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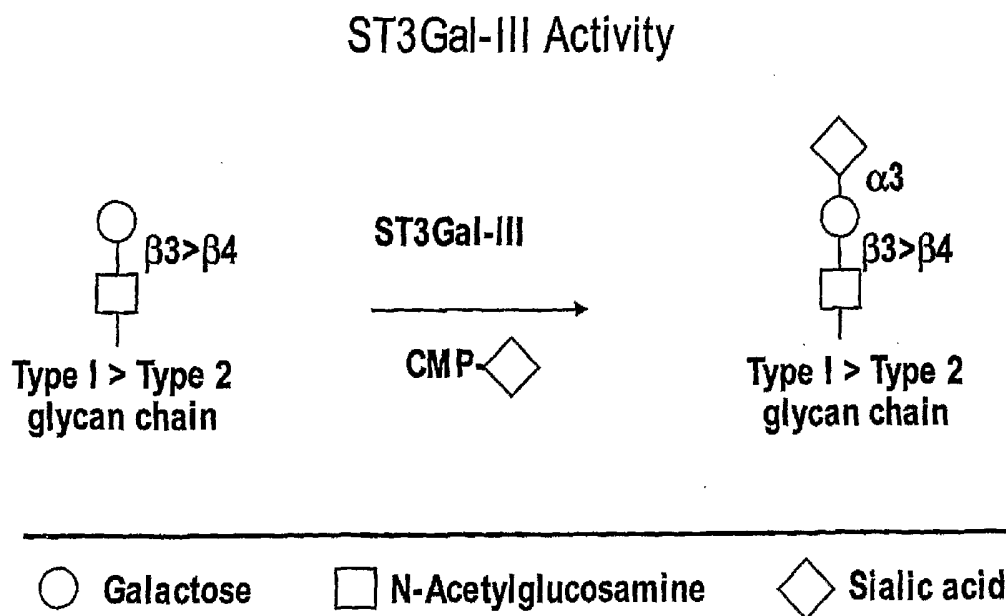
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[Continued on next page]

(54) Title: TREATMENT OF EPILEPSY BY EXPRESSING ST3GAL-III



(57) Abstract: The present invention provides methods of diagnosing epilepsy in a mammal by detecting ST3 β -galactoside α -2,3-sialyltransferase 3 (ST3Gal-III) activity or by detecting for one or more mutations in a *ST3Gal-III* gene that decrease that activity of a ST3Gal-III polypeptide. The invention further provides methods of treating an epileptic condition associated with decreased ST3Gal-III activity by administering one or more agents that increase the activity of ST3Gal-III. Also provided are methods of identifying one or more agents that increase the activity of ST3Gal-III.



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TREATMENT OF EPILEPSY BY EXPRESSING ST3GAL-III

CROSS-REFERENCES TO RELATED APPLICATIONS

[0001] This application claims the benefit of U.S. Provisional Application No. 60/591,720, filed July 27, 2004, the entire disclosure of which is hereby incorporated herein by reference in its entirety for all purposes.

STATEMENT AS TO RIGHTS TO INVENTIONS MADE UNDER FEDERALLY SPONSORED RESEARCH AND DEVELOPMENT

[0002] This invention was made with Government support under Grant Nos. DK48247 and HL57345, awarded by the National Institutes of Health. The Government has certain rights in this invention.

FIELD OF THE INVENTION

[0003] The present invention relates to the prevention or treatment of an epileptic condition associated with a ST3Gal-III deficiency. The invention further relates to the identification of agents used to prevent or treat an epileptic condition associated with a ST3Gal-III deficiency by increasing ST3Gal-III activity.

BACKGROUND OF THE INVENTION

[0004] Epilepsy refers to a disorder of brain function characterized by the periodic and unpredictable occurrence of seizures (*see*, Chapter 21 of Hardman and Limbird, *Goodman & Gilman's The Pharmacological Basis of Therapeutics*, 10th Edition, 2001, McGraw-Hill; and Chapter 348 of Kaspar, *et al*, *Harrison's Principles of Internal Medicine*, 16th Edition, 2005, McGraw-Hill. The various forms of epilepsy or "epilepsy syndromes" have disparate causes. Several genes have been associated with the presence of an epilepsy syndrome, including CHRNA4, CHRNB2, KCNQ2, KCNQ3, SCN1B, LGI1, CSTB, EPM2A, and *Doublecortin*.

[0005] ST3 β -galactoside α -2,3-sialyltransferase 3 (ST3Gal-III) is a sialyltransferase that catalyzes the transfer of a sialic acid to either a sialylate type 1 (Gal β 1-3GlcNAc) or a type 2 (Gal β 1-4GlcNAc) oligosaccharide to produce a Siao2-3Gal β 1-3GlcNAc or a Siao2-3Gal β 1-4GlcNAc oligosaccharide moiety, respectively. The Siao2-3Gal β 1-3/4GlcNAc moieties

produced by ST3Gal-III can be further substituted, for example, with fucosyl moieties, to produce selectin (*i.e.* E-, P- or L-selectin) ligand structures. ST3Gal-III is widely expressed in different tissues, including in embryonic stem cells, brain, heart, kidney, liver, colon, skeletal muscle, and ovary (*see, Ellies, et al., Blood* (2002) 100:3618-3625). This invention is based, in part, on the discovery that a deficiency of ST3Gal-III activity in a mammal results in symptoms of epilepsy.

BRIEF SUMMARY OF THE INVENTION

[0006] The invention provides methods of treating epilepsy by upregulating expression of ST3Gal-III. For example, the invention provides 1) methods to treat epilepsy by delivering the gene or gene product for ST3Gal-III, 2) methods for diagnosing epilepsy by identifying and detecting mutations in the ST3Gal-III gene, 3) animal models for epilepsy, and 4) methods for screening compounds for the treatment of epilepsy using the animal models.

[0007] Accordingly, in a first aspect, the present invention provides methods for detecting an epileptic condition associated with decreased ST3Gal-III activity in a mammal, the methods comprising detecting ST3Gal-III activity in a sample from the mammal.

[0008] The invention further provides methods for detecting an epileptic condition in a mammal by detecting a carbohydrate structure in a sample from the mammal. In this case, the epileptic condition may or may not result from decreased ST3Gal-III activity.

[0009] In a related aspect, the invention provides methods for identifying an increased risk for an epileptic condition associated with decreased ST3Gal-III activity, the method comprising identifying one or more mutations in a *ST3Gal-III* gene, wherein the one or more mutations decrease the activity of the encoded ST3Gal-III polypeptide.

[0010] In a further aspect, the invention provides for methods of treating an epileptic condition associated with decreased ST3Gal-III activity in a mammal, the method comprising administering to the mammal a therapeutically effective amount of one or more agents that increase the activity of ST3Gal-III in the mammal.

[0011] The invention further provides methods for increasing the levels of one or more Sia α 2-3Gal β 1-3/4GlcNAc moieties in a central nervous system (CNS) cell, the method comprising, introducing into a CNS cell an expression vector comprising a nucleic acid that encodes a ST3Gal-III polypeptide or enzymatically active fragment thereof.

[0012] The invention also provides methods of identifying one or more agents for the treatment of an epileptic condition associated with decreased ST3Gal-III activity in an individual, the method comprising identifying a candidate agent that increases the activity of ST3Gal-III.

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BRIEF DESCRIPTION OF THE DRAWINGS

[0013] Figure 1 illustrates a sialyltransferase reaction of ST3Gal-III sialyltransferase.

[0014] Figure 2 illustrates the ST3Gal-III sialyltransferase deficiency alters locomotor activity and the contextual fear response.

10 [0015] Figure 3 illustrates impairments in muscular strength and coordination among ST3Gal-III sialyltransferase deficient mice.

[0016] Figure 4 illustrates increased metabolism in ST3Gal-III sialyltransferase deficient mice.

[0017] Figure 5 illustrates that ST3Gal-III sialyltransferase deficiency induces seizures.

15 [0018] Figure 6 illustrates that ST3Gal-III sialyltransferase deficiency induces early adult age of seizure onset.

[0019] Figure 7 illustrates the seizure state in ST3Gal-III sialyltransferase deficient mice. ST3Gal-III sialyltransferase deficient mice in a seizure state display a raised tail and splayed limbs.

DETAILED DESCRIPTION

20 Definitions

[0020] “Epilepsy” or “epileptic condition” refers to a disorder of brain function characterized by the periodic and unpredictable occurrence of seizures (*see, Goodman & Gilman’s The Pharmacological Basis of Therapeutics, and Harrison’s Principles of Internal Medicine, supra*).

25 [0021] Epilepsy or an epileptic condition “associated with” a ST3Gal-III deficiency or decrease ST3Gal-III activity includes those epileptic conditions directly or indirectly resulting from decreased ST3Gal-III presence or activity, for example, due to a mutation in a *ST3Gal-III* gene, abnormally low transcription of ST3Gal-III mRNA, abnormally low

translation of a ST3Gal-III polypeptide, or a post-translational mutation in a ST3Gal-III polypeptide.

[0022] As used herein, "ST3Gal-III" refers to all mammalian, including human, isoforms and variants of an α 2-3 sialyltransferase that catalyzes the transfer of a sialic acid moiety to either a sialylate type 1 (Gal β 1-3GlcNAc) or a type 2 (Gal β 1-4GlcNAc) oligosaccharide to produce a Sia α 2-3Gal β 1-3GlcNAc or a Sia α 2-3Gal β 1-4GlcNAc oligosaccharide moiety, respectively. These are known in the art. Accordingly, "ST3Gal-III polypeptides" refer to naturally-occurring sequences such as the exemplary sequences provided in SEQ ID NOs:2, 4, 6, 8, 10, 12, 14, 16, 18, 20, 22 or 24, as well as variants or specific fragments thereof, that have α 2-3 sialyltransferase activity. Exemplary human and mouse nucleic acid and protein sequences are provided in SEQ ID NOs:1-24. A "ST3Gal-III" polypeptide for use in the invention therefore refers to a polypeptide that: (1) has an amino acid sequence that has greater than about 60% amino acid sequence identity, 65%, 70%, 75%, 80%, 85%, 90%, preferably 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98% or 99% or greater amino acid sequence identity, preferably over a window of at least about 25, 50, 100, 200, or 500, or more amino acids, to one or more amino acid sequences of SEQ ID NOs:2, 4, 6, 8, 10, 12, 14, 16, 18, 20, 22 or 24; (2) bind to antibodies raised against an immunogen comprising an amino acid sequence of SEQ ID NOs:2, 4, 6, 8, 10, 12, 14, 16, 18, 20, 22 or 24; (3) or have at least 15 contiguous amino acids, more often, at least 20, 25, 30, 35, 40, 50 or 100, 200, 300, 400, or 500 contiguous amino acids, of SEQ ID NOs:2, 4, 6, 8, 10, 12, 14, 16, 18, 20, 22 or 24. Similarly, a "ST3Gal-III" polynucleotide for use in the invention therefore refers to a polynucleotide that: (1) has a nucleic acid sequence that has greater than about 60% nucleic acid sequence identity, 65%, 70%, 75%, 80%, 85%, 90%, preferably 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98% or 99% or greater nucleic acid sequence identity, preferably over a window of at least about 25, 50, 100, 200, 300, 400, 500, or more contiguous nucleic acids, to one or more nucleic acid sequences of SEQ ID NOs:1, 3, 5, 7, 9, 11, 13, 15, 17, 19, 21 or 23.

