Expanding the genotypic and phenotypic spectrum of the *B3GAT3* linkeropathy

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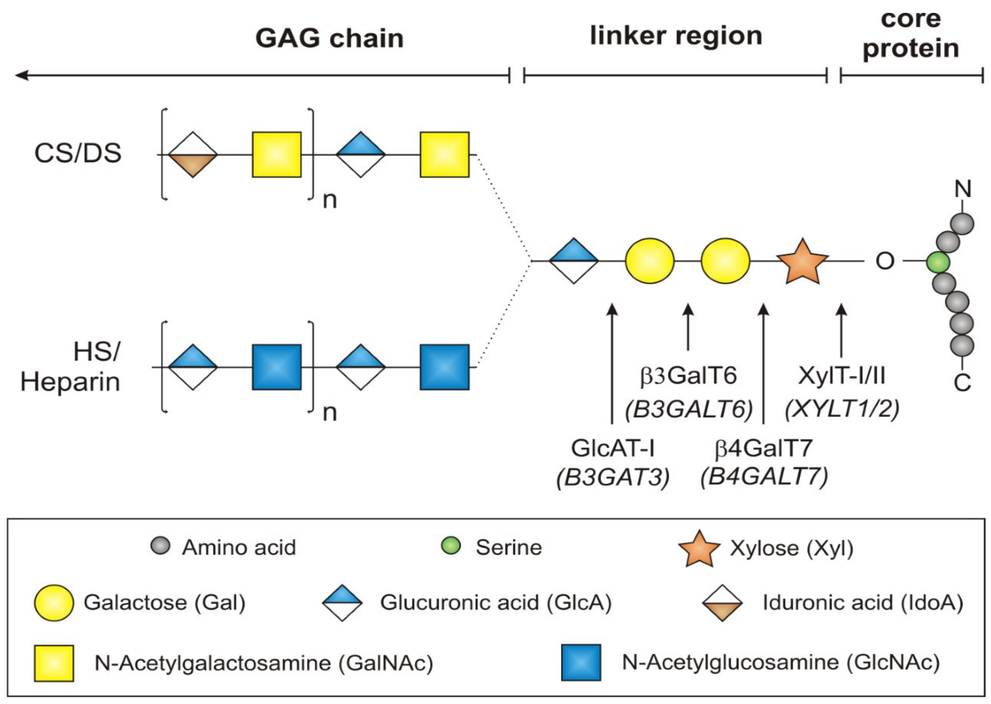
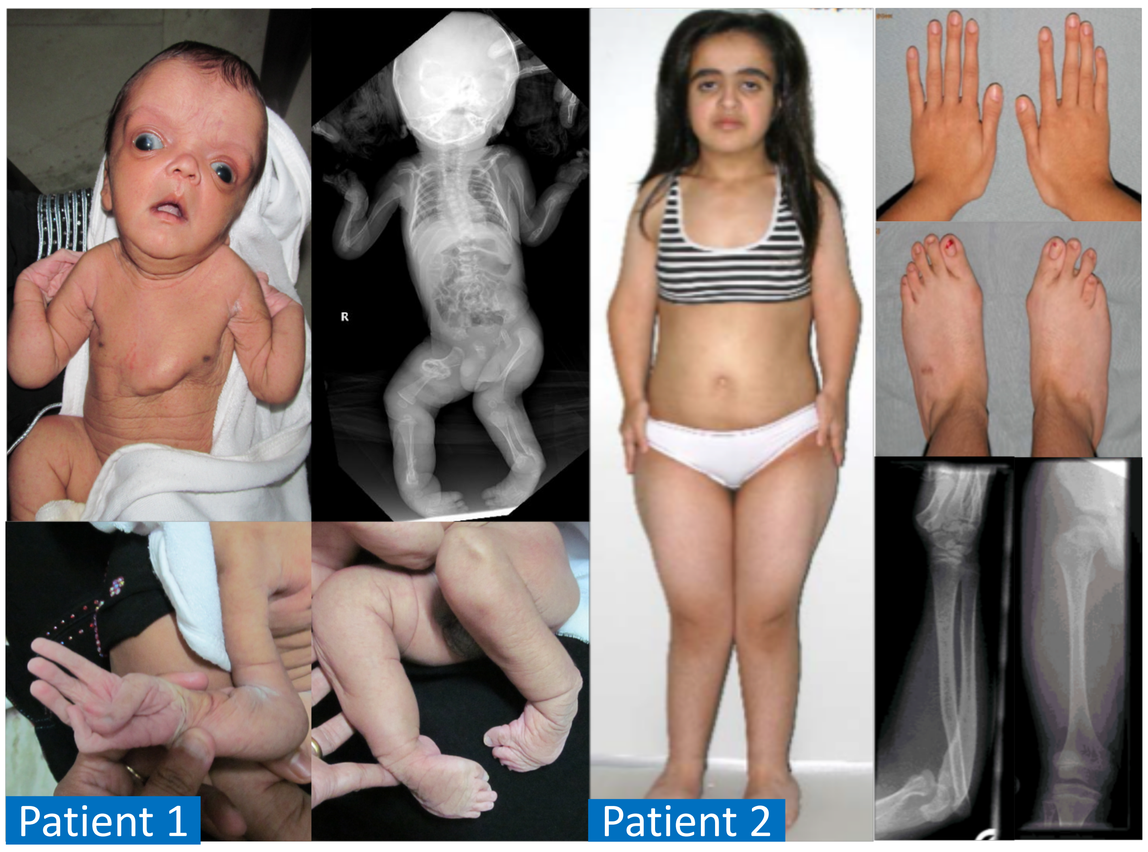
Defects in the enzymes responsible for the formation of the tetrasaccharide linker region between the proteoglycan core protein and the glycosaminoglycan side chains, lead to a spectrum of severe and overlapping autosomal recessive connective tissue disorders, collectively coined 'glycosaminoglycan linkeropathies'.

