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Review

Neurology of inherited glycosylation disorders

Hudson H Freeze, Erik A Eklund, Bobby G Ng, Marc C Patterson

Congenital disorders of glycosylation comprise most of the nearly 70 genetic disorders known to be caused by impaired synthesis of glycoconjugates. The effects are expressed in most organ systems, and most involve the nervous system. Typical manifestations include structural abnormalities (eg, rapidly progressive cerebellar atrophy), myopathies (including congenital muscular dystrophies and limb-girdle dystrophies), strokes and stroke-like episodes, epileptic seizures, developmental delay, and demyelinating neuropathy. Patients can also have neurological symptoms associated with coagulopathies, immune dysfunction with or without infections, and cardiac, renal, or hepatic failure, which are common features of glycosylation disorders. The diagnosis of congenital disorder of glycosylation should be considered for any patient with multisystem disease and in those with more specific phenotypic features. Measurement of concentrations of selected glycoconjugates can be used to screen for many of these disorders, and molecular diagnosis is becoming more widely available in clinical practice. Disease-modifying treatments are available for only a few disorders, but all affected individuals benefit from early diagnosis and aggressive management.

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Sanford-Burnham Medical Research Institute, La Jolla, CA, USA (Prof H H Freeze PhD, B G Ng BS); **Section of Experimental Paediatrics, Department of Clinical Sciences, Lund University, Lund, Sweden** (E A Eklund MD); **and Division of Child and Adolescent Neurology, Mayo Clinic, Rochester, MN, USA** (Prof M C Patterson MD)

Correspondence to:
Dr Hudson H Freeze, Sanford-Burnham Medical Research Institute, 10901 North Torrey Pines Road, La Jolla, CA 92037, USA
hudson@sanfordburnham.org

Introduction

A hypotonic child presents with seizures, hypoglycaemia, mild liver fibrosis and high transaminase concentrations. Another child with intrauterine growth retardation and dysmorphic features, including a long, thin face with large protruding ears and a micropenis, presents with delayed speech and motor development. A third child is referred with retinitis pigmentosa and stroke-like episodes in the context of heart failure secondary to cardiomyopathy. An active athletic adult aged 25 years has recently developed peripheral neuropathy and progressive foot drop. These patients have very different phenotypes, but they all have inherited defects in glycosylation—the process of adding complex sugar chains to proteins and lipids. Nearly 70 genetic disorders of glycosylation have been discovered, mostly within the past 15 years, and the catalogue continues to grow. A simple biochemical test can confirm the general diagnosis in most cases, although a few disorders require more invasive procedures, and all require definitive genetic confirmation. We present an overview of these diseases, with an emphasis on phenotypes, diagnostic approaches, and treatment.

Common features of glycosylation pathways

The glycome—all the sugar chain structures in a cell or organism—is orders of magnitude larger than the expressed genome. Its daunting complexity claims 1–2% of the genome to encode the known glycosylation machinery.[1] Sugar chains (glycans) are added to mammalian proteins and lipids through eight distinct pathways (table 1, figure 1). Each pathway requires a different enzyme or transferase complex to initiate glycosylation. The first sugar unit (monosaccharide) linked to the protein or lipid defines the pathway, to which a single sugar or a preformed sugar chain might be added (figure 1). All pathways require activated monosaccharides in the form of nucleotide sugars, which are delivered to correct locations in the endoplasmic reticulum (ER) or Golgi apparatus to enable glycan biosynthesis. Because pathway precursors are shared, low concentrations or inefficient delivery could affect several pathways, although such effects have generally been studied in only one pathway at a time. Effects on multiple pathways have been reported in some instances and might be more common than is appreciated at present. Most of the effects of defects in the early steps of glycosylation are highly pathway specific, whereas those later in the process can affect multiple pathways. One protein can carry multiple glycans from different pathways. The outcome is not pathway driven, and many factors determine the spectrum of glycan structures. Examples include protein structure, availability of donor substrates, and the amounts of different sugar transferases and their kinetic constants. The effects of these factors on a particular glycan can exclude or enhance subsequent extension, or can place proteins in an environment where other transferases compete for a single glycan. Transferases are transcriptionally regulated, but their localisation and efficiency of recycling through the dynamic ER-Golgi network is crucial.[2] The effect of faulty glycosylation on the function of any individual protein is unpredictable and ranges from trivial to essential. Effects must, therefore, be determined for each protein and for each function.[3]