[0023] A number of transcripts from the human ST3Gal-III gene have been identified and cloned. Grahn *et al. Glycoconj J.* 2002 Mar;19(3):197-210 (*see* Genbank accession numbers NM_174963-174972 for human coding sequences and NM_009176 and BC006710 for mouse coding sequences).

[0024] The following abbreviations are used herein:

Gal = galactosyl;

GlcNAc = N-acetylglucosyl;

Fuc = fucosyl

Sia = sialyl, sialic acid.

[0025] Oligosaccharides are considered to have a reducing end and a non-reducing end, whether or not the saccharide at the reducing end is in fact a reducing sugar. In accordance with accepted nomenclature, oligosaccharides are depicted herein with the non-reducing end on the left and the reducing end on the right.

[0026] All oligosaccharides described herein are described with the name or abbreviation for the non-reducing saccharide (*e.g.*, Gal), followed by the configuration of the glycosidic bond (α or β), the ring position of the reducing saccharide involved in the bond, and then the name or abbreviation of the reducing saccharide (*e.g.*, GlcNAc). The linkage between two sugars may be expressed, for example, as Gal β 4GlcNAc. Each saccharide is a pyranose. Glycoside linkages described herein are assumed to originate from the C1 hydroxyl group except for sialic acids, which are linked from the C2 hydroxyl.

[0027] An "activator" or "agonist" in the context of this invention generally refers to an agent that binds to, increases, facilitates, enhances activation, *e.g.*, by enhancing sialyl transferase activity. In some embodiments, an "activator" or "agonist" increases the activity or expression of a glycosyltransferase, *e.g.*, a ST3Gal-III.

[0028] As used herein, the "central nervous system" or "CNS" refers to tissues and cells of the brain and spinal cord.

[0029] "Antibody," as used herein, refers to a polypeptide substantially encoded by an immunoglobulin gene or immunoglobulin genes, or fragments thereof that specifically bind and recognize an analyte (antigen). The recognized immunoglobulin genes include the kappa, lambda, alpha, gamma, delta, epsilon and mu constant region genes, as well as the myriad immunoglobulin variable region genes. Light chains are classified as either kappa or lambda. Heavy chains are classified as gamma, mu, alpha, delta, or epsilon, which in turn define the immunoglobulin classes, IgG, IgM, IgA, IgD and IgE, respectively.

[0030] An exemplary immunoglobulin (antibody) structural unit comprises a tetramer. Each tetramer is composed of two identical pairs of polypeptide chains, each pair having one "light" (about 25 kD) and one "heavy" chain (about 50-70 kD). The N-terminus of each chain defines a variable region of about 100 to 110 or more amino acids primarily responsible

for antigen recognition. The terms variable light chain (V_L) and variable heavy chain (V_H) refer to these light and heavy chains respectively.

[0031] Antibodies exist, *e.g.*, as intact immunoglobulins or as a number of well-characterized fragments produced by digestion with various peptidases. Thus, for example, 5 pepsin digests an antibody below the disulfide linkages in the hinge region to produce $F(ab)'_2$, a dimer of Fab which itself is a light chain joined to V_H - C_H1 by a disulfide bond. The $F(ab)'_2$ may be reduced under mild conditions to break the disulfide linkage in the hinge region, thereby converting the $F(ab)'_2$ dimer into an Fab' monomer. The Fab' monomer is essentially an Fab with part of the hinge region (*see*, Paul (Ed.) *Fundamental Immunology*, Third 10 Edition, Raven Press, NY (1993)). While various antibody fragments are defined in terms of the digestion of an intact antibody, one of skill will appreciate that such fragments may be synthesized *de novo* either chemically or by utilizing recombinant DNA methodology. Thus, the term antibody, as used herein, also includes antibody fragments either produced by the modification of whole antibodies or those synthesized *de novo* using recombinant DNA 15 methodologies (*e.g.*, single chain Fv, humanized antibodies, chimeric antibodies, etc.).

[0032] The term "nucleic acid" or "polynucleotide" refers to deoxyribonucleotides or ribonucleotides and polymers thereof in either single- or double-stranded form. Unless specifically limited, the term encompasses nucleic acids containing known analogues of natural nucleotides that have similar binding properties as the reference nucleic acid. Unless 20 otherwise indicated, a particular nucleic acid sequence also implicitly encompasses conservatively modified variants thereof (*e.g.*, degenerate codon substitutions) and complementary sequences as well as the sequence explicitly indicated. Specifically, degenerate codon substitutions may be achieved by generating sequences in which the third position of one or more selected (or all) codons is substituted with mixed-base and/or 25 deoxyinosine residues (Batzer *et al.*, *Nucleic Acid Res.* 19:5081 (1991); Ohtsuka *et al.*, *J. Biol. Chem.* 260:2605-2608 (1985); and Cassol *et al.* (1992); Rossolini *et al.*, *Mol. Cell. Probes* 8:91-98 (1994)).

[0033] The term "recombinant" when used with reference to a cell indicates that the cell replicates a heterologous nucleic acid, or expresses a peptide or protein encoded by a 30 heterologous nucleic acid. Recombinant cells can contain genes that are not found within the native (non-recombinant) form of the cell. Recombinant cells can also contain genes found in the native form of the cell wherein the genes are modified and re-introduced into the cell

by artificial means. The term also encompasses cells that contain a nucleic acid endogenous to the cell that has been modified without removing the nucleic acid from the cell; such modifications include those obtained by gene replacement, site-specific mutation, and related techniques.

- 5 [0034] A “heterologous sequence” or a “heterologous nucleic acid”, as used herein, is one that originates from a source foreign to the particular host cell, or, if from the same source, is modified from its original form.

[0035] A “subsequence” refers to a sequence of nucleic acids or amino acids that comprise a part of a longer sequence of nucleic acids or amino acids (e.g., polypeptide) respectively.

- 10 [0036] A “recombinant expression cassette” or simply an “expression cassette” is a nucleic acid construct, generated recombinantly or synthetically, with nucleic acid elements that are capable of affecting expression of a structural gene in hosts compatible with such sequences. Expression cassettes include at least promoters and optionally, transcription termination signals as well as other desired sequences that influence gene expression.

- 15 [0037] The term “isolated” is meant to refer to material which is substantially or essentially free from components which normally accompany the enzyme as found in its native state. Thus, the enzymes of the invention do not include materials normally resulting from their *in situ* environment. Typically, isolated proteins of the invention are at least about 80% pure, usually at least about 90%, and preferably at least about 95% pure as measured by band
20 intensity on a silver stained gel or other method for determining purity. Protein purity or homogeneity can be indicated by a number of means known in the art, such as polyacrylamide gel electrophoresis of a protein sample, followed by visualization upon staining. For certain purposes high resolution will be needed and HPLC or a similar means for purification utilized.

- 25 [0038] The terms “polypeptide,” “peptide” and “protein” are used interchangeably herein to refer to a polymer of amino acid residues. The terms apply to amino acid polymers in which one or more amino acid residue is an artificial chemical mimetic of a corresponding naturally occurring amino acid, as well as to naturally occurring amino acid polymers and non-naturally occurring amino acid polymers. As used herein, the terms encompass amino acid
30 chains of any length, including full-length proteins (*i.e.*, antigens), wherein the amino acid residues are linked by covalent peptide bonds.

[0039] The term “amino acid” refers to naturally occurring and synthetic amino acids, as well as amino acid analogs and amino acid mimetics that function in a manner similar to the naturally occurring amino acids. Naturally occurring amino acids are those encoded by the genetic code, as well as those amino acids that are later modified in naturally-occurring cells, *e.g.*, hydroxyproline, γ -carboxyglutamate, and O-phosphoserine. Amino acid “analogs” refers to compounds that have the same basic chemical structure as a naturally occurring amino acid, *i.e.*, an α carbon that is bound to a hydrogen, a carboxyl group, an amino group, and an R group, *e.g.*, homoserine, norleucine, methionine sulfoxide, methionine methyl sulfonium. Such analogs have modified R groups (*e.g.*, norleucine) or modified peptide backbones, but retain the same basic chemical structure as a naturally occurring amino acid. “Amino acid mimetics” refers to chemical compounds that have a structure that is different from the general chemical structure of an amino acid, but which functions in a manner similar to a naturally occurring amino acid.

[0040] Amino acids may be referred to herein by either the commonly known three letter symbols or by the one-letter symbols recommended by the IUPAC-IUB Biochemical Nomenclature Commission. Nucleotides, likewise, may be referred to by their commonly accepted single-letter codes.

[0041] With reference to amino acid sequences, one of skill will recognize that individual substitutions, deletions or additions to a nucleic acid, peptide, polypeptide, or protein sequence which alters, adds or deletes a single amino acid or a small percentage of amino acids in the encoded sequence is a “conservatively modified variant” where the alteration results in the substitution of an amino acid with a chemically similar amino acid.

Conservative substitution tables providing functionally similar amino acids are known in the art. Such conservatively modified variants are in addition to and do not exclude polymorphic variants, interspecies homologs, and alleles of the invention.

