

# Gene Section

## Review

# THBS1 (thrombospondin-1)

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## Abstract

Thrombospondins are encoded in vertebrates by a family of 5 THBS genes. THBS1 is infrequently mutated in most cancers, but its expression is positively regulated by several tumor suppressor genes and negatively regulated by activated oncogenes and promoter hypermethylation. Consequently, loss of thrombospondin-1 expression is frequently lost during oncogenesis and is correlated with a poor prognosis for some cancers. Thrombospondin-1 is a secreted protein that acts in the tumor microenvironment to inhibit angiogenesis, regulate antitumor immunity, stimulate tumor cell migration, and regulate the activities of extracellular proteases and growth factors.

Differential effects of thrombospondin-1 on the sensitivity of normal versus malignant cells to ischemic and genotoxic stress also regulate the responses to tumors to therapeutic radiation and chemotherapy.

### Keywords

thrombospondin-1, matricellular, tumor angiogenesis, metastasis, resistance to genotoxic therapy

## Identity

**HGNC (Hugo):** THBS1

**Location:** 15q14

### Other names

THBS, TSP, THBS-1, TSP-1, TSP1

### Local order

Telomeric to FLJ39531, centromeric to FSIP1 (fibrous sheath interacting protein 1)

## DNA/RNA

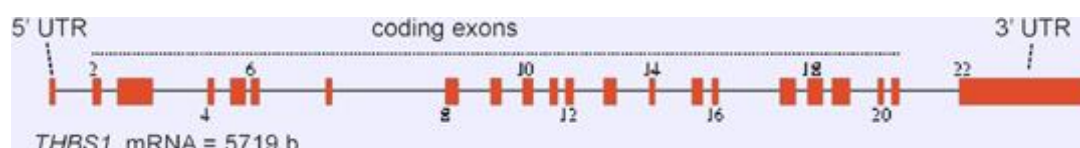
### Description

The THBS1 gene is 16,393 bases in size and is composed of 22 exons.

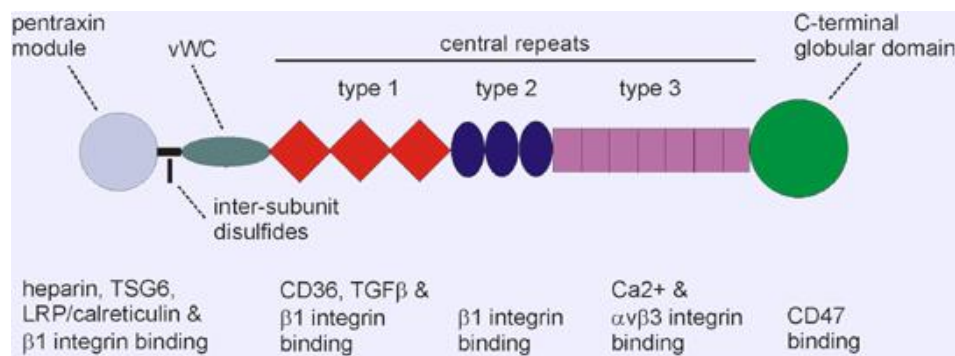
Exons 2-21 encode the 5729 b mRNA.

### Transcription

Egr-1 and Sp1 sites function in the transcription of THBS1 stimulated in most cell types by culture in the presence of serum (Shingu and Bornstein, 1994). Transcription is regulated by JUN (c\_jun or AP1) in cooperation with the repressor Yin Yang-1 (YY1) and by TP53.



Exon/intron organization of the THBS1 gene.



Domain organization and localization of selected ligand binding sites in THBS1. THBS1 is a homotrimer linked via disulfide bonds.

USF2 and the aryl hydrocarbon receptor (AHR) mediate glucose-induced THBS1 transcription (Wang et al., 2004; Dabir et al., 2008). ID1 represses THBS1 transcription (Volpert et al., 2002).

