

ORIGINAL ARTICLE

Clinical features and genetic analysis of Korean patients with Loey–Dietz syndrome

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Loey–Dietz syndrome (LDS) is an inherited disorder that is characterized by the triad of arterial tortuosity and aneurysms, hypertelorism and a bifid uvula or cleft palate. The disease is caused by heterozygous mutations in the genes encoding transforming growth factor β receptors 1 and 2 (*TGFBR1* and *TGFBR2*, respectively). However, studies of patients with LDS are limited in Korea. From June 2000 to December 2010, 13 patients (10 probands) diagnosed with LDS were enrolled. The multidisciplinary data of the patients were reviewed retrospectively. The frequency of each clinical manifestation in Korean patients with LDS was compared with Western populations as described in the report by Loey *et al.* Twelve (92%) of the 13 LDS patients had arterial tortuosity, 9 (69%) patients had hypertelorism and 11 (85%) patients had bifid uvula or cleft palate. Mutations in either *TGFBR1* or *TGFBR2* were detected in nine probands (90%). Of the mutations, five novel mutations were detected; three in *TGFBR2* and two in *TGFBR1*. Blue sclera and atrial septal defect were not observed in the Korean patients, and the frequency of blue sclera was significantly lower in our Korean population than previously-described Western population (0 vs 40%; $P=0.005$). Despite the restricted number of patients in our study, we identified five novel mutations in the *TGFBR1* and *TGFBR2* genes and, except for blue sclera, no differences in phenotype are apparent between Korean patients and Western patients. *Journal of Human Genetics* (2012) 57, 52–56; doi:10.1038/jhg.2011.130; published online 24 November 2011

Keywords: arterial tortuosity; bifid uvula; hypertelorism; Loey–Dietz syndrome; transforming growth factor β receptors

INTRODUCTION

Loey–Dietz syndrome (LDS), a genetic disorder affecting the connective tissue, is caused by mutations in the genes encoding transforming growth factor β receptors 1 and 2 (*TGFBR1* and *TGFBR2*, respectively).¹ LDS is characterized by the triad of hypertelorism, a bifid uvula or cleft palate and generalized arterial tortuosity with widespread vascular aneurysm and dissection.² The diagnosis of LDS is made according to clinical presentations in the proband and family members, and molecular genetic testing of the *TGFBR1* and *TGFBR2* genes.³ Early and accurate diagnosis is essential to patients with LDS because they are at increased risk for aortic dissection or rupture at an early age. To date, most studies related to LDS are based on data obtained from the European and American populations. There are few data regarding the clinical and genetic characteristics of the Korean patients with LDS,

leaving doubt as to whether or not there are racial differences in the physical presentation of LDS between the Oriental and Western populations.

Therefore, we investigated the clinical and genetic characteristics in the Korean patients with LDS, and compared clinical manifestations between Korean patients and Western populations as reported by Loey *et al.*²

MATERIALS AND METHODS

Subjects

We reviewed 22 consecutive patients who were suspicious of having LDS from June 2000 to December 2010. All had undergone genetic analysis of the *TGFBR1* and *TGFBR2*. Of them, we examined 13 Korean patients who were diagnosed with LDS. The diagnoses of these patients were made based on clinical presentation, physical examinations, radiological findings and genetic

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Received 7 April 2011; revised 18 October 2011; accepted 25 October 2011; published online 24 November 2011

tests. Information about deceased family members, as well as other family members who were suspected of being affected, was obtained from the probands. Clinical data were obtained from clinical database and medical records. This study received Institutional Review Board approval, and informed consent was waived for this retrospective study.

DNA sequence analysis

Genomic DNA was extracted from peripheral blood leukocytes with the Wizard Genomic DNA Purification Kit (Promega, Madison, WI, USA), following the manufacturer's instructions. The coding exons and the flanking introns of the *TGFBR1* and *TGFBR2* on chromosome 9q33-q34 and 3p22, respectively, were amplified using primers designed by the authors (available upon request). Direct sequencing was performed with the BigDye Terminator Cycle Sequencing Ready Reaction kit (Applied Biosystems, Foster City, CA, USA) on an ABI 3100 Genetic Analyzer (Applied Biosystems).