[0042] The following eight groups each contain amino acids that are conservative substitutions for one another:

- 1) Alanine (A), Glycine (G);
- 2) Aspartic acid (D), Glutamic acid (E);
- 3) Asparagine (N), Glutamine (Q);
- 4) Arginine (R), Lysine (K);
- 5) Isoleucine (I), Leucine (L), Methionine (M), Valine (V);

6) Phenylalanine (F), Tyrosine (Y), Tryptophan (W);

7) Serine (S), Threonine (T); and

8) Cysteine (C), Methionine (M)

(see, e.g., Creighton, *Proteins* (1984)).

5 [0043] "Percentage of sequence identity" is determined by comparing two optimally aligned sequences over a comparison window, wherein the portion of the polynucleotide sequence in the comparison window may comprise additions or deletions (*i.e.*, gaps) as compared to the reference sequence (which does not comprise additions or deletions) for optimal alignment of the two sequences. The percentage is calculated by determining the
10 number of positions at which the identical nucleic acid base or amino acid residue occurs in both sequences to yield the number of matched positions, dividing the number of matched positions by the total number of positions in the window of comparison and multiplying the result by 100 to yield the percentage of sequence identity.

[0044] The terms "identical" or percent "identity," in the context of two or more nucleic
15 acids or polypeptide sequences, refer to two or more sequences or subsequences that are the same.

[0045] The term "substantially identical" refers to two or more sequences that have a specified percentage of amino acid residues or nucleotides that are the same (*i.e.*, 60% identity, optionally 65%, 70%, 75%, 80%, 85%, 90%, or 95% identity over a specified region
20 or over an entire sequence when no region is specified), when compared and aligned for maximum correspondence over a comparison window, or designated region as measured using one of the following sequence comparison algorithms or by manual alignment and visual inspection. Optionally, the identity exists over a region that is at least about 25 nucleotides or amino acids in length, or more preferably over a region that is 50, 100, 200,
25 500 or more nucleotides or amino acids in length.

[0046] The present invention provides polynucleotides and polypeptides substantially identical to SEQ ID NOs: 1, 3, 5, 7, 9, 11, 13, 15, 17, 19, 21, 23; and 2, 4, 6, 8, 10, 12, 14, 16, 18, 20, 22 or 24, respectively. Thus, a ST3Gal-III polypeptide that is substantially identical, *e.g.*, to one or more of SEQ ID NOs: 2, 4, 6, 8, 10, 12, 14, 16, 18, 20, 22 or 24, typically has
30 an amino acid sequence that is at least 60% identical, often at least 65%, 70%, 75%, 80%, 85%, or 90% identical; and preferably at least 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98% or 99% identical; to one or more of SEQ ID NOs: 2, 4, 6, 8, 10, 12, 14, 16, 18, 20, 22 or 24.

Similarly, a ST3Gal-III polynucleotide that is substantially identical, *e.g.*, to one or more of SEQ ID NOs: 1, 3, 5, 7, 9, 11, 13, 15, 17, 19, 21 or 23, typically has a nucleic acid sequence that is at least 60% identical, often at least 65%, 70%, 75%, 80%, 85%, or 90% identical; and preferably at least 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98% or 99% identical; to one or more of SEQ ID NOs: 1, 3, 5, 7, 9, 11, 13, 15, 17, 19, 21 or 23. The percent identity is preferably over a window of at least 50, 100, 200, 300, 500 or more nucleic acids or amino acids, or over the complete length of the sequence.

[0047] For sequence comparison, typically one sequence acts as a reference sequence, to which test sequences are compared. When using a sequence comparison algorithm, test and reference sequences are entered into a computer, subsequence coordinates are designated, if necessary, and sequence algorithm program parameters are designated. Default program parameters can be used, or alternative parameters can be designated. The sequence comparison algorithm then calculates the percent sequence identities for the test sequences relative to the reference sequence, based on the program parameters.

[0048] A “comparison window”, as used herein, includes reference to a segment of any one of the number of contiguous positions selected from the group consisting of from 20 to 600, usually about 50 to about 200, more usually about 100 to about 150 in which a sequence may be compared to a reference sequence of the same number of contiguous positions after the two sequences are optimally aligned. Methods of alignment of sequences for comparison are known in the art. Optimal alignment of sequences for comparison can be conducted, *e.g.*, by the local homology algorithm of Smith and Waterman (1970) *Adv. Appl. Math.* 2:482c, by the homology alignment algorithm of Needleman and Wunsch (1970) *J. Mol. Biol.* 48:443, by the search for similarity method of Pearson and Lipman (1988) *Proc. Nat’l. Acad. Sci. USA* 85:2444, by computerized implementations of these algorithms (GAP, BESTFIT, FASTA, and TFASTA in the Wisconsin Genetics Software Package, Genetics Computer Group, 575 Science Dr., Madison, WI), or by manual alignment and visual inspection (*see, e.g.*, Ausubel *et al.*, *Current Protocols in Molecular Biology* (1995 supplement)).

[0049] An example of an algorithm that is suitable for determining percent sequence identity and sequence similarity are the BLAST and BLAST 2.0 algorithms, which are described in Altschul *et al.* (1977) *Nuc. Acids Res.* 25:3389-3402, and Altschul *et al.* (1990) *J. Mol. Biol.* 215:403-410, respectively. Software for performing BLAST analyses is publicly available through the National Center for Biotechnology Information

(<http://www.ncbi.nlm.nih.gov/>). This algorithm involves first identifying high scoring sequence pairs (HSPs) by identifying short words of length W in the query sequence, which either match or satisfy some positive-valued threshold score T when aligned with a word of the same length in a database sequence. T is referred to as the neighborhood word score threshold (Altschul *et al.*, *supra*). These initial neighborhood word hits act as seeds for initiating searches to find longer HSPs containing them. The word hits are extended in both directions along each sequence for as far as the cumulative alignment score can be increased. Cumulative scores are calculated using, for nucleotide sequences, the parameters M (reward score for a pair of matching residues; always > 0) and N (penalty score for mismatching residues; always < 0). For amino acid sequences, a scoring matrix is used to calculate the cumulative score. Extension of the word hits in each direction are halted when: the cumulative alignment score falls off by the quantity X from its maximum achieved value; the cumulative score goes to zero or below, due to the accumulation of one or more negative-scoring residue alignments; or the end of either sequence is reached. The BLAST algorithm parameters W , T , and X determine the sensitivity and speed of the alignment. The BLASTN program (for nucleotide sequences) uses as defaults a wordlength (W) of 11, an expectation (E) or 10, $M=5$, $N=-4$ and a comparison of both strands. For amino acid sequences, the BLASTP program uses as defaults a wordlength of 3, and expectation (E) of 10, and the BLOSUM62 scoring matrix (*see* Henikoff and Henikoff (1989) *Proc. Natl. Acad. Sci. USA* 89:10915) alignments (B) of 50, expectation (E) of 10, $M=5$, $N=-4$, and a comparison of both strands.

[0050] The BLAST algorithm also performs a statistical analysis of the similarity between two sequences (*see, e.g.*, Karlin and Altschul (1993) *Proc. Natl. Acad. Sci. USA* 90:5873-5787). One measure of similarity provided by the BLAST algorithm is the smallest sum probability ($P(N)$), which provides an indication of the probability by which a match between two nucleotide or amino acid sequences would occur by chance. For example, a nucleic acid is considered similar to a reference sequence if the smallest sum probability in a comparison of the test nucleic acid to the reference nucleic acid is less than about 0.2, more preferably less than about 0.01, and most preferably less than about 0.001.

[0051] An indication that two nucleic acid sequences or polypeptides are substantially identical is that the polypeptide encoded by the first nucleic acid is immunologically cross reactive with the antibodies raised against the polypeptide encoded by the second nucleic acid, as described below. Thus, a polypeptide is typically substantially identical to a second

polypeptide, for example, where the two peptides differ only by conservative substitutions. Another indication that two nucleic acid sequences are substantially identical is that the two molecules or their complements hybridize to each other under stringent conditions, as described below. Yet another indication that two nucleic acid sequences are substantially identical is that the same primers can be used to amplify the sequence.

[0052] The phrase “selectively (or specifically) hybridizes to” refers to the binding, duplexing, or hybridizing of a molecule only to a particular nucleotide sequence under stringent hybridization conditions when that sequence is present in a complex mixture (e.g., total cellular or library DNA or RNA).

[0053] The phrase “stringent hybridization conditions” refers to conditions under which a probe will hybridize to its target subsequence, typically in a complex mixture of nucleic acid, but to no other sequences. Stringent conditions are sequence-dependent and will be different in different circumstances. Longer sequences hybridize specifically at higher temperatures. An extensive guide to the hybridization of nucleic acids is found in Tijssen, *Techniques in Biochemistry and Molecular Biology--Hybridization with Nucleic Probes*, “Overview of principles of hybridization and the strategy of nucleic acid assays” (1993). Generally, stringent conditions are selected to be about 5-10° C lower than the thermal melting point (T_m) for the specific sequence at a defined ionic strength pH. The T_m is the temperature (under defined ionic strength, pH, and nucleic concentration) at which 50% of the probes complementary to the target hybridize to the target sequence at equilibrium (as the target sequences are present in excess, at T_m , 50% of the probes are occupied at equilibrium). Stringent conditions will be those in which the salt concentration is less than about 1.0 M sodium ion, typically about 0.01 to 1.0 M sodium ion concentration (or other salts) at pH 7.0 to 8.3 and the temperature is at least about 30°C for short probes (e.g., 10 to 50 nucleotides) and at least about 60° C for long probes (e.g., greater than 50 nucleotides). Stringent conditions may also be achieved with the addition of destabilizing agents such as formamide. For selective or specific hybridization, a positive signal is at least two times background, optionally 10 times background hybridization. Exemplary stringent hybridization conditions can be as following: 50% formamide, 5X SSC, and 1% SDS, incubating at 42°C, or 5X SSC, 1% SDS, incubating at 65°C, with wash in 0.2X SSC, and 0.1% SDS at 55°C, 60°C, or 65°C. Such washes can be performed for 5, 15, 30, 60, 120, or more minutes.

[0054] Nucleic acids that do not hybridize to each other under stringent conditions are still substantially identical if the polypeptides that they encode are substantially identical. This occurs, for example, when a copy of a nucleic acid is created using the maximum codon degeneracy permitted by the genetic code. In such cases, the nucleic acids typically hybridize under moderately stringent hybridization conditions. Exemplary “moderately stringent hybridization conditions” include a hybridization in a buffer of 40% formamide, 1 M NaCl, 1% SDS at 37°C, and a wash in 1X SSC at 45°C. Such washes can be performed for 5, 15, 30, 60, 120, or more minutes. A positive hybridization is at least twice background. Those of ordinary skill will readily recognize that alternative hybridization and wash conditions can be utilized to provide conditions of similar stringency.

