

and *TGFB2*, along with “other TGF- β signaling pathway genes yet to be associated with disease” for which the clinical characteristics have yet to be defined.

DISCLOSURE

The authors declare no conflict of interest.

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Response to Pyeritz et al.

To the Editor: Subsequent to the meeting of the “Montalcino Consortium,” the Marfan Foundation convened a more inclusive gathering in Boston of all invested parties to discuss the important issue of nosology for inherited presentations of thoracic aortic aneurysm. In addition to representatives from the Montalcino Consortium, participants included leaders from many additional centers of excellence in the care of thoracic aortic disease and patients and representatives from patient advocacy groups including the US and Canadian Marfan foundations and the US Loeys–Dietz Syndrome Foundation. Virtually all of the comments and concerns raised by Pyeritz et al.¹ in their letter, “Loeys–Dietz Syndrome Is a Specific Phenotype and Not a Concomitant of Any Mutation in a Gene Involved in TGF- β Signaling,” were discussed in detail. We welcome this opportunity to more thoroughly present the prevailing themes of this meeting.

There was uniform consensus that knowledge about the gene or specific mutation underlying a disease can serve as a proxy for the biochemical and cellular events that drive disease initiation or progression and that influence response to therapy. This knowledge often provides predictive value with regard to when and where disease will manifest; the character of the disease (e.g., mild or severe, and more or less predictable than average); the best diagnostic, follow-up, and therapeutic protocols to apply; and the spectrum of risks for family members (present and future). The ability to “bin” patients into a specific predisposition class (based on commonality of phenotype/genotype/mechanism) increases the potential for anticipatory counseling and management while minimizing bias or other confounding factors. Such principles underlie current practices in the diagnosis and management of Marfan syndrome (MFS), in which the presence of a pathogenic *FBN1* mutation or an unequivocally affected family member, in combination with aortic root enlargement, is sufficient for the

REFERENCES

1. MacCarrick G, Black JH III, Bowdin S, et al. Loeys-Dietz syndrome: a primer for diagnosis and management. *Genet Med* 2014;16:576–587.
2. Mizuguchi T, Collod-Beroud G, Akiyama T, et al. Heterozygous *TGFBR2* mutations in Marfan syndrome. *Nat Genet* 2004;36:855–860.
3. Loeys BL, Chen J, Neptune BR, et al. A syndrome of altered cardiovascular, craniofacial, neurocognitive and skeletal development caused by mutations in *TGFBR1* or *TGFBR2*. *Nat Genet* 2005;37:275–281.
4. Attias D, Stheneur C, Roy C, et al. Comparison of clinical presentations and outcomes between patients with *TGFBR2* and *FBN1* mutations in Marfan syndrome and related disorders. *Circulation* 2009;120:2541–2549.
5. Tran-Fadulu V, Pannu H, Kim DH, et al. Analysis of multigenerational families with thoracic aortic aneurysms and dissections due to *TGFBR1* or *TGFBR2* mutations. *J Med Genet* 2009;46:607–613.
6. Morris SA, Orbach DB, Geva T, et al. Increased vertebral artery tortuosity index is associated with adverse outcomes in children and young adults with connective tissue disorders. *Circulation* 2011;124:388–396.
7. Pyeritz RE. Heritable thoracic aortic disorders. *Curr Opin Cardiol* 2014;29:97–102.

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diagnosis of MFS irrespective of the presence and/or severity of other systemic findings, ranging from catastrophic infantile presentations that often associate with striking dysmorphism to exceedingly mild adult presentations in individuals who do not show outward features of MFS. This alerts caregivers with variable familiarity with the intricacies of diagnosis to the spectrum of possibilities and informs patient management (e.g., the need for ophthalmologic evaluations, proper imaging modalities, and surgical thresholds). A description of these widely endorsed and applied priorities and nosologic practices included the leadership of the Montalcino Consortium as authors, and similar practices are in place (and productive) for other presentations of aneurysm, prominently including vascular Ehlers–Danlos syndrome.^{2,3}

