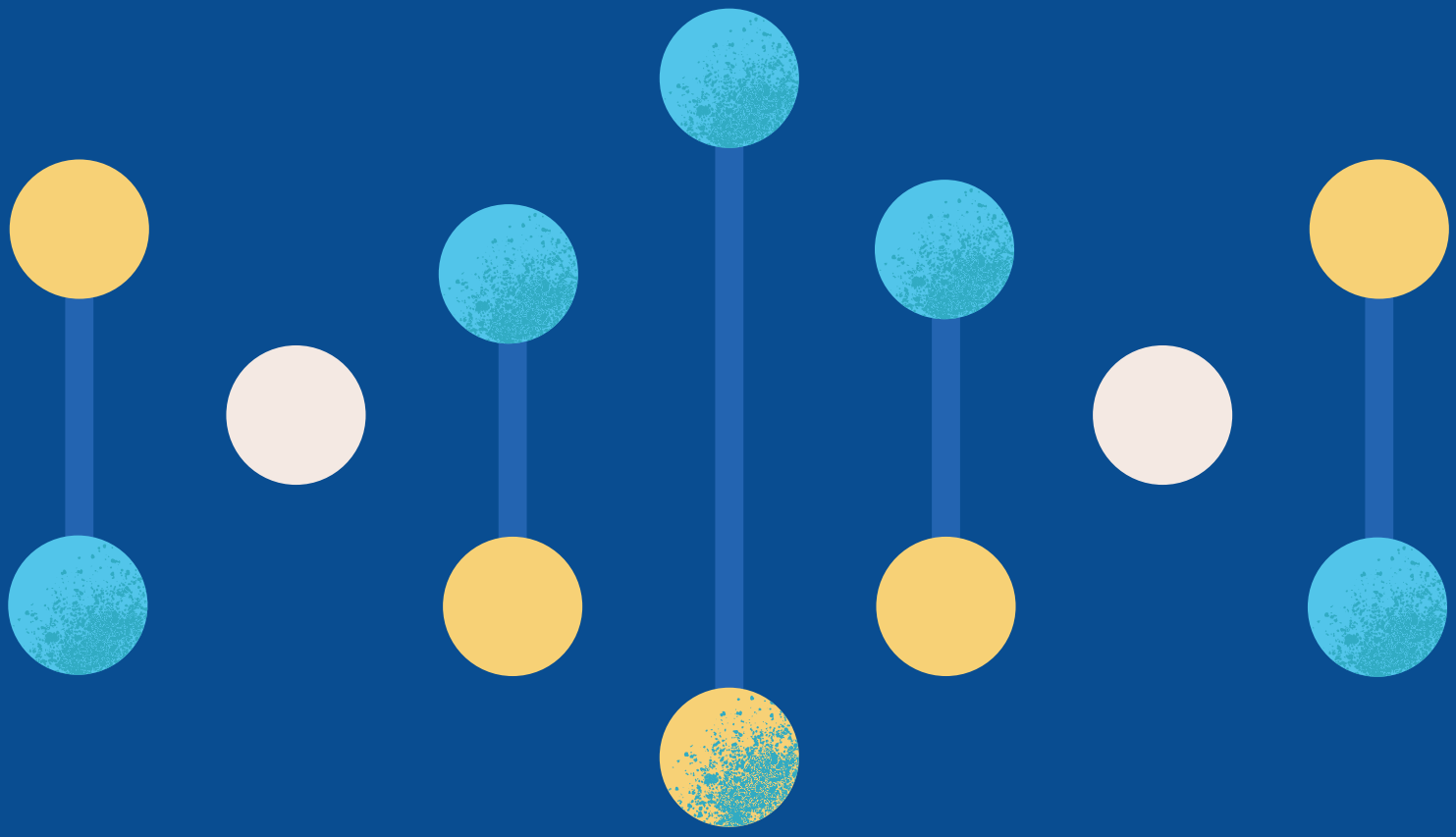
TGF-BR2 GENE COMPENDIUM

A Curated Reference for Thoracic Aortic Aneurysm and Dissection (TAAD)



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Notices
This compendium is provided as an educational resource.
Medical and genetic knowledge evolves rapidly, and users are advised to consult up-to-date literature and clinical guidance when interpreting genetic variants.

Curators have made every effort to ensure accuracy but bear no liability for clinical or diagnostic outcomes based on this document. All variant classifications and recommendations should be considered in context and with professional clinical judgment.