[0055] “Activators” of expression or of activity are used to refer to activating, stimulating, enhancing molecules, respectively, identified using *in vitro* and *in vivo* assays for expression or activity. Samples or assays comprising a polypeptide of interest, *e.g.*, a glycosyltransferase, *e.g.* ST3Gal-III, that are treated with a potential agonist can be compared to control samples without the agonist to examine the extent of effect. Control samples (untreated with agonists) are assigned a relative activity value of 100%. Activation of the polypeptide is achieved when the polypeptide activity value relative to the control is 110%, optionally 150%, optionally 200%, 300%, 400%, 500%, or 1000-3000% or more higher activity.

[0056] A “therapeutically effective amount”, “pharmacologically acceptable dose”, “pharmacologically acceptable amount” means that a sufficient amount of a ST3Gal-III activity enhancer is present to achieve a desired result, *e.g.*, activating, agonizing, increasing, enhancing the sialyltransferase activity of ST3Gal-III.

Detailed Embodiments

[0057] In a first aspect, the present invention provides methods for detecting an epileptic condition associated with decreased ST3Gal-III activity in a mammal, the methods comprising detecting ST3Gal-III activity in a sample from the mammal. ST3Gal-III polypeptides and their activity can be detected using standard assays (*e.g.*, polypeptides can be detected using antibodies; activity can be detected using standard enzymology techniques). An epileptic condition, whether or not associated with a decrease in ST3Gal-III activity, can be diagnosed by detecting the levels of carbohydrate structures used or made by ST3Gal-III, for example, by detecting decreasing levels of substrate (*e.g.*, an activated sialic acid or a

Gal β 1-3/4GlcNAc) or increasing levels of product (e.g., a Sia α 2-3Gal β 1-3GlcNAc or a Sia α 2-3Gal β 1-4GlcNAc oligosaccharide moiety). Carbohydrate structures can be detected directly (e.g., using antibodies, high performance liquid chromatography (HPLC), NMR) or indirectly (e.g., by detecting binding to one or more antibodies, lectins (i.e., *Maackia*
5 *Amurensis* II (MAL II)), selectins, CD33, or sialoadhesin). ST3Gal-III activity additionally can be detected by detecting an increase or decrease in the transcription of a ST3Gal-III coding sequence or translation of a ST3Gal-III polypeptide.

[0058] The invention further provides methods of detecting an epileptic condition, the method comprising detecting one or more carbohydrate structures in a sample from the
10 mammal. In cases where the epileptic condition results from decreased ST3Gal-III activity, the carbohydrate structure can be a product of ST3Gal-III, for example, one or more of a Sia α 2-3Gal β 1-3GlcNAc or a Sia α 2-3Gal β 1-4GlcNAc oligosaccharide moiety. The carbohydrate structure can also be one or more of a substrate of ST3Gal-III, for example, a Gal β 1-3GlcNAc or a Gal β 1-4GlcNAc oligosaccharide moiety. The carbohydrate structure
15 can be detected using methods known in the art, as described herein. In some embodiments the presence of the carbohydrate structure is abnormally high or abnormally low in comparison to the presence of the carbohydrate structure in a sample from a mammal not suffering an epileptic condition. In some embodiments, the one or more carbohydrate structures are detected on a CNS cell, including a brain cell.

[0059] In a related aspect, the invention provides methods for identifying an increased risk for an epileptic condition associated with decreased ST3Gal-III activity, the method comprising identifying one or more mutations in a *ST3Gal-III* gene, wherein the one or more mutations decrease the activity of the encoded ST3Gal-III polypeptide. The decrease in
25 ST3Gal-III activity of a ST3Gal-III polypeptide expressed from a mutant gene can be made in comparison to the activity of a ST3Gal-III polypeptide expressed from a wild-type gene. The one or more mutations can be in an active site of the ST3Gal-III enzyme, and typically occur in regions of the enzyme highly conserved among mammals. Such highly conserved regions can be identified by aligning nucleic acid and/or amino acid sequences of known ST3Gal-III sequences from different mammalian species, for example, from human, mouse,
30 rat, cow, pig and hamster. This can be done using readily available algorithms known in the art (e.g., BLAST; Lipman and Pearson's Align program).

[0060] In a further aspect, the invention provides for methods of treating an epileptic condition associated with decreased ST3Gal-III activity in a mammal, the method comprising administering to the mammal a therapeutically effective amount of one or more agents that increase the activity of ST3Gal-III in the mammal. In some embodiments, the agent is a nucleic acid encoding an enzymatically active ST3Gal-III or an enzymatically active fragment thereof. The agent that increases the activity of ST3Gal-III also can be a ST3Gal-III polypeptide. In some embodiments, the agent increases the level of ST3Gal-III protein expression, or increases the level of ST3Gal-III mRNA expression.

[0061] The invention further provides methods for increasing the levels of one or more Sia α 2-3Gal β 1-3/4GlcNAc moieties in a central nervous system (CNS) cell, the method comprising, introducing into a CNS cell an expression vector comprising a nucleic acid that encodes a ST3Gal-III polypeptide or enzymatically active fragment thereof. In some embodiments, the CNS cell is a differentiated brain cell. In some embodiments, the CNS cell is an undifferentiated stem cell. The expression vector can be introduced into the CNS cell either *ex vivo* or *in vivo*.

[0062] The invention also provides methods of identifying one or more agents for the treatment of an epileptic condition associated with decreased ST3Gal-III activity in an individual, the method comprising identifying a candidate agent that increases the activity of ST3Gal-III. In some embodiments, the agent that increases the activity of ST3Gal-III is identified by contacting the candidate agent with a ST3Gal-III polypeptide or enzymatically active fragment thereof. In some embodiments, the agent that increases the activity of ST3Gal-III is identified by contacting the candidate agent with a substrate (*e.g.*, an activated sialic acid or a Gal β 1-3/4GlcNAc) or a product (*e.g.*, a Sia α 2-3Gal β 1-3GlcNAc or a Sia α 2-3Gal β 1-4GlcNAc oligosaccharide moiety) of a ST3Gal-III. Candidate agents of interest increase the amount of Sia α 2-3Gal β 1-3GlcNAc or Sia α 2-3Gal β 1-4GlcNAc moieties in a CNS cell, particularly a brain cell.

Identification of ST3Gal-III activity enhancers

[0063] A number of different screening protocols can be utilized to identify agents that increase the level of expression or activity of ST3Gal-III in cells, particularly mammalian cells, and especially human cells. In general terms, the screening methods involve screening a plurality of agents to identify an agent that increases the activity of ST3Gal-III.

[0064] This invention involves routine techniques in the field of recombinant genetics. Basic texts disclosing the general methods of use in this invention include Sambrook *et al.*, *Molecular Cloning, A Laboratory Manual* (3rd ed. 2001); Kriegler, *Gene Transfer and Expression: A Laboratory Manual* (1990); and *Current Protocols in Molecular Biology* (Ausubel *et al.*, eds., 1994-2005)).

[0065] Activators of ST3Gal-III, *e.g.*, ST3Gal-III agonists (*i.e.*, agents that increase the activity or expression of ST3Gal-III) are useful for increasing or replacing ST3Gal-III sialyltransferase activity in individuals having an epileptic condition associated with deficient ST3Gal-III activity.

10 *ST3Gal-III activating agents*

[0066] ST3Gal-III activating agents can be any small chemical compound, or a biological entity, such as a protein, sugar, nucleic acid or lipid.

[0067] A wide variety of methods can be used to identify agents that increase ST3Gal-III activity or level. Typically, test compounds will be small chemical molecules and/or peptides. Essentially any chemical compound can be used as a potential activity enhancer. In the assays of the invention, although most often compounds that can be dissolved in aqueous or organic (especially DMSO-based) solutions are used. The assays can be designed to screen large chemical libraries by automating the assay steps and providing compounds from any convenient source to assays, which are typically run in parallel (*e.g.*, in microtiter formats on microtiter plates in robotic assays). It will be appreciated that there are many suppliers of chemical compounds, including Sigma (St. Louis, MO), Aldrich (St. Louis, MO), Sigma-Aldrich (St. Louis, MO), Fluka Chemika-Biochemica Analytika (Buchs, Switzerland) and the like.

[0068] In some embodiments, high throughput screening methods involve providing a combinatorial chemical or peptide library containing a large number of potential therapeutic compounds (potential activity enhancing compounds). Such “combinatorial chemical libraries” or “ligand libraries” are then screened in one or more assays, as described herein, to identify those library members (particular chemical species or subclasses) that display a desired characteristic activity. The compounds thus identified can serve as conventional “lead compounds” or can themselves be used as potential or actual therapeutics.

[0069] A combinatorial chemical library is a collection of diverse chemical compounds generated by either chemical synthesis or biological synthesis, by combining a number of chemical "building blocks" such as reagents. For example, a linear combinatorial chemical library such as a polypeptide library is formed by combining a set of chemical building blocks (amino acids) in every possible way for a given compound length (*i.e.*, the number of amino acids in a polypeptide compound). Millions of chemical compounds can be synthesized through such combinatorial mixing of chemical building blocks.

