Title: *GNPTAB*-Related Disorders *GeneReview* – Scientific history of *GNPTAB*-related disorders
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Scientific History of *GNPTAB*-Related Disorders

The two standard clinical phenotypes of *GNPTAB*-related disorder were delineated following differing clinical observations initially considered to have one of the glycosaminoglycans storage disorders (mucopolysaccharidoses: MPS). The early-onset type differed significantly from MPS type I (Hurler disease) and correlated directly with the "in vitro" finding of innumerable cytoplasmic inclusions in the cultured fibroblasts that were called "Inclusion" or "I"-cells" [Leroy & DeMars 1967]. Already in 1966 Maroteaux had delineated the childhood-onset disorder as Pseudo-Hurler polydystrophy [Maroteaux et al 1966] also with absence of excessive urinary excretion of GAGs. Taylor et al [1973] reported that fibroblast cultures from "pseudo-Hurler polydystrophy" showed the "I-Cell" phenotype, contained many deficient lysosomal acid hydrolases and had an increased activity of the same enzymes in the culture media. These facts had been reported earlier in the early-onset type of the disorder [Wiesmann et al 1971, Leroy et al 1972]. The excessive activity in the plasma of either type of patient having been established, the hypothesis of the allelic nature of the phenotypes became robust. Before the end of that decade, research had shown that lysosomal enzymes are glycoproteins and bear glycan side chains at several N-glycosylation sites. As at least some of the oligosaccharylglycans have terminal mannose-6-phosphate receptor recognition markers, normally equipped hydrolases are adequately targeted from the Golgi stacks to their lysosomal destination [Hasilik & Neufeld 1980a, Hasilik & Neufeld 1980b] where at mildly acid pH they catalyze the breakdown of several types of macromolecules.

Lysosomes and the membranes of the in-between vesicular structures in the subcellular trafficking pathway bear two types of M6P receptors to which normal hydrolases effectively bind. Lysosomal enzymes in *GNPTAB*-related disorders lack the M6P recognition marker. The responsible enzyme defect was discovered to be UDP-GlcNAc-1-phosphotransferase (GNPT with IUBMB N°2.7.8.17) [Hasilik et al 1981, Reitman et al 1981] and later isolated and structurally characterized as a heterohexameric protein complex [Bao et al 1996a, Bao et al 1996b] composed of two α, two β, and two γ polypeptides. *GNPTAB* encodes the αβ precursor protein of 1256 amino acids proteolytically cleaved by protease-1 into the larger α subunit that is contained in the catalytic site and the shorter β subunit [Marschner et al 2011]. The former contains domains that contribute to recognition of the lysosomal proteins and substrates, and to binding of the soluble γ subunits (encoded by *GNPTG*) [Qian et al 2010, Franke et al 2013, Qian et al 2013, De Pace et al 2014, Qian et al 2015, Velho et al 2015, De Pace et al 2016, Velho et al 2016].

The GNPT enzyme is composed of polypeptides encoded by two different genes. Variant *GNPTG* genotypes cause the nonallelic mild MLIII γ [Raas-Rotschild et al 2000, Raas-Rotschild et al 2004]. The normal GNPT complex remains bound to the Golgi membrane and recruits the soluble γ polypeptides in order for them to become fully functional. The specific role of the latter is not completely known. It contributes to the recognition of the hydrolase substrates. In the most recent years impressive progress has been made in the functional characterization of the various protein domains in the enzyme complex.

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