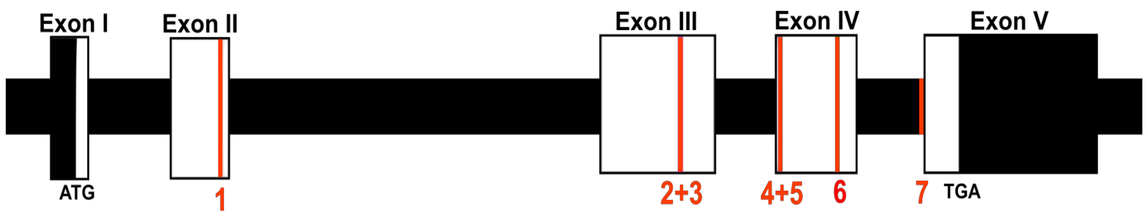
We report the clinical findings of two novel patients with biallelic mutations in *B3GAT3*, encoding glucuronosyltransferase I (GlcAT-I), which catalyzes the addition of the ultimate saccharide to the linker region.





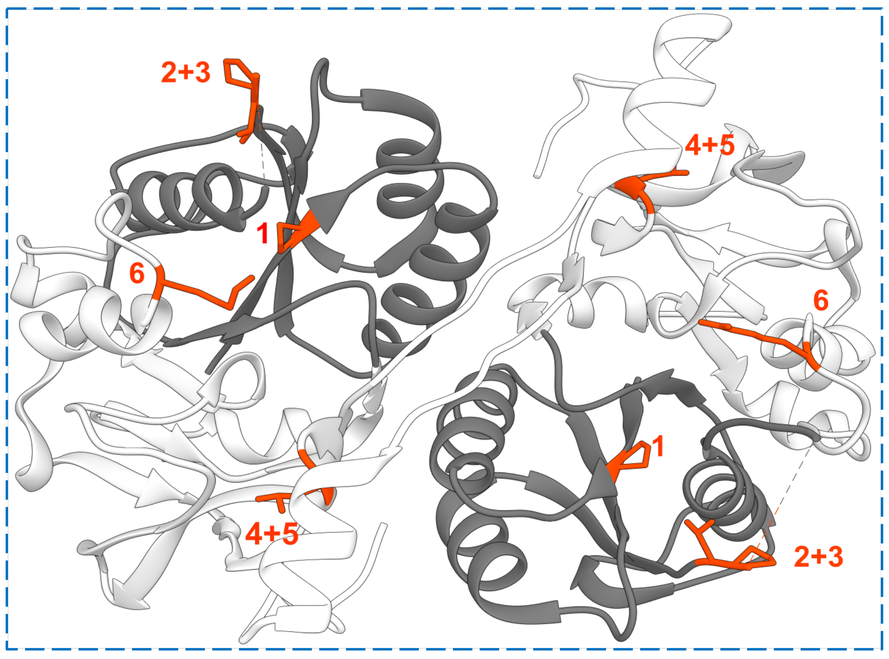
Patient 1 with bulging of the thoracic cage, blue sclerae, corneal clouding, cutis laxa, long fingers, campylodactyly, spatulate distal phalanges and club feet. Radiography shows osteopenia, fractures and joint contractures. He died at age of 2,5 months due to unknown reasons. The previously reported homozygous c.667G>A, p.(Gly223Ser) missense mutation was identified.

Patient 2 with a short stature, genu valgum, a flat face and prominent eyes, long fingers, spatulate distal phalanges and pes planus. Radiography shows radial head dislocation and a short femoral neck. An unreported homozygous c.416C>T, p.(Thr139Met) missense mutation was found.



1. c.245C>T; p.(Pro82Leu)
2. c.416C>T; p.(Thr139Met)
3. c.419C>T; p.(Pro140Leu)
4. c.667G>A; p.(Gly223Ser)
5. c.671T>A; p.(Leu224Gln)
6. c.830G>A; p.(Arg277Gln)
7. c.888+262T>G

Schematic representation of all reported mutations in the *B3GAT3* gene and a representation of all missense mutations on an *in silico* model of GlcAT-I in which the substrate donor is colored in dark grey and the substrate acceptor subdomain is colored light grey.



Overview of the clinical features present in the different linkeropathies

	XYLT1 n=15	XYLT2 n=17	B4GALT7* n=8	B3GALT6 n=27	B3GAT3 n=26
Short stature	100%	53%	100%	100%	83%
Skeletal dysplasia*	100%	94%	100%	100%	100%
Joint hypermobility	40%	NR	100%	88%	53%
Bone fragility	7%	94%	62%	48%	67%
Joint contractures	NR	NR	37%	59%	69%
Facial dysmorphology*	100%	65%	87%	100%	100%
Hyperextensible/lax skin	NR	NR	87%	68%	12%
Cardiovascular involvement	7%	35%	NR	16%	60%
Intellectual disability	100%	35%	75%	20%	14%
Ocular involvement	NR	88%	62%	NR	15%
Hearing loss	7%	53%	25%	NR	8%

Table summarizing some of the clinical features in all reported patients of each linkeropathy.
*With exclusion of the Larsen of Reunion Island syndrome cohort from Crathault et al.
NR= Not Reported

Loss-of-function mutations in *B3GAT3* are associated with a complex connective tissue phenotype characterized by disproportionate short stature, skeletal dysplasia, facial dysmorphism, spatulate distal phalanges and - to a lesser extent - joint contractures, joint hypermobility with dislocations, cardiac defects and bone fragility. The more severe phenotypes seem to have mutations located in the substrate acceptor subdomain of the catalytic domain while more mildly affected phenotypes seem to have mutations in the donor substrate binding subdomain.

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