Definitions

The methods used for assessing clinical and radiological examinations and cutoff limits are described below. To evaluate aortic root aneurysm, we measured the aortic diameter at the level of the sinuses of Valsalva from at least two images of transthoracic echocardiography. The diameter was corrected for age and body surface area, and interpreted as a Z-score.⁴ If transthoracic echocardiographic evaluations were not available, we measured at the level of the sinuses of Valsalva on multi-detector computed tomography angiography. Aortic root aneurysm was defined as an aortic diameter at the sinus of Valsalva ≥ 2 Z-score. The diagnosis of ectopia lentis was based on slit-lamp examination after maximal dilatation of the pupil. Scoliosis was evaluated using coronal reformatted multi-detector computed tomography images. The Lippman-Cobb method was used to measure the degree of scoliotic curvature with a Cobb angle $> 20^\circ$ representing a positive finding.

Statistical analysis

The significances of differences in percentages were evaluated using Fisher's exact test with SPSS software (version 17.0; SPSS Inc., Chicago, IL, USA). Descriptive statistics are reported as medians (ranges). Statistical significance was determined as a *P*-value < 0.05 .

RESULTS

Clinical findings

Clinical features of the 13 Korean patients are summarized in Table 1. The 13 patients, six males and seven females, ranged in age from 5 to 56 years, with a median age of 24 years at last follow-up. Aortic root aneurysm or dissection was present in 12 (92%) patients. Nine patients (69%) underwent graft surgery in the ascending aorta at a median age of 17 years. Arterial tortuosity was found in 12 (92%) patients. Cleft palate or abnormal uvula was found in 11 (85%) patients. Hypertelorism, craniosynostosis, arachnodactyly and scoliosis were found in nine (69%) patients. Pectus deformity and joint laxity were found in eight patients, patent ductus arteriosus in four and dural ectasia in three. Blue sclera and atrial septal defect were not observed in this study. None of our patients had ectopia lentis, but three (23%) had dolichostenomelia, findings that are typical of Marfan syndrome. Of the 13 patients, 2 (patient 3 and 10-II) fulfilled the Ghent nosology and 1 (patient 3) fulfilled the revised Ghent nosology for Marfan syndrome.

Table 2 summarizes the frequency of phenotypic manifestations in the Korean and Western patients. Incidences of hypertelorism, cleft palate/bifid uvula, aortic root aneurysm/dissection, arterial tortuosity and other clinical manifestations described by Loey *et al.*² were not significantly different between the Korean and Western populations. The frequency of blue sclera was significantly lower in the Korean population than in the Western population (0 vs 40%; *P*=0.005). Ectopia lentis was not observed either in the Korean or Western populations.

Genetic analysis

The nature and location of each detected mutation is shown in Figure 1. We identified heterogenous mutations in the *TGFBR1* or *TGFBR2* genes in 9 out of 10 probands. *TGFBR2* mutations were found in six probands and *TGFBR1* mutations were found in three probands. The mutations in probands 2–9 occurred *de novo*, whereas mutation p.Arg495X segregated with disease in proband 1. Pedigrees of the family 1 and 10 are shown in Figure 2. Four mutations have previously been described in the literature including three in *TGFBR2* (p.Arg495X,² p.Ser449Phe,⁵ p.Trp504X⁶) and one in *TGFBR1* (p.Arg487Gln⁷). Four of the five novel mutations identified in this study were missense mutations in the serine–threonine kinase domain mutations including p.Asp266Tyr (c.796G>T) and p.Thr375Arg (c.1124C>T) in the *TGFBR1*, and p.His378Arg (c.1130A>G) and p.Cys514Arg (c.1540T>C) in the *TGFBR2*. The remaining mutation was a complex deletion-insertion mutation in the *TGFBR2* gene with preservation of the open reading frame (c.915_916delCCinsTCATG; p.Gln306delinsHisGlu). Additionally, we performed direct sequencing analysis of the fibrillin-1 gene (*FBN1*) in eight patients and detected no mutations.