[0070] Preparation and screening of combinatorial chemical libraries is known to those of skill in the art. Such combinatorial chemical libraries include, but are not limited to, peptide libraries (*see, e.g.*, U.S. Patent 5,010,175, Furka, *Int. J. Pept. Prot. Res.* 37:487-493 (1991) and Houghton *et al.*, *Nature* 354:84-88 (1991)). Other chemistries for generating chemical diversity libraries can also be used. Such chemistries include, but are not limited to: peptoids (*e.g.*, PCT Publication No. WO 91/19735), encoded peptides (*e.g.*, PCT Publication WO 93/20242), random bio-oligomers (*e.g.*, PCT Publication No. WO 92/00091), benzodiazepines (*e.g.*, U.S. Pat. No. 5,288,514), diversomers such as hydantoins, benzodiazepines and dipeptides (Hobbs *et al.*, *Proc. Nat. Acad. Sci. USA* 90:6909-6913 (1993)), vinylogous polypeptides (Hagihara *et al.*, *J. Amer. Chem. Soc.* 114:6568 (1992)), nonpeptidal peptidomimetics with glucose scaffolding (Hirschmann *et al.*, *J. Amer. Chem. Soc.* 114:9217-9218 (1992)), analogous organic syntheses of small compound libraries (Chen *et al.*, *J. Amer. Chem. Soc.* 116:2661 (1994)), oligocarbamates (Cho *et al.*, *Science* 261:1303 (1993)), and/or peptidyl phosphonates (Campbell *et al.*, *J. Org. Chem.* 59:658 (1994)), nucleic acid libraries (*see* Ausubel, Berger and Sambrook, all *supra*), peptide nucleic acid libraries (*see, e.g.*, U.S. Patent 5,539,083), antibody libraries (*see, e.g.*, Vaughn *et al.*, *Nature Biotechnology*, 14(3):309-314 (1996) and PCT/US96/10287), carbohydrate libraries (*see, e.g.*, Liang *et al.*, *Science*, 274:1520-1522 (1996) and U.S. Patent 5,593,853), small organic molecule libraries (*see, e.g.*, benzodiazepines, Baum C&EN, Jan 18, page 33 (1993); isoprenoids, U.S. Patent 5,569,588; thiazolidinones and metathiazanones, U.S. Patent 5,549,974; pyrrolidines, U.S. Patents 5,525,735 and 5,519,134; morpholino compounds, U.S. Patent 5,506,337; benzodiazepines, 5,288,514, and the like).

[0071] Devices for the preparation of combinatorial libraries are commercially available (*see, e.g.*, 357 MPS, 390 MPS, Advanced Chem Tech, Louisville KY, Symphony, Rainin, Woburn, MA, 433A Applied Biosystems, Foster City, CA, 9050 Plus, Millipore, Bedford, MA). In addition, numerous combinatorial libraries are themselves commercially available

(see, e.g., ComGenex, Princeton, N.J., Tripos, Inc., St. Louis, MO, 3D Pharmaceuticals, Exton, PA, Martek Biosciences, Columbia, MD, etc.).

ST3Gal-III polypeptides

[0072] ST3Gal-III sequences are highly conserved amongst mammals. For example, mouse and human ST3Gal-III polypeptides share about 90-95% sequence identity (isoform B1 shares about 97% identity). Mouse and human ST3Gal-III encoding polynucleotide sequences share about 70% sequence identity. ST3Gal-III nucleic acid and amino acid sequences for other mammalian species, including pig, cow and hamster, also have been identified.

[0073] ST3Gal-III polypeptides for use in the invention include ST3Gal-III polypeptides comprising: a naturally-occurring amino acid sequence including a human ST3Gal-III (e.g., one or more of SEQ ID NOs:2, 4, 6, 8, 10, 12, 14, 16, 18 or 20), or other animal ortholog, e.g., mouse ST3Gal-III (e.g., SEQ NOs:22 or 24). Other naturally occurring variants (relative to the exemplary sequences provided herein); or engineered ST3Gal-III polypeptides can also be employed. Accordingly, substantial information is available to those of skill in identifying and/or generating such variant ST3Gal-III polypeptides.

[0074] ST3Gal-III polypeptide variants for use in the invention can be tested, e.g., by assessing the ability of the polypeptide to transfer a sialic acid moiety onto a sialylate type 1 (Gal β 1-3GlcNAc) or a type 2 (Gal β 1-4GlcNAc) oligosaccharide. Such ST3Gal-III polypeptides can then be used in assays to identify activators of ST3Gal-III activity.

Methods of Screening for Activity Enhancers of ST3Gal-III.

[0075] A number of different screening protocols can be utilized to identify agents that enhance the activity of ST3Gal-III.

[0076] Screening can be performed using isolated, purified or partially purified reagents. In some embodiments, purified or partially purified ST3Gal-III (e.g., cell fractions comprising a ST3Gal-III polypeptide) can be used.

[0077] Alternatively, cell-based methods of screening can be used. For example, cells that naturally-express ST3Gal-III or that recombinantly express ST3Gal-III can be used. In some embodiments, the cells used are mammalian cells, including but not limited to, human cells.

In general terms, the screening methods involve screening a plurality of agents to identify an

agent that increases the activity of ST3Gal-III by, *e.g.*, binding to and/or increasing the activity of a ST3Gal-III polypeptide, preventing an activator from binding to ST3Gal-III, increasing association of activator with ST3Gal-III, or activating expression of ST3Gal-III.

ST3Gal-III Binding Assays

- 5 [0078] Optionally, preliminary screens can be conducted by screening for agents that bind to ST3Gal-III. Binding assays are also useful, *e.g.*, for identifying endogenous, or other proteins, that interact with ST3Gal-III. For example, antibodies or other molecules that bind ST3Gal-III can be identified in binding assays. Such antibodies have use, *e.g.*, as diagnostic agents.
- 10 [0079] Binding assays usually involve contacting a ST3Gal-III protein with one or more test agents and allowing the ST3Gal-III protein and test agent(s) to form a binding complex. Binding complexes that are formed can be detected using any of a number of established analytical techniques. Protein binding assays include, but are not limited to, methods that measure co-precipitation or co-migration on non-denaturing SDS-polyacrylamide gels, and
- 15 co-migration on Western blots (see, *e.g.*, Bennet, J.P. and Yamamura, H.I. (1985) "Neurotransmitter, Hormone or Drug Receptor Binding Methods," in *Neurotransmitter Receptor Binding* (Yamamura, H. I., et al., eds.), pp. 61-89. Other binding assays involve the use of mass spectrometry or NMR techniques to identify molecules bound to ST3Gal-III or displacement of labeled substrates. The ST3Gal-III protein utilized in such assays can be
- 20 naturally expressed, cloned or synthesized.
- [0080] In addition, mammalian or yeast two-hybrid approaches (*see, e.g.*, Bartel, P.L. *et al. Methods Enzymol*, 254:241 (1995)) can be used to identify polypeptides or other molecules that interact or bind when expressed together in a cell.

ST3Gal-III Activity

- 25 [0081] ST3Gal-III activators can be identified by screening for agents that alter an activity of ST3Gal-III. Analysis of ST3Gal-III activity is performed according to general biochemical procedures. Such assays include cell-based assays as well as *in vitro* assays involving purified or partially purified ST3Gal-III polypeptides or cellular fractions comprising ST3Gal-III.
- 30 [0082] In some embodiments, ST3Gal-III activators are identified by screening a plurality of agents (generally in parallel) for the ability to enhance ST3Gal-III activity. The level of

ST3Gal-III activity in a cell or other sample can be determined and compared to a baseline value (e.g., a control value or the ST3Gal-III activity in a sample not contacted with an agent or the ST3Gal-III activity in a sample contacted to a different agent).

[0083] ST3Gal-III catalyzes the transfer of a sialic acid moiety to a sialylate type 1 (Gal β 1-3GlcNAc) or a type 2 (Gal β 1-4GlcNAc) oligosaccharide. Thus, ST3Gal-III activity can be determined using any number of direct and indirect indicators of activity. For example, the transferase activity can be determined directly (e.g., using the standard enzymology techniques, for example, by measuring the increase of a product (i.e., a Sia α 2-3Gal β 1-3/4GlcNAc) or the decrease of a substrate (i.e., activated sialic acid or a sialylate type 1 or type 2 oligosaccharide). Carbohydrate structures can be detected using methods known in the art, for example, by using antibodies specific for particular oligosaccharide moieties, chromatographic techniques (e.g., HPLC), mass spectrometry, or nuclear magnetic resonance (NMR). For instance, specific lectins, selectins, sialoadhesin, CD33 or antibodies raised against the ligand can be used. Methods suitable for use in the diagnostic methods of the invention described in WO 00/33076. Alternatively, the level of glycosylation can be determined indirectly, typically by measuring the level of lectin or selectin binding, e.g., P-, E- or L- selectin binding. Any lectin or selectin that binds to a Sia α 2-3Gal β 1-3/4GlcNAc can be used, for example, *Maackia Amurensis* II (MAL II) lectin.

[0084] In some embodiments, cells transiently transfected with ST3Gal-III are measured for ST3Gal-III activity in suspension or adhered to the plate, within an isotonic buffer. The cells are then contacted to one or more agents and tested for ST3Gal-III activity.

[0085] Screening methods to identify enhancers of ST3Gal-III activity typically employ in at least one of the steps, an assay that uses a ST3Gal-III polypeptide.

Expression Assays

[0086] Screening methods for a compound that increases the expression of ST3Gal-III are also provided. Screening methods generally involve conducting cell-based assays in which test compounds are contacted with one or more cells expressing ST3Gal-III, and then detecting an increase or decrease in ST3Gal-III expression (either transcript, translation product). Assays can be performed with cells that naturally express ST3Gal-III or in cells recombinantly altered to express a ST3Gal-III.

[0087] ST3Gal-III expression can be detected in a number of different ways. For example, the expression level of ST3Gal-III in a cell can be determined by evaluating mRNA expression using known methods, *e.g.*, northern blot analysis, *in situ* hybridization and the like. Alternatively, ST3Gal-III protein can be detected, *e.g.*, using immunological methods, such as ELISA, immunoblotting, immunoprecipitations, and other well-known techniques.

[0088] Other cell-based assays involve reporter assays conducted with cells using standard reporter gene assays. These assays can be performed in either cells that do, or do not, express ST3Gal-III. Some of these assays are conducted with a heterologous nucleic acid construct that comprises a ST3Gal-III promoter that is operably linked to a reporter gene that encodes a detectable product. A number of different reporter genes can be utilized, including, green fluorescent protein, and enzyme reporters such as β -glucuronidase, CAT (chloramphenicol acetyl transferase; Alton and Vapnek (1979) *Nature* 282:864-869), luciferase, β -galactosidase and alkaline phosphatase (Toh, *et al.* (1980) *Eur. J. Biochem.* 182:231-238; and Hall *et al.* (1983) *J. Mol. Appl. Gen.* 2:101).