The term “Loeys–Dietz syndrome” (LDS) was initially applied to describe a condition, caused by mutations in either of the genes that encode subunits of the transforming growth factor (TGF)- β receptor (*TGFBR1* or *TGFBR2*), that associates many features of MFS (arachnodactyly, pectus deformity, scoliosis, dural ectasia, and aortic root aneurysm) with other discriminating features in the craniofacial (hypertelorism, cleft palate, bifid uvula, and craniosynostosis), skeletal (cervical spine malformation and/or instability and clubfoot deformity), and cutaneous (translucent skin, easy bruising, and dystrophic scars) systems.⁴ Most importantly, patients with LDS often show a widespread and aggressive vasculopathy (arterial tortuosity, aneurysms throughout the arterial tree, dissections at young ages and at relatively small vascular dimensions that do not infer risk or provoke surgery in MFS, and many other conditions). Within 1 year (in 2006), a second publication expanded the phenotypic spectrum of LDS to include individuals with *TGFBR1* or *TGFBR2* mutations with a similarly diffuse and aggressive vascular phenotype but only subtle or even absent craniofacial and/or skeletal manifestations.⁵ Around the same time, others proposed use of the diagnosis of familial thoracic aortic aneurysm and dissection for such patients, a term previously applied for patients with mutations in genes encoding components of

the vascular smooth muscle cell contractile apparatus with predominant or exclusive aneurysms of the thoracic aorta that tended to be well served by imaging and surgical practices that had previously been developed for MFS.⁶ This practice might have merit if the diagnosis adequately captured the extent of predisposition for such patients, if true phenotype–genotype correlations exist, and if phenotypes bred true in families; none of these suppositions proved valid. Indeed, in the published literature and in many examples shared by multiple groups at the Boston meeting, such patients commonly showed aneurysms distant from the thoracic aorta, dissections at small dimensions as compared with those of MFS, and family members with classic craniofacial, skeletal, cutaneous, and cardiovascular manifestations of LDS. Furthermore, data were presented showing that virtually every familial thoracic aortic aneurysm and dissection–associated *TGFBR1/TGFBR2* mutation had been observed in other individuals and/or families with classic and unequivocal LDS.

In the initial and subsequent reports describing *SMAD3* mutations in individuals with a syndromic presentation of aneurysms, it was clear that virtually all craniofacial, skeletal, cutaneous, and cardiovascular manifestations of LDS were commonly observed, prominently including diffuse and aggressive vascular disease.⁷ The impression of this group at that time was that a predisposition for early and severe osteoarthritis was a predominant distinguishing feature, prompting the proposal of use of the designation aneurysms–osteoarthritis syndrome. However, with further experience, they have refined this position to accommodate the finding of osteoarthritis in many etiologies of LDS (and many other connective tissue disorders) and the defining aggressive vascular course reminiscent of LDS, leading to their adoption of the designation LDS-type 3 for this condition, as expressed at the Boston meeting. Likewise, our initial description of mutations in the gene encoding the TGF- β ligand (*TGFBR2*) described frequent LDS-associated features including hypertelorism, cleft palate, bifid uvula, clubfoot deformity, arterial tortuosity, and widespread aneurysms with a propensity for early dissection.⁸ Given this substantial clinical overlap with LDS caused by other etiologies, we proposed the designation LDS-type 4, an observation and conclusion now shared by others (Leutermann et al.⁹). Although other reports have described patients with familial thoracic aortic aneurysm and dissection with or without systemic features reminiscent of MFS in patients with mutations in *SMAD3* and *TGFBR2*, phenotypic descriptions were often vague, clinical pictures were not provided, and aneurysms and dissections distant from the thoracic aorta were also described. Importantly, there were no distinguishing characteristics regarding the location, nature, or cellular consequence of the mutations, with absolute consensus that heterozygous mutations in *TGFBR1*, *TGFBR2*, *SMAD3*, and *TGFBR2* impair the performance of positive effectors of TGF- β signaling in cell culture systems but lead to paradoxically enhanced TGF- β signaling in the vessel wall in affected patients and mouse models. This is in striking contrast to Camurati–Engelmann disease or Myhre syndrome, in which site-specific mutations in the *TGFBR1* or *SMAD4* genes

