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### ► **To cite this version:**

Melissa Yana Frederic, Dalil Hamroun, Laurence Faivre, Catherine Boileau, Guillaume Jondeau, et al.. A new locus-specific database (LSDB) for mutations in the TGFBR2 gene: UMD-TGFBR2.. *Human Mutation*, 2008, 29 (1), pp.33-8. <10.1002/humu.20602>. <inserm-00343980v2>

**HAL Id: inserm-00343980**

**<https://inserm.hal.science/inserm-00343980v2>**

Submitted on 20 Dec 2017

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# A New Locus-Specific Database (LSDB) for Mutations in the *TGFBR2* Gene: UMD-*TGFBR2*

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The implication of mutations in the *TGFBR2* gene, known to be involved in cancers, in Marfan syndrome (MFS) and later in Loeys-Dietz syndrome (LDS) and Familial Thoracic Aortic Aneurysms and Dissections (TAAD2) gives a new example of the complexity of one gene involved in multiple diseases. To date, known *TGFBR2* mutations are not disease-specific and many mutations have to be accumulated before genotype-phenotype relationships emerge. To facilitate mutational analysis of the *TGFBR2* gene, a locus-specific database has been set up with the Universal Mutation Database (UMD) software. The version of the computerized database contains 85 entries. A total of 12 mutations are reported to be involved in MFS, six in incomplete MFS, 30 in LDS type I, 10 in LDS type II, seven in TAAD2, and 20 in various cancers. The database is accessible online at <http://www.umd.be>

KEY WORDS: *TGFBR2*; TGF beta signalopathies; Marfan syndrome; Loeys Dietz syndrome; locus-specific database

## INTRODUCTION

Many diseases are caused by an inherited variation in just one gene. Among more than 7,000 human rare diseases inherited in a Mendelian fashion (one gene-one disease), nearly 4,000 genes associated with a given phenotype have now been mapped. These molecular genetic analyses identify a more complex scenario in which the same gene can be involved in disorders thought to be clinically distinct. The *TGFBR2* gene (MIM# 190182) belongs to this more complex category. Transforming growth factor beta receptor type II (T $\beta$ R-II) is a transmembrane protein serine/threonine kinase well known as having a tumor suppressor role and inhibiting cell proliferation. Receptor activation occurs upon binding of TGF $\beta$  to T $\beta$ R-II, which then recruits and phosphorylates T $\beta$ R-I, which propagates the signal to downstream targets, Smads (Fig. 1). Smad complexes then translocate to the nucleus, where together with a coactivator or a corepressor they regulate transcription of target genes [Attisano et al., 1996; Souhelnytskyi et al., 1996; Ullrich and Schlessinger, 1990; Wieser et al., 1995; Wrana et al., 1994a, 1994b]. Perturbations of the TGF $\beta$ /Smad signaling system are the cause of various forms of human cancers as well as developmental disorders [Massague, 1998]. With somatic mutations and loss of expression of genes for various components of the TGF $\beta$ /SMAD signaling pathway, growth inhibition is lost, resulting in unregulated cell growth with tumor formation. A large number of pancreatic and colorectal cancers have mutations in some component of the pathway. Mutations in the gene encoding T $\beta$ R-II, *TGFBR2*, usually reported in colon and

gastric cancer lead to truncated, inactive *TGFBR2* product by mutations in a polyadenosine tract (*BatII* region) [Markowitz et al., 1995]. In most of these cases, both *TGFBR2* alleles present with a mutation in the *BatII* sequence. In some cases, however, a different mutation inactivates the second allele such as loss of heterozygosity, addition of a GT dinucleotide to a (GT)<sub>3</sub> sequence in the kinase domain coding region, or missense mutations predicted to inactivate this kinase domain. *TGFBR2* then shares the two-hit inactivation mechanism of other tumor suppressor genes.