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1. Basic Information for TAAD Gene

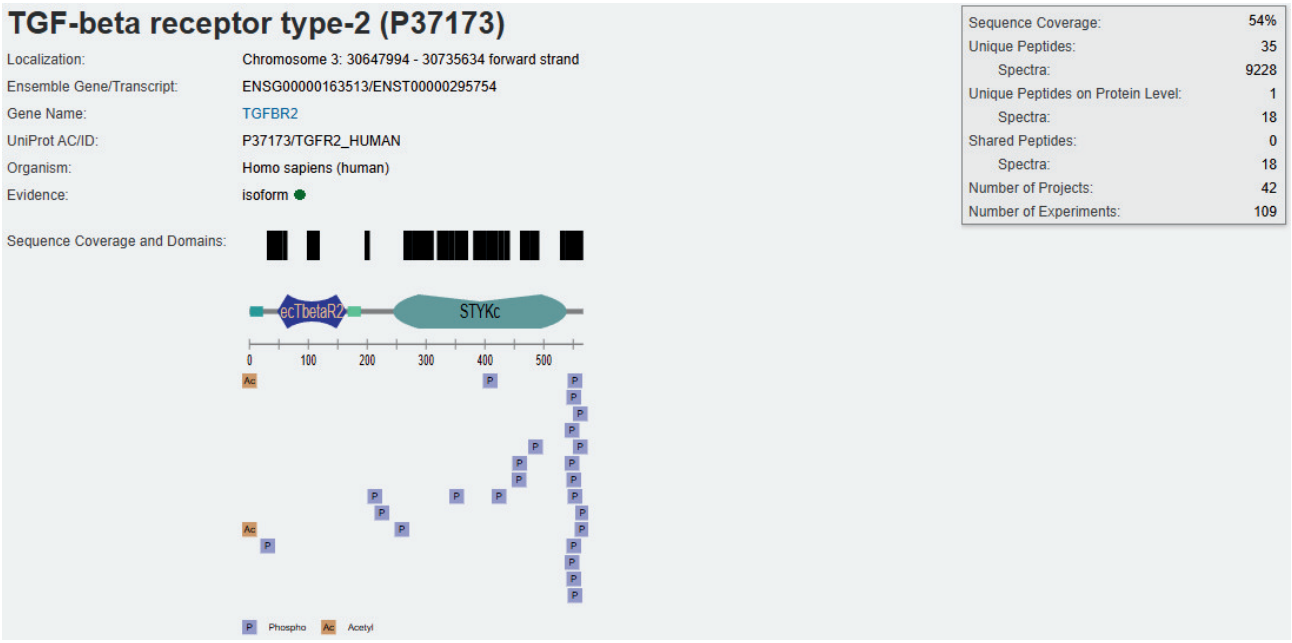
1.1 Gene Identifiers

Gene MIM Number	190182
Phenotype MIM Number	610168 Loeys-Dietz syndrome 2
Orphanet code	ORPHA: 60030 Loeys-Dietz syndrome ORPHA: 91387 Familial thoracic aortic aneurysm and aortic dissection ORPHA: 284973 Marfan syndrome type 2
Chromosomal Position (hg19/GRCh37)	NC_000003.11 (chr3:30 648 093-30 735 634)
Chromosomal Position (hg38/GRCh38)	NC_000003.12 (chr3: 30 606 601-30 694 140)
Total Number of Amino Acids	567
MANE Transcript	NM_003242.6
Are there pseudogenes?	No
Other pitfalls (e.g. retrocopy insertion polymorphisms)?	

No other condition(s) associated with this gene with no or low prevalence of aneurysm.

2. Protein Structure Overview

2.1. Scheme with important domains within the protein



Source: https://www.proteomicsdb.org/proteomicsdb/#protein/proteinDetails/55264/summary

Table: Overview of TGF-βR2 protein with Amino Acid (AA) boundaries

Domain	From AA	To AA
Signal peptide	1	22
Extracellular	23	159
Trans-membrane	160	188
Cytoplasmic	189	245
Serine-Threonine Protein kinase	246	543
Cytoplasmic	544	567

Source: www.umd.be/TGFBR1

2.2 List of Exon Boundaries (at cDNA Level)

MANE transcript NM_003242.6	Nucleotide Range	Amino Acid Range
5'UTR / Exon 1	c.-283 to 94	1 to 32

