

ORIGINAL ARTICLE

Aneurysm Syndromes Caused by Mutations in the TGF- β Receptor

Bart L. Loeys, M.D., Ph.D., Ulrike Schwarze, M.D., Tammy Holm, M.D., Bert L. Callewaert, M.D., George H. Thomas, Ph.D., Hariyadarshi Pannu, Ph.D., Julie F. De Backer, M.D., Gretchen L. Oswald, M.S., Sofie Symoens, B.S., Sylvie Manouvrier, M.D., Ph.D., Amy E. Roberts, M.D., Francesca Faravelli, M.D., M. Alba Greco, M.D., Reed E. Pyeritz, M.D., Ph.D., Dianna M. Milewicz, M.D., Ph.D., Paul J. Coucke, Ph.D., Duke E. Cameron, M.D., Alan C. Braverman, M.D., Peter H. Byers, M.D., Anne M. De Paepe, M.D., Ph.D., and Harry C. Dietz, M.D.

ABSTRACT

BACKGROUND

From the McKusick–Nathans Institute for Genetic Medicine (B.L.L., T.H., G.H.T., G.L.O., H.C.D.) and the Department of Surgery (D.E.C.), Johns Hopkins University School of Medicine, and the Kennedy Krieger Institute (G.H.T.) — both in Baltimore; the Departments of Pathology and Medicine, University of Washington, Seattle (U.S., P.H.B.); the Center for Medical Genetics, Ghent University Hospital, Ghent, Belgium (B.L.L., B.L.C., J.F.D.B., S.S., P.J.C., A.M.D.P.); the Department of Medicine, University of Texas, Houston (H.P., D.M.M.); the Department of Clinical Genetics, University Hospital, Lille, France (S.M.); the Department of Clinical Genetics, Harvard Medical School, Boston (A.E.R.); the Department of Human Genetics, Ospedale Galliera, Genoa, Italy (F.F.); the Department of Pathology, New York University School of Medicine, New York (M.A.G.); the Department of Medicine, University of Pennsylvania, Philadelphia (R.E.P.); the Department of Medicine, Washington University School of Medicine, St. Louis (A.C.B.); and Howard Hughes Medical Institute, Chevy Chase, Md. (H.C.D.). Address reprint requests to Dr. Loeys at the Center for Medical Genetics, Ghent University Hospital, Bldg. 0K5, De Pintelaan 185, 9000 Ghent, Belgium, or at bart.loeys@ugent.be.

The Loeys–Dietz syndrome is a recently described autosomal dominant aortic-aneurysm syndrome with widespread systemic involvement. The disease is characterized by the triad of arterial tortuosity and aneurysms, hypertelorism, and bifid uvula or cleft palate and is caused by heterozygous mutations in the genes encoding transforming growth factor β receptors 1 and 2 (*TGFBR1* and *TGFBR2*, respectively).

METHODS

We undertook the clinical and molecular characterization of 52 affected families. Forty probands presented with typical manifestations of the Loeys–Dietz syndrome. In view of the phenotypic overlap between this syndrome and vascular Ehlers–Danlos syndrome, we screened an additional cohort of 40 patients who had vascular Ehlers–Danlos syndrome without the characteristic type III collagen abnormalities or the craniofacial features of the Loeys–Dietz syndrome.

RESULTS

We found a mutation in *TGFBR1* or *TGFBR2* in all probands with typical Loeys–Dietz syndrome (type I) and in 12 probands presenting with vascular Ehlers–Danlos syndrome (Loeys–Dietz syndrome type II). The natural history of both types was characterized by aggressive arterial aneurysms (mean age at death, 26.0 years) and a high incidence of pregnancy-related complications (in 6 of 12 women). Patients with Loeys–Dietz syndrome type I, as compared with those with type II, underwent cardiovascular surgery earlier (mean age, 16.9 years vs. 26.9 years) and died earlier (22.6 years vs. 31.8 years). There were 59 vascular surgeries in the cohort, with one death during the procedure. This low rate of intraoperative mortality distinguishes the Loeys–Dietz syndrome from vascular Ehlers–Danlos syndrome.

CONCLUSIONS

Mutations in either *TGFBR1* or *TGFBR2* predispose patients to aggressive and widespread vascular disease. The severity of the clinical presentation is predictive of the outcome. Genotyping of patients presenting with symptoms like those of vascular Ehlers–Danlos syndrome may be used to guide therapy, including the use and timing of prophylactic vascular surgery.