In 2004, we demonstrated the implication of six *TGFBR2* mutations in Marfan syndrome (MFS) [Mizuguchi et al., 2004]. MFS, the founding member of heritable disorders of connective tissue,

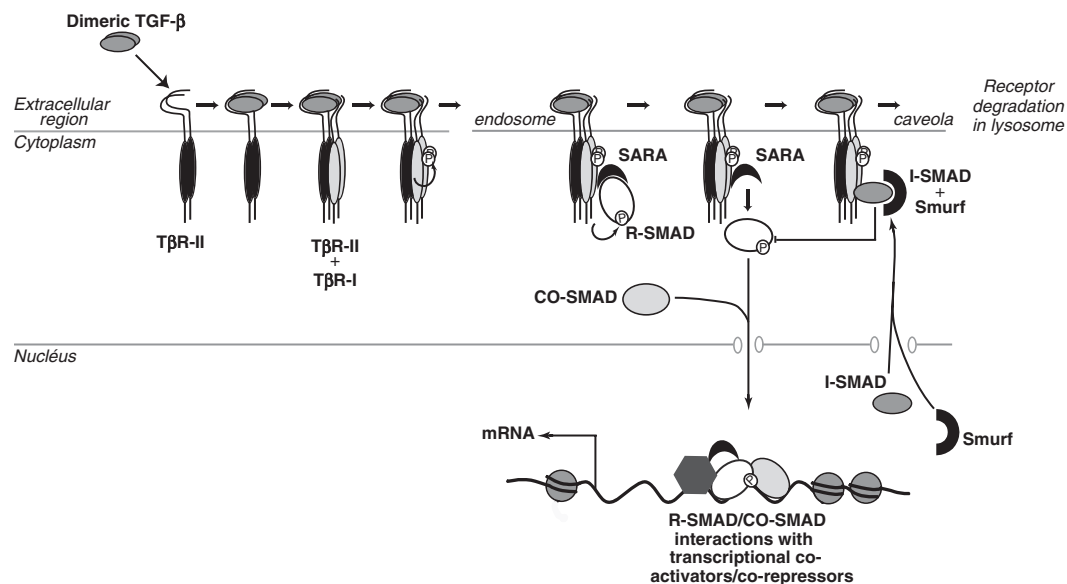
is a dominantly inherited condition characterized by tall stature and skeletal deformities, dislocation of the lens, and propensity to aortic dissection. The syndrome is characterized by considerable variation in the clinical presentation between families and also within the same family. The leading cause of premature death is progressive dilation of the aortic root and ascending aorta, causing aortic incompetence and dissection. The average life expectancy has risen significantly since 1972, which is partly due to the benefit arising from aortic follow-up with echocardiography, aortic surgery, and medical therapy with beta blockers. The first mutations involved in classical MFS phenotypes have been found in the *FBN1* gene encoding fibrillin-1, the major component of the extracellular matrix [Dietz et al., 1991]. *FBN1* mutations have now been identified in a spectrum of phenotypically-related connective tissue disorders, termed type 1 fibrillinopathies, including severe neonatal Marfan syndrome [Kainulainen et al., 1994], autosomal dominantly inherited ectopia lentis [Kainulainen et al., 1994], isolated skeletal features (or Marfanoid skeletal syndrome) [Ades et al., 2002; Hayward et al., 1994; Milewicz et al., 1995], "MASS phenotype" (MASS is an acronym that designates the involvement of the mitral valve, aorta, skeleton, and skin) [Dietz et al., 1993], familial or isolated forms of aortic aneurysms [Milewicz et al., 1996], and autosomal dominant Weill-Marchesani syndrome [Favre et al., 2003]. Heterozygous mutations in *TGFBR2*, a putative tumor-suppressor gene involved in several malignancies, are also associated with MFS [Mizuguchi et al., 2004]. The implication of *TGFBR2* mutations, not only in MFS [Boileau et al., 2005] but also in other autosomal dominant Mendelian disorders such as Loeys-Dietz syndrome (LDA) [Loeys et al., 2005] and Familial Thoracic Aortic Aneurysms and Dissections (TAAD2) [Pannu et al., 2005], revealed all the complexity of the TGF- $\beta$  signal transduction network. Mutations in the *TGFBR2* gene in MFS2, LDS, and TAAD2 define a new group of Marfan syndrome-related connective tissue disorders: TGF $\beta$  signalopathies.