lead to tissue-specific (predominantly skeletal and not vascular) phenotypic features through a mechanism that is not well defined and to multiple self-healing epitheliomas (Ferguson–Smith syndrome) and in which a germ-line null allele of *TGFBR1* is paired with somatic loss of the opposite allele. There are many situations in which the conditions caused by genes in a common pathway with a common molecular and predominant phenotypic consequence share a single designation—with Noonan syndrome caused by mutations in genes encoding effectors and regulators of the RAS–RAF–MEK–ERK axis serving as a prime example. Use of a numbering system that designates both the condition and locus (i.e., LDS-1, LDS-2, LDS-3, and LDS-4 for the conditions caused by mutations in *TGFBR1*, *TGFBR2*, *SMAD3*, and *TGFBR2*, respectively), as we have proposed, would alert clinicians to the commonalities of phenotype while accommodating current and future recognition of potentially important locus-specific differences.

In our proposed guidelines for the management of LDS we do not advocate a “one-shoe-fits-all” approach. Existing evidence from all groups would strongly support widespread cardiovascular imaging on an intermittent basis and imaging of the cervical spine at diagnosis. We have proposed that surgical repair of aortic root aneurysms be “considered” with measurements around 4 cm, but we stress that other factors such as family history, historical knowledge about the specific genotype (gene and/or mutation), severity of systemic findings, and the patient’s personal assessment of risk versus benefit should influence this decision. The decision regarding the use of medications such as angiotensin receptor blockers and/or β -blockers can and should be influenced by each center’s analysis of available data. Given the data regarding the underlying mechanism of disease, the ability of angiotensin receptor blockers to suppress TGF- β signaling in the aortic wall, the evidence that angiotensin receptor blockers can attenuate the progression of aortic root enlargement in LDS mouse models and in both mouse models and people with MFS (another TGF- β vasculopathy), the excellent tolerance profile for this class of medications, and the aggressive, diffuse, and often catastrophic course of untreated LDS, we believe that the use of these agents for LDS remains a responsible choice in patients who are fully informed regarding what is known and what remains to be learned. The selection of dose will require additional study, but we are compelled by the evidence for both safety and superior efficacy of ultra-high dose angiotensin receptor blocker regimens in the management of chronic kidney disease and other TGF- β -related pathologies. Although the proposed management guidelines remain descriptive rather than prescriptive, we believe that they make a genuine attempt to integrate the prevailing tenets of both evidence-based and individualized medicine, with the sole and unwavering priority of best serving our patients and their families. Refinement will undoubtedly occur with further research and knowledge.

DISCLOSURE

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REFERENCES

1. Pyeritz R, Jondeau G, Moran R, et al., for the Montalcino Aortic Consortium. Loeys–Dietz syndrome is a specific phenotype and not a concomitant of any mutation in a gene involved in TGF- β signaling. *Genet Med* 2014; this issue, page 641.
2. Loeys BL, Dietz HC, Braverman AC, et al. The revised Ghent nosology for the Marfan syndrome. *J Med Genet* 2010;47:476–485.
3. Beighton P, De Paepe A, Steinmann B, Tsipouras P, Wenstrup RJ. Ehlers-Danlos syndromes: revised nosology, Villefranche, 1997. Ehlers-Danlos National Foundation (USA) and Ehlers-Danlos Support Group (UK). *Am J Med Genet* 1998;77:31–37.