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MUTATIONS IN THE GENES ENCODING transforming growth factor β (TGF- β) receptors 1 and 2 (*TGFBR1* and *TGFBR2*, respectively) have recently been found in association with a continuum of clinical features. On the mild end, the mutations have been found in association with a presentation similar to that of Marfan's syndrome or with familial thoracic aortic aneurysm and dissection,^{1,2} and on the severe end, they are associated with a complex phenotype in which aortic dissection or rupture commonly occurs in childhood.³ This complex phenotype is characterized by the triad of widely spaced eyes (hypertelorism); a bifid uvula, cleft palate, or both; and generalized arterial tortuosity with widespread vascular aneurysm and dissection. Previously described in 10 families, the phenotype has been classified as the Loeys–Dietz syndrome (Online Mendelian Inheritance in Man number, 609192).³

Affected patients have a high risk of aortic dissection or rupture at an early age and at aortic diameters that ordinarily would not be predictive of these events. Surgical intervention is generally successful, and this characteristic distinguishes patients with the Loeys–Dietz syndrome from those with vascular Ehlers–Danlos syndrome, a differential diagnosis often considered in patients with mutations in *TGFBR1* and *TGFBR2*. The importance of careful clinical and molecular characterization to identify patients and families at risk for arterial dissection and rupture cannot be overemphasized, because it allows the use of a structured approach to intervention and leads to informed counseling regarding the risk of recurrence, concerns related to pregnancy, and guidelines for clinical management. To examine the range of the clinical effects resulting from mutations in *TGFBR1* and *TGFBR2*, we identified mutations in the 10 original probands³ and an additional 42 probands and their family members.

METHODS

STUDY SUBJECTS

The study was approved by the institutional review board at each participating institution. Written informed consent was obtained from all adult patients and from the parents or guardians of children who were unable to give consent but did provide assent when possible.

Patients and families were evaluated prospectively at the time of presentation to a medical

genetics clinic for the diagnosis and management of conditions associated with aortic aneurysm. Families were assigned to the Loeys–Dietz syndrome type I category if craniofacial involvement consisting of cleft palate, craniosynostosis, or hypertelorism was observed. Families assigned to the Loeys–Dietz syndrome type II category had no evidence of these findings but some had an isolated bifid uvula. All probands with type II had at least two of the findings associated with vascular Ehlers–Danlos syndrome (visceral rupture, easy bruising, wide and atrophic scars, joint laxity, and translucent skin, velvety skin, or both). They had previously received a provisional diagnosis of vascular Ehlers–Danlos syndrome after evaluation by a medical geneticist, but the diagnosis had been ruled out by studies of type III collagen biosynthesis before the start of this study.

The natural-history component of the study involved the 10 families previously reported to have Loeys–Dietz syndrome type I.³ Relatives of all probands were included if they carried the same mutation as the proband or if their clinical presentation allowed for the assignment of affected status.

CRANIOFACIAL SEVERITY INDEX

The craniofacial severity index was used to determine the severity of symptoms of the Loeys–Dietz syndrome. Scores were assigned by two of the study investigators. The scores can range from 0 to 11, with higher scores indicating more severe abnormalities. Patients were given a score of 2 for marked hypertelorism, 1 for subtle hypertelorism (interpupillary distance at or around the 97th percentile), or 0 for no hypertelorism. Patients received a score of 0 in the absence of cleft palate and craniosynostosis, a score of 6 if both were present, and a score of 3 if one was present. For malformations of the uvula, a bifid uvula was given a score of 3, midline raphe a score of 2, a broad uvula with no cleft a score of 1, and a normal uvula a score of 0.

BIOCHEMICAL AND MOLECULAR STUDIES

The synthesis of type III collagen by cultured dermal fibroblasts was evaluated in all patients who had presented with vascular Ehlers–Danlos syndrome before the study, as described previously.⁴ Sequencing of the *TGFBR1* and *TGFBR2* genes was performed as described previously.³ The causal nature of the missense mutations was inferred on the basis of new occurrence in

sporadic cases, on the basis of segregation with disease in familial cases, or on the basis of the absence of mutation in at least 200 ethnically matched control chromosomes or substitution of evolutionarily conserved residues (see Table 1 of the Supplementary Appendix, available with the full text of this article at www.nejm.org).