To date, known *TGFBR2* mutations are not disease-specific and many mutations have to be accumulated before genotype-phenotype

relationships emerge. To facilitate mutational analysis of the *TGFBR2* gene, and as for *FBN1* [Collod et al., 1996; Collod-Beroud et al., 1997, 1998, 2003], we have created a human *TGFBR2* mutation database, Universal Mutation Database (UMD)-*TGFBR2*. The information regarding these mutations is standardized to facilitate their mutational analysis and, when a greater number of mutations has been collected, identify structure-function and phenotype-genotype relationships. This database gives access to a software package that provides specific routines and optimized multicriteria research and sorting tools [Beroud et al., 2000, 2005].

## THE *TGFBR2* GENE AND T $\beta$ R-II

*TGFBR2* gene maps to 3p22 [Mathew et al., 1994]. The T $\beta$ R-II protein is encoded by 567 codons in seven exons (Fig. 2A) [Takenoshita et al., 1996]. The translated product of the *TGFBR2* gene is composed of several subdomains (Fig. 2B). Starting from the N-terminus, there is a signal peptide (1–22) [Lin et al., 1992], a relatively short cysteine-rich extracellular domain (51–142), serine/threonine protein kinase catalytic domains (codons 246–544), and the C-terminus. The extracellular region is N-glycosylated [Wells et al., 1997] and contains 12 cysteines probably involved in the general folding of this region. Three of these cysteines form a characteristic cluster near the transmembrane sequence [Childs et al., 1993; Massague, 1992]. The transmembrane region and the cytoplasmic juxtamembrane region have no singular structural features. The cytoplasmic region contains kinase domains conforming to the canonical sequence of a serine/threonine protein kinase domain (Hanks et al., 1988). T $\beta$ R-II is regulated intricately by autophosphorylation on at least three serine residues (Ser213 in the juxtamembrane region and Ser409 et Ser416 in the T-loop region of the kinase domain [Luo and Lodish, 1997]). The T $\beta$ R-II exists in an alternative form arising from the presence of a 25-amino acid insert following the signal sequence [Hirai and Fujita, 1996; Suzuki et al., 1994].



**FIGURE 1. TGF- $\beta$  signaling.** Binding of dimeric TGF- $\beta$  to type II receptor (T $\beta$ R-II) in concert with type I receptor (T $\beta$ R-I) leads to the formation of a receptor complex and the phosphorylation of T $\beta$ R-I. Thus activated, T $\beta$ R-I subsequently phosphorylates a receptor-regulated SMAD (R-SMAD), allowing this protein to associate with coactivator (CO-SMAD) and move into the nucleus. In the nucleus, the SMAD complex associates with a DNA-binding partner and this complex binds to specific enhancers in target genes, activating transcription. Smurfs (Smad-ubiquitin regulatory factor) bind to the activated TGF- $\beta$  receptor complex via I-Smads. Smurf then ubiquitinates the receptor, causing its rapid proteasomal degradation. The CO-SMAD/R-SMAD can interact with a great number of transcriptional coactivators/corepressors to positively or negatively regulate effector genes, so that the interpretation of a signal depends on the cell-type and cross-talk with other signaling pathways.



colon cancer [Lu et al., 1995], in MFS [Mizuguchi et al., 2004], and in LDS type I [Loeys et al., 2006]. Today, two recurrent mutations are only involved in LDS type I: p.C461Y and p.R528C [Loeys et al., 2006]. When looking at reported transmissions, 20 somatic mutations are involved in cancers and 17 de novo mutations vs. 16 familial cases are observed. For 28 mutations, detailed data are not available. Mutations are mainly missense with 78 reported cases among which 46 concern highly conserved amino acids. Two nonsense mutations, p.R495X [Loeys et al., 2006] and p.R497X [Singh et al., 2006], are located in the same region, the cytoplasmic serine/threonine kinase domain DXI. Four splice-site mutations are described. Three concern the canonical splice site sequences (c.95-2A>G, c.1397-2A>G, and c.1397-1G>A) and one is a synonymous amino acid substitution in the last nucleotide of exon 6 resulting in abnormal splicing [Mizuguchi et al., 2004]. For each of the four mutations, insertion or deletion sequences have been experimentally characterized (see Table 1). Only one insertion is reported, corresponding to the duplication of one base, c.1600\_1601dup [Markowitz et al., 1995].