DISCUSSION

In the present study, we describe 13 patients from 10 families with LDS characterized by hypertelorism, bifida uvula or cleft palate, and generalized arterial tortuosity with ascending aortic aneurysm and dissection. All 13 patients showed the typical manifestations of LDS with variable individual expressions of the clinical features. Incidences of clinical manifestations, except for blue sclera, did not show significant differences between the Korean and Western populations. Furthermore, we found three novel mutations in the *TGFBR2* gene and two novel mutations in the *TGFBR1* gene.

Clinical findings

Accurate diagnosis of LDS has important medical and personal implications for patients, yet diagnostic criteria have not been well established. In current practice, the diagnosis of LDS is based on characteristic clinical findings in the proband and family members, and confirmation by molecular genetic testing of the *TGFBR1* and *TGFBR2* genes.³ However, to date, characteristic clinical findings are based on data obtained from Europeans and Americans, and data supporting racial differences in patients with LDS from other populations have not been documented. Although the relatively small size of our study population have influenced our results, our data indicate that the frequencies of clinical manifestations in our patients and in patients described by Loey *et al.* are similar, except for blue sclera. These similarities may reflect the fact that characters varying across populations, such as height, arm span and body weight, are not considered in the diagnosis for LDS. Therefore, our observations suggest that clinical findings derived from the analyses of Caucasians are sufficient for diagnosing the Korean patients.

In previous studies, ~75% of affected individuals had LDS type I with craniofacial manifestations (bifida uvula/cleft palate, craniosynostosis and hypertelorism) and ~25% had LDS type II with cutaneous manifestations (velvety and translucent skin, easy bruising and atrophic scar), whereas all of our patients had features typical of LDS type I.^{3,8} To our knowledge, in previous studies of Oriental populations, patients with LDS type II were not identified.^{9–13} Accordingly, a large-scale clinical study is needed to identify whether differences in the frequencies of LDS type I and II can be attributed to racial differences.

Table 1 Clinical results for the 13 Korean patients with LDS

Mutation	TGFB _{R2}						TGFB _{R1}			TGFB _{R1/2} (-)									
	1		2		3		4		5		6		7		8		9		10
Individual	1-I	1-II	2	3	4	5	6	7	8	9	10-I	10-II	10-III						
Age (years)	56	34	11	22	12	48	17	5	33	13	53	24	25						
Sex	F	F	M	M	F	F	M	F	F	M	M	M	F						
<i>Typical</i>																			
Hypertelorism	+	+	+	+	+	-	-	+	-	+	-	+	+						
Cleft palate or abnormal uvula	+	+	+	+	+	-	+	+	+	-	+	+	+						
Aortic-root aneurysm	+	+	+	+	+	+	+	+	+	+	+	-	+						
Arterial tortuosity	+	+	+	+	+	+	+	+	+	-	+	+	+						
<i>Craniofacial</i>																			
Craniosynostosis	+	-	+	+	+	+	-	+	+	+	-	-	+						
Malar hypoplasia	-	-	+	+	+	-	-	-	-	+	-	-	-						
Retrognathia	+	-	+	-	+	-	-	-	-	+	-	-	-						
Blue sclera	-	-	-	-	-	-	-	-	-	-	-	-	-						
Ectopia lentis	-	-	-	-	-	-	-	-	-	-	-	-	-						
<i>Skeletal</i>																			
Dolichostenomelia	-	-	+	+	+	-	-	-	-	-	-	-	-						
Arachnodactyly	-	-	+	+	+	-	+	+	-	+	+	+	+						
Pectus deformity	-	-	+	+	-	-	+	+	+	+	-	+	+						
Scoliosis	-	+	+	+	+	-	+	+	+	+	-	+	-						
Talipes equinovarus	-	-	-	-	+	-	-	-	-	-	-	+	+						
Camptodactyly	-	-	-	-	-	-	-	-	-	-	+	+	-						
Joint laxity	-	-	-	+	+	-	+	+	-	+	+	+	+						
Cervical-spine instability	-	-	-	+	+	-	+	-	-	-	-	-	-						
Dural ectasia	-	-	-	-	+	-	+	-	-	-	-	-	+						
<i>Cutaneous</i>																			
Velvety skin	-	-	-	-	-	-	-	-	-	-	-	+	-						
Translucent skin	-	-	-	-	+	-	-	-	-	-	-	-	-						
<i>Other</i>																			
Patent ductus arteriosus	-	-	+	+	+	-	-	+	-	-	-	-	-						
Atrial septal defect	-	-	-	-	-	-	-	-	-	-	-	-	-						
Developmental delay	-	-	-	-	+	-	-	+	-	-	-	-	-						
Mutations in the fibrillin-1 gene	-	-	-	-	NA	-	NA	-	-	NA	NA	NA	-						
The Ghent criteria	-	-	-	+	-	-	-	-	-	-	-	+	-						
The revised Ghent criteria	-	-	-	+	-	-	-	-	-	-	-	-	-						

