DEFECTS IN GLYCOSAMINOGLYCAN BIOSYNTHESIS CAUSE THE *C. ELEGANS* SQV PHENOTYPE AND HUMAN EHLERS-DANLOS SYNDROME

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Mutations in eight *sqv* (squashed vulva) genes result in several developmental abnormalities, including defective vulval invagination and maternal-effect lethality. The molecular identities of the six *sqv* genes cloned to date now suggest that the molecular basis for these defects lies in the disruption of the biosynthesis of glycosaminoglycans (GAG) of the structure (serine residue in the protein core)-xylose-galactose-galactose-glucuronic acid-(X-glucuronic acid)$_n$, where X is either N-acetylgalactosamine or N-acetylglucosamine.

Biosynthesis of GAGs requires the synthesis of nucleotide sugars in the cytoplasm and translocation of nucleotide sugars into the endoplasmic reticulum (ER) and/or Golgi, where polymerization of sugars is catalyzed by glycosyltransferases. SQV-4 is a UDP-glucose dehydrogenase, a key enzyme in UDP-glucuronic acid synthesis. SQV-7 is a multi-pass transmembrane protein that transports UDP-glucuronic acid, UDP-N-acetylgalactosamine and UDP-galactose from the cytoplasm into the ER and/or Golgi (see abstract by Berninsone *et al*.). Recently cloned mammalian homologs of *sqv-3* and *sqv-8* encode glycosyltransferases necessary for the biosynthesis of the GAG-protein linkage region of proteoglycans. SQV-3 is similar to galactosyltransferase I, and SQV-8 is similar to glucuronyltransferase I. SQV-1 is a cytoplasmic protein with weak similarities to nucleotide-sugar modifying enzymes, and SQV-5 is a novel protein with a single predicted transmembrane domain. We postulate that *sqv-1* and *sqv-5* are components of the same GAG biosynthesis pathway and that the GAGs are important for cell-cell or cell-matrix interactions in embryonic and vulval development.

Mutations in the human homolog of *sqv-3* are implicated as the cause of a progeroid variant of the connective-tissue disorder Ehlers-Danlos syndrome. The other five *sqv* genes also have close human counterparts, which suggest that a common pathway for modifying important cell surface and/or extracellular GAGs is present in humans and in *C. elegans*. Defects in the human counterparts of other *sqv* genes therefore may be responsible for aging disorders and connective tissue diseases such as Ehlers-Danlos syndrome.