4. Loeys BL, Chen J, Neptune ER, et al. A syndrome of altered cardiovascular, craniofacial, neurocognitive and skeletal development caused by mutations in TGFBR1 or TGFBR2. *Nat Genet* 2005;37:275–281.
5. Loeys BL, Schwarze U, Holm T, et al. Aneurysm syndromes caused by mutations in the TGF- β receptor. *N Engl J Med* 2006;355:788–798.
6. Pannu H, Fadulu VT, Chang J, et al. Mutations in transforming growth factor- β receptor type II cause familial thoracic aortic aneurysms and dissections. *Circulation* 2005;112:513–520.
7. van der Linde D, van de Laar IM, Bertoli-Avella AM, et al. Aggressive cardiovascular phenotype of aneurysms-osteoarthritis syndrome caused by pathogenic SMAD3 variants. *J Am Coll Cardiol* 2012;60:397–403.
8. Lindsay ME, Schepers D, Bolar NA, et al. Loss-of-function mutations in TGFBR2 cause a syndromic presentation of thoracic aortic aneurysm. *Nat Genet* 2012;44:922–927.
9. Leutermann R, Sheikhzadeh S, Brockstädt L, et al. A 1-bp duplication in TGFBR2 in three family members with a syndromic form of thoracic aortic aneurysm. *Eur J Hum Genet* 2013; e-pub ahead of print 6 November 2013.

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Michael J. Fox Foundation LRRK2 Consortium: geographical differences in returning genetic research data to study participants

In 2004, several mutations in the gene encoding leucine-rich repeat kinase 2 (*LRRK2*) were identified as being a genetic cause for Parkinson disease (PD).¹ The most common *LRRK2* mutation, G2019S, has been identified in 1% of all sporadic PD cases and in 4% of all familial PD cases.² Among selected populations, the frequency of the G2019S mutation is much higher. Up to 18% of all Ashkenazi Jewish PD cases³ and 40% of North African Berbers with familial PD carry the G2019S mutation.⁴ PD penetrance is age dependent and very controversial, with estimates ranging between 24 and 80%.⁵ Clinically, *LRRK2*-related PD is indistinguishable from idiopathic PD on an individual patient level.² As a group, mutation carriers may have less tremor and more postural and gait difficulties.^{6,7} Most autopsies of *LRRK2*-related PD brains show pathology similar to that seen in idiopathic PD, including the presence of Lewy bodies in the substantia nigra and cortex.^{8,9}

In 2008, the Michael J. Fox Foundation established an international consortium to investigate *LRRK2*, which, eventually, included nine countries across four continents (Canada, China, France, Germany, Israel, Norway, Spain, Tunisia, and the United States). The methodology for subject recruitment is similar in most centers; PD participants are examined and screened for *LRRK2* mutations, and a more thorough investigation is performed on those with mutations (and a subset of those without mutations). All willing family members are then recruited so that *LRRK2* carriers with and without PD, as well as noncarriers, may be examined.

The study design raised an ethical question: should the genetic testing results be reported to participants? Currently,

the clinical implications of carrying an *LRRK2* mutation among PD patients are unknown, and treatment is the same for carriers and noncarriers. Even so, investigators and ethics committees in different countries reached different conclusions regarding whether to inform study participants of their genetic test results.

With regard to PD participants, none of the centers in the United States offered the results of genetic testing performed for research purposes to participants. In New York state, reporting of results from a laboratory not approved per the Clinical Laboratory Improvement Amendments is against regulations; a minority of participants chose to pursue formal genetic counseling and clinical testing. By contrast, review committees in Israel concluded that it would be unethical not to provide the data to study participants with PD, and, as a result, all participants who requested results (the vast majority) received them.

The ethical dilemma among nonmanifesting *LRRK2* carrier family members is even more complicated. Carrying a mutation is more clinically meaningful in this population than in the probands with PD because it implies a 24–80% risk for PD. However, there are no known modifying interventions that may prevent PD in this population (developing such interventions is one of the major aims of the Michael J. Fox Foundation Consortium). Therefore, most centers chose, at the start of recruitment, not to reveal mutation status to non-PD participants, unless they first received genetic counseling and clinical testing. Most centers have reported that only a handful of non-PD participants were interested in receiving these data.

In many centers, the protocol for sharing genetic results with all participants was changed partway through the study. After initially reporting genetic data (if requested), the Toronto research team obtained ethics committee approval to stop revealing these results because they felt that the participants were confused by the information and/or did not understand how to interpret it. By contrast, the ethics committee in Trondheim asked researchers to alter the protocol so that study participants who were told of the risks associated with having a mutation could be notified of their genetic status. As a result,