Exon 2	c.95 to 263	32 to 88
Exon 3	c.264 to 454	88 to 152
Exon 4	c.455 to 1254	152 to 418
Exon 5	c.1255 to 1396	419 to 466
Exon 6	c.1397 to 1524	466 to 508
Exon 7-3'UTR	c.1525 to *2543	509 to 567

Source: Alamut

2.3. Mutational hotspot or recurrent/founder variants

Yes, amino acids Arg460, Arg528 and Arg537 appear to be highly important functionally, with different amino acids changes reported in databases and literature.

cDNA annotation	**Protein annotation**	**Number of submissions in ClinVar**	**Number of Submissions in UMD**
c.1336G>A	p.Asp446Asn	6 VarID 265447	5
c.1378C>A	p.Arg460Ser	1 VarID 1332770	
c.1378C>T	p.Arg460Cys	6 VarID 12514	6
c.1379G>C	p.Arg460Pro	2 VarID 1332771	
c.1379G>T	p.Arg460Leu	1 VarID 543900	1
c.1379G>A	p.Arg460His	7 VarID 12515	22
c.1483C>T	p.Arg495Ter	7 VarID 12519	7
c.1489C>T	p.Arg497Ter	8 VarID 213934	2
c.1570G>A	p.Asp524Asn	6 VarID 180541	4
c.1582C>G	p.Arg528Gly	1 VarID 1702293	

c.1582C>A	p.Arg528Ser	1 VarID 1299545	1
c.1582C>T	p.Arg528Cys	7 VarID 12512	9
c.1583G>A	p.Arg528His	5 VarID 12511	11
c.1583G>T	p.Arg528Leu		1
c.1609C>T	p.Arg537Cys	8 VarID 12507	9 personal communication Paris

2.4. Major domain(s) that involves more pathogenic variants

Almost all pathogenic variants are located in the protein kinase domain: aa246- aa544 (Loeys et al. 2006; Singh et al. 2006).

Clinvar database: ClinVar - TGFBR2
GnomAD database: gnomAD.v4.1 TGFBR2
Mutscore: MutScore TGFBR2

3. Mode of Inheritance

Loeys-Dietz syndrome (LDS) is inherited in an autosomal dominant manner. Wide intrafamilial phenotypic variability has been documented. Rare examples of non-penetrance in LDS have been documented (Baban et al, 2018).

4. Constraint Matrices and Mutational Subtypes

pLI score	pLI=0,96 o/e= 0,35 (0.24-0.51)	gnomad v.4.1
Missense constraint	Z=3,65; o/e=0.6 (0.55-0.66)	gnomad v.4.1
Haplo-insufficiency (nonsense or out of frame splice)	No*	Goudie et al, 2011
Full gene deletion	No**	Redon et al, 2006
Multi-exon deletion	Yes***	Bichat lab
Full gene duplication	No****	Breckpot et al, 2010
Multi-exon duplication	No	

* All currently described pathogenic nonsense mutations are shown or predicted to escape NMD, so haplo–insufficiency is not believed to be a pathogenic mechanism for the

aneurysmal phenotype.
** One paper describing a full gene deletion but the patient had microcephaly, mild dysmorphic features, and global developmental delay but not LDS-aneurysmal features at the time of reporting (was a 20 month old girl) (Campbell et al, 2011).
*** Four probands with entire exon 6 deletion were identified and in one it was a de novo event (Paris, personal communication).

5. Mode of Action of the Pathogenic Variants

Gain-of-function	Unknown*	Lindsey and Dietz et al 2014. MacFarlane et al 2017.
Haploinsufficiency (as defined by allele that undergoes (or predicted to undergo NMD) or full gene deletion	No**	Lindsey and Dietz et al 2014. MacFarlane et al 2017.
Dominant-negative	Unknown*	Lindsey and Dietz et al 2014. MacFarlane et al 2017.
Loss-of-function (not driven by haplo-insufficiency)	Unknown*	Lindsey and Dietz et al 2014. MacFarlane et al 2017.

* The precise mechanism for TGF-βR2 variant is not clear. Various mechanisms have been proposed to explain how LDS mutations can result in increased TGF-β signaling in vivo, however, none of these mechanisms has been validated to date.
** All currently described pathogenic nonsense mutations are shown or predicted to escape NMD, so haplo–insufficiency is not believed to be a pathogenic mechanism for the aneurysmal phenotype.