STATISTICAL ANALYSIS

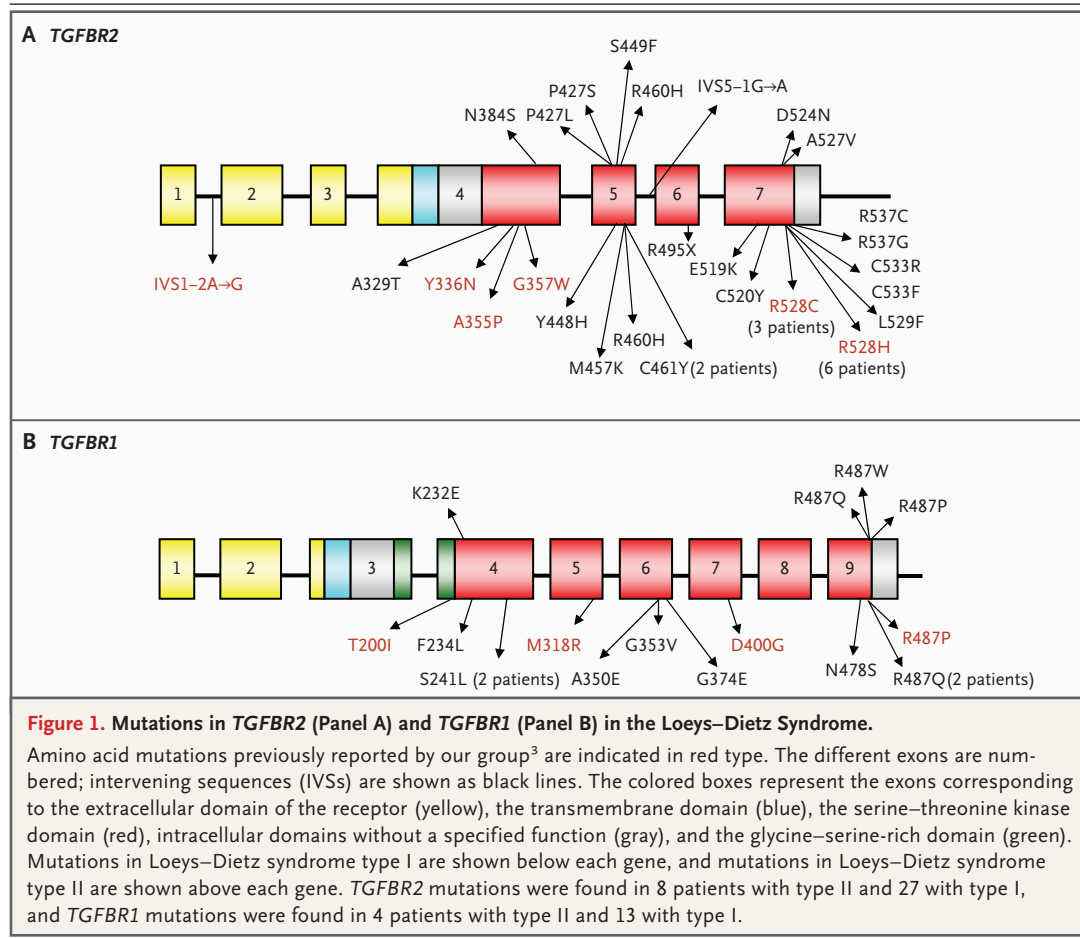
Pearson's analysis was used to calculate the correlation between the craniofacial-severity-index score and the age at the first cardiovascular event. We used life-table methods (SPSS statistical software, version 12.0) to construct Kaplan–Meier curves and to estimate the median survival.

RESULTS

SPECTRUM OF TGFBR MUTATIONS

We identified 52 families with the Loey–Dietz syndrome, including the 10 we described in our earlier report.³ We identified causative TGFBR

mutations in 42 new probands. Overall, 29 mutations were found in TGFBR2 and 13 were found in TGFBR1. The nature and location of each mutation are shown in Figure 1. Six amino acid mutations have been previously described in the literature: five in TGFBR2 (R537C,¹ S449F,¹ R528H,³ R528C,³ and R460H^{2,5}) and one in TGFBR1 (R487P³). The mutation occurred as a new event in the context of sporadic disease in 27 of 42 families (64 percent). With the exception of one splice-site mutation (IVS5–1G→A) and one nonsense mutation (R495X), both in TGFBR2, all newly identified mutations in this series were missense mutations in or immediately flanking the serine–threonine kinase domains of either receptor. The splice-site mutation resulted in the inclusion of 30 nucleotides in intron 5 in the mature messenger RNA, leading to the insertion of 10 amino acids (data not shown). One patient was heterozygous for two mutations in TGFBR2: P427S and V387M. The latter substitution has previously been described as a somatic mutation in breast



cancer,⁶ but we found it in 2 of 200 control chromosomes. We identified another variant in *TGFBR2* (M373I) that was present in 1 of 200 control chromosomes but has previously been reported as a somatic event in a primary squamous-cell carcinoma.⁷ Finally, we did not identify any *TGFBR* mutations in a cohort of 70 unrelated patients with aortic or arterial aneurysms but no systemic findings of connective-tissue disease.

CLINICAL PRESENTATION OF PROBANDS

We identified mutations in all 30 new probands whose phenotype was consistent with Loeys–Dietz

syndrome type I. Their clinical characteristics, along with those of the 10 previously described probands,³ are presented in Table 1. Of the 30 newly identified probands, 21 had mutations in *TGFBR2* and 9 in *TGFBR1* (Fig. 1). Besides the triad of hypertelorism, cleft palate or bifid uvula, and arterial tortuosity with aneurysms, patients in this group had additional cardiovascular, skeletal, and cutaneous findings (Table 1 and Fig. 2A). Neurocognitive signs included delayed development in six patients, hydrocephalus in six patients, and Arnold–Chiari malformation in four patients. When present, delayed development was not al-

