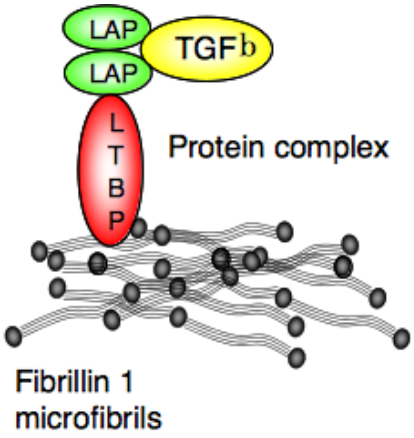
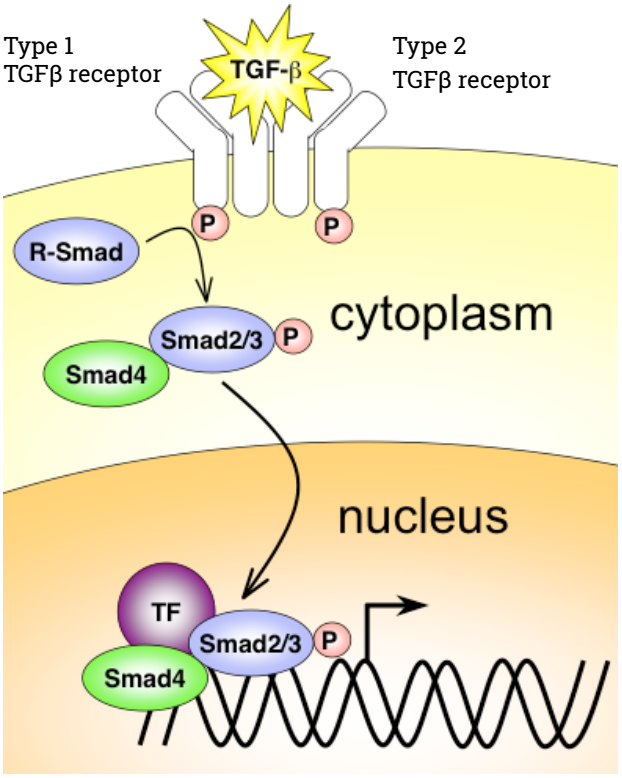
GENE ASSOCIATIONS

This sheet is meant to be a brief overview of the genes associated with Loeys-Dietz syndrome (LDS) and the corresponding clinical features. Information is still evolving and much of the information is based on small populations reported in the literature.

GENES & PROTEINS

Genes encode for proteins, which have certain functions within the cells of the body. The following is an illustration of how the proteins associated with Loeys-Dietz syndrome (and Marfan syndrome) interact.





GENES ASSOCIATED WITH ANEURYSM DISEASE IN THE TGF BETA PATHWAY

TGFBR1=transforming growth factor beta receptor 1 (LDS 1)

TGFBR2= transforming growth factor beta receptor 2 (LDS 2)

SMAD3= mothers against decapentaplegic, drosophila, homolog of, 3 (LDS 3; Aneurysm-Osteoarthritis syndrome)

TGFB2= transforming growth factor beta ligand 2 (LDS 4, aortic aneurysm with MFS-like skeletal features)

FBN1=Fibrillin-1 (Marfan syndrome)

Fibrillin-1 binds to a complex of proteins that then binds tgfbeta ligands (molecules). TGFBR1 and 2 are cell surface receptors that are activated (turned on) by the binding of the released TGF-beta ligands. Once activated, the receptors add a phosphate chemical to SMAD2 and 3 proteins to allow association with SMAD4 and subsequent continuing of the tgfbeta signaling pathway. This pathway is responsible for a variety of cell responses including cell movement, proliferation and death.

MUTATIONS

A mutation (change) in any of these genes causes the corresponding protein to not be made or function correctly. Because these varying genes encode for proteins that interact in the same pathway there is clinical overlap in the medical features of people with Loeys-Dietz syndrome even though they may have different mutations in different genes in this pathway.

We will continue to learn more information about the similiarities/differences as more people are diagnosed with these gene mutations. There are other TGFBeta ligands (TGFB1 and TGFB3) whose contribution to aneurysm development is not currently known. As well, we would expect that more genes encoding for proteins in the tgfbeta signaling pathway will continue to be discovered as causing disorders in humans. Gene mutations in TGFBR1 and 2 were discovered as causing Loeys-Dietz syndrome in 2005. SMAD3 was discovered in 2011, and TGFB2 ligand in 2012.

ASSOCIATION OF GENES WITH CLINICAL PRESENTATION

FEATURE	TGFβR1/2	SMAD3	TGFβ2	FBN1
Cleft palate / bifid uvula	++	+	+	-
Hypertelorism	++	+	+	-
Eye muscle problems	+	Unknown	Unknown	-
Lens Dislocation	-	-	-	++
Pectus Deformity	++	++	++	++
Scoliosis	+	+	++	++
Cervical Spine Instability	+	Unknown	Unknown	-
Spondylolisthesis	+	++	+	+
Osteoarthritis	+	+++	+	++
Clubfoot	++	+	++	-
Aortic Root Aneurysm	++	++	++	++
Arterial Tortuosity	++	++	++	-/+
Other Aneurysm/dissection	++	++	+ (cerebral)	+ (mostly distal aorta)
Joint Flexibility	++	+	++	+
Hernias	+	++	++	+
Allergic Disease	+	Unknown	Unknown	-
GI Disease	+	Unknown	Unknown	-

+++ = very common

++ = common

+ = somewhat common

- = not reported

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