which aortic root dilatation was detected echocardiographically was 11.0 (3.9) years. In two unrelated familial children there were no other family members with major aortic involvement. The remaining 11 familial children all had a family history of major aortic involvement. The earliest age at which aortic root dilatation was documented was 18 months. The affected parent of this child had an aortic dissection at the age of 17 years.

DNA marker studies

In 10 families, intragenic polymorphic markers allowed the particular copy of the fibrillin gene that co-segregated with Marfan's syndrome to be identified in affected family members. Eighteen children who were at risk from these 10 families were tested and found to carry this copy of the fibrillin gene, suggesting that they had inherited the condition. In 12 children with familial Marfan's syndrome from nine different kindreds it was not possible to perform gene tracking as there were inadequate numbers of unequivocally affected individuals in previous generations. In these small families in which few meioses are available for scoring, there is potential for error as genetic heterogeneity has been reported by one group of investigators.²⁴

Discussion

Previous reports of children with Marfan's syndrome have concentrated on severely affected individuals with prominent cardiovascular involvement and have included patients with the more severe sporadic neonatal form of this condition.^{9–12, 17} Neonatal Marfan's syndrome has a poor prognosis with death from cardiovascular involvement occurring usually in the first year of life.¹⁸ All reported cases to date have been sporadic, some of which have been due to new dominant mutations clustering in the same region of the fibrillin gene.^{25, 26} As such, neonatal Marfan's syndrome is a separate condition and it has been excluded from this study. The clinical features of 40 patients with classical Marfan's syndrome under the age of 16 years are presented here. Thirty patients had a family history of the syndrome and were therefore screened to make an early diagnosis and institute appropriate follow up and preventive care. The identification of two or more unequivocally affected individuals within a family has enabled the use of a gene tracking technique to confirm clinical diagnosis in a child with a 50% risk of the condition in whom evolution of the phenotype is incomplete at initial assessment. This allows appropriate ophthalmic, cardiac, and orthopaedic follow up and intervention to be planned and has enabled observation of the development of the phenotypic characteristics with increasing age.

The most frequent musculoskeletal findings at presentation were a combination of tall stature (>97th centile), limb disproportion, pectus deformity, classical facial features, high arched palate, and arachnodactyly. A pectus deformity and development of a scoliosis often became more prominent during the pubertal growth spurt, at which time many children developed noticeable red striae distensae over the lumbar region and shoulders. A minimum of four skeletal features was present in each patient at the time of last evaluation.

Severe cardiovascular abnormalities were not documented as frequently suggested in previous studies.^{9–12, 14} This possibly may be explained by the exclusion of neonatal patients with Marfan's syndrome. Some 55% of patients less than 16 years of age had

cardiovascular involvement but remained asymptomatic. Echocardiographic findings of mild aortic root dilatation were found in 17 patients, usually becoming evident about the age of 9–15 years. This suggests that the absence of aortic root enlargement cannot be used to exclude a diagnosis of Marfan's syndrome in a 'marfanoid' child before skeletal growth is complete. A previous study of serial measurements of the aortic root diameter in children with Marfan's syndrome suggested that the aortic root diameter was at or just above the upper limits of normal throughout childhood. In most individuals serial measurements demonstrated that growth velocity of the aortic root resembles that in normal individuals¹⁴; however, an increase in growth velocity of the aorta may signify increasing likelihood of aortic dissection or rupture. Although this is rare in childhood or adolescence, it is well documented in the late teens and early twenties. Annual echocardiographic assessment is essential throughout childhood to detect early aortic root dilatation and follow the rate of change of aortic root diameter. Not all patients who satisfy the diagnostic criteria for Marfan's syndrome are at risk of severe cardiovascular complications and a reliable assessment of cardiovascular risk cannot be safely made on the basis of events in preceding generations.²⁷

Ophthalmological assessment in our study found that lens dislocation and severe myopia occurred in only about 25% of patients with Marfan's syndrome. A previous study prospectively evaluated 62 children with Marfan's syndrome who were diagnosed before the age of 5 years and suggested that the mean (range) age of lens dislocation was 2.7 years with a range of 2 months to 6 years of age.^{28, 29} This suggests that repeat ocular examination is necessary in early childhood to detect lens dislocation but that myopia is likely to be the main complication after the age of about 6 years. Attention must be paid to correction of acuity in early childhood to prevent development of amblyopia.

Diagnosis in patients with familial Marfan's syndrome is confounded by considerable intra-familial phenotypic heterogeneity. From the families represented in this study severe aortic complications clearly do not affect all individuals within a given pedigree and the age at which aortic events occur within a family is also widely variable. Likewise ocular features do not necessarily 'breed true'. Musculoskeletal characteristics also show intrafamilial variability but to a lesser extent. As with the sporadic syndrome, the phenotype will evolve with age. Gene tracking is useful to provide an early diagnosis when no or minimal skeletal characteristics are evident at the first referral in childhood. It is also of benefit in excluding the diagnosis in a child with a 50% risk of Marfan's syndrome.

Diagnosis of Marfan's syndrome in a child with no family history of the condition is more difficult and diagnostic dilemmas arise as the full phenotype may not be manifest at the initial assessment. There is a high prevalence of

isolated features of Marfan's syndrome in the general population, such as joint hypermobility, mitral valve prolapse, early myopia, and scoliosis, which contributes to the difficulty in making a specific diagnosis of sporadic Marfan's syndrome. Furthermore, genetic heterogeneity must be recognised as many of these skeletal features are found in other connective tissue disorders such as the related condition Beal's congenital contractural arachnodactyly, caused by mutations within the fibrillin gene on chromosome 5,³⁰ homocysteinuria, and Ehlers-Danlos syndrome.

The detection rate of mutations within the fibrillin gene on chromosome 15 is extremely low (10–20%), and with one exception, all mutations identified have been unique to a single family.^{3, 31, 32} This precludes the widespread use of direct mutation analysis for the diagnosis of sporadic Marfan's syndrome. Some 25% of individuals with Marfan's syndrome will have no family history of the condition and diagnosis will therefore rely on clinical criteria. Children who do not fulfil these criteria but who have at least four skeletal features, particularly a pectus deformity, scoliosis, and limb disproportion in association with tall stature, in the absence of overt cardiovascular or ocular manifestations, should undergo periodic re-evaluation as more diagnostic features may become apparent with increasing age.

We recommend that annual review should be undertaken to assess growth and vertebral column abnormality in children in whom sporadic Marfan's syndrome is suspected on the basis of four or more skeletal characteristics. Annual slit lamp examination to the age of 6 years will detect ectopia lentis in most children.²⁸ Thereafter visual acuity testing is appropriate. Yearly echocardiographic examination is recommended even in the absence of overt cardiovascular abnormality as aortic dilatation is clinically silent. By the time that skeletal maturity is attained and the full musculoskeletal phenotype is apparent, most affected individuals will have evidence of cardiovascular abnormality and clinical diagnosis of Marfan's syndrome is simplified. There may still be individuals who will develop cardiovascular features for the first time during adulthood and therefore continued echocardiographic surveillance may be appropriate in a few individuals who do not fulfil the full clinical diagnostic criteria³ but who have six or more musculoskeletal features in adulthood.

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