6. Additional Supportive Evidence for Pathogenicity

6.1. Clinical evidence

No features are specific for TGF-βR2.

6.2. Functional evidence

Currently, no functional tests are available that could help for missense variants interpretation in TGF-βR2. In the case of a nonsense mutation, efforts to examine nonsense-mediated decay (NMD) should be performed to demonstrate NMD escape before concluding on pathogenicity.

7. Mutation Database or Expert

7.1. Gene-specific mutation database

- UMD: http://www.umd.be/TGFBR2/
- LOVD: https://databases.lovd.nl/shared/genes/TGFBR2
- ClinVar: https://www.ncbi.nlm.nih.gov/clinvar/?term=TGFBR2%5bgene%5d

7.2 Uniprot 3D protein structure

The UniProt database provides access to the 3D structure and functional annotation of TGF-βR2: https://www.uniprot.org/uniprotkb/P37173/entry#structure

7.3 Lab "expert" for this gene that can be contacted for advice on specific cases

For questions about specific variants or complex TGF-βR2 cases, expert consultation is available at:
Center for Medical Genetics, University Hospital Antwerp, Belgium

- Bart.loeys@uza.be

Genetics Department, Bichat hospital, Paris, France

- pauline.arnaud@aphp.fr

8. Phenotype Characteristics

8.1. Estimated prevalence of the disease

The exact prevalence of LDS is unknown but estimated to be 1:50,000. More than 1,000 families with LDS have been described in the literature.

8.2. Youngest age of onset of aortic aneurysm

Prenatal identification of an aortic root aneurysm in a fetus of 19 week of gestation in (Viassolo et al. 2006). Also, neonatal presentation (since 2 days of life to 6 months old) with aortic root dilatation has been described in the literature (Yetman et al 2007, Baldo et al 2022, Valenzuela et al, 2017).

8.3. Youngest age of onset of aortic dissection

Aortic dissection has been reported as early as 6 months of age with aortic diameter of 4.2 cm (Williams et al. 2016).

8.4. Genotype-phenotype correlation validated for this gene

No, current data suggest there might be an early onset and more severe presentation for pathogenic variants affecting Arg528. So far, this observation does not change the clinical management of patients with this variant.

8.5. Is there any consensus on management of the disease?

Yes, not specific for TGF-βR2 but for LDS in general (Mac Carrick et al, 2014). Also consult general TAAD guidelines (Isselbacher et al 2022, Mazzolai et al, 2024, Morris et al, 2024).

