Title: Sialuria *GeneReview*
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Molecular Genetics

Abnormal gene product (continued). Over-expression of *GNE* with the pathologic variant p.Arg263Leu in Chinese hamster ovary (CHO) cell culture resulted in overproduction of sialic acid and significant increase of polysialic acid bound to neural cell adhesion molecules (NCAM). Persons with sialuria may still have harmful consequences upon maintenance of cerebral and/or neural functions. One can but wonder whether inappropriate polysialylation of NCAM may not increase the risk for harmful effects in brain development, learning, and neural regeneration [Bork et al 2005]. The *GNE* sialuria mutation in the model CHO-cell expression system that produces recombinant human erythropoietin (rhEPO), a cytokine for erythrocyte precursors, expresses homogeneous highly sialylated EPO of the desired therapeutic value instead of the incompletely and heterogeneously sialylated expressed product [Bork et al 2007].

In vitro silencing of a *GNE* mutation by RNA interference (RNAi) with synthetic small interfering RNAs (siRNAs) in primary sialuria fibroblasts resulted in significantly decreased levels of free sialic acid. Feedback inhibition by CMP-neu5Ac was restored. This result is important as a principle demonstration of the possible therapeutic potential [Klootwijk et al 2008].

Loss of GNE activity itself is apparently often only partial as measured enzymatically in in vitro cell systems. It clearly interferes however with sialic acid production and precludes adequate sialylation of many glycoconjugates. That oral feeding of ManNAc to knock-in mutant mouse strains has postponed or prevented the expected hIBM has become the most robust argument in proving the importance of sialylation in adequate function and maintenance of muscular tissue.

References

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