Abbreviations: F, female; LDS, Loey-Dietz syndrome; M, male; NA, not available; TGFB_R, transforming growth factor β receptor.

LDS has many similarities to Marfan syndrome with regard to cardiovascular disorders or skeletal manifestations.^{14,15} In fact, two patients in our study fulfilled the Ghent criteria for Marfan syndrome and one patient fulfilled the revised Ghent criteria. One patient (patient 3) was confirmed by having no mutations in the fibrillin-1 gene and mutation of TGFB_{R2}. The other patient (patient 10-II) was suspected LDS as he did not reveal TGFB_{R1} or TGFB_{R2} mutation despite conventional clinical findings and a positive family history.

Genetic analysis

Due to difficulties in the clinical approach to patients with various vascular involvements, with or without aortic root dilatation and LDS

cardinal features, genetic analysis is essential to clarify the diagnosis and to assess the management and prognosis of the patient.^{11,16} In our study, although 10 patients with the TGFB_R mutations had phenotypic variability, genetic analysis can be used to differentiate LDS from Marfan syndrome or from familial thoracic aortic aneurysm and dissection. Prior studies have suggested that some TGFB_{R2} mutations are present in families whose members have not only LDS (p.Arg495X),² but also classic Marfan syndrome (p.Ser449Phe),⁵ or incomplete Marfan syndrome (p.Trp504X)⁶ and TGFB_{R1} mutations are present in patients with familial thoracic aortic aneurysm and dissection (p.Arg487Gln).⁷ However, our patients with the p.Arg495X, p.Ser449Phe, p.Trp504X and p.Arg487Gln had features typical of LDS type I. These findings suggest that patients who carried the same

Table 2 Frequency of clinical features of LDS in Korean patients versus Western patients

	Present study (n=13)	Loeys <i>et al.</i> ² (n=40)	P-value
Hypertelorism	9/13 (69)	36/40 (90)	0.090
Cleft palate or abnormal uvula	11/13 (85)	36/40 (90)	0.627
Aortic-root aneurysm	12/13 (92)	39/40 (98)	0.434
Arterial tortuosity	12/13 (92)	21/25 (84)	0.643
Craniosynostosis	9/13 (69)	19/40 (48)	0.213
Malar hypoplasia	4/13 (31)	24/40 (60)	0.109
Retrognathia	4/13 (31)	20/40 (50)	0.338
Blue sclera	0/13 (0)	16/40 (40)	0.005
Ectopia lentis	0/13 (0)	0/40 (0)	—
Dolichostenomelia	3/13 (23)	7/40 (18)	0.692
Arachnodactyly	9/13 (69)	28/40 (70)	1.0
Pectus deformity	8/13 (62)	27/40 (68)	0.743
Scoliosis	9/13 (69)	20/40 (50)	0.338
Talipes equinovarus	3/13 (23)	18/40 (40)	0.204
Camptodactyly	2/13 (15)	15/40 (38)	0.183
Joint laxity	8/13 (62)	27/40 (68)	0.743
Cervical-spine instability	3/13 (23)	7/40 (18)	0.692
Velvety skin	1/13 (8)	11/40 (28)	0.253
Translucent skin	1/13 (8)	13/40 (33)	0.145
Patent ductus arteriosus	4/13 (31)	14/40 (35)	1.0
Atrial septal defect	0/13 (0)	9/40 (17)	0.092
Developmental delay	2/13 (15)	6/40 (15)	1.0

Abbreviation: LDS, Loews-Dietz syndrome.
 Values are n (%).