References

- Baldo F, Morra L, Feresin A, Faletra F, Al Naber Y, Memo L, Travan L. Neonatal presentation of Loeys-Dietz syndrome: two case reports and review of the literature. Ital J Pediatr. 2022 Jun 6;48(1):85. doi: 10.1186/s13052-022-01281-y. PMID: 35668506; PMCID: PMC9169291.
- Campbell IM, Kolodziejska KE, Quach MM, Wolf VL, Cheung SW, Lalani SR, Ramocki MB, Stankiewicz P. TGFBR2 deletion in a 20-month-old female with developmental delay and microcephaly. Am J Med Genet A. 2011 Jun;155A(6):1442-7. doi: 10.1002/ajmg.a.34015. Epub 2011 May 12. PMID: 21567932; PMCID: PMC3646644.
- Chung BH, Bradley T, Grosse-Wortmann L, Blaser S, Dirks P, Hinek A, Chitayat D. Hand and fibrillin-1 deposition abnormalities in Loeys-Dietz syndrome--expanding the clinical spectrum. Am J Med Genet A. 2014 Feb;164A(2):461-6. doi: 10.1002/ajmg.a.36246. Epub 2013 Nov 5. PMID: 24194458.
- Isselbacher EM, Preventza O, Hamilton Black J 3rd, Augoustides JG, Beck AW, Bolen MA, Braverman AC, Bray BE, Brown-Zimmerman MM, Chen EP, Collins TJ, DeAnda A Jr, Fanola CL, Girardi LN, Hicks CW, Hui DS, Schuyler Jones W, Kalahasti V, Kim KM, Milewicz DM, Oderich GS, Ogbechie L, Promes SB, Gyang Ross E, Schermerhorn ML, Singleton Times S, Tseng EE, Wang GJ, Woo YJ; Peer Review Committee Members. 2022 ACC/AHA Guideline for the Diagnosis and Management of Aortic Disease: A Report of the American Heart Association/American College of Cardiology Joint Committee on Clinical Practice Guidelines. Circulation. 2022 Dec 13;146(24):e334-e482. doi: 10.1161/CIR.0000000000001106. Epub 2022 Nov 2. PMID: 36322642; PMCID: PMC9876736.
- Jondeau G, Ropers J, Regalado E, Braverman A, Evangelista A, Teixedo G, De Backer J, Muiño-Mosquera L, Naudion S, Zordan C, Morisaki T, Morisaki H, Von Kodolitsch Y, Dupuis-Girod S, Morris SA, Jeremy R, Odent S, Adès LC, Bakshi M, Holman K, LeMaire S, Milleron O, Langeois M, Spentchian M, Aubart M, Boileau C, Pyeritz R, Milewicz DM; Montalcino Aortic Consortium. International Registry of Patients Carrying TGFBR1 or TGFBR2 Mutations: Results of the MAC (Montalcino Aortic Consortium). Circ Cardiovasc Genet. 2016 Dec;9(6):548-558. doi:10.1161/CIRCGENETICS.116.001485. Epub 2016 Nov 21. PMID: 27879313; PMCID: PMC5177493.
- Lindsay ME, Dietz HC. The genetic basis of aortic aneurysm. Cold Spring Harb Perspect Med. 2014 Sep 2;4(9):a015909. doi: 10.1101/cshperspect.a015909. PMID: 25183854; PMCID: PMC4143103.
- Loeys BL, Schwarze U, Holm T, Callewaert BL, Thomas GH, Pannu H, De Backer JF, Oswald GL, Symoens S, Manouvrier S, Roberts AE, Faravelli F, Greco MA, Pyeritz RE, Milewicz DM, Coucke PJ, Cameron DE, Braverman AC, Byers PH, De Paepe AM, Dietz HC. Aneurysm syndromes caused by mutations in the TGF-beta receptor. N Engl J Med. 2006 Aug 24;355(8):788-98. doi: 10.1056/NEJMoa055695. PMID: 16928994.
- Loeys BL, Chen J, Neptune ER, Judge DP, Podowski M, Holm T, Meyers J, Leitch CC, Katsanis N, Sharifi N, Xu FL, Myers LA, Spevak PJ, Cameron DE, De Backer J, Hellemans J, Chen Y, Davis EC, Webb CL, Kress W, Coucke P, Rifkin DB, De Paepe AM, Dietz HC. A syndrome of altered cardiovascular, craniofacial, neurocognitive and skeletal development caused by mutations in TGFBR1 or TGFBR2. Nat Genet. 2005 Mar;37(3):275-81. doi: 10.1038/ng1511. Epub 2005 Jan 30. PMID: 15731757.
- MacCarrick G, Black JH 3rd, Bowdin S, El-Hamamsy I, Frischmeyer-Guerrerio PA, Guerrerio AL, Sponseller PD, Loeys B, Dietz HC 3rd. Loeys-Dietz syndrome: a primer for diagnosis and management. Genet Med. 2014 Aug;16(8):576-87. doi: 10.1038/gim.2014.11. Epub 2014 Feb 27. PMID: 24577266; PMCID: PMC4131122.