[0089] In these assays, cells harboring the reporter construct are contacted with a test compound. Increased expression is monitored by detecting the level of a detectable reporter. A number of different kinds of ST3Gal-III expression enhancers can be identified in this assay. For example, a test compound that activates the promoter by binding to it, or by binding to and activating a transcription factor that binds to the promoter, or by inducing a cascade that produces a molecule that activates the promoter, or that otherwise activates the promoter can be identified. Similarly, a test compound that, *e.g.*, enhances the promoter by binding to it, or by binding to a transcription factors or other regulatory factor that results in activating a ST3Gal-III promoter can also be identified.

[0090] The level of expression or activity can be compared to a baseline value. The baseline value can be a value for a control sample or a statistical value that is representative of ST3Gal-III expression levels for a control population (*e.g.*, individuals not having or at risk for epilepsy) or cells (*e.g.*, tissue culture cells not exposed to a ST3Gal-III agonist or antagonist). Expression levels can also be determined for cells that do not express a ST3Gal-III as a negative control. Such cells generally are otherwise substantially genetically the same as the test cells.

[0091] Various controls can be conducted to ensure that an observed activity is authentic including running parallel reactions with cells that lack the reporter construct or by not contacting a cell harboring the reporter construct with test compound.

Computer-Based Assays

5 [0092] Other assays for compounds that increase the activity of ST3Gal-III involves computer-assisted drug design, in which a computer system is used to generate a three-dimensional structure of ST3Gal-III based on the structural information encoded by its amino acid sequence. The input amino acid sequence interacts directly and actively with a pre-established algorithm in a computer program to yield secondary, tertiary, and quaternary
10 structural models of the protein. The models of the protein structure are then examined to identify regions (e.g., the active site) of the structure that have the ability to bind ligands or otherwise be enhance ST3Gal-III activity. These regions are then used to identify polypeptides that bind to ST3Gal-III.

[0093] Once the tertiary structure of a protein of interest has been generated, potential
15 activity enhancers can be identified by the computer system. Three-dimensional structures for potential activity enhancers are generated by entering chemical formulas of compounds. The three-dimensional structure of the potential activity enhancer is then compared to that of ST3Gal-III to identify potential activity enhancer binding sites to ST3Gal-III. Binding affinity between the protein and activity enhancer is determined using energy terms to
20 determine which ligands have an enhanced probability of binding to the protein.

Validation of candidate activators

[0094] Agents that are initially identified by any of the foregoing screening methods can be further tested to validate the apparent activity and/or determine other biological effects of the agent. In some cases, the identified agent is tested for the ability to increase ST3Gal-III
25 activity and/or the levels of Sia α 2-3Gal β 1-3GlcNAc or Sia α 2-3Gal β 1-4GlcNAc oligosaccharide moieties.

[0095] *In vitro* assays using isolated CNS cells, particularly brain cells (normal or epileptic) can be performed in the presence or absence of the candidate activator. In some embodiments, validation studies are conducted with suitable animal models. The basic
30 format of such methods involves administering a lead compound identified during an initial screen to an animal that serves as a model for humans and then determining if ST3Gal-III

activity and/or expression, *e.g.*, selectin binding, sialyltransferase activity and the like, is in fact activated following administration of the ST3Gal-III activator. The animals can also be monitored for the increase or decrease of seizure activity by EEG analysis or subject to behavioral monitoring (locomotor activity, contextual fear responses, muscular strength and coordination). The animal models utilized in validation studies generally are mammals of any kind, but usually mice. Specific examples of suitable animals include mice having a knocked-out *ST3Gal-III* gene or a *ST3Gal-III* gene having one or more mutations such that the ST3Gal-III sialyltransferase activity is decreased in comparison to a mouse having a wild-type *ST3Gal-III* gene. Mice genetically deficient for a *ST3Gal-III* gene are described in Ellies, *et al.*, *Blood* (2002) 100:3618-25. Other established animal epilepsy models can find use in the screening and validation of ST3Gal-III activity enhancer, whether using the animals themselves or the methods of monitoring for epileptic symptoms, including those described in Yang and Frankel, *Adv Exp Med Biol* (2004) 548:1-11; Stables, *et al.*, *Epilepsia* (2002) 43:1410-20; Kupferberg, *Epilepsia* (2001) 4:7-12; and Seyfried, *et al.*, (1999) 79:279-90.

Administration and Pharmaceutical Compositions

[0096] Activators of ST3Gal-III (*e.g.*, ST3Gal-III agonists) can be administered directly to the mammalian subject in need thereof for activation of ST3Gal-III activity *in vivo*.

Individuals in need of activators of ST3Gal-III include, for example, individuals with an epileptic condition or another seizure disorder associated with deficient ST3Gal-III activity.

Administration can be by any of the routes normally used for introducing a compound into ultimate contact with the tissue to be treated and is known to those of skill in the art.

Although more than one route can be used to administer a particular composition, a particular route can often provide a more immediate and more effective reaction than another route.

[0097] The pharmaceutical compositions of the invention may comprise a pharmaceutically acceptable carrier. Pharmaceutically acceptable carriers are determined in part by the particular composition being administered, as well as by the particular method used to administer the composition. Accordingly, there is a wide variety of suitable formulations of pharmaceutical compositions of the present invention (*see, e.g., Remington: The Science and Practice of Pharmacy*, 20th ed. 2003)).

[0098] Activators, alone or in combination with other suitable components, can be made into aerosol formulations (*i.e.*, they can be “nebulized”) to be administered via inhalation.

Aerosol formulations can be placed into pressurized acceptable propellants, such as dichlorodifluoromethane, propane, nitrogen, and the like.

[0099] Formulations suitable for administration include aqueous and non-aqueous solutions, isotonic sterile solutions, which can contain antioxidants, buffers, bacteriostats, and solutes that render the formulation isotonic, and aqueous and non-aqueous sterile suspensions that can include suspending agents, solubilizers, thickening agents, stabilizers, and preservatives. The formulations of compounds can be presented in unit-dose or multi-dose sealed containers, such as ampoules and vials. Solutions and suspensions can be prepared from sterile powders, granules, and tablets of the kind previously described. The activators can also be administered as part of a prepared food or drug.

[0100] In the practice of this invention, compositions can be administered, for example, orally, nasally, topically, intravenously, intraperitoneally, or intrathecally. Optimally, an activator or a ST3Gal-III polypeptide is delivered to brain tissue. Strategies for delivery of an activator or a polypeptide across the blood-brain barrier include, for example, double-coated poly (butylcyanoacrylate) nanoparticulate delivery systems (Das and Lin, *J Pharm Sci.* (2005) 94:1343-53); convection-enhanced delivery (Lonser, *et al.*, *Ann Neurol.* (2005) 57:542-8); ST3Gal-III conjugation to a transferring receptor (TfR)-specific ligand, including an anti-TfR antibody (Zhang and Pardridge, *J Pharmacol Exp Ther.* (2005) 313:1075-81; *see also*, U.S. Patent Nos. 5,977,307 and 5,672,683); formulations which include the amphiphilic block copolymer Pluronic P85 (P85) (Batrakova, *et al. Pharm Res.* (2004) 21:1993-2000); formulations which include Zonula occludens toxin (Zot) or its biologically active fragment, DeltaG (Salama, *et al.*, *J Pharmacol Exp Ther.* (2005) 312:199-205); nanoparticles (U.S. Patent Publication No. 2004/0131692) and co-administration with hyaluronidase (U.S. Patent Publication No. 2003/0215432).

[0101] The dose administered to a patient, in the context of the present invention should be sufficient to induce a beneficial response in the subject over time. The optimal dose level for any patient will depend on a variety of factors including the efficacy of the specific activator employed, the age, body weight, physical activity, and diet of the patient, on a possible combination with other drugs, and on the severity of the case of epilepsy. It is recommended that the daily dosage of the activator be determined for each individual patient by those skilled in the art in a similar way as for known compositions used to treat epilepsy. The size of the dose also will be determined by the existence, nature, and extent of any adverse side-

effects that accompany the administration of a particular compound or vector in a particular subject.

[0102] In determining the effective amount of the activator to be administered a physician may evaluate circulating plasma levels of the activator, activator toxicity, and the production of anti-activator antibodies. In general, the dose equivalent of an activator is from about 1 ng/kg to 10 mg/kg for a typical subject.

[0103] ST3Gal-III activators can be administered at a rate determined by the LD-50 of the activator, and the side-effects of the activator at various concentrations, as applied to the mass and overall health of the subject. Administration can be accomplished via single or divided doses.

[0104] The compounds of the present invention can also be used effectively in combination with one or more additional active agents currently used to treat epilepsy, depending on the desired target therapy, including carbamazepine, phenytoin, valproate, phenobarbital, primidone, and ethosuximide (*see*, Chapter 21 of *Goodman and Gilman's, supra*).

Combination therapy includes administration of a single pharmaceutical dosage formulation that contains a ST3Gal-III activator of the invention and one or more additional active agents, as well as administration of a ST3Gal-III activator and each active agent in its own separate pharmaceutical dosage formulation. For example, a ST3Gal-III activator and another active agent used to treat epilepsy can be administered to the human subject together in a single oral dosage composition, such as a tablet or capsule, or each agent can be administered in separate oral dosage formulations. Where separate dosage formulations are used, a ST3Gal-III activator and one or more additional active agents can be administered at essentially the same time (i.e., concurrently), or at separately staggered times (i.e., sequentially). Combination therapy is understood to include all these regimens.

[0105] Pharmaceutically acceptable carriers are determined in part by the particular composition being administered, as well as by the particular method used to administer the composition. Accordingly, there is a wide variety of suitable formulations of pharmaceutical compositions of the present invention, as described below (*see, e.g., Remington: The Science and Practice of Pharmacy*, 20th ed., 2003).

Administration of nucleic acid activators

[0106] In one aspect of the present invention, ST3Gal-III activators can also comprise nucleic acid molecules that express ST3Gal-III. Conventional viral and non-viral based gene transfer methods can be used to introduce nucleic acids encoding ST3Gal-III polypeptides in mammalian cells or target tissues, for example CNS tissue or brain tissue. Such methods can be used to administer nucleic acids encoding polypeptides of the invention to cells *in vitro*.