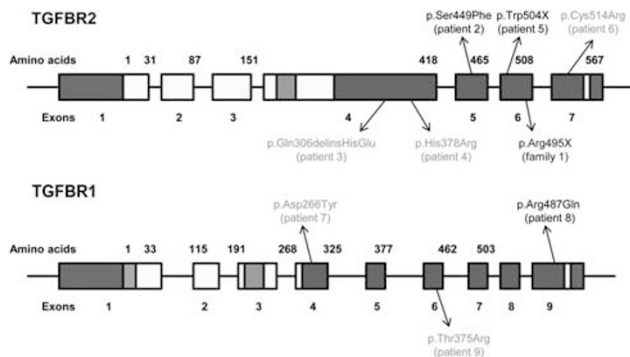


Figure 1 Mutations in the *TGFBR2* and the *TGFBR1* genes. Novel mutations are indicated in red type. The different exons are numbered and intervening sequences are shown as black lines. The colored boxes represent the exons encoding the extracellular domain of the receptor (yellow), the transmembrane domain (green) and the serine-threonine kinase domain (blue). *TGFBR2* mutations were found in seven patients (six probands), and *TGFBR1* mutations were found in three patients (three probands). A full color version of this figure is available at the *Journal of Human Genetics* journal online.

mutation as the affected proband could still exhibit phenotypic variability. In addition, the novel mutations that were found in this study further expand the spectrum of known *TGFBR1* and *TGFBR2* mutations in LDS patients.

In agreement with previous reports, the mutations were located on the intracellular kinase domain of the receptor in exon 4–7 of the *TGFBR2* gene and exon 4, 6 and 9 of the *TGFBR1* gene.^{1,5,7,10,12} Mutations found in the *TGFBR* gene associated with LDS are essentially missense and only rare instances of nonsense or deletions have been identified.^{2,6} In our study, two probands had a mutation leading to a premature termination codon, whereas seven probands had a mutation leading to an altered protein. Interestingly, family 1 and patient 5, both with a nonsense mutation of *TGFBR2*, had few systemic manifestations and underwent their first cardiovascular surgery at a late age. Patient 1-II suffered from acute aortic dissection type B at the age of 33, and patient 5 suffered from acute aortic dissection type A at the age of 45. Our study and previous studies show that patients with nonsense mutations of either the *TGFBR1* or *TGFBR2* genes are generally older than patients with missense mutations, with the exception of one 7-year-old patient (Table 3). On the other hand, the seven patients with missense mutations of the *TGFBR1* or *TGFBR2* genes who underwent graft surgery in the ascending aorta due to acute root aneurysm or dissection ranged in age from 4 to 22 years, with a median age of 11. Accordingly, further studies of a large sample are needed to understand the relationship between the mutation type and the phenotype, and to identify whether nonsense mutation of *TGFBR* may have milder systemic features and later-onset cardiovascular event than missense mutation of *TGFBR*.

Patients in the family of proband 10 did not show mutations in *TGFBR* despite having clinical features typical of LDS. It is reported that 5% of LDS patients are negative in the genetic study of *TGFBR1* or *TGFBR2* mutations.^{3,17} Theoretically, sequence analysis of these two genes can only detect point mutations so that a large deletion or duplication, deep intronic mutation, and promoter site mutations may be possible to miss a diagnosis for LDS. However, as of yet, family 10 should be regarded as a suspected LDS patient as there has been no report that a large deletion or duplication, deep intronic mutation or promoter site mutation was found in LDS case.