- MacFarlane EG, Haupt J, Dietz HC, Shore EM. TGF-β Family Signaling in Connective Tissue and Skeletal Diseases. Cold Spring Harb Perspect Biol. 2017 Nov 1;9(11):a022269. doi: 10.1101/cshperspect.a022269. PMID: 28246187; PMCID: PMC5666637.
- Mazzolai L, Teixido-Tura G, Lanzi S, Boc V, Bossone E, Brodmann M, Bura-Rivière A, De Backer J, Deglise S, Della Corte A, Heiss C, Kałużna-Oleksy M, Kurpas D, McEniery CM, Mirault T, Pasquet AA, Pitcher A, Schaubroeck HAI, Schlager O, Sirnes PA, Sprynger MG, Stabile E, Steinbach F, Thielmann M, van Kimmenade RRJ, Venermo M, Rodriguez-Palomares JF; ESC Scientific Document Group. 2024 ESC Guidelines for the management of peripheral arterial and aortic diseases. Eur Heart J. 2024 Sep 29;45(36):3538-3700. doi: 10.1093/eurheartj/ehae179. PMID: 39210722.
- Morris SA, Flyer JN, Yetman AT, Quezada E, Cappella ES, Dietz HC, Milewicz DM, Ouzounian M, Rigelsky CM, Tierney S, Lacro RV; American Heart Association Council on Lifelong Congenital Heart Disease and Heart Health in the Young (Young Hearts); Council on Cardiovascular and Stroke Nursing; Council on Peripheral Vascular Disease; Council on Cardiopulmonary, Critical Care, Perioperative and Resuscitation; and Council on Cardiovascular Surgery and Anesthesia. Cardiovascular Management of Aortopathy in Children: A Scientific Statement From the American Heart Association. Circulation. 2024 Sep 10;150(11):e228-e254. doi: 10.1161/CIR.0000000000001265. Epub 2024 Aug 12. PMID: 39129620.
- Muramatsu Y, Kosho T, Magota M, Yokotsuka T, Ito M, Yasuda A, Kito O, Suzuki C, Nagata Y, Kawai S, Ikoma M, Hatano T, Nakayama M, Kawamura R, Wakui K, Morisaki H, Morisaki T, Fukushima Y. Progressive aortic root and pulmonary artery aneurysms in a neonate with Loeys-Dietz syndrome type 1B. Am J Med Genet A. 2010 Feb;152A(2):417-21. doi: 10.1002/ajmg.a.33263. PMID: 20101701.
- Singh KK, Rommel K, Mishra A, Karck M, Haverich A, Schmidtke J, Arslan-Kirchner M. TGFBR1 and TGFBR2 mutations in patients with features of Marfan syndrome and Loeys-Dietz syndrome. Hum Mutat. 2006 Aug;27(8):770-7. doi: 10.1002/humu.20354. PMID: 16799921.
- Stheneur C, Collod-Béroud G, Faivre L, Gouya L, Sultan G, Le Parc JM, Moura B, Attias D, Muti C, Sznajder M, Claustres M, Junien C, Baumann C, Cormier-Daire V, Rio M, Lyonnet S, Plauchu H, Lacombe D, Chevallier B, Jondeau G, Boileau C. Identification of 23 TGFBR2 and 6 TGFBR1 gene mutations and genotype-phenotype investigations in 457 patients with Marfan syndrome type I and II, Loeys-Dietz syndrome and related disorders. Hum Mutat. 2008 Nov;29(11):E284-95. doi: 10.1002/humu.20871. PMID: 18781618.
- Valenzuela I, Fernández-Alvarez P, Munell F, Sanchez-Montanez A, Giralt G, Vendrell T, Tizzano EF. Arthrogryposis as neonatal presentation of Loeys-Dietz syndrome due to a novel TGFBR2 mutation. Eur J Med Genet. 2017 Jun;60(6):303-307. doi: 10.1016/j.ejmg.2017.03.010. Epub 2017 Mar 24. PMID: 28344185.
- Viassolo V, Lituania M, Marasini M, Dietz H, Benelli F, Forzano F, Faravelli F. Fetal aortic root dilation: a prenatal feature of the Loeys-Dietz syndrome. Prenat Diagn. 2006 Nov;26(11):1081-3. doi: 10.1002/pd.1565. PMID: 16981219.
- Williams JA, Loeys BL, Nwakanma LU, Dietz HC, Spevak PJ, Patel ND, François K, DeBacker J, Gott VL, Vricella LA, Cameron DE. Early surgical experience with Loeys-Dietz: a new syndrome of aggressive thoracic aortic aneurysm disease. Ann Thorac Surg. 2007 Feb;83(2):S757-63; discussion S785-90. doi: 10.1016/j.athoracsur.2006.10.091. PMID: 17257922.
- Yetman AT, Beroukhim RS, Ivy DD, Manchester D. Importance of the clinical recognition of Loeys-Dietz syndrome in the neonatal period. Pediatrics. 2007 May;119(5):e1199-202. doi: 10.1542/peds.2006-2886. PMID: 17470566; PMCID: PMC3131201.

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VASCERN, the European Reference Network on Rare Multisystemic Vascular Diseases, is dedicated to gathering the best expertise in Europe in order to provide accessible cross-border healthcare to patients with rare vascular diseases (an estimated 1.3 million affected). These include arterial diseases (affecting the aorta to small arteries), arterio-venous anomalies, vascular malformations, and lymphatic diseases.

VASCERN currently comprises 48 expert teams from 39 highly specialised multidisciplinary HCPs coming from 19 EU Member States, as well as various European Patient Organisations, and is coordinated in Paris, France.

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