The most recent nomenclature for glycosylation disorders proposes using the gene name followed by CDG to denote a congenital disorder of glycosylation.[4] While this system is not the only one in use, we find it useful and convenient, and we use it in this Review. Where relevant we also provide other common or traditional names, such as CDG-I or CDG-II.

Specific glycosylation pathways

Genetic defects are known to occur in seven of the eight major ER-Golgi network glycan-generating pathways (table 1). The best known, and by far the most studied, is the *N*-linked glycosylation pathway, especially in terms of defects located in the ER (figure 1). Protein *O*-linked glycosylation is more diverse than *N*-linked glycosylation. Serine or threonine residues are linked to glycans

	Number of disorders	Typical clients	Functions
N-linked	38	Nearly all cell-surface receptors, ECM, and secreted proteins	Assistance in folding, stabilisation of target proteins, signalling
O-linked			
O-xylose	10	ECM proteins, heparan and chondroitin sulphate	Growth-factor binding, structure of ECM
O-mannose	6	α-Dystroglycan	Bridging neuromuscular 1α-receptor junction
O-fucose	2	Notch and Notch ligands	Notch signalling, developmental patterning
O-GalNAc	2	Mucins, leucocyte receptors	Pathogen decoys, lubrication, protection of cell surface
O-glucose	0	Notch and Notch ligands	Notch signalling, developmental patterning
GPI-anchor glycans	5	Proteins in lipid rafts, signalling molecules	Organisation of plasma-membrane domains
Glycosphingolipid	1	Brain (highest concentration), synapses	Membrane organisation, signalling
Multiple	13	Soluble and membrane-bound molecules to provide substrates or Golgi-ER homoeostasis	Trafficking of Golgi resident proteins, synthesis of precursors

ECM=extracellular matrix. GalNAc=*N*-acetylgalactosamine. GPI=glycophosphatidylinositol. ER=endoplasmic reticulum.

