

GLMN (Glomulin)

Identity

Other names	GLMN FAP68 FAP48
Hugo	GLMN
Location	1p22.1
Note	The gene was identified by linkage mapping and positional cloning. There is no evidence for locus heterogeneity. Haplotype sharing has been reported for an important number of families.

DNA/RNA

Description	The genomic DNA of the glomulin gene spans about 55 kbp and contains 19 exons coding for 1785 bp. The first exon is non coding, the start codon is located on the second exon and the stop codon in the last exon.
Transcription	In all human and murine tissues tested, a about 2 kb transcript was observed by Northern blot hybridization, suggesting that glomulin expression is ubiquitous. This could be due to the presence of glomulin-expressing blood vessels in the various tissues analysed. By in situ hybridisation on murine embryos, glomulin expression was evident at embryonic E10.5 days post-coitum (dpc) and localized to the cardiac outflow tract. Between E11.5 to 14.5 dpc, glomulin mRNA is most abundant in the walls of large vessels (e.g. dorsal aorta). At E14.5 dpc, E16.5 dpc, and in adult tissues, expression of glomulin is clearly restricted to vascular smooth muscle cells. The high level of glomulin expression in the murine vasculature indicates that glomulin may have an important role in blood vessel development and/or maintenance. A truncated form of glomulin, called FAP48, with an altered carboxy-terminal end, was isolated from a Jurkat-cell library. However FAP48, which presents 70% homology with glomulin, was not detected in other tissues and cells tested. Thus, it might be an aberrant transcript in this library.
Pseudogene	In man, no paralogue exists. Yet, a pseudogene is located on chromosome 21. It contains only a few exons (exons 6 to 10), without intervening introns and with several nucleotide differences. Thus, glomulin seems to be unique in the human genome.

Protein

Note	Glomulin was identified by reverse genetics, and its function is currently unknown.
Description	Glomulin gene encodes a protein of 594 amino acids (68 kDa). In silico analysis reveals no known functional or structural domains, but a few potential phosphorylation and glycosylation sites.
Expression	(see above, para Transcription)
Localisation	By <i>in silico</i> analysis, no signal sequence or clear transmembrane domain in glomulin has been identified. Glomulin (FAP68) is likely an intracellular protein.
Function	The exact function of glomulin is unknown. Glomulin (under the name of FAP48) has been described to interact with FKBP12, an immunophilin that binds the immunosuppressive drugs FK506 and rapamycin. FKBP12 interacts with the TGF β type I receptor, and prevents its phosphorylation by the type II receptor in the absence of TGF β . Thus, FKBP12 safeguards against the ligand-independent activation of this pathway. Glomulin, through its interaction with FKBP12, could act as a repressor of this inhibition. Glomulin has also been described to interact with the last 30 amino acids of the C-terminal part of the HGF receptor, c-MET. This receptor is a transmembrane tyrosine

kinase, which becomes tyrosine-phosphorylated upon activation by HGF. Glomulin interacts with the inactive, non phosphorylated form of c-MET. When c-MET is activated by HGF, glomulin is released in a phosphorylated form. This leads to p70 S6 protein kinase (p70S6K) phosphorylation. This activation occurs synergistically with the activation by the c-MET-activated PI3 kinase. It is not known whether glomulin activates p70S6K directly or indirectly. The p70S6K is a key regulator of protein synthesis. Glomulin could thereby control cellular events such as migration and cell division.

The third reported glomulin partner is Cul7, a Cul1 homologue. This places glomulin in an SCF-like complex, which is implicated in protein ubiquitination and degradation.