The p.T315M variation, which was reported initially in familial nonpolyposis colorectal cancer [Lu et al., 1998], was observed in two patients with MFS and in nine of 497 controls by Ki et al. [2005]. Ki et al. [2005] presumed then that this variation is a rare polymorphism in the Korean population (estimated allele frequency of 0.01). This variation is however considered as probably pathogenic based on chemical properties (Blosum62 [Henikoff and Henikoff, 1992], and biochemical value [Yu, 2001]). In the absence of conclusive data, this variation has been classified as a polymorphism. In the same way, sequence variations, c.944C>T [Lu et al., 1998], c.1159G>A [Lucke et al., 2001; Matyas et al., 2006], and c.1159G>C [Matyas et al., 2006], for which no clear argument for their pathogenicity has been reported are considered as polymorphism until more data are collected (see Supplementary Table S2).

The diagnosis of Shprintzen-Goldberg syndrome reported by Kosaki et al. [2006] in a Korean patient is debatable (c.IVS5-2A>G or c.1397-2A>G mutation). This patient fulfills the preliminary guidelines suggested for the diagnosis of Shprintzen-Goldberg syndrome. However, Robinson et al. [2006] argued that the diagnosis of Loeys-Dietz syndrome would also be appropriate for this individual, especially in light of the presence of bifid uvula and the sigmoid configuration of the brachycephalic, left common carotid, and left subclavian arteries. This patient is then reported as having LDS type I.

Further studies will be now necessary to characterize a large number of germline mutations in this gene and determine if the spectrum of clinical features associated with *TGFBR2* gene mutations is as large as that of *FBNI* gene mutations.

## DATABASE UPDATE

The current database and subsequent updated versions are available at [www.umd.be](http://www.umd.be).

Notification of omissions and errors in the current version as well as specific phenotypic data would be gratefully received by the corresponding author ([g.collod-beroud@montp.inserm.fr](mailto:g.collod-beroud@montp.inserm.fr)). The software package is available on a collaborative basis. The software will be expanded as the database grows and according to the requirements of its users. New functions could be implemented. Users of the database must cite this article.

TABLE 1. Evaluation of Splice-Site Consequences

Mutation	Reference	Splice site type	Wild type sequence	Wild type CV	Mutant sequence	Mutant CV	Variation	Observed consequences
c.IVS1-2A>G (c.95-2A>G)	Loeys et al. [2005]	Acceptor	TTCTCTCTCTCAgt	92,43	TTCTCTCTCTCGgt	76,5	-17,23	Experimentally demonstrated (skipping of nucleotides 95-112)
c.IVS5-2A>G (c.1397-2A>G)	Kosaki et al. [2006]	Acceptor	GGCTTTCTTCACAgA	93,96	GGCTTTCTTCACGGgA	78,04	-16,95	Experimentally demonstrated (inclusion of 30 nt)
c.IVS5-1G>A (c.1397-1G>A)	Loeys et al. [2006]	Acceptor	GGCTTTCTTCACAgA	93,96	GGCTTTCTTCACAAa	78,04	-16,95	Experimentally demonstrated (inclusion of 30 nt)
c.1524G>G (p.Gin508Gin)>A	Mizuguchi et al. [2004]	Donor	CAGgtaagg	98,07	CAAgtaagg	87,07	-10,79	Experimentally demonstrated (inclusion of 23 nt)

\*Consensus values for each potential donor or acceptor splice site are calculated for wild type (WT) and mutant sequence according to Shapiro and Senapathy [1987] and Senapathy et al. [1990] (100 = strong splice site; 0 = not a splice site). Observed consequences describes the abnormalities found at the mRNA level.

## ACKNOWLEDGMENTS

This work was supported by grants from GIS-Institut des Maladies Rares 2004 and ANR-05PCOD-14-02 (both to C.B. and G.J.). M.Y.F. is supported by a grant from Association Française contre les Myopathies (AFM).

