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Does genotype predict development of the spinal deformity in patients with diastrophic dysplasia?

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Abstract This study analyzed whether genotype can be used to predict development of spinal deformity in patients with diastrophic dysplasia (DD). Severity and natural history of scoliosis vary among patients, but the magnitude of the curves is similar among siblings. Plain radiographs were taken of 69 patients aged 16 years or older. The degree of scoliosis was measured according to Cobb's method. Blood samples were collected from patients clinically diagnosed as having DD and the genotype was determined. Fifty-six patients were found to be homozygous for the Finnish founder DTD mutation, DTDST_{Fin}. Of these 56, 51 (91%) had scoliosis, with an average curve of 43° (range 12°–188°). The DTDST_{Fin}/R279 W genotype was found in nine patients, and of these, eight (89%) had scoliosis, with an average curve of 34° (range 11°–70°). The DTDST_{Fin}/nondetermined genotype was found in four patients. Three (75%) of them had scoliosis,

with an average curve of 126° (range 77°–188°). Statistical analysis found no difference in the prevalence or magnitude of curves between subgroups. The development and severity of the scoliosis cannot, therefore, be predicted from the genotype. It seems possible that scoliosis development is affected by several genes as well as by external factors.

Keywords Osteochondrodysplasia · Diastrophic dysplasia · Scoliosis · Genotype · DTDST gene

Introduction

Diastrophic dysplasia (DD) is a rare skeletal dysplasia with autosomal recessive inheritance. Pathognomonic clinical and radiological findings are short-limbed short stature, multiple joint contractures and early degeneration of joints [8, 11, 19]. Spinal deformities, including scoliosis, cervical kyphosis and exaggerated lumbar lordosis, are often associated with DD [11, 12, 13] (Fig. 1).

The DD gene, located in chromosome 5 [3, 4], encodes a sulfate transporter (diastrophic dysplasia sulfate transporter, DTDST), whose defective function leads to depletion of intracellular sulfate and undersulfation of sulfated macromolecules such as cartilage matrix proteoglycans [4]. This in turn leads to abnormally soft cartilage with compromised resistance to loading.

Scoliosis is common in patients with DD [2, 11, 17, 19]. In the largest study, the prevalence of scoliosis was 88% in patients aged 16 years or older [13]. The severity

Fig. 1A, B Clinical findings in an 11-year-old girl with DD. Note the disproportionate short stature, joint contractures of the limbs, and rigid thoracolumbar scoliosis

of scoliosis varies greatly both clinically and radiologically [11, 13, 19]. Although clinical variability is known among siblings [5], the magnitude of their curves tends to be similar [13]. It is not known to what extent genotype, i.e. different mutations in the DTDST gene [4], affects the development of the spinal deformity.

We investigated the natural history of scoliosis in adult patients with DD and compared our findings with genotype data to establish whether the development and severity of the scoliosis could be predicted from the genotype.

Materials and methods

Patients

We studied 69 unselected patients, 46 of them females and 23 males from all over Finland. The age of the patients at the time of the first radiograph of the spine ranged from newborn to 78 years (average 16.3 years). All patients were 16 years or older at the time of their last radiograph. Eight families had two affected adult siblings and three families had three affected adult siblings.

Genotype

Blood samples were collected from patients clinically diagnosed as having DD, and their genotypes were determined as previously described [4].

Radiographs

Standard anteroposterior and lateral radiographs of the spine were taken in an upright standing position. Consecutive radiographs (two or more) were available for 58 patients (84%), with an average follow-up of 20 years (range 2–41 years). Only radiographs taken before the operation were included for four patients who had undergone surgical treatment of the thoracic and/or lumbar deformity.

Statistical analysis

The statistical significance of the prevalence of scoliosis between patients with different genotypes was analyzed by the chi-squared test, and the severity of scoliosis in different groups by Kruskal-Wallis analysis of variance. The statistically significant *P*-value was defined as *P*<0.05 and the highly significant value as *P*<0.01.

Results

Genotype

The most prevalent mutation in our patients, designated DTDST_{Fin}, is a GT>GC transition in the splice donor site of a 5' untranslated exon leading to reduced levels of DTDST RNA. Fifty-six patients were homozygous for this mutation (DTDST_{Fin}/DTDST_{Fin}). An arginine-to-tryptophan substitution at residue 279 (R279 W) was found in nine

Fig. 2 A, B Posteroanterior standing radiographs of two female siblings, aged 24 and 29 years old, with the DTDST_{Fin}/DTDST_{Fin} genotype. They had 82° and 91° deformities, respectively. C Posteroanterior standing radiograph of a male patient with DTDST_{Fin}/R279 W genotype. At the age of 16 years, scoliosis was 70°. Note the similarities in magnitude between all three curves

Table 1 Distribution of curve patterns in different subgroups (Th thoracic, Th-L thoracolumbar, L lumbar)

Subgroup	Th	Th-L	L
DTDST _{Fin} /DTDST _{Fin}	31	6	14
DTDST _{Fin} /R279 W	3	3	2
DTDST _{Fin} /?	2	1	—

patients; all were compound heterozygotes (DTDST_{Fin}/R279 W). In four patients one mutant allele could not be determined (DTDST_{Fin}/?).