Table 1: **Overview of glycan types by pathway**

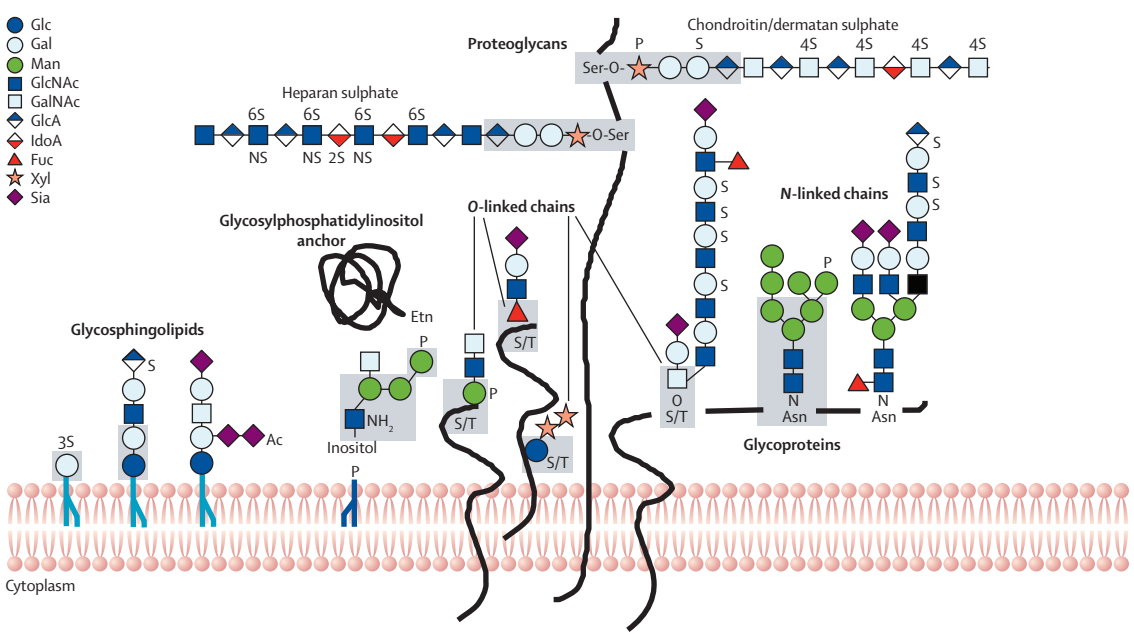

Figure 1: **Pathways of glycosylation in the endoplasmic reticulum-Golgi network of mammalian cells**
The main types of glycosylation are shown. Various representative sugar chain structures are given as examples. The grey shaded areas denote common core regions. Most of the glycosylation disorders that affect the nervous system involve alterations in *N*-linked and *O*-mannosylated glycoproteins. Some glycophosphatidylinositol-anchor and glycosphingolipid disorders also involve these alterations, but most proteoglycan and *O*-GalNAc defects do not. Other types of glycosylation exist, such as cytoplasmic *O*-GlcNAc and *C*-mannosylation, but are not shown. Glc=glucose. Gal=galactose. Man=mannose. GlcNAc=*N*-acetylglucosamine. GalNAc=*N*-acetylgalactosamine. GlcA=glucuronic acid. IdoA=Iduronic acid. Fuc=fucose. Xyl=xylose. Sia=sialic acid. S=sulphation. P=phosphorylation. Ac=acetylation. S/T=serine or threonine. Adapted from Stanley and colleagues,[5] by permission of the Consortium of Glycobiology Editors, La Jolla, CA, USA.

through *N*-acetylgalactosamine, xylose, mannose or fucose (figure 1). Chains are extended by specific glycosyltransferases, whereas terminal sugars are in many cases added by non-specific transferases that service multiple pathways.

N-linked glycosylation

N-acetylglucosamine is bound to asparagine on nascent proteins in the ER lumen, but it is not added as a single sugar. Rather, a universal 14-sugar precursor containing two *N*-acetylglucosamine, nine mannose, and three glucose units is assembled on a lipid carrier (dolichol) to form a lipid-linked oligosaccharide.[5] The entire glycan is transferred to asparagine by the multisubunit oligosaccharyltransferase complex.[6,7] The glucose units and up to six of the mannose units are often removed after transfer, and *N*-acetylglucosamine, galactose, sialic acid, and fucose are added on to multiple branches. The order of remodelling

of the chains is prescribed, but, as with all glycosylation, it is not template driven.

Essentially, all proteins (except albumin) that travel through the ER-Golgi network undergo *N*-linked glycosylation. Glycans promote protein folding, stability, trafficking, localisation, and oligomerisation.[5] They play vital parts in cell–cell interactions and intracellular signalling.[8]

The dolichol carrier lipid also carries mannose, which serves three other pathways: glycophosphatidylinositol anchors, *O*-mannosylation, and *C*-mannosylation. The first two are described below. No *C*-mannosylation disorders have been reported.[9,10]

O-linked glycosylation

O-linked protein glycosylation involves initial linkage between serine or threonine residues and mannose, xylose, *N*-acetylgalactosamine, fucose, or glucose (figure 1). The *O*-linked α-mannose glycans contain *N*-acetylglucosamine, galactose, *N*-acetylgalactosamine, and sialic acid.[11,12] α-Dystroglycan, which has a crucial role as a link between the extracellular matrix and the cytoskeleton in skeletal muscle cells, is the major identified carrier for *O*-linked α-mannose glycans. Other proteins certainly carry them, but are yet to be identified. Defects in this pathway often cause neurological deficits.[13]

O-linked α-*N*-acetylgalactosamine-based glycans link to serine or threonine, after which one of four sugars is added to form a disaccharide. Sequential addition of galactose, *N*-acetylglucosamine, fucose, and sialic acid generates linear or multibranched chains[14] that are found on secreted or cell-surface mucins of epithelial cells. These chains can lubricate and are effective pathogen decoys. None causes neurological pathology.