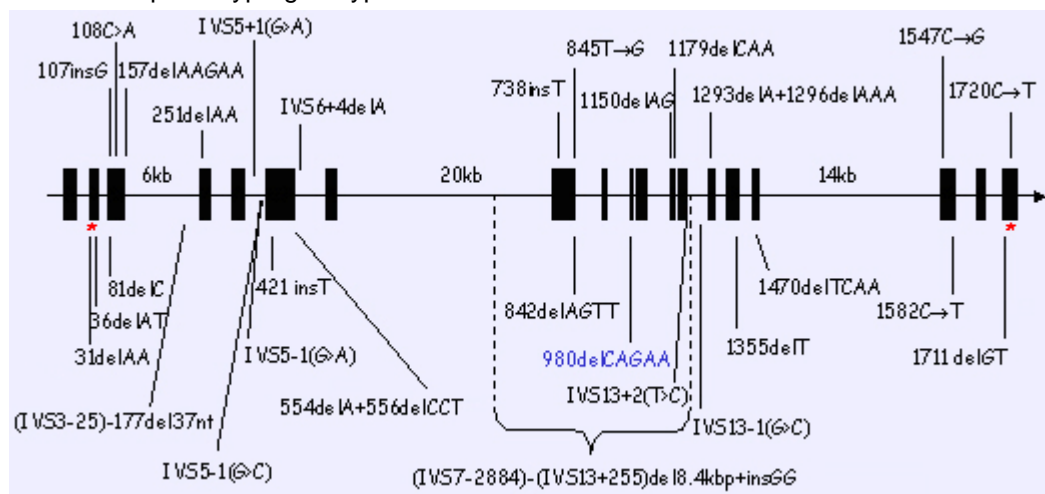
Homology

Glomulin seems to be a unique protein. No paralogue has been found and its lack in GVM is not compensated by another protein. Orthologues of glomulin have been identified in other species (cat, chimpanzee, cow, dog, mouse, rat, rhesus macaque, xenopus, zebrafish) and thus it is present in all vertebrates but not in insects or bacteria.

Mutations

Note

There is no phenotype-genotype correlation in GVM.



Schematic representation of glomulin : The two stars (*) indicate the start and the stop codons, in exon 2 and 19 respectively. All known mutations are shown. Somatic second hit is in blue.

Germinal

To date, 29 different inherited mutations (deletions, insertions and nonsense substitutions) have been identified. The most 5' mutations are located in the first coding exon. The majority of them cause premature truncation of the protein and likely result in loss-of-function. One mutation deletes 3 nucleotides resulting in the deletion of an asparagine at position 394 of the protein.

More than 70% of GVMs are caused by eight different mutations in glomulin: 157delAAGAA (40,7%), 108C>A (9,3%), 1179delCAA (8,1%), 421insT and 738insT (4,65% each), 554delA+556delCCT (3,5%), 107insG and IVS5-1(G>A) (2,3% each).

Somatic

The phenotypic variability observed in GVM could be explained by the need of a somatic second-hit mutation. Such a mechanism was discovered in one GVM (somatic mutation 980delCAGAA), suggesting that the lesion is due to a complete localized loss-of-function of glomulin. This concept can explain why some patients have bigger lesions than others, why new lesions appear, and why they are multifocal. This could also explain, why some mutation carriers are unaffected.

Implicated in

Entity

[Glomuvenous malformation](#) (GVM)

Note

GVM is often, if not always, hereditary, and transmitted as an autosomal dominant disorder.

Disease

GVM is a localized bluish-purple cutaneous vascular lesion, histologically consisting of distended venous channels with flattened endothelium surrounded by variable number of maldifferentiated smooth muscle-like "glomus cells" in the wall. GVM account for 5% of venous anomalies referred to centers for vascular anomalies.

Seven features characterize GVM lesions : (1) Colour: GVMs can be pink in infants, the most are bluish-purple; (2) Affected tissues: the lesions are localized to the skin and subcutis; (3) Localization: lesions are more often located on the extremities; (4) Appearance : lesions are usually nodular and multifocal. They are often hyperkeratotic; (5) The lesions are not compressible; The lesions are painful on palpation; (7) New lesions can appear with time, likely after trauma
 GVM has no neoplastic histological characteristics and never becomes malignant.