The ATF1 transcription factor also down-regulates transcription of THBS1 through an ATF/cAMP-responsive element-binding protein binding site (Ghoneim et al., 2007). In contrast, MYC increases turnover of thrombospondin-1 mRNA (Janz et al., 2000). Transcription of THBS1 in some human cancers is suppressed through hypermethylation (Li et al., 1999; Yang et al., 2003). THBS1 expression is also regulated post-transcriptionally by micro-RNAs including MIR17HG (miR-17-92), MIR18A, MIR19A, MIR27B, MIR98, miR-194, MIR221, and MIRLET7I (let-7i-5p) (van Almen et al., 2011; Sundaram et al., 2011; Italiano et al., 2012; Yang et al., 2019; Miao et al., 2018; Farberov and Meidan 2018; Chen et al., 2017).

### Pseudogene

None identified.

## Protein

### Description

The THBS1 precursor contains 1170 amino acids; 129,412 Da. The mature secreted protein comprises residues 19-1170 after removal of the N-terminal signal peptide and assembles into a disulfide linked homotrimer. Secreted THBS1 is a glycoprotein with a molecular mass of 150-180 kDa that contains approximately 12 Asn-linked mono-, bi- tri-, and tetraantennary complex oligosaccharides and variable numbers of C-mannosylated Trp residues in the type 1 repeats, and O-fucosylation (Furukawa et al., 1989; Hofsteenge et al., 2001).

### Expression

THBS1 is expressed in many tissues during embryonic development but has limited expression in the healthy adult. THBS1 is the most abundant protein in alpha granules of platelets, but normal plasma levels are very low (typically 100-200 ng/ml). Expression in other cell types and tissues is

induced by wounding, ischemia, ischemia reperfusion, during tissue remodeling, in atherosclerotic lesions, rheumatoid synovium, glomerulonephritis, in response to high glucose and fat, and in the stroma of many tumors. THBS1 expression increases with aging and in age-related conditions including type 2 diabetes and cardiovascular disease. THBS1 may also play a role in hematologic conditions such as sickle cell disease. Conversely, most but not all malignant cells in tumors exhibit loss of THBS1 expression during malignant progression (Isenberg et al., 2009). This loss is due to diminished positive regulation of the THBS1 gene by suppressor genes such as TP53 and NME1 and increased negative regulation by oncogenes including RAS and MYC. THBS1 expression is induced by TGF-beta, vitamin A, progesterone, and retinoids and suppressed by nickel, ID1, and HGF (hepatocyte growth factor).

### Localisation

THBS1 is secreted by many cell types in response to injury or specific cytokines, THBS1 is and present transiently in extracellular matrix but is rapidly internalized for degradation by fibroblasts and endothelial cells. THBS1 is abundant in megakaryocytes and platelets and is constitutively expressed at the dermal-epidermal boundary in skin and in subendothelial matrix of some blood vessels. However, THBS1 levels are generally low or undetectable in most healthy adult tissues.

### Function

THBS1 binds to extracellular matrix ligands including fibrinogen, fibronectin, some collagens, latent and active TGF $\beta$ 1 (transforming growth factor-beta-1), TNFAIP6 (TSG6), heparin, plasmin, CTSG (cathepsin G), ELANE (neutrophil elastase), some MMPs, tissue factor pathway inhibitor, and heparan sulfate proteoglycans (Resovi et al., 2014). THBS1 binds to cell surface receptors including CD36, CD47, some syndecans, LRP1 (LDL receptor-related protein-1) (via CALR (calreticulin)) and the integrins ITGA5/ ITGB3 (alpha-5/beta-3), ITGA3/ ITGB1 (alpha-3/beta-1), ITGA4/ITGB1

(alpha-4/beta-1), and ITGA6/ITGB1 (alpha-6/beta-1) (Calzada and Roberts, 2005). THBS1 is a slow tight inhibitor of several proteases including plasmin, cathepsin G, and neutrophil elastase. THBS1 directly binds and activates latent TGF $\beta$ 1 (Murphy-Ullrich and Suto, 2018).

THBS1 in a context-dependent and cell-specific manner stimulates or inhibits cell adhesion, proliferation, motility, and survival. THBS1 is a potent inhibitor of angiogenesis, but N-terminal proteolytic and recombinant parts of THBS1 have clear pro-angiogenic activities mediated by beta-1 integrins. In the immune system, THBS1 is a potent inhibitor of T cell and dendritic cell activation and mediates clearance of apoptotic cells by phagocytes (Soto-Pantoja et al., 2015). In the CNS, THBS1 secreted by astrocytes promotes synaptogenesis (Risher and Eroglu, 2012).