Our study has several limitations. First, our study sample is unlikely to represent an unbiased fraction of individuals from the general population, as many of the enrolled patients were referred to our hospital to undergo aortic surgery. Second, the relatively small size of our study population may have influenced our results. Therefore, further studies with larger numbers of patients are needed to verify clinical and genetic features of LDS in the Korean patients. Such studies will help clinicians to better understand this serious, but

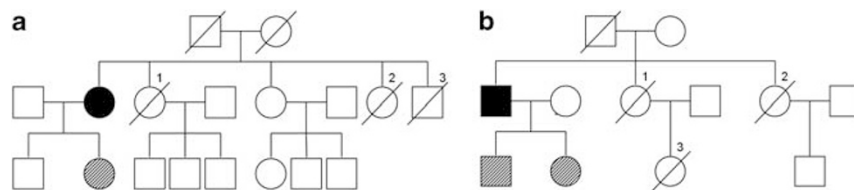


Figure 2 Pedigrees of the family of proband 1 and 10. Squares indicate male family members, circles indicate female family members, and symbols with slashes indicate deceased family members. Open symbols indicate unaffected family members, filled symbols indicate probands, and shaded symbols indicate family members who are or were probably affected. (a) Pedigree of the family of proband 1. Individual 1 suffered from acute aortic dissection type A at the age of 48 and died a sudden death at the age of 50. Individual 2 and 3 died a sudden death at the age of 4 and the month of 7, respectively. (b) Pedigree of the family of proband 10. Individual 1 died of non-cardiovascular disease at the age of 34, individual 2 suffered from acute aortic dissection type A at the age of 42 and individual 3 died a sudden death at the age of 22.

Table 3 Clinical features in patients with nonsense mutations of the *TGFBR* in previous and present studies

Age	Sex	Gene	Location	Nucleotide change	Amino-acid change	Age at graft surgery of aorta (years)	Cardiovascular system	LDS-specific symptoms	Inheritance	Reference number
35	M	TGFBR2	Exon 6	c.1483C>T	p.Arg495X	34	Acute aortic dissection, type B	Pectus excavatum, exotropia	NA	10
NA	M	TGFBR2	Exon 6	c.1483C>T	p.Arg495X	NA	Aortic aneurysm and dissection	Bifid uvula, hypertelorism, club feet, pectus deformity	Familial	2
24	M	TGFBR2	Exon 6	c.1483C>T	p.Arg495X	-	Arterial tortuosity	Hypertelorism, bifid uvula, joint laxity, scoliosis, camptodactyly, pectus excavatum, retrognathia	Familial	9
34	F	TGFBR2	Exon 6	c.1483C>T	p.Arg495X	30	Acute aortic dissection, type B	Hypertelorism, bifid uvula, scoliosis, Pectus excavatum, arachnoidactyly	Familial de novo	Present study 17
40	M	TGFBR2	Exon 6	c.1489C>T	p.Arg497X	NA	Dilated ascending aorta	-	Familial	6
33	M	TGFBR2	Exon 6	c.1489C>T	p.Arg497X	NA	+	-	Familial	6
43	F	TGFBR2	Exon 6	c.1511G>A	p.Trp504X	-	-	Bifid uvula	Familial de novo	6
48	F	TGFBR2	Exon 6	c.1512G>A	p.Trp504X	45	Acute aortic dissection, type A	Craniosynostosis, flat foot	Familial de novo	Present study 6
7	F	TGFBR2	Exon 7	c.1531C>T	p.Gln511X	NA	+	-	Familial	6
25	M	TGFBR2	Exon 7	c.1562G>A	p.Trp521X	NA	+	-	Familial de novo	6

Abbreviations: F, female; LDS, Loews-Dietz syndrome; M, male; NA, not available; TGFBR, transforming growth factor β receptor. +, organ system involved; -, organ system not involved.

overlooked, disorder and to develop more appropriate therapeutic strategies.

In conclusion, although the number of the patients was limited, we identified five novel mutations in the *TGFBR1* and *TGFBR2* genes in 13 patients affected with LDS. We suggested that no differences in phenotype are apparent between Korean patients and Western patients, except for the manifestation of blue sclera.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

ACKNOWLEDGEMENTS

We thank the patients for their participation in this study and members of the Cardiac and Vascular Center, Department of Laboratory Medicine and Genetics, Department of Thoracic and Cardiovascular Surgery, Department of Orthopedic Surgery, Department of Pediatrics and Department of Ophthalmology.

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