## REFERENCES

- Ades LC, Sreetharan D, Onikul E, Stockton V, Watson KC, Holman KJ. 2002. Segregation of a novel FBN1 gene mutation, G1796E, with kyphoscoliosis and radiographic evidence of vertebral dysplasia in three generations. *Am J Med Genet* 109:261–270.
- Attisano L, Wrana J, Montalvo E, Massague J. 1996. Activation of signalling by the activin receptor complex. *Mol Cell Biol* 16:1066–1073.
- Beroud C, Colod-Beroud G, Boileau C, Soussi T, Junien C. 2000. UMD (Universal mutation database): a generic software to build and analyze locus-specific databases. *Hum Mutat* 15:86–94.
- Beroud C, Hamroun D, Colod-Beroud G, Boileau C, Soussi T, Claustres M. 2005. UMD (Universal Mutation Database): 2005 update. *Hum Mutat* 26:184–191.
- Boileau C, Jondeau G, Mizuguchi T, Matsumoto N. 2005. Molecular genetics of Marfan syndrome. *Curr Opin Cardiol* 20:194–200.
- Carcamo J, Zentella A, Massague J. 1995. Disruption of transforming growth factor beta signaling by a mutation that prevents transphosphorylation within the receptor complex. *Mol Cell Biol* 15:1573–1581.
- Childs S, Wrana J, Arora K, Attisano L, O'Connor M, Massague J. 1993. Identification of a Drosophila activin receptor. *Proc Natl Acad Sci USA* 90:9475–9479.
- Colod G, Beroud C, Soussi T, Junien C, Boileau C. 1996. Software and database for the analysis of mutations in the human FBN1 gene. *Nucleic Acids Res* 24:137–140.
- Colod-Beroud G, Beroud C, Ades L, Black C, Boxer M, Brock DJ, Godfrey M, Hayward C, Karttunen L, Milewicz D, Peltonen L, Richards RI, Wang M, Junien C, Boileau C. 1997. Marfan Database (second edition): software and database for the analysis of mutations in the human FBN1 gene. *Nucleic Acids Res* 25:147–150.
- Colod-Beroud G, Beroud C, Ades L, Black C, Boxer M, Brock DJ, Holman KJ, de Paepe A, Francke U, Grau U, Hayward C, Klein HG, Liu W, Nuytinck L, Peltonen L, Alvarez Perez AB, Rantamaki T, Junien C, Boileau C. 1998. Marfan Database (third edition): new mutations and new routines for the software. *Nucleic Acids Res* 26:229–233.
- Colod-Beroud G, Le Bourdelles S, Ades L, Ala-Kokko L, Booms P, Boxer M, Child A, Comeglio P, De Paepe A, Hyland JC, Holman K, Kaitila I, Loeys B, Matyas G, Nuytinck L, Peltonen L, Rantamaki T, Robinson P, Steinmann B, Junien C, Beroud C, Boileau C. 2003. Update of the UMD-FBN1 mutation database and creation of an FBN1 polymorphism database. *Hum Mutat* 22:199–208.
- Dietz H, Cutting G, Pyeritz R. 1991. Defects in the fibrillin gene cause the Marfan syndrome; linkage evidence and identification of a missense mutation. *Nature* 352:337–339.
- Dietz H, McIntosh I, Sakai L, Corson G, Chalberg S, Pyeritz R, Francomano C. 1993. Four novel FBN1 mutations: significance for mutant transcript level and EGF-like domain calcium binding in the pathogenesis of Marfan syndrome. *Genomics* 17:468–475.
- Disabella E, Grasso M, Marziliano N, Ansaldi S, Lucchelli C, Porcu E, Tagliani M, Pilotto A, Diegoli M, Lanzarini L, Malattia C, Pelliccia A, Ficcadenti A, Gabrielli O, Arbustini E. 2006. Two novel and one known mutation of the TGFBR2 gene in Marfan syndrome not associated with FBN1 gene defects. *Eur J Hum Genet* 14:34–38.
- Faivre L, Gorlin RJ, Wirtz MK, Godfrey M, Dagonneau N, Samples JR, Le Merrer M, Colod-Beroud G, Boileau C, Munnich A, Cormier-Daire V. 2003. In frame fibrillin-1 gene deletion in autosomal dominant Weill-Marchesani syndrome. *J Med Genet* 40:34–36.
- Garrigue-Antar L, Munoz-Antonia T, Antonia S, Gesmonde J, Vellucci V, Reiss M. 1995. Missense mutations of the transforming growth factor beta type II receptor in human head and neck squamous carcinoma cells. *Cancer Res* 55:3982–3987.