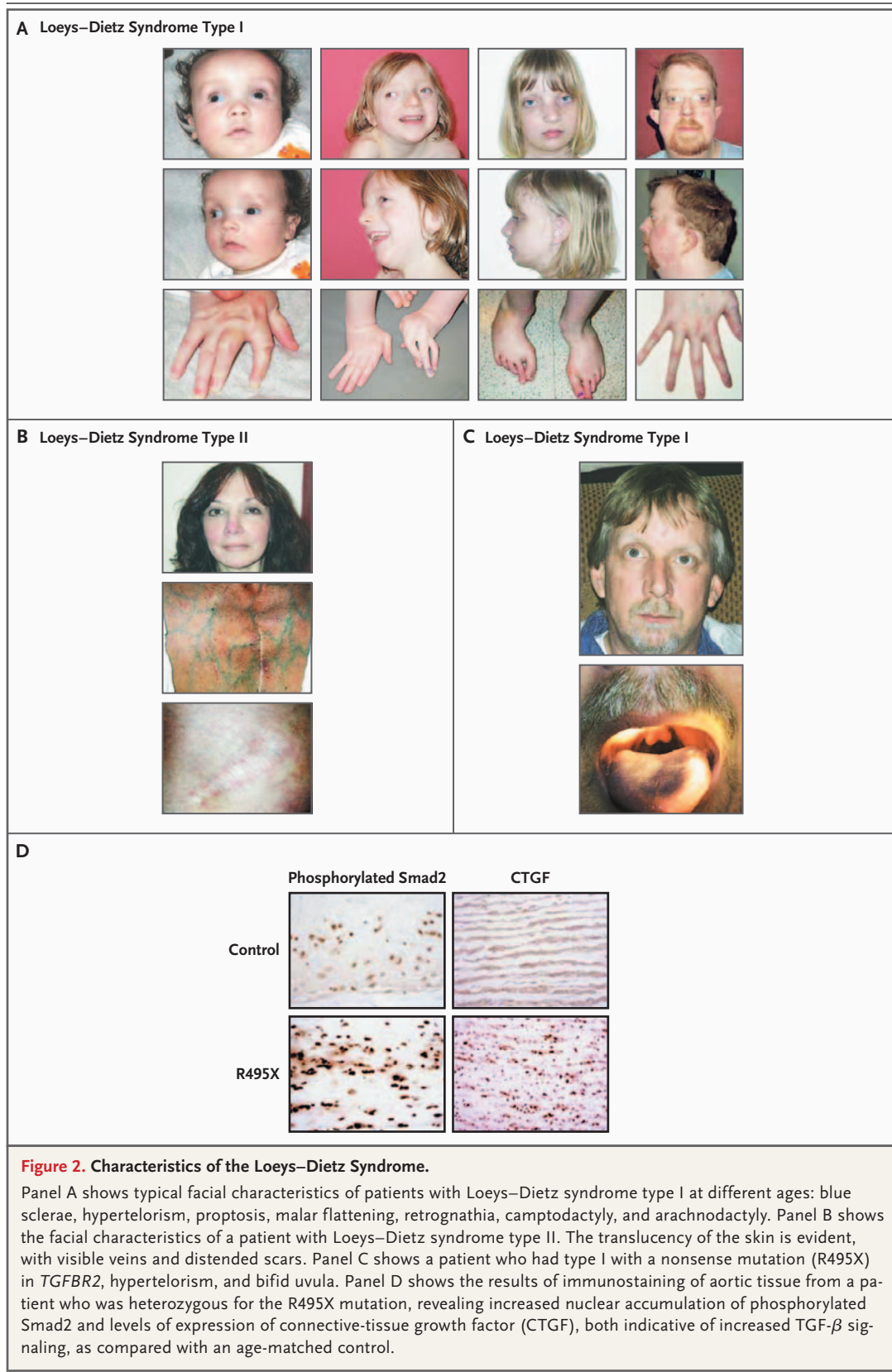
Table 1. Clinical Characteristics of 40 Probands with Loeys–Dietz Syndrome Type I.

Characteristic	Current Cohort	Previous Cohort	Total
	(N = 30)	(N = 10)*	(N = 40)
	<i>no. of patients</i>		<i>no. (%)</i>
Typical			
Hypertelorism†	26	10	36 (90)
Cleft palate or abnormal uvula†	27	9	36 (90)
Aortic-root aneurysm†	29	10	39 (98)
Aneurysm of other vessels†	13	8	21 (52)
Arterial tortuosity†	11‡	10	21 (84)
Craniofacial			
Craniosynostosis†	15	4	19 (48)
Malar hypoplasia	17	7	24 (60)
Retrognathia	15	5	20 (50)
Blue sclerae†	10	6	16 (40)
Ectopia lentis†	0	0	0
Skeletal			
Dolichostenomelia†	4	3	7 (18)
Arachnodactyly†	22	6	28 (70)
Pectus deformity	21	6	27 (68)
Scoliosis	14	6	20 (50)
Talipes equinovarus†	15	3	18 (45)
Camptodactyly	10	5	15 (38)
Joint laxity	18	9	27 (68)
Cervical-spine instability†	6	1	7 (18)
Cutaneous			
Velvety skin	9	2	11 (28)
Translucent skin†	9	4	13 (32)
Other			
Patent ductus arteriosus	10	4	14 (35)
Atrial septal defect	5	4	9 (22)
Developmental delay	3	3	6 (15)

* Data are from Loeys et al.³

† This abnormality is considered rare in the general population.