Based on studies of Thbs1 null mice, platelet THBS1 is not essential for platelet aggregation, but THBS1 null mice have impaired excisional but improved ischemic wound repair, increased retinal angiogenesis, and are hyper-responsive to several inflammatory stimuli (Soto-Pantoja et al., 2015).

Time stimulates pathologic production of reactive oxygen species (ROS) by targeting NOX1. Mitochondria from CD47 null mice produce less ROS. Inhibition of H2S signaling contributes to the inhibition of T cell activation by THBS1 mediated through the CD47 receptor (Miller et al., 2015).

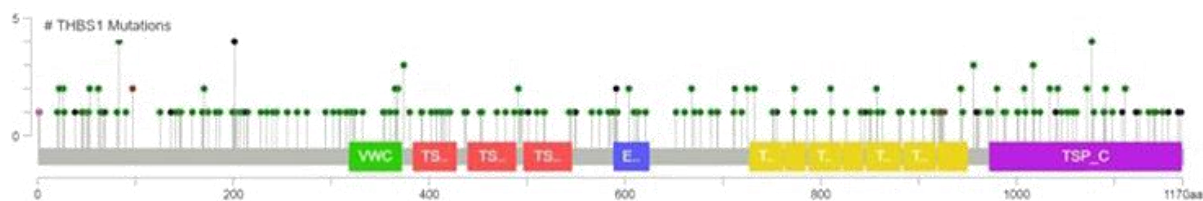
THBS1 through interacting with CD47, plays a broader role in primary non-cancer and cancer tissue survival of genotoxic damage caused by ionizing radiation and chemotherapy (Soto-Pantoja et al., 2015; Feliz-Mosquea et al., 2018). Animals lacking either THBS1 or CD47 tolerated high-dose regional radiation with minimal soft-tissue injury or loss of bone marrow (Isenberg et al., 2008). Suppressing THBS1-CD47 signaling renders non-cancer cells and tissues resistant to radiation- and

chemotherapy-mediated injury by promoting protective autophagy and enhancing anabolic metabolic repair pathways (Soto-Pantoja et al., 2012; Miller et al., 2015). Blocking the THBS1-CD47 axis also enhanced survival to lethal whole-body radiation (Soto-Pantoja et al., 2013). Conversely, interruption of THBS1-CD47 signaling increases radiation- and chemotherapy-mediated killing of cancers (Maxhimer et al., 2009; Feliz-Mosquea et al., 2018). This latter effect is mediated through activation of T and NK cell killing of tumors (Soto-Pantoja et al., 2014; Nath et al., 2019).