- Grady W, Myeroff L, Swinler S, Rajput A, Thiagalingam S, Lutterbaugh J, Neumann A, Brattain M, Chang J, Kim S, Kinzler K, Vogelstein B, Willson J, Markowitz S. 1999. Mutational inactivation of transforming growth factor beta receptor type II in microsatellite stable colon cancers. *Cancer Res* 59:320–324.
- Hanks S, Quinn A, Hunter T. 1988. The protein kinase family: conserved features and deduced phylogeny of the catalytic domains. *Science* 241:42–52.
- Hayward C, Porteous MEM, Brock DJH. 1994. A novel mutation in the fibrillin gene (FBN1) in familial arachnodactyly. *Mol Cell Probe* 8:325–327.
- Henikoff S, Henikoff JG. 1992. Amino acid substitution matrices from protein blocks. *Proc Natl Acad Sci USA* 89:10915–10919.
- Hirai R, Fujita T. 1996. A human transforming growth factor-beta type II receptor that contains an insertion in the extracellular domain. *Exp Cell Res* 223:135–141.
- Kainulainen K, Karttunen L, Puhakka L, Sakai L, Peltonen L. 1994. Mutations in the fibrillin gene responsible for dominant ectopia lentis and neonatal Marfan syndrome. *Nat Genet* 6:64–69.
- Ki CS, Jin DK, Chang SH, Kim JE, Kim JW, Park BK, Choi JH, Park IS, Yoo HW. 2005. Identification of a novel TGFBR2 gene mutation in a Korean patient with Loeys-Dietz aortic aneurysm syndrome; no mutation in TGFBR2 gene in 30 patients with classic Marfan's syndrome. *Clin Genet* 68:561–563.
- Knaus PI, Lindemann D, DeCoteau JF, Perlman R, Yankelev H, Hille M, Kadin ME, Lodish HF. 1996. A dominant inhibitory mutant of the type II transforming growth factor beta receptor in the malignant progression of a cutaneous T-cell lymphoma. *Mol Cell Biol* 16:3480–3489.
- Kosaki K, Takahashi D, Udaka T, Kosaki R, Matsumoto M, Ibe S, Isobe T, Tanaka Y, Takahashi T. 2006. Molecular pathology of Shprintzen-Goldberg syndrome. *Am J Med Genet A* 140:104–108; author reply: 109–110.
- Law C, Bunyan D, Castle B, Day L, Simpson I, Westwood G, Keeton B. 2006. Clinical features in a family with an R460H mutation in transforming growth factor beta receptor 2 gene. *J Med Genet* 43:908–916.
- LeMaire SA, Pannu H, Tran-Fadulu V, Carter SA, Coselli JS, Milewicz DM. 2007. Severe aortic and arterial aneurysms associated with a TGFBR2 mutation. *Nat Clin Pract Cardiovasc Med* 4:167–171.
- Lin H, Wang X, Ng-Eaton E, Weinberg R, Lodish H. 1992. Expression cloning of the TGF-beta type II receptor, a functional transmembrane serine/threonine kinase. *Cell* 68:775–785.
- Loeys B, Chen J, Neptune E, Judge D, Podowski M, Holm T, Meyers J, Leitch C, Katsanis N, Sharifi N, Xu F, Myers L, Spevak P, Cameron D, De Backer J, Hellems J, Chen Y, Davis E, Webb C, Kress W, Coucke P, Rifkin D, De Paepe A, Dietz H. 2005. A syndrome of altered cardiovascular, craniofacial, neurocognitive and skeletal development caused by mutations in TGFBR1 or TGFBR2. *Nat Genet* 37:275–281.
- 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. 2006. Aneurysm syndromes caused by mutations in the TGF-beta receptor. *N Engl J Med* 355:788–798.
- Lu S, Akiyama Y, Nagasaki H, Saitoh K, Yuasa Y. 1995. Mutations of the transforming growth factor-beta type II receptor gene and genomic instability in hereditary nonpolyposis colorectal cancer. *Biochem Biophys Res Commun* 216:452–457.
- Lu S, Kawabata M, Imamura T, Akiyama Y, Nomizu T, Miyazono K. 1998. HNPCC associated with germline mutation in the TGF-beta type II receptor gene. *Nat Genet* 19:17–18.
- Lucke C, Philpott A, Metcalfe J, Thompson A, Hughes-Davies L, Kemp P, Hesketh R. 2001. Inhibiting mutations in the transforming growth factor beta type 2 receptor in recurrent human breast cancer. *Cancer Res* 61:482–485.
- Luo K, Lodish H. 1997. Positive and negative regulation of type II TGF-beta receptor signal transduction by autophosphorylation on multiple serine residues. *EMBO J* 16:1970–1981.