Prevalence of scoliosis

Sixty-two (90%) of the 69 patients had scoliosis. Of the patients with mutation of the DTDST_{Fin}/DTDST_{Fin} genotype, scoliosis was found in 51 patients (91%) (Fig. 2A,B); the average deformity was 43° (range 12°–188°). Scoliosis with an average curve of 34° (range 11°–70°) was found in eight (89%) of the patients with DTDST_{Fin}/R279 W genotype (Fig. 2C). Scoliosis with an average curve of 126° (range 77° to 188°) was found in three (75%) of the patients with the DTDST_{Fin}/? genotype.

Different patterns of curvature and their distribution in the whole patient population are given in Table 1. Patterns of curvature among siblings are given in Table 2.

In statistical analysis, there was no difference in the prevalence of scoliosis ($P=0.586$) or magnitude of the curves ($P=0.320$) between different subgroups.

Discussion

Scoliosis is common in patients with DD, and in this study the prevalence was even higher than reported previously [11, 17, 19]. Scoliosis appears to be an almost constant feature in this rare disease. However, we found no correlation between genotype and the development and severity of the scoliosis. This may be due to the small number of patients with DTDST_{Fin}/? genotype. If this group had been larger, the difference between this subgroup and the other two subgroups probably would have been statistically significant.

We chose spine and scoliosis to study the correlation between genotype and phenotype, as there is only little, if any, progression in severity after the cessation of growth [11, 14], which is in contrast, for example, to early degeneration and contractures in joints, which proceed in adulthood [7, 10, 18, 19]. On the other hand, a definite value for comparison between subgroups (magnitude of the curve) can be obtained.

Matsui et al. studied the correlation between genotype and phenotype in patients with achondroplasia and hypochondroplasia [9], two allelic disorders with different mutations. Their findings showed a firm statistical correlation between genotype and phenotype, although there were a few exceptional cases with phenotypic overlap between the two conditions. The mode of inheritance may be associated with differences in correlation between genotype and phenotype. Achondroplasia and hypochondroplasia are inherited dominantly [15], whereas DD is inherited recessively. On the other hand, mutations in pa-

Table 2 Scoliosis in 11 families with siblings. Details of sex, age at time of the last radiograph, location of the apex of the primary curve (Th, Th-L, or L), side of the curve, and magnitude of the curve in the last radiograph

	Sex	Age	Genotype	Apex	Convexity	Magnitude (°)
Family 1	F	34	DTDST _{Fin} /?	Th	Right	188
	M	28	DTDST _{Fin} /?	Th	Left	112
Family 2	M	50	DTDST _{Fin} /DTDST _{Fin}	L	Left	40
	M	39	DTDST _{Fin} /DTDST _{Fin}	Th	Right	26
	F	52	DTDST _{Fin} /DTDST _{Fin}	Th-L	Left	36
Family 3	F	56	DTDST _{Fin} /R279 W	L	Left	37
	F	63	DTDST _{Fin} /R279 W	Th-L	Left	35
Family 4	F	29	DTDST _{Fin} /DTDST _{Fin}	Th	Left	91
	F	24	DTDST _{Fin} /DTDST _{Fin}	Th	Right	82
Family 5	F	21	DTDST _{Fin} /DTDST _{Fin}	Th	Left	20
	F	32	DTDST _{Fin} /DTDST _{Fin}	Th-L	Left	36
Family 6	F	43	DTDST _{Fin} /DTDST _{Fin}	L	Right	12
	F	53	DTDST _{Fin} /DTDST _{Fin}	Th	Right	14
Family 7	F	33	DTDST _{Fin} /DTDST _{Fin}	Th-L	Right	14
	M	25	DTDST _{Fin} /DTDST _{Fin}	Th	Left	12
Family 8	F	52	DTDST _{Fin} /R279 W	Th	Right	11
	F	51	DTDST _{Fin} /R279 W	Th	Left	20
Family 9	F	47	DTDST _{Fin} /DTDST _{Fin}	Th	Left	15
	F	45	DTDST _{Fin} /DTDST _{Fin}	L	Left	20
	F	50	DTDST _{Fin} /DTDST _{Fin}	Th	Right	23
Family 10	M	33	DTDST _{Fin} /DTDST _{Fin}	L	Left	20
	F	40	DTDST _{Fin} /DTDST _{Fin}	Th	Right	60
Family 11	F	41	DTDST _{Fin} /DTDST _{Fin}	L	Left	35
	F	30	DTDST _{Fin} /DTDST _{Fin}	L	Right	22
	F	34	DTDST _{Fin} /DTDST _{Fin}	Th	Left	12

tients with achondroplasia and hypochondroplasia are “gain of function mutations”, whereas mutations in patients with DD are “loss of function mutations”. Mutations in the fibroblast growth factor receptor 3 (FGFR3) gene [1, 16] cause continuous activation of fibroblast growth factor receptor 3 and thus ultimately inhibition of linear bone growth [6]. Mutations in the DTDST gene, on the other hand, cause impaired function of its product and lead to undersulfation of proteoglycans in cartilage matrix [4].