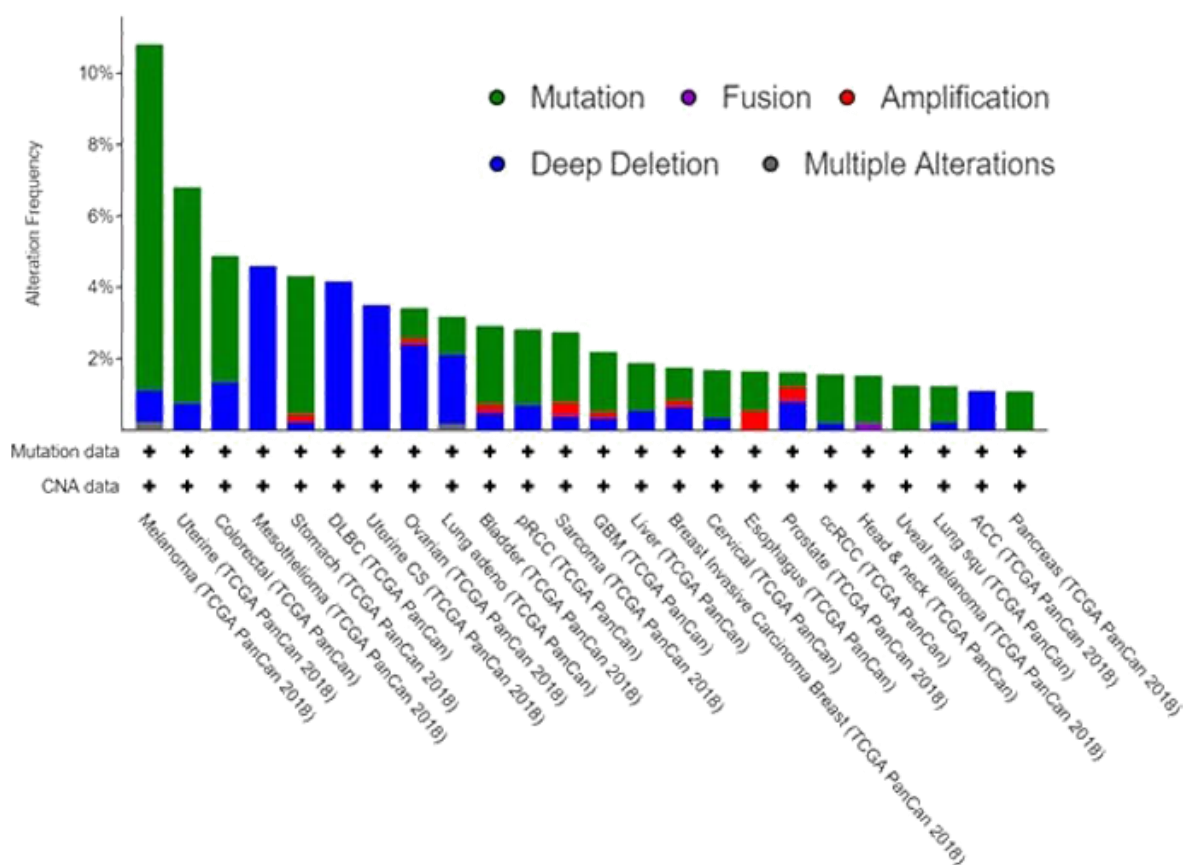
THBS1 is also a proximate inhibitor of stem cell self-renewal (Kaur et al., 2013). Acting via its cell surface receptor CD47, THBS1 limits the expression of important self-renewal transcription factors including POU5F1 (Oct3/4), SOX2, KLF4, and MYC in nonmalignant cells (Kaur et al., 2013). However, the ability of THBS1 to limit stem cell self-renewal is lost in cancer cells where MYC is amplified or dysregulated, and loss of CD47 expression or function consequently can suppress cancer stem cells (Kaur et al., 2013; Lee et al., 2014; Kaur and Roberts, 2016).

### Homology

THBS1 is a member of the thrombospondin family that also contains THBS2, THBS3, THBS4, and COMP (cartilage oligomeric matrix protein) which arose from gene duplication of a single primordial thrombospondin in insects (Adams and Lawler, 2012). The central type 1 repeats are also known as thrombospondin-repeats (TSRs) and are shared with the larger thrombospondin/properdin repeat superfamily (Adams and Tucker, 2000; Apte 2009; deLau et al., 2012). Orthologs of THBS1 are widely conserved in mammals and have also been identified in birds (*Gallus gallus* NP\_001186382.1), amphibians (*Xenopus tropicalis* XP\_002937245.1) and fish (*Dania rerio* XP\_005160819.1).



Identified mutations in thrombospondin-1 in human cancers include 187 missense (green), 41 truncating nonsense (black), 3 inframe (brown), and 2 other (purple). Data is from The Cancer Genome Atlas (TCGA) using cBioPortal tools to analyze data from 10,953 patients.



Frequency of THBS1 mutations in TCGA PanCancer data classified by cancer type using cBioPortal tools (green = mutation, purple = fusion, blue = deletion, red = amplification, grey = multiple alterations).