- Markowitz S, Wang J, Myeroff L, Parsons R, Sun L, Lutterbaugh J, Fan RS, Zborowska E, Kinzler KW, Vogelstein B, Brattain MB, Willson JK. 1995. Inactivation of the type II TGF-beta receptor in colon cancer cells with microsatellite instability. *Science* 268:1336–1338.
- Massague J. 1992. Receptors for the TGF-beta family. *Cell* 69:1067–1070.
- Massague J. 1998. TGF-beta signal transduction. *Annu Rev Biochem* 67: 753–791.
- Mathew S, Murty VV, Cheifetz S, George D, Massague J, Chaganti RS. 1994. Transforming growth factor receptor gene TGFBR2 maps to human chromosome band 3p22. *Genomics* 20:114–115.
- Matyas G, Arnold E, Carrel T, Baumgartner D, Boileau C, Berger W, Steinmann B. 2006. Identification and in silico analyses of novel TGFBR1 and TGFBR2 mutations in Marfan syndrome-related disorders. *Hum Mutat* 27:760–769.
- Milewicz DM, Grossfield J, Cao S-N, Kielty C, Covitz W, Jewett T. 1995. A mutation in FBN1 disrupts profibrillin processing and results in isolated skeletal features of the Marfan syndrome. *J Clin Invest* 95:2373–2378.
- Milewicz DM, Michael K, Fisher N, Coselli JS, Markello T, Biddinger A. 1996. Fibrillin-1 (FBN1) mutations in patients with thoracic aortic aneurysms. *Circulation* 94:2708–2711.
- Mizuguchi T, Collod-Beroud G, Akiyama T, Abifadel M, Harada N, Morisaki T, Allard D, Varret M, Claustres M, Morisaki H, Ihara M, Kinoshita A, Yoshiura K, Junier C, Kajii T, Jondeau G, Ohta T, Kishino T, Furukawa Y, Nakamura Y, Niikawa N, Boileau C, Matsumoto N. 2004. Heterozygous TGFBR2 mutations in Marfan syndrome. *Nat Genet* 36: 855–860.
- Myeroff L, Parsons R, Kim S, Hedrick L, Cho K, Orth K, Mathis M, Kinzler K, Lutterbaugh J, Park K, Bang Y, Lee H, Park J, Lynch H, Roberts A, Vogelstein B, Markowitz S. 1995. A transforming growth factor beta receptor type II gene mutation common in colon and gastric but rare in endometrial cancers with microsatellite instability. *Cancer Res* 55: 5545–5547.
- Pannu H, Fadulu V, Chang J, Lafont A, Hasham S, Sparks E, Giampietro P, Zaleski C, Estrera A, Safi H, Shete S, Willing M, Raman C, Milewicz D. 2005. Mutations in transforming growth factor-beta receptor type II cause familial thoracic aortic aneurysms and dissections. *Circulation* 112: 513–520.
- Parsons R, Myeroff L, Liu B, Willson J, Markowitz S, Kinzler K, Vogelstein B. 1995. Microsatellite instability and mutations of the transforming growth factor beta type II receptor gene in colorectal cancer. *Cancer Res* 55: 5548–5550.
- Robinson PN, Arteaga-Solis E, Baldock C, Collod-Beroud G, Booms P, De Paepe A, Dietz HC, Guo G, Handford PA, Judge DP, Kielty CM, Loey s B, Milewicz DM, Ney A, Ramirez F, Reinhardt DP, Tiedemann K, Whiteman P, Godfrey M. 2006. The molecular genetics of Marfan syndrome and related disorders. *J Med Genet* 43:769–787. (PMID: 16571647).
- Sakai H, Visser R, Ikegawa S, Ito E, Numabe H, Watanabe Y, Mikami H, Kondoh T, Kitoh H, Sugiyama R, Okamoto N, Ogata T, Fodde R, Mizuno S, Takamura K, Egashira M, Sasaki N, Watanabe S, Nishimaki S, Takada F, Nagai T, Okada Y, Aoka Y, Yasuda K, Iwasa M, Kogaki S, Harada N, Mizuguchi T, Matsumoto N. 2006. Comprehensive genetic analysis of relevant four genes in 49 patients with Marfan syndrome or Marfan-related phenotypes. *Am J Med Genet A* 140:1719–1725.