‡ Value is based on the 15 patients from whom the data could be collected.



ways associated with craniosynostosis or hydrocephalus, suggesting that learning disability is a rare primary manifestation. Other recurrent findings in this study included congenital hip dislocation in three patients, dural ectasia in six, spondylolisthesis in five, cervical dislocation or instability in seven, submandibular branchial cysts in three, osteoporosis with multiple fractures at a young age in four, and defective tooth enamel in two. No patient had ectopia lentis, and few patients (18 percent) had dolichostenomelia, findings that are typical of Marfan's syndrome.

In the cohort of 40 patients with a presentation suggestive of vascular Ehlers–Danlos syndrome (Loeys–Dietz syndrome type II), 12 had a heterozygous mutation (30 percent): 8 in *TGFBR2* and 4 in *TGFBR1* (Fig. 1). Physical findings in these patients (Table 2 and Fig. 2B) included prominent joint laxity, easy bruising, wide and atrophic scars, velvety and translucent skin with easily visible veins, spontaneous rupture of the spleen or bowel, diffuse arterial aneurysms and dissections, and catastrophic complications of pregnancy, including rupture of the gravid uterus and the arteries, either during pregnancy or in the immediate postpartum period. None of these patients had cleft palate, hypertelorism, or craniosynostosis. Three patients had an isolated bifid uvula, and one had a family history of cleft palate. The extent of vascular and skin involvement was similar in the patients with vascular Ehlers–Danlos syndrome with *TGFBR* mutations and in those without *TGFBR* mutations; only joint laxity was significantly more prevalent in those with *TGFBR* mutations (12 of 12 vs. 18 of 28, $P=0.03$).

NATURAL HISTORY

We reviewed the clinical data for all 52 probands and 38 relatives who were known to have the Loeys–Dietz syndrome (Table 3). The median survival for the entire cohort was 37.0 years (Fig. 3A). Of these 90 patients, 27 died before or during the study period (Table 3); the mean age at death was 26.0 years (range, 0.5 to 47.0) with thoracic aortic dissection as the leading cause of death (67 percent), followed by abdominal aortic dissection (22 percent) and cerebral bleeding (7 percent). The mean age at first vascular dissection was 26.7 years (range, 0.5 to 47.0), and the mean age at first vascular surgery — most often for ascending aortic aneurysm or dissection — was 19.8 years (range, 1.2 to 46.0). Twenty-

nine patients (32 percent) had vascular dissection, underwent surgery for vascular aneurysm or dissection, or died of vascular dissection or rupture before 19 years of age. Arterial involvement was widespread beyond the aorta and most commonly involved the thoracic arterial circulation (Table 3). About 20 percent of patients had aneurysms in the arteries of the head and neck or in abdominal arterial branches. Arterial tortuosity was commonly observed in the head and neck vessels but was also found throughout the body. All patients underwent echocardiography and computed tomography or magnetic resonance angiography; aneurysms distant from the aortic root were found in 53 percent of those with Loeys–Dietz syndrome type I.

We next determined whether the presence and severity of craniofacial abnormalities were predictive of the cardiovascular outcome. The number of deaths was similar in the two groups, but the mean age at death tended to be lower in the group with Loeys–Dietz syndrome type I than in the group with type II (22.6 years vs. 31.8 years, $P=0.06$). The mean age at first surgery was significantly younger in the group with type I than in the group with type II (16.9 years vs. 26.9 years, $P=0.03$). The correlation between craniofacial and cardiovascular abnormalities was further evaluated after the assignment of craniofacial-severity-index scores to all patients with mutations in *TGFBR*. We found a negative correlation between the score and age at the first cardiovascular event ($R^2=0.28$, $P<0.001$) (Fig. 3B).

There was a total of 21 pregnancies among 12 women (5 with type I and 7 with type II). Six of these women (five with type II and one with type I) had a major complication either during pregnancy or in the immediate postpartum period — aortic dissection in four and uterine rupture in two. Two of these events occurred during the first pregnancy, three during the second pregnancy, and one during a subsequent pregnancy. Severe uterine hemorrhage that was independent of pregnancy was reported in two women; in one woman, the hemorrhage was associated with uterine dilation and curettage, and in the other, it was a spontaneous event that required hysterectomy.