External links

[Hugo](#)
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[Entrez_Gene](#)

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[GeneCards](#)

[Ensembl](#)

[Genatlas](#)
[GeneLynx](#)
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Nomenclature

[GLMN](#)
[GLMN](#)
[GLMN 11146](#) glomulin, FKBP associated protein

Cards

[GLMNID43022ch1p22](#)
[GLMN](#)
[GLMN](#) [Search_View] [ENSG00000174842](#) [Gene_View]
[GLMN](#)
[GLMN](#)
[GLMN](#)
[11146](#)

Genomic and cartography

[GLMN - 1p22.1 chr1:92484545-92537154 - 1p22.1](#) (hg18-Mar_2006)
[GLMN - 1p22.1 \[CytoView\]](#)
[Mapview](#)
[Disease map \[OMIM\]](#)
[GLMN](#)

Gene and transcription

[AJ302735](#) [ENTREZ]
[AJ347709](#) [ENTREZ]
[AK130581](#) [ENTREZ]
[BC001257](#) [ENTREZ]
[BG187128](#) [ENTREZ]
[NM_053274](#) [SRS] [NM_053274](#) [ENTREZ]
[AC_000044](#) [SRS] [AC_000044](#) [ENTREZ]
[NC_000001](#) [SRS] [NC_000001](#) [ENTREZ]
[NT_032977](#) [SRS] [NT_032977](#) [ENTREZ]
[NW_921795](#) [SRS] [NW_921795](#) [ENTREZ]
[GLMN](#) AceView - NCBI
[Hs.49105](#) [SRS] [Hs.49105](#) [NCBI] [HS49105](#) [spliceNest]
[16775](#) (alternative variants)

Protein : pattern, domain, 3D structure

[13671](#)

Protein Interaction databases

Polymorphism : SNP, mutations, diseases

[138000;601749](#) [\[map \]](#)
[138000;601749](#)

[SNP](#)

[SNP](#)

[SNP](#)

[HAPMAP](#)

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[SAGE](#)

[GO](#)

[GO](#)

[GO](#)

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Bibliography

Multiple glomus tumors. A clinical and electron microscopic study.

Goodman TF, Abele DC.
Arch Dermatol 1971; 103(1): 11-23.
Medline [4321799](#)

FAP48, a new protein that forms specific complexes with both immunophilins FKBP59 and FKBP12. Prevention by the immunosuppressant drugs FK506 and rapamycin.

Chambraud B, Radanyi C, Camonis JH, Shazand K, Rajkowski K, Baulieu EE.
J Biol Chem 1996; 271(51): 32923-32929.
Medline [8955134](#)

TGFbeta receptor inhibition by FKBP12.

Chen YG, Liu F, Massague J.
EMBO J. 1997; 16(13): 3866-3876.
Medline [9233797](#)

[GLMN](#) [dbSNP-NCBI]

[NM_053274](#) [SNP-NCI]

[GLMN](#) [GeneSNPs - Utah] [GLMN](#) [HGBASE - SRS]

[GLMN](#) [HAPMAP]

[GLMN](#) [Somatic mutation (COSMIC-CGP-Sanger)]

[GLMN](#)

General knowledge

[GLMN](#) [UCSC Family Browser]

[NM_053274](#)

[Hs.49105](#)

[Hs.49105](#)

[vasculogenesis](#) [Amigo] [vasculogenesis](#)

[hepatocyte growth factor receptor binding](#) [Amigo] [hepatocyte growth factor receptor binding](#)

[protein binding](#) [Amigo] [protein binding](#)

[protein binding](#) [Amigo] [protein binding](#)

[intracellular](#) [Amigo] [intracellular](#)

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[positive regulation of interleukin-2 biosynthetic process](#) [Amigo] [positive regulation of interleukin-2 biosynthetic process](#)

[positive regulation of cytokine secretion](#) [Amigo] [positive regulation of cytokine secretion](#)

[GLMN](#)

Other databases

[Probes](#)

[PubMed](#)

[14 Pubmed reference\(s\) in LocusLink](#)

A gene for inherited cutaneous venous anomalies ("glomangiomas") localizes to chromosome 1p21-22.

