S1 | **Genetics of collagen XVIII, XV and perlecan**

Genetics	Genotype and mutant forms	Phenotype
Collagen XVIII		
Human: *Knobloch* syndrome	Autosomal recessive, mutations in the *COL18A1* gene and truncation of the short form of collagen XVIII	High myopia, vitreoretinal degeneration with retinal detachment, macular abnormalities and occipital encephalocele[1]
Mouse: Knockout	Null mutation	Delay in postnatal regression of retinal hyaloid vessels, abnormal outgrowth of retinal vessels, accumulation of deposits in retinal pigment epithelium and reduced visual function[2,3]. Enhanced angiogenic response in aortic explants[4]. Hydrocephalus and dilation of brain ventricles, BM broadening[5].
Mouse: Transgene	Overexpression of endostatin in lens and skin driven by keratin 14 promoter	Cataracts and skin BM abnormalities[6]
Collagen XVIII/ApoE		
Mouse: Double knockout	Double null mutation	Enhanced neovascularization and vascular permeability in atherosclerosis[7]
Collagen XV		
Mouse: Knockout	Null mutation	Viable and fertile; reduced inotropic response to cardiac perfusion; exercise-induced cardiac injury[8]
Collagen XVIII/XV		
Mouse: Double knockout	Double null mutation	Viable and fertile; phenotypes similar to the individual knockouts, indicating separate biological roles
Collagen XVIII		
C. elegans: *cle-1*	Deletion of the C-terminal NC1 domain and other mutant forms	Defects in cell migration and axon guidance[9], and abnormal neuromuscular structure[10]
Perlecan		
Human		
Dyssegmental Dysplasia, Silver-Handmaker type (DDSH)	Autosomal recessive, deletions or point mutations produce truncated, non-secreted/non-functional perlecan	Lethal skeletal dysplasia characterized by anisospondyly and micromelia[11,12]
Schwartz–Jampel Syndrome (SJS)	Homozygous missense and splicing mutations produce truncated partially functional or reduced wild-type perlecan	Non-lethal, myotonia, chondrodysplasia[13,14]
Mouse: Knockout	Null mutation	Mostly embryonic lethal with severe cephalic and cartilage abnormalities; complete transposition of aorta and pulmonary artery, and abnormal attachment of coronary arteries[15-18]
Deletion of exon 3 (*Hspg2*$^{\Delta 3/\Delta 3}$)	Homozygous deletion mutant. Loss of HS attachment sites in domain I, but remaining protein core is fully expressed	Viable and fertile. Small eyes with perinatal degeneration of lens. *Col18a1*$^{-/-}$, *Hspg2*$^{\Delta 3/\Delta 3}$ double mutants show accelerated lens degeneration[19], increased stenosis in injured carotid artery[20], and impaired angiogenesis and tumour growth[21]
Drosophila melanogaster (*Trol* (terribly reduced optical lobes))	Multiple deletion mutants	Lethal, reduced optical lobes and abnormal imaginal discs, abnormal proliferation of neuroblasts and modulation of FGF and Hedgehog[22,23]
Caenorhabditis elegans (*Unc-5* (uncoordinated phenotype))	Null mutation	Pat (paralyzed, arrested at twofold); lethal
	Mutations in exons 16, 17 and 18 affecting some, but not all, *Unc-52* isoforms	Larvae move normally, adults paralyzed owing to progressive disruption of body wall[24]. Abnormal gonadogenesis owing to deregulation of several growth factor signalling pathways[25]

BM, basement membrane; FGF, fibroblast growth factor; NC1, non-collagenous domain-1.

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