The involvement of other organs included splenic rupture in association with minor trauma (in two patients, both with type II) and chronic gastrointestinal disease (in three patients, two with

Table 2. Characteristics of 12 Probands with Loeys-Dietz Syndrome Type II.*

Characteristic	Proband No.												No./ Total No.
	1	2	3	4	5	6	7	8	9	10	11	12	
Mutation	R1, R487Q	R2, P427L	R2, R460H	R2, P427S	R2, D524N	R1, R487W	R2, S449F	R1, R487P	R2, N384S	R2, IVS5-1G→A	R1, K232E	R2, A527V	
Aortic-root aneurysm with dissection††	+	+	+	+	+	+	+	+	+	+	+	+	12/12
Other arterial aneurysm‡	+	+	+	-	+	+	-	-	+	ND	+	+	8/11
Arterial tortuosity††	+	+	+	-	-	+	-	ND	+	ND	+	ND	6/9
Vascular rupture during pregnancy†	+	+	-	NA	-	+	NA	NA	-	NA	NA	NA	3/6
Uterine rupture†	-	+	+	NA	-	-	NA	NA	-	NA	NA	NA	2/6
Uterine hemorrhage	-	-	-	NA	-	+	NA	NA	-	NA	NA	NA	1/6
Splenic or bowel rupture††	-	+	-	+	-	+	-	-	-	-	-	-	3/12
Inguinal hernia	-	-	+	+	+	+	-	ND	-	-	-	-	4/11
Easy bruising	+	+	+	+	-	-	+	+	+	+	-	-	8/12
Translucent skin†	+	-	+	-	-	-	+	+	+	ND	+	+	7/11
Velvety skin	+	+	+	+	+	+	-	+	+	ND	-	+	9/11
Skin hyperextensibility	-	-	-	-	+	+	-	ND	-	ND	-	-	2/10
Atrophic scars	-	-	+	+	+	+	-	ND	+	ND	-	-	5/10
Joint laxity	+	+	+	+	+	+	+	+	+	+	+	+	12/12

* R1 denotes TGFBR1, R2 TGFBR2, plus sign the presence of a characteristic, minus sign the absence of a characteristic, ND not determined, and NA not applicable.
 † This abnormality or condition is considered rare in the general population.
 ‡ All probands had splenic rupture except proband 6, who had bowel rupture.

type II and one with type I), consisting of diverticulitis or inflammatory bowel disease complicated by recurrent hemorrhage and spontaneous bowel perforation.

RESPONSE TO DISEASE MANAGEMENT

We used vascular management principles derived from past experience with Marfan's syndrome to treat our patients.⁸ These principles included the use of beta-blockade, exercise restrictions, frequent cardiovascular imaging, and prophylactic surgical repair when the aortic root exceeded 5.0 cm in diameter in adults and older children or when the growth rate of the aorta exceeded 1.0 cm in diameter per year in younger children. Two adult patients had dissection of the ascending aorta and died within weeks after the documentation of maximal aortic dimensions of 3.9 and 4.0 cm.

A total of 59 vascular surgeries (38 in patients with Loeys–Dietz syndrome type I and 21 in patients with type II), largely involving the aorta and major branch vessels, were performed in this cohort; only one resulted in intraoperative death. This death was due to the friability of the tissues, which precluded the formation of vascular anastomosis. Among the other patients, there were no deaths or short-term complications during follow-up (range, 1 to 154 months). Since our initial description of the Loeys–Dietz syndrome and the recognition of the aggressive nature of the vascular disease, 14 elective repairs of the aortic root have been performed, all with the use of the valve-sparing approach, in patients ranging in age from 9 months to 40 years.

GENOTYPE–PHENOTYPE CORRELATIONS

Overall, there were no apparent differences in the clinical presentations between patients with mutations in *TGFBR1* and patients with mutations in *TGFBR2*. Of the mutations we identified in the 42 new probands, three had been reported previously in association with type I (R487P in *TGFBR1* and R528C and R528H in *TGFBR2*).³ In addition, we identified two patients with the C461Y mutation in *TGFBR2* and the S241L mutation in *TGFBR1* and three patients with the R487Q mutation in *TGFBR1*. All patients in the six families with the R528H mutation and in the three families with the R528C mutation had Loeys–Dietz syndrome type I, as did the patients with the C461Y mutation. One patient with the R487Q mutation in

Table 3. Cardiovascular Involvement in 90 Patients with Loeys–Dietz Syndrome Type I or II from 52 Families.

Characteristic	Type I (N=64)	Type II (N=26)
Mean craniofacial-severity-index score*	4.8	0.8
Mean age at first major event (yr)†	24.5	29.8
Age at death (yr)		
Mean	22.6	31.8
Range	0.5–45.0	18.0–47.0
Cause of death (no.)		
Thoracic aortic dissection	12	6
Abdominal aortic dissection	3	3
Subclavian-artery dissection	0	1
Cerebral bleeding	2	0
Age at first cardiovascular surgery (yr)		
Mean	16.9	26.9
Range	1.2–46.0	14.0–38.0
Distribution of aneurysms (no.)		
Ascending aorta	54	22
Transverse aorta	3	6
Descending thoracic aorta	4	5
Abdominal aorta	5	4
Thoracic arterial branches	17	2
Head or neck arterial branches	7	2
Abdominal arterial branches	2	4

* Scores can range from 0 to 11, with higher scores indicating more severe abnormalities.

† A major event was defined as vascular surgery, dissection, or death.