In some embodiments, the nucleic acids encoding polypeptides of the invention are administered for *in vivo* or *ex vivo* gene therapy uses. Non-viral vector delivery systems include DNA plasmids, naked nucleic acid, and nucleic acid complexed with a delivery vehicle such as a liposome. Viral vector delivery systems include DNA and RNA viruses, which have either episomal or integrated genomes after delivery to the cell. For a review of gene therapy procedures, see Anderson, *Science* 256:808-813 (1992); Nabel & Felgner, *TIBTECH* 11:211-217 (1993); Mitani & Caskey, *TIBTECH* 11:162-166 (1993); Dillon, *TIBTECH* 11:167-175 (1993); Miller, *Nature* 357:455-460 (1992); Van Brunt, *Biotechnology* 6(10):1149-1154 (1988); Vigne, *Restorative Neurology and Neuroscience* 8:35-36 (1995); Kremer & Perricaudet, *British Medical Bulletin* 51(1):31-44 (1995); Haddada et al., in *Current Topics in Microbiology and Immunology* Doerfler and Böhm (eds) (1995); and Yu et al., *Gene Therapy* 1:13-26 (1994).

[0107] Methods of non-viral delivery of nucleic acids encoding engineered polypeptides of the invention include lipofection, microinjection, biolistics, virosomes, liposomes, immunoliposomes, polycation or lipid:nucleic acid conjugates, naked DNA, artificial virions, and agent-enhanced uptake of DNA. Lipofection is described in e.g., US 5,049,386, US 4,946,787; and US 4,897,355) and lipofection reagents are sold commercially (e.g., Transfectam and Lipofectin). Cationic and neutral lipids that are suitable for efficient receptor-recognition lipofection of polynucleotides include those of Felgner, WO 91/17424, WO 91/16024. Delivery can be to cells (*ex vivo* administration) or target tissues (*in vivo* administration).

[0108] The preparation of lipid:nucleic acid complexes, including targeted liposomes such as immunolipid complexes, is known to one of skill in the art (see, e.g., Crystal, *Science* 270:404-410 (1995); Blaese et al., *Cancer Gene Ther.* 2:291-297 (1995); Behr et al., *Bioconjugate Chem.* 5:382-389 (1994); Remy et al., *Bioconjugate Chem.* 5:647-654 (1994); Gao et al., *Gene Therapy* 2:710-722 (1995); Ahmad et al., *Cancer Res.* 52:4817-4820 (1992);

U.S. Pat. Nos. 4,186,183, 4,217,344, 4,235,871, 4,261,975, 4,485,054, 4,501,728, 4,774,085, 4,837,028, and 4,946,787).

[0109] The use of RNA or DNA viral based systems for the delivery of ST3GAL III nucleic acids is known in the art. RNA or DNA viral based systems for the delivery of nucleic acids encoding polypeptides of the invention take advantage of highly evolved processes for targeting a virus to specific cells in the body and trafficking the viral payload to the nucleus. Viral vectors can be administered directly to patients (*in vivo*) or they can be used to treat cells *in vitro* and the modified cells are administered to patients (*ex vivo*).

Conventional viral based systems for the delivery of polypeptides of the invention could include retroviral, lentivirus, adenoviral, adeno-associated and herpes simplex virus vectors for gene transfer. Viral vectors are currently the most efficient and versatile method of gene transfer in target cells and tissues. Integration in the host genome is possible with the retrovirus, lentivirus, and adeno-associated virus gene transfer methods, often resulting in long term expression of the inserted transgene. Additionally, high transduction efficiencies have been observed in many different cell types and target tissues.

[0110] Gene therapy vectors can be delivered *in vivo* by administration to an individual patient, typically by systemic administration (e.g., intravenous, intraperitoneal, intramuscular, subdermal, or intracranial infusion) or topical application, as described below. Alternatively, vectors can be delivered to cells *ex vivo*, such as cells explanted from an individual patient (e.g., lymphocytes, bone marrow aspirates, fetal tissue, umbilical tissue, tissue biopsy) or universal donor hematopoietic stem cells, followed by reimplantation of the cells into a patient, usually after selection for cells which have incorporated the vector. Optimally, a nucleic acid encoding a ST3Gal-III or an enzymatically active fragment thereof is delivered to brain tissue. Strategies for delivery of a nucleic acid across the blood brain barrier include, for example, virally transduced bone marrow cells (Makar, *et al.*, *Neurosci Lett.* (2004) 356:215-9); poly-L-lysine modified iron oxide nanoparticles (IONP-PLL) (Xiang, *et al.*, *J Gene Med.* (2003) 5:803-17); liposomes (U.S. Patent No. 6,372,250); transfection of one or more neurons which "straddle" the blood-brain barrier (U.S. Patent Publication No. 2003/0083299) and co-administration with hyaluronidase (U.S. Patent Publication No. 2003/0215432). *See also*, Schlachetzki, *et al.*, *Neurology.* (2004) 62:1275-81.

[0111] *Ex vivo* cell transfection for diagnostics, research, or for gene therapy (e.g., via re-infusion of the transfected cells into the host organism) is known to those of skill in the art.

In some embodiments, cells are isolated from the subject organism, transfected with a nucleic acid (gene or cDNA) encoding a polypeptides of the invention, and re-infused back into the subject organism (e.g., patient). Various cell types suitable for *ex vivo* transfection are known to those of skill in the art (see, e.g., Freshney *et al.*, *Culture of Animal Cells, A Manual of Basic Technique* (3rd ed. 1994)) and the references cited therein for a discussion of how to isolate and culture cells from patients).

[0112] In one embodiment, stem cells are used in *ex vivo* procedures for cell transfection and gene therapy. The advantage to using stem cells is that they can be differentiated into other cell types *in vitro*, e.g., CNS or brain tissue.

[0113] Stem cells are isolated for transduction and differentiation using known methods. For example, stem cells are isolated from bone marrow cells by panning the bone marrow cells with antibodies which bind unwanted cells, such as CD4+ and CD8+ (T cells), CD45+ (panB cells), GR-1 (granulocytes), and Iad (differentiated antigen presenting cells) (see Inaba *et al.*, *J. Exp. Med.* 176:1693-1702 (1992)).

[0114] In other embodiments, nucleic acids encoding a ST3Gal-III, can be introduced into CNS cells, brain cells or stem cells *ex vivo* and then reintroduced into the patient.

[0115] Vectors (e.g., retroviruses, adenoviruses, liposomes, etc.) containing therapeutic nucleic acids can also be administered directly to the organism for transduction of cells *in vivo*. Alternatively, naked DNA can be administered. Administration is by any of the routes normally used for introducing a molecule into ultimate contact with blood or tissue cells. Suitable methods of administering such nucleic acids are available and known to those of skill in the art, and, although more than one route can be used to administer a particular composition, a particular route can often provide a more immediate and more effective reaction than another route.

[0116] In some embodiments, transcription of an administered ST3Gal-III nucleic acid sequence is under the control of an inducible or a CNS-specific (brain-specific or neuron specific) promoter. Promoters for inducible expression or tissue-specific expression are known in the art. Exemplified inducible promoters include a metallothionein promoter or a brain natriuretic peptide promoter. Exemplified brain specific promoters include promoters for actin-binding LIM domain protein (ABLIM) (Klimov, *et al.*, *Biochim Biophys Acta* (2005) July 7; PMID 16005990), brain aromatase exon 1f (Harada and Honda, *J Steroid Biochem Mol Biol* (2005) June 12; PMID 15955692), estrogen receptor alpha and beta

(Hamada, *et al.*, *Brain Res Mol Brain Res*, (2005) June 10; PMID 15953656; and Hu, *et al.*, *J Neurobiol* (2005) 64:298-309), melanocortin 4 receptor (Daniel, *et al.*, *Mol Cell Endocrinol* (2005) 239:63-71), and brain natriuretic peptide (Ma, *et al.*, *Regul Pept* (2005) 128:169-76) genes. Exemplified neuron specific promoters include promoters for the enolase (Pillai-Nair, *et al.*, *J Neurosci* (2005) 25:4659-71), Thy 1.2 (Araki, *et al.*, *Genesis* (2005) 42:53-60) and tyrosine hydroxylase (Sorensen, *et al.*, *Eur J Neurosci* (2005) 21:2793-9) genes.

Diagnosis of risk for disease

[0117] In some embodiments, the invention provides methods of diagnosing a risk for an epileptic condition associated with decreased ST3Gal-III activity. Risk for epilepsy can be assessed for example, by determining the presence of one or more mutations in a *ST3Gal-III* gene that decrease or inhibit the activity of a ST3Gal-III sialyltransferase. Such mutations can lead to decreased levels of Sia α 2-3Gal β 1-3GlcNAc or a Sia α 2-3Gal β 1-4GlcNAc oligosaccharide moieties. Methods for detecting ST3Gal-III nucleic acids or mutants thereof are well known. For example, PCR, nucleic acid hybridization methods, and the like can be used to detect a particular mutant.

[0118] In other embodiments, disease risk can be assessed, for example, by determining whether mutations are present in ST3Gal-III genes or genes that regulate ST3-Gal-III transcription or translation lead to abnormal expression of ST3Gal-III, particularly in CNS or brain tissues.

Transgenic Animals

[0119] The invention also provides chimeric and transgenic nonhuman animals which contain cells that lack a functional ST3Gal-III sialyltransferase gene. The animals can be used to test therapies of the invention. A “chimeric animal” includes some cells that lack the functional ST3Gal-III gene and other cells that do not have the inactivated gene. A “transgenic animal,” in contrast, is made up of cells that have all incorporated the specific modification which renders the ST3Gal-III gene inactive. While a transgenic animal is capable of transmitting the inactivated sialyltransferase gene to its progeny, the ability of a chimeric animal to transmit the mutation depends upon whether the inactivated gene is present in the animal’s germ cells. The modifications that inactivate the gene can include, for example, insertions, deletions, or substitutions of one or more nucleotides. The modifications can interfere with transcription of the gene itself, with translation and/or stability of the

resulting mRNA, or can cause the gene to encode an inactive sialyltransferase polypeptide. Mice deficient for ST3Gal-III are described in Ellies, *et al*, *supra*.

[0120] The claimed methods are useful for producing transgenic and chimeric animals of most vertebrate species. Such species include, but are not limited to, nonhuman mammals, including rodents such as mice and rats, rabbits, ovines such as sheep and goats, porcines such as pigs, and bovines such as cattle and buffalo. Methods of obtaining transgenic animals are described in, for example, Puhler, A., Ed., *Genetic Engineering of Animals*, VCH Publ., 1993; Murphy and Carter, Eds., *Transgenesis Techniques : Principles and Protocols (Methods in Molecular Biology, Vol. 18)*, 1993; Pinkert, CA, Ed., *Transgenic Animal Technology : A Laboratory Handbook*, Academic Press, 2003; Houdebine, *et al.*, *Animal Transgenesis and Cloning*, 2003, John Wiley & Sons.

