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Genomic Medicine and the Plain Populations of North America

As the result of a founder effect, the Old Order Amish population is plagued with a nonsense mutation that results in the early termination of the protein product of *SIAT9*, GM3 synthase. This results in GM3 Synthase Deficiency. This disease is inherited in an autosomal recessive fashion, and causes blindness and profound developmental delay. Ganglioside GM3, the product of GM3 synthase, is present in all eukaryotic cells, where it plays a variety of roles, among them cell adhesion, cell signaling, and central nervous system (CNS) development. GM3 is also the biosynthetic precursor to all other a- and b-series gangliosides, which have similar functions.

Ganglioside replacement therapy by subcutaneous injection of GM3 is plausible. A source of 7–10 grams of pure GM3 per patient per year, however, is needed. The present study endeavors to develop a laboratory synthesis of GM3. The route will build up and protect the ceramide and trisaccharide moieties of the molecule separately, and will conclude by coupling these portions of GM3 by chemical or chemoenzymatic means. The chemical method accomplishes this using a trichloroacetimidate derived from the trisaccharide, and couples to the ceramide primary alcohol in the presence of BF_3 as a Lewis acid catalyst. On the other hand, the chemoenzymatic method will fluorinate the trisaccharide, and couple this compound to the unprotected ceramide using the *endo*-glycoceramidase II E351S mutant. Progress on accomplishing the chemical coupling is here reported.