TGFBR1 died from aortic dissection at six months of age, whereas in two other families with this same mutation, affected patients survived into adulthood.

With rare exceptions, all family members who carried the same mutation as the affected proband had concordant findings. One male proband had major craniofacial and vascular features of type I, whereas his father had no craniofacial manifestations but required aortic-root replacement at 45 years of age. The sequencing analysis of genomic DNA derived from leukocytes revealed a reduced ratio of the mutant allele (R537G in *TGFBR2*) and the wild-type allele in the father than in his severely affected son (data not shown), suggesting mosaicism. In two other families, severely affected children had fathers with a non-penetrant mutation. Although somatic mosaicism

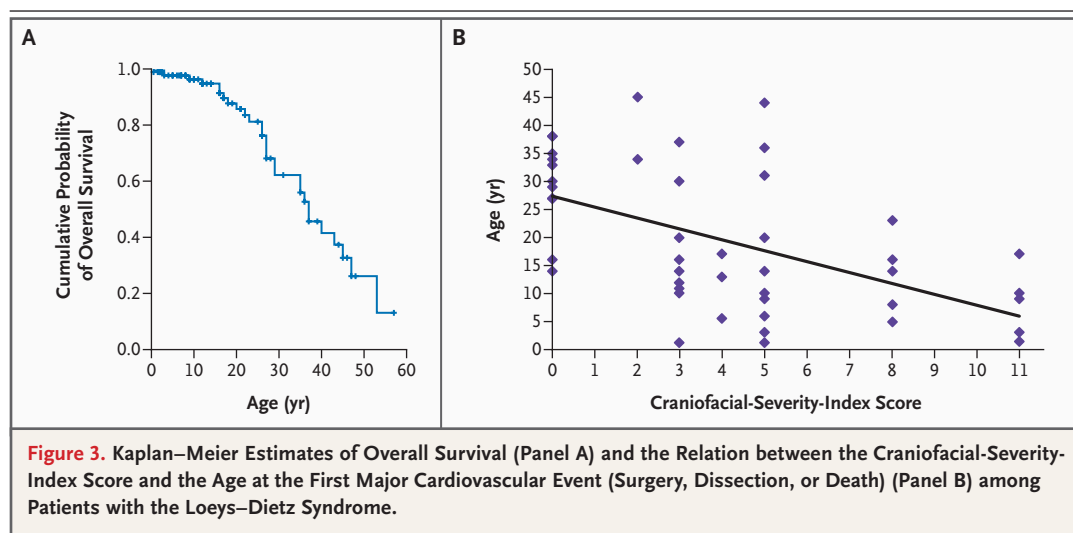


Figure 3. Kaplan–Meier Estimates of Overall Survival (Panel A) and the Relation between the Craniofacial–Severity–Index Score and the Age at the First Major Cardiovascular Event (Surgery, Dissection, or Death) (Panel B) among Patients with the Loeys–Dietz Syndrome.

cannot be excluded, the analysis of genomic DNA from these fathers and their affected daughters revealed equal representation of the mutant alleles (A329T in *TGFBR2* and N478S in *TGFBR1*) in leukocytes (data not shown).

We also identified a germ-line nonsense mutation in *TGFBR* (R495X in *TGFBR2*) in a family with bifid uvula, hypertelorism, club feet, pectus deformity, and aggressive aortic aneurysm and dissection, allowing for the diagnosis of Loeys–Dietz syndrome type I (Fig. 2C). The histologic assessment of the aortic wall from a patient with this mutation revealed increased signaling by TGF- β , as evidenced by the accumulation of phosphorylated Smad2 in the nucleus and increased levels of expression of genes responsive to TGF- β , such as connective-tissue growth factor (*CTGF*) (Fig. 2D).

DISCUSSION

The natural histories of Loeys–Dietz syndrome type I and type II differ considerably from those of other connective-tissue disorders, mandating individualized counseling and disease management. The median survival in our cohort was 37 years, as compared with 48 years among patients with vascular Ehlers–Danlos syndrome⁹ and 70 years among patients with Marfan’s syndrome who have been treated.¹⁰ The mean age at the first major vascular event in our group with Loeys–Dietz syndrome type II (29.8 years) is similar to that among patients with vascular Ehlers–Danlos syndrome caused by a deficiency of type

III collagen (24.6 years).⁹ In both the Loeys–Dietz syndrome and vascular Ehlers–Danlos syndrome, dissection can occur without marked arterial dilatation. However, the incidence of fatal complications during or immediately after vascular surgery is about 45 percent in vascular Ehlers–Danlos syndrome^{9,11} but only 1.7 percent in Loeys–Dietz syndrome overall and 4.8 percent in type II. Thus, genotyping is beneficial in patients who present with features of vascular Ehlers–Danlos syndrome. Current experience favors first performing biochemical analysis of type III collagen, with or without screening of *COL3A1* for mutations, with subsequent screening of the *TGFBR* genes in patients with negative results. This sequence should be switched in a patient with a personal or family history of the craniofacial features typical of the Loeys–Dietz syndrome or documented arterial tortuosity.