- Senapathy P, Shapiro MB, Harris NL. 1990. Splice junctions, branch point sites, and exons: sequence statistics, identification, and applications to genome project. *Methods Enzymol* 183:252–278.
- Shapiro MB, Senapathy P. 1987. RNA splice junctions of different classes of eukaryotes: sequence statistics and functional implications in gene expression. *Nucleic Acids Res* 15:7155–7174.
- Singh KK, Rommel K, Mishra A, Karck M, Haverich A, Schmidtke J, Arslan-Kirchner M. 2006. TGFBR1 and TGFBR2 mutations in patients with features of Marfan syndrome and Loey s-Dietz syndrome. *Hum Mutat* 27:770–777.
- Souchelnytskiy S, ten Dijke P, Miyazono K, Heldin C. 1996. Phosphorylation of Ser165 in TGF-beta type I receptor modulates TGF-beta1-induced cellular responses. *EMBO J* 15:6231–6240.
- Suzuki A, Shioda N, Maeda T, Tada M, Ueno N. 1994. Cloning of an isoform of mouse TGF-beta type II receptor gene. *FEBS Lett* 355: 19–22.
- Takenoshita S, Hagiwara K, Nagashima M, Gemma A, Bennett WP, Harris CC. 1996. The genomic structure of the gene encoding the human transforming growth factor beta type II receptor (TGF-beta RII). *Genomics* 36:341–344.
- Takenoshita S, Tani M, Nagashima M, Hagiwara K, Bennett WP, Yokota, J, Harris, CC. 1997. Mutation analysis of coding sequences of the entire transforming growth factor beta type II receptor gene in sporadic human colon cancer using genomic DNA and intron primers. *Oncogene* 14: 1255–1258.
- Tanaka S, Mori M, Mafune K, Ohno S, Sugimachi K. 2000. A dominant negative mutation of transforming growth factor-beta receptor type II gene in microsatellite stable oesophageal carcinoma. *Br J Cancer* 82:1557–1560.
- Ullrich A, Schlessinger J. 1990. Signal transduction by receptors with tyrosine kinase activity. *Cell* 61:203–212.
- Waldmuller S, Muller M, Warnecke H, Rees W, Schols W, Walterbusch G, Ennker J, Scheffold T. 2007. Genetic testing in patients with aortic aneurysms/dissections: a novel genotype/phenotype correlation? *Eur J Cardiothorac Surg* 31:970–975.
- Wells R, Yankelev H, Lin H, Lodish H. 1997. Biosynthesis of the type I and type II TGF-beta receptors. Implications for complex formation. *J Biol Chem* 272:11444–11451.
- Wieser R, Wrana J, Massague J. 1995. GS domain mutations that constitutively activate T beta R-I, the downstream signaling component in the TGF-beta receptor complex. *EMBO J* 14:2199–2208.
- Wrana J, Attisano L, Wieser R, Ventura F, Massague J. 1994a. Mechanism of activation of the TGF-beta receptor. *Nature* 370:341–347.
- Wrana J, Tran H, Attisano L, Arora K, Childs S, Massague J, O'Connor M. 1994b. Two distinct transmembrane serine/threonine kinases from *Drosophila melanogaster* form an activin receptor complex. *Mol Cell Biol*. 14:944–950.
- Yu K. 2001. Theoretical determination of amino acid substitution Groups based on qualitative physicochemical properties. Available at: <http://cmgm.stanford.edu/biochem218/Projects%202001/Yu.pdf> Last accessed: 2 August 2007.