Boon LM, Brouillard P, Irrthum A, Karttunen L, Warman ML, Rudolph R, Mulliken JB, Olsen BR, Vikkula M.

Am J Hum Genet. 1999; 65(1): 125-133.

Medline [10364524](#)

High-resolution physical and transcript map of the locus for venous malformations with glomus cells (VMGLOM) on chromosome 1p21-p22.

Brouillard P, Olsen BR, Vikkula M.

Genomics 2000; 67(1): 96-101.

Medline [10945676](#)

Ligand-regulated binding of FAP68 to the hepatocyte growth factor receptor.

Grisendi S, Chambraud B, Gout I, Comoglio PM, Crepaldi T.

J Biol Chem 2001; 276(49): 46632-46638.

Medline [11571281](#)

Linkage disequilibrium narrows locus for venous malformation with glomus cells (VMGLOM) to a single 1.48 Mbp YAC.

Irrthum A, Brouillard P, Enjolras O, Gibbs NF, Eichenfield LF, Olsen BR, Mulliken JB, Boon LM, Vikkula M.

Eur J Hum Genet 2001; 9(1): 34-38.

Medline [11175297](#)

Mutations in a novel factor, Glomulin, are responsible for glomuvenous malformations ("Glomangiomas").

Brouillard P, Boon LM, Mulliken JB, Enjolras O, Ghassibé M, Matthew L, Warman O, Tan T, Olsen BR, Vikkula M.

Am J Hum Genet 2002; 70: 866-874.

Medline [11845407](#)

Targeted disruption of P185/Cul7 gene results in abnormal vascular morphogenesis.

Arai T, Kasper JS, Skaar JR, Ali SH, Takahashi C, DeCaprio JA.

Proc Natl Acad Sci USA 2003; 100(17): 9855-9860.

Medline [12904573](#)

Glomuvenous malformations (glomangioma) and Venous malformations, Distinct clinicopathologic and genetic entities.

Boon LM, Mulliken JB, Enjolras O, Vikkula M.

Arch Dermatol 2004; 140: 971-976.

Medline [15313813](#)

Glomulin is predominantly expressed in vascular smooth muscle cells in the embryonic and adult mouse.

McIntyre BA, Brouillard P, Aerts V, Gutierrez-Roelens I, Vikkula M.

Gene Expr Patterns 2004; 4(3): 351-358.

Medline [15053987](#)

Four common glomulin mutation cause two thirds of glomuvenous malformations ("familial glomangiomas") : evidence for a founder effect.

Brouillard P, Ghassibé M, Penington A, Boon LM, Domp Martin a, Temple IK, Cordisco M, Adams D, Piette F, Harper JI, Syed S, Boralevi F, Taieb A, Danda S, Baselga E, Enjolras O, Mulliken JB, Vikkula M.

J Med Genet 2005; 42(2): e13.

Medline [15689436](#)

Medical and surgical treatment of venous malformations.

Boon LM, Vanwijck R.

Ann Chir Plast Esthet 2006; 51(4-5): 403-411.
Medline [17005307](#)

Congenital plaque-type glomuvenous malformations presenting in childhood.

Mallory SB, Enjolras O, Boon LM, Rogers E, Berk DR, Blei F, Baselga E, Ros AM, Vikkula M.
Arch Dermatol 2006; 142(7): 892-896.
Medline [16847206](#)

GLMN and Glomuvenous Malformation.

Brouillard P, Enjolras O, Boon LM, Vikkula M.
Inborn Errors of Development 2e, edited by Charles Epstein, Robert Erickson and Anthony Wynshaw-Boris, Oxford University Press, Inc. In press.

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