We conclude that scoliosis is almost a hallmark feature of DD. Although curve patterns are similar among sib-

lings, development and severity of the scoliosis cannot be predicted from the genotype. As well as external factors, several genes appear to affect the development of the scoliosis.

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References

1. Bellus GA, McIntosh I, Smith EA, Aylsworth AS, Kaitila I, Horton WA, Greenhaw GA, Hecht JT, Francomano CA (1995) A recurrent mutation in the tyrosine kinase domain of fibroblast growth factor receptor 3 causes hypochondroplasia. *Nat Genet* 10:357–359
2. Bethem D, Winter RB, Lowell L, Moe JH, Bradford DS, Loenstein JE, Langer LO (1981) Spinal disorders of dwarfism. *J Bone Joint Surg Am* 63:1412–1425
3. Hastbacka J, Kaitila I, Sistonen P, de la Chapelle A (1990) Diastrophic dysplasia gene maps to the distal long arm of chromosome 5. *Proc Natl Acad Sci* 87:8056–8059
4. Hastbacka J, de la Chapelle A, Mahtani MM, Clines G, Reeve-Daly MP, Daly M, Hamilton BA, Kusumi K, Trivedi B, Weaver A, Coloma A, Lovett M, Buckler A, Kaitila I, Lander ES (1994) The diastrophic dysplasia gene encodes a novel sulfate transporter: positional cloning by fine-structure linkage disequilibrium mapping. *Cell* 78:1073–1087
5. Horton WA, Rimoin DL, Lachman RS, Skovby F, Hollister DW, Spranger J, Scott CI, Hall JG (1978) The phenotypic variability of diastrophic dysplasia. *J Pediatr* 93:609–613
6. Horton WA (1997) Fibroblast growth factor receptor 3 and the human chondrodysplasias. *Curr Opin Pediatr* 9:437–442
7. Kopits SE (1976) Orthopedic complications of dwarfism. *Clin Orthop* 114:153–179

8. Lamy M, Maroteaux P (1960) Le nanisme diastrophique. *Presse Med* 68:1977–1980
9. Matsui Y, Yasui N, Kimura T, Tsumaki N, Kawabata H, Ochi T (1998) Genotype phenotype correlation in achondroplasia and hypochondroplasia. *J Bone Joint Surg Br* 80:1052–1056
10. Peltonen JJ, Hoikka V, Poussa M, Paavilainen T, Kaitila I (1992) Cementless hip arthroplasty in diastrophic dysplasia. *J Arthroplasty* 7S:369–376
11. Poussa M, Merikanto J, Ryoppy S, Marttinen E, Kaitila I (1991) The spine in diastrophic dysplasia. *Spine* 16:881–887
12. Remes V, Marttinen E, Poussa M, Kaitila I, Peltonen J (1999) Cervical kyphosis in diastrophic dysplasia. *Spine* 24:1990–1995
13. Remes V, Poussa M, Peltonen J (2001) Scoliosis in patients with diastrophic dysplasia – a new classification. *Spine* 26:1689–1697
14. Remes V, Tervahartiala P, Poussa M, Peltonen J (2001) Thoracic and lumbar spine in diastrophic dysplasia. A clinical and magnetic resonance imaging analysis. *Spine* 26:187–195
15. Scott CI Jr (1976) Achondroplastic and hypochondroplastic dwarfism. *Clin Orthop* 114:18–30
16. Shiang R, Thompson LM, Zhu YZ, Church DM, Fielder TJ, Bocian M, Winokur, ST, Wasmuth JJ (1994) Mutations in the transmembrane domain of FGFR3 cause the most common genetic form of dwarfism, achondroplasia. *Cell* 78:335–342
17. Tolo VT, Kopits SE (1983) Spinal deformity in diastrophic dysplasia. *Orthop Trans* 7:31–32
18. Vaara P, Peltonen J, Poussa M, Merikanto J, Nurminen M, Kaitila I, Ryoppy S (1998) Development of the hip in diastrophic dysplasia. *J Bone Joint Surg Br* 80:315–320
19. Walker BA, Scott CI, Hall JG, Murdoch JL, McKusick VA (1972) Diastrophic dwarfism. *Medicine (Baltimore)* 51:41–59