O-linked β-xylose glycans on serine generate glycosaminoglycans, such as heparan sulphate, heparin, chondroitin, and dermatan sulphates.[15] Long repeating disaccharides of glucuronic acid-*N*-acetylgalactosamine (chondroitin and dermatan sulphates) or glucuronic acid-*N*-acetylglucosamine (heparin and heparan sulphate) are extended from a small core glycan.[13] Some glucuronic acid is epimerised to iduronic acid. Sulphation occurs on de-*N*-acetylated *N*-acetylglucosamine NH_2 groups or OH groups. Proteins carrying chondroitin are used for physical integrity and cushioning. Cell-surface heparin-sulphate chains bind growth factors (eg, fibroblast growth factors), cytokines, and morphogens during development to establish gradients of these molecules.[16,17]

O-linked α-fucose-based glycans occur in selected epidermal growth factor modules in Notch and Notch ligands, and are extended by Fringe family *N*-acetylglucosamine transferases and other glycosyltransferases.[18,19] The presence of these glycans has a strong effect on Notch signalling. Thrombospondin type I repeats can be *O*-fucosylated by a different transferase, and fucose is extended with one or two glucose units.[20]

Lipid-bearing glycans

Glycosphingolipids link glucose to ceramide. If galactose is also added, lactosylceramide is formed. This core can be variably extended to more complex glycosphingolipids, including the sialylated gangliosides.[21] The greatest diversities in types and concentrations of glycosphingolipids occur in the brain and peripheral nervous system. Glycosphingolipids bind to each other or to proteins, such as integrins, which enables them to affect signalling.[22] Glycophosphatidylinositol-anchor glycans substitute for transmembrane regions of many proteins. They contain mannose and glucosamine, and are assembled in the ER on a phosphatidylinositol backbone. The entire glycolipid is transferred to C-terminal regions of proteins.[23] Glycophosphatidylinositol anchors also have roles in membrane diffusion, intracellular protein sorting, and signalling.[24,25] Defects in glycosphingolipid and glycophosphatidylinositol pathways can cause neurological complications.[26–29]

Trafficking and homoeostasis

Client proteins travel through the dynamic ER-Golgi network, where glycosylation occurs. Genetic defects in proteins needed to recycle the glycosylation machinery between the ER and the Golgi apparatus can affect the process.[2] Most of the known genes encode soluble cytoplasmic proteins that transiently associate with the Golgi apparatus and help to guide vesicles containing the glycosylation machinery to their location. Most patients with these defects have neurological deficits that, along with skeletal abnormalities and dysmorphic features, are probably due to their effects on multiple glycosylation pathways.[30]

Selected specific defects

Space limitations prevent description of all 66 glycosylation disorders in this Review. In tables 2–4 we list the glycosylation disorders with neurological manifestations and their most common symptoms. A list of disorders without or with minor neurological complications is available online (appendix). Many of the listed congenital disorders of glycosylation, such as deficiencies in sulphation, primarily affect glycosaminoglycan structure, and their classification as glycosylation disorders is the subject of debate. In this section we highlight disorders that have been documented in at least ten patients.

See Online for appendix

PMM2-CDG (CDG-Ia)

PMM2-CDG is the most frequent *N*-linked congenital disorder of glycosylation and accounts for around 80% of all diagnosed cases.[31] Mutations in *PMM2*, which encodes the phosphomannomutase 2 enzyme that catalyses conversion of mannose-6-phosphate to mannose-1-phosphate, cause the disorder. The CNS and peripheral nervous system are prime targets, but multisystem abnormalities cause substantial residual

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