## Mutations

### Germinal

Deep exon sequencing of THBS1 from 60,706 humans identified 4 putative loss of function mutations, which was significantly below the 37.6 expected loss of function mutations for a non-essential gene of this size (Lek et al., 2016). The resulting calculated probability that THBS1 is loss intolerant ( $pLI = 1.0$ ) exceeds the  $pLI > 0.9$  cut-off, which predicts a strong selective pressure against inactivation of this gene. The basis for this apparent selective pressure against loss of THBS1 in humans remains unclear. *Thbs1*<sup>-/-</sup> mice are viable and fertile but exhibit defects in inflammatory responses and wound repair that may compromise their viability outside a protected laboratory environment (Lawler et al., 1998; Crawford et al., 1998; Lamy et al., 2007; Qu et al., 2018). Coding polymorphisms in THBS1 associated with altered disease risk in humans include a2210g (Asn700Ser), which is associated with premature familial myocardial infarction and small for gestational age infants. This mutation alters calcium binding to THBS1 and protein stability (Carlson et al., 2008; Hannah et al., 2004). The coding polymorphism g1678a (Thr523Ser) was

identified as a genetic risk factor of cerebral thrombosis in a Chinese population (Liu et al., 2004). Several noncoding SNPs in THBS1 have been associated with cancer risk as detailed below.

### Somatic

The frequency of somatic THBS1 mutation in human cancers is low. Somatic mutations have been identified at a frequency of 1.9% in The Cancer Genome Atlas (cBioportal.org). A total of 233 mutations have been identified, most of which are missense or nonsense. However, the random distribution of these mutations indicates a lack of cancer-specific mutation hotspots. THBS1 is most frequently mutated in cutaneous melanomas (12%) followed by uterine cancers (7%), but rare or absent in other cancer types. The higher mutation rate of THBS1 in melanomas may simply reflect the high overall mutation burden of this malignancy.

### Epigenetics

Most down-regulation of THBS1 in cancers is epigenetic, resulting from promoter hypermethylation (Yang et al., 2003), altered expression of regulatory noncoding RNAs (van Almen et al., 2011; Sundaram et al., 2011; Italiano et al., 2012; Yang et al., 2019; Miao et al., 2018; Farberov and Meidan 2018; Chen et al., 2017), or



altered levels of oncogenic transcription factor. Epigenetic silencing of THBS1 is associated with a poor prognosis in several cancers (Guerrero et al., 2008; Isenberg et al., 2009).

## Implicated in

### Gastric carcinoma

#### Disease

#### THBS1 rs1478605 T>C

Carriers of the CC genotype exhibited a decreased risk of developing gastric cancer compared to the carriers of the CT and TT genotypes [adjusted OR, 0.56; 95% confidence interval (CI), 0.39-0.79; P=0.001] (Hong et al., 2015). The CC genotype of rs1478605 was negatively associated with gastric cancer lymph node metastasis (OR, 0.41; 95% CI, 0.23-0.71; P=0.001) and was associated with a reduced risk of lymph node metastasis in male patients (OR, 0.27; 95% CI, 0.14-0.52; P

#### THBS1 rs2292305 T>C, rs1478604 A>G

Significant association was found between the homozygous CC variant of THBS1 (rs2292305 T>C) and development of highly differentiated gastric carcinoma (Lin et al., 2012). The rs1478604 A>G variant was associated with invasion and lymph node metastasis in gastric cancer. Based on logistic regression and stratification analysis, rs1478604 A>G was more strongly associated with lymph node metastasis in highly differentiated gastric cancer.

#### Oncogenesis

The mechanism by which this polymorphism regulates carcinogenesis remains to be determined.

### Bladder cancer

#### Disease

#### THBS1 696 C/T polymorphism (rs2664139)

Compared with the CT/TT genotypes, the CC genotype was associated with a significantly increased risk of bladder cancer (adjusted odds ratio [OR] 1.43, 95% CI 1.01-2.04) (Gu et al., 2014).

#### Oncogenesis

The mechanism by which this polymorphism regulates carcinogenesis remains to be determined.

### Colorectal cancer

Cancer progression associated with loss of THBS1 expression in the absence of known gene mutations.

#### Prognosis

Mutation of THBS1 is rare in most cancers, but loss of THBS1 expression due to hypermethylation, transcriptional regulation by oncogenes or tumor suppressor genes, or altered mRNA stability is commonly reported (Isenberg et al., 2009). Decreased THBS1 expression has been correlated with malignant progression and decreased survival in several cancers (Isenberg et al., 2009). To date, the

strongest data is for colorectal carcinomas. Multiple independent studies have shown significant association of reduced THBS1 expression with increased invasion, microvascular densities, and poor prognosis (Miyanaga et al., 2002; Maeda et al., 2001; Isenberg et al., 2009; Teraoku et al., 2016). Increased circulating levels of THBS1 were also a favourable prognostic marker in patients with colon cancer (HR 0.43, p = 0.007) (Marisi et al., 2018).