Prior studies have suggested that some *TGFBR2* mutations are present in families whose members have classic Marfan’s syndrome (R537C, S449F, and R460H)^{1,5} or familial thoracic aortic aneurysm and dissection (R460H).² Many of these families had findings that were atypical for these diagnoses, including cervical-spine instability, dysmorphic facies, patent ductus arteriosus, and cardiac septal defects in patients designated as having Marfan’s syndrome^{1,5} and clinically significant skeletal abnormalities and aneurysms with primary dissections distant from the thoracic aorta in those designated as having familial thoracic aortic aneurysm and dissection.¹² All these features have been associated with the Loeys–Dietz

syndrome phenotype. Our patient with the R537C mutation had features typical of type I, whereas the patient with the S449F mutation had features typical of type II. We observed the R460H mutation in two families, one with typical type I and the other with type II. In our experience, all patients with *TGFBR* mutations have had clinical features that can be used to discriminate the Loeys–Dietz syndrome from Marfan’s syndrome or from familial thoracic aortic aneurysm and dissection. Some features of both types are subtle and may have been overlooked (e.g., bifid uvula and skin findings) or missed in the absence of specialized imaging (e.g., arterial tortuosity) on examination of the families described as having Marfan’s syndrome or familial thoracic aortic aneurysm and dissection. A reevaluation of these families might shed light on this important issue.

Given the recent description of the Loeys–Dietz syndrome and its substantial overlap with Marfan’s syndrome, including the extensive involvement of the aorta, skeleton, and dura, it is no longer meaningful simply to ask whether someone has sufficient features to be given a diagnosis of Marfan’s syndrome without considering findings that are not expected in the disease. We found no *TGFBR* mutations in 93 consecutive, unrelated patients with classic Marfan’s syndrome³ or in 70 unrelated patients with vascular disease and no systemic findings of a connective-tissue disorder. These data suggest that a comprehensive clinical evaluation is critical for making these important diagnostic distinctions and that genotyping of *TGFBR* will be most useful in patients with features of the Loeys–Dietz syndrome or vascular Ehlers–Danlos syndrome.

Using three-dimensional reconstruction of images from the head to the pelvis obtained by computed tomography with intravenous contrast material or magnetic resonance angiography, we identified aneurysms distant from the aortic root in 53 percent of our patients with Loeys–Dietz syndrome type I; these aneurysms would not have been detected with the use of echocardiography. The majority of these lesions were amenable to surgical repair. This imaging approach also detects arterial tortuosity, a finding of diagnostic importance.

The criteria for the surgical repair of ascending aortic aneurysms have not been determined empirically. Although the severity of craniofacial findings is somewhat predictive of the outcome,

the average age at a first cardiovascular event in patients with or without clinically significant craniofacial findings was lower than that for patients with untreated Marfan’s syndrome or vascular Ehlers–Danlos syndrome. In patients with the Loeys–Dietz syndrome, aortic dissection often occurred in childhood and in aortas with diameters well under 50 mm, the threshold above which surgical intervention is currently recommended in patients with Marfan’s syndrome. Given the safety of surgical repair at centers with experienced staff and the availability of the valve-sparing procedure, surgery should be considered for young children — especially those with pronounced craniofacial features — once the maximal dimension of the ascending aorta exceeds the 99th percentile and the diameter of the aortic annulus exceeds 1.8 cm. The use of these criteria allows for the placement of a graft of sufficient size to accommodate growth. For adolescents and adults, surgical repair of the ascending aorta should be considered once the maximal diameter approaches 4.0 cm. This practice may not eliminate the risk of dissection or death, however, and earlier intervention may be indicated, depending on the family history and the patient’s personal assessment of the risks and benefits.

Patients with the Loeys–Dietz syndrome should be advised of and evaluated for the life-threatening manifestations of the disease that are treatable, including cervical-spine instability, spontaneous or traumatic organ rupture, and catastrophic complications of pregnancy. The counseling of a prospective parent who is affected or of a parent who has an affected child is complicated by the wide intrafamilial variation in the clinical severity of the disease and the occurrence of apparent nonpenetrance. With the exception of somatic mosaicism, the factors that contribute to intrafamilial variation are currently unknown, but they presumably include genetic modification of the TGF- β signaling cascade.

The mechanism by which mutations in the TGF- β receptor cause the multisystem manifestations of the Loeys–Dietz syndrome is complex and poorly understood. Similar to missense mutations,³ a nonsense mutation that is expected to truncate the kinase domain and preclude signal transduction resulted in paradoxically enhanced TGF- β signaling in the vessel wall of one of our patients. TGF- β antagonists have the ability to alleviate or eliminate many manifestations, includ-

ing aortic aneurysm, in mouse models of Marfan's syndrome.¹³ Although the application of this approach to the Loeys–Dietz syndrome may prove beneficial, caution is warranted, pending validation in genetically defined animal models.

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