#### Oncogenesis

The specific role of THBS1 in colorectal oncogenesis has been studied in the APC<sup>Min/+</sup> mouse model. Mice lacking THBS1 on the Apc<sup>Min/+</sup> background exhibited increased intestinal adenoma formation with increased vascularization compared to Thbs1<sup>+/+</sup>: Apc<sup>Min/+</sup> mice, consistent with the known anti-angiogenic activity of THBS1 (Gutierrez et al., 2003). Lack of THBS1 also decreased colorectal carcinogenesis in mice exposed to the carcinogen azoxymethane in combination with oral administration of dextran sulfate to induce intestinal inflammation (Lopez-Dee, et al., 2015). Again, angiogenesis was increased in the lesions formed in the Thbs1<sup>-/-</sup> mice. However, the protective role of THBS1 expression to limit colorectal carcinogenesis was lost when Apc<sup>Min/+</sup> mice were fed a high fat Western diet, and metabolomic analysis identified systemic alterations including in eicosanoid metabolism that may mediate this effect (Soto-Pantoja et al., 2016).

### Various cancers

#### Disease

Cancer progression associated with loss of THBS1 expression in the absence of known gene mutations.

#### Prognosis

Studies have shown associations of decreased THBS1 with poor prognosis in various cancers including non-small cell lung carcinoma (Rouanne et al., 2016), pancreatic adenocarcinoma, gastric (Nakao, et al., 2011), invasive cervical carcinoma, and oral squamous cell carcinomas (Isenberg et al., 2009). Reports are mixed regarding THBS1 as a prognostic factor in breast cancers (Rice et al., 2002). Stromal THBS1 expression in breast cancer was inversely related to lymph node involvement (Ioachim et al., 2012). Evidence indicates that the failure of THBS1 to protect in breast cancer is due to an escape mechanism involving increased VEGFA expression (Fontana et al., 2005). Hypermethylation of THBS1 was associated with a poor prognosis in prostate cancers (Guerrero et al., 2008). However, THBS1 was positively correlated with invasion in hepatocellular carcinomas (Poon et al 2004). Evidence is mixed regarding the clinical significance of THBS1 expression in prostate cancer, and urothelial cancer (Miyata and Sakai, 2013).

#### Oncogenesis

Several transgenic mouse models support an indirect tumor suppressor activity of THBS1. Mice lacking THBS1 developed tumors earlier in a tp53 null background (Lawler et al., 2001). Loss of THBS1 expression was associated with local invasive behavior, tumor neovascularization, and metastasis. A study of UVB-induced skin carcinogenesis in wildtype versus Thbs1<sup>-/-</sup> hairless SKH1 mice found that the protective activity of the flavone apigenin was lost in the absence of THBS1 (Mirzoeva et al., 2018). The protective role of THBS1 to limit carcinogenesis in skin was associated with decreased levels of circulating inflammatory cytokines and infiltrating macrophages and neutrophils. Conversely, transgenic mice overexpressing THBS1 in skin or mammary tissue were resistant to chemical or oncogene-driven carcinogenesis (Streit et al., 1999; Rodriguez-Manzaneque et al., 2001). In addition to inhibiting the angiogenic switch required for tumor growth and hematologic metastasis, overexpression of THBS1 in tumor cells was associated with increased M1 polarization of tumor-associated macrophages in xenograft tumors, and THBS1 treatment increased superoxide production and killing of tumor cells by macrophages in vitro (Martin-Manos et al., 2008).

### **Familial pulmonary artery hypertension**

#### **Disease**

#### **THBS1 missense mutant Asp362Asn**

The THBS1 missense mutation (Asp362Asn) alters a residue in the first type 1 repeat of THBS1 (Maloney et al., 2012). The Asp362Asn THBS1 mutant had less than half of the ability of wild-type THBS1 to activate latent TGFβ1. Mutant 362Asn THBS1 also lost the ability to inhibit growth of pulmonary arterial smooth muscle cells and was over three-fold less effective at inhibiting endothelial cell growth.

The mutation was found in two unrelated probands from 60 familial pulmonary arterial hypertension (PAH) kindreds but not in any healthy or chronic disease control cohorts. Several affected family members carried a mutation in BMPR2, which is known to be associated with PAH risk, and one family member with the THBS1 mutation but lacking the BMPR2 mutation was not diagnosed with PAH. Therefore, the THBS1 mutation alone may not be sufficient to cause PAH, and THBS1 was proposed to be a modifier gene for familial PAH. The frequency of other common THBS1 polymorphisms did not differ between PAH and control cohorts.

#### **THBS1 intronic mutation (IVS8+255 G/A)**

THBS1 intronic mutation (IVS8+255 G/A) was identified in a proband with familial pulmonary hypertension (Maloney et al., 2012). This mutation

decreased and/or eliminated local binding of the transcription factors SP1 and MAZ in aortic smooth muscle cells. The mutation was confirmed to not alter splicing of THBS1 mRNA but is predicted to alter gene expression.

The mutation was found in multiple members of the single proband family with nine members diagnosed with PAH but absent in healthy and chronic disease control cohorts. Some of the affected family members were known to have BMPR2 mutations that are associated with PAH risk, and two family members with the THBS1 mutation but lacking the BMPR2 mutation were not diagnosed with PAH. Therefore, THBS1 was proposed to be a modifier gene. Because only one family was reported to date, the relative risk associated with this mutation remains to be determined.

### **Post-refractive surgery chronic ocular surface inflammation**

#### **Disease**

**THBS1 SNPs (rs1478604 T >?C, rs2228262 missense AAT > AGT, rs2292305 missense ACA > GCA)**

Increased risk for developing chronic inflammation in patients undergoing refractive eye surgery or receiving corneal allografts.

#### **Prognosis**

Patients with the minor alleles were more susceptible to developing chronic keratoconjunctivitis (rs1478604: odds ratio [OR], 2.5; 95% confidence interval [CI], 1.41-4.47; P = 2.5 × 10<sup>-3</sup>; rs2228262 and rs2292305: OR, 1.9; 95% CI, 1.05-3.51; P = 4.8 × 10<sup>-2</sup>. The rs1478604 A SNP was significantly associated with increased risk of corneal allograft rejection (odds ratio [OR], 1.58; 95% confidence interval [CI], 1.02-2.45; P = 0.04) (Contreras-Ruiz et al., 2014; Winton et al., 2014).

### **Familial premature myocardial infarction, Small for gestational age (SGA) infants**

#### **Disease**

#### **THBS1 variant A2210G (Ser700Asn)**

The THBS1 S700N variant is a significant risk factor for familial premature myocardial infarction in both homozygous and heterozygous carriers of the variant allele (Topol et al., 2001; Zwicker et al., 2006; Stenina et al., 2004).

Paternal and neonatal THBS1 A2210G was also associated with small gestational age. Maternal THBS1 A2210G was associated with reduced maternal birth weight adjusted for gestational age at delivery (P = 0.03) (Andraweera et al., 2011).

#### **Prognosis**

The THBS1 S700N variant may be a general risk factor for vascular disorders throughout life.

## Sickle cell disease

### Disease

#### THBS1 SNPs (rs1478605 T > C and rs1478604 T > C)

The THBS1 SNPs rs1478604 (minor allele frequencies (MAF) 0.291) and rs1478605 (MAF 0.286) were negatively associated [OR 0.45 (95% CI 0.19, 1.08;  $p=0.069$ ) and OR 0.33 (95% CI 0.12, 0.88;  $p=0.017$ , respectively)] with tricuspid regurgitant velocity (TRV)  $\geq 2.5$  in sickle cell disease patients (Jacob et al., 2017). Elevated TRV is a marker of pulmonary dysfunction. Of note, rs1478605 and rs1478604 are proximal to the THBS1 transcription start site and may alter THBS1 expression in patients with sickle cell disease.

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