[0121] One method of obtaining a transgenic or chimeric animal having an inactivated ST3Gal-III sialyltransferase gene in its genome is to contact fertilized oocytes with a vector that includes a sialyltransferase-encoding polynucleotide that is modified to contain an inactivating modification. Alternatively, the modified sialyltransferase gene can be introduced into embryonic stem cells (ES). These cells are obtained from preimplantation embryos cultured *in vitro*. See, e.g., Hooper, ML, *Embryonal Stem Cells : Introducing Planned Changes into the Animal Germline* (Modern Genetics, v. 1), Int'l. Pub. Distrib., Inc., 1993; Bradley *et al.* (1984) *Nature* 309, 255-258. Transformed ES cells are combined with blastocysts from the non-human animal. See, Jaenisch (1988) *Science* 240: 1468-1474.

EXAMPLES

The following examples are offered to illustrate, but not to limit the claimed invention.

Example 1: ST3Gal-III deficient mice

[0122] ST3Gal-III deficient mice have been described in Ellies, *et al.*, *Blood* (2002) 100:3618-3625. Briefly, genomic clones of the *ST3Gal-III* gene were isolated from a 129/SvJ phage library (Stratagene, La Jolla, CA), and *Cre-loxP* gene targeting constructs prepared by approaches and procedures described in Priatel, *et al.*, *Glycobiology* (1997) 7:45-56. Mice bearing mutant genotypes were produced and bred by procedures described in

Shafi, *et al.*, *Proc Natl Acad Sci USA* (2000) 97:5735-5739. Genotyping was performed by polymerase chain reaction (PCR) by using oligonucleotide primers:

LE-110 (5'-CCAGCCAGCAGAGGATCTGATAC) and

LE-115 (5'-CGCAGGGGGCGTTTCTAGAC) to detect the 450-bp ST3Gal-III wild type

5 allele, and LE-110 and rlox (5'-CTCGAATTGATCCCCGGGTAC) to detect the 300-bp ST3Gal-III Δ allele.

Example 2: Measurement of metabolic and behavioral parameters

[0123] Protocols for the measurement of metabolic and behavioral parameters are

described in Angata, *et al.*, *J Biol Chem* 279:32603-13. Briefly, two separate cohorts of

10 4-month-old male mice were analyzed. The first consisted of equal numbers of wild-type and ST3Gal-III-deficient littermates. These were assessed in a behavioral test battery modified from that used by McIlwain, *et al.*, *Physiol Behav* (2001) 73:705-17, and described in Corbo, *et al.*, *J Neurosci* (2002) 22:7548-57. This included parameters such as metabolic performance, physical appearance, sensorimotor reflexes, motor activity, nociception,

15 acoustic startle, sensorimotor gating, and assessments of learning and memory. Concern that testing mice in such a large battery could influence behavior in any individual task and that multiple assessments increased the probability of a type I statistical error error, a second cohort of mice was also analyzed (wild-type, $n = 16$; Δ/Δ , $n = 15$). In the open field test, activity was measured in a 30-min test period in an area of 45×45 cm using a Digiscan

20 apparatus (Accuscan Electronics, Columbus, OH). Vertical activity (rearing) and distance (total and center) were recorded.

[0124] Passive avoidance analysis involved a two-compartment light/dark apparatus ($35 \times 18 \times 30$ cm, Coulbourn Instruments, Allentown, PA). Each mouse was placed in the lighted compartment. When the animal entered the dark compartment, a guillotine door closed

25 behind and a foot shock of 0.4 mA was delivered through the grid floor of the dark compartment for 3 s. If the mouse did not enter the dark compartment within 10 min, it was excluded from the retrieval test. In the retrieval trial performed 24 h later, the latency for the mice to enter the dark compartment was recorded. The maximum latency was 600 s.

[0125] Fear conditioning analyses used chambers ($26 \times 22 \times 18$ cm high) made of clear

30 Plexiglas placed in a 2×2 array (Med Associates). A video camera was used for recording and analysis (FreezeFrame, Actimetrics, St. Evanston, IL). The conditioned stimulus (CS) was an 85-db, 2,800-Hz, 20-s tone, and the unconditioned stimulus was a scrambled foot

shock at 0.75 mA presented during the last 3 s of the CS. Mice were placed in the test chamber for 3 min before recording CS and freezing behavior. Freezing was defined as the absence of movement other than breathing, and thresholds were selected via the software of high correlation with human observers. Three CS/unconditioned stimulus pairings were given with 1-min spacing, and freezing during the CS was also recorded. Each mouse was returned to the shock chamber 24 h later, and freezing responses were recorded for 3 min (context test). The chambers were modified to present a different environmental context (shape, odor, color changes), and 2 h later the mice were placed in this novel environment. Freezing behavior was recorded for 3 min before and during three CS presentations (cued conditioning). The time spent freezing was converted to a percent value.

[0126] The water maze task constituted a pretraining phase during which all mice from both cohorts were tested for 2 days in a straight-swim pretraining protocol. Mice received 16 trials (8 trials over 2 days) in a 31 × 60-cm rectangular tank that was located in a different room than the circular tank used in the hidden platform trials. The platform was located 1 cm below the water opposite from the start location. Latency to climb onto the platform was the dependent measure. Criteria for advancing to the hidden platform trials was completing 6 of 8 trials under 10 s on the 2nd day. This pretraining procedure provided experience with swimming and climbing onto a submerged platform without exposing the mice to the spatial cues used in the hidden platform trials. This procedure both screens for mice with severe motor deficits and reduces behavioral variability often seen on the 1st day of hidden platform testing. All mice successfully passed this pretraining phase. Hidden platform testing followed in which extra-maze visual cues were hung from a curtain located around a 1.26-m diameter circular tank. The water was made opaque with the addition of non-toxic paint. The 10-cm diameter escape platform was located 1 cm below the surface of the water, and a Polytrack video-tracking system (San Diego Instruments) was used to collect mouse movement data (location, distance, and latency) during training and probe trials. Each mouse was given eight trials a day, in two blocks of four trials for 4 consecutive days. After 36 trials, each animal was given a 60-s probe trial. During the probe test, the platform was removed, and quadrant search times were measured. Visual cue testing was performed 1 day after the last hidden platform training trial, wherein mice were trained to locate a visible cued platform. The visible cue was a gray plastic cube (9 cm) attached to a pole so that it was 10 cm above the platform. On each trial of the visible platform test, the platform was randomly

located in one of the four quadrants. Mice were given eight trials, in blocks of four trials, and the latency to find the platform was recorded for each trial.

[0127] Metabolic chambers termed CLAMS (Comprehensive Lab Animal Monitoring System; Columbus Instruments, Columbus, OH) automatically recorded metabolic

5 parameters including volume of carbon dioxide produced (VCO_2), volume of oxygen consumed (VO_2), respiration (respiratory exchange ratio) = VCO_2/VO_2 , and caloric (heat) value $((3.815 + 1.232 \times \text{respiratory exchange ratio}) \times VO_2)$, motion in all three axes in time, and consumption of food and water. Data were collected every 30 min over three 12-h dark cycles and two 12-h light cycles and analyzed as mean values over each 12-h period with the
10 exception of food and water intake which were added to the total during subsequent cycles.

[0128] Pulmonary function was scored by measurement of the uptake of CO. A carbon monoxide uptake monitor (Columbus Instruments) measured the CO level in a sealed chamber after exposing the mouse to a 60-s interval of air with 0.17% CO. The mean breath per min was also recorded. Each animal was tested once.

15 [0129] Blood pressure was determined by a noninvasive blood pressure tail-cuff system (Columbus Instruments) that measures systolic blood pressure in addition to heart rate and relative changes in diastolic and mean blood pressure. Individual mice were placed in a small cylinder chamber; occlusion and sensor cuffs were placed on the tail, and the tail was warmed to 37 °C. Mice were first acclimated to the restraining chamber, tail cuffs, and the heat fan for
20 30 min for 2 days prior to testing. The mean of four measurements on the 3rd day was reported and analyzed by the Student's t test.

Example 3: Detection of seizures

[0130] Electrocorticographic recordings. Silver wire electrodes (0.005 inch diameter) soldered to a microminiature connector were implanted bilaterally into the subdural space
25 over the frontal and parietal cortex of mice under anesthesia several days before recording. Simultaneous cortical activity and behavioral video/electrographic monitoring was performed using a digital electroencephalograph (Stellate Systems, Montreal, Canada) from ST3GalIII +/- and Δ/Δ mice moving freely in the test cage for prolonged periods, including sleep (Noebels, *et al.*, (1984) *Nature* 310:409–411). Seizure behavior was observed directly and
30 annotated on all recordings.

[0131] It is understood that the examples and embodiments described herein are for illustrative purposes only and that various modifications or changes in light thereof will be suggested to persons skilled in the art and are to be included within the spirit and purview of this application and scope of the appended claims. All publications, patents, and patent
5 applications cited herein are hereby incorporated by reference in their entirety for all purposes.

WHAT IS CLAIMED IS:

- 1 1. A method of detecting epilepsy in a mammal, the method comprising
2 detecting ST3Gal-III activity in a sample from the mammal.
- 1 2. The method of claim 1, wherein ST3Gal-III activity is detected by
2 detecting the increase in one or more Sia α 2-3Gal β 1-3/4GlcNAc moieties.
- 1 3. The method of claim 1, wherein ST3Gal-III activity is detected by
2 detecting the decrease in one or more Gal β 1-3/4GlcNAc moieties.
- 1 4. A method of detecting epilepsy in a mammal, the method comprising
2 detecting a carbohydrate structure in a sample from the mammal.
- 1 5. The method of claim 4, wherein the carbohydrate structure is one or
2 more Sia α 2-3Gal β 1-3/4GlcNAc moieties.
- 1 6. The method of claim 4, wherein the carbohydrate structure is one or
2 more Gal β 1-3/4GlcNAc moieties.
- 1 7. A method of identifying an increased risk for an epileptic condition,
2 the method comprising identifying a mutation in a *ST3Gal-III* gene, wherein the mutation
3 decreases the activity of the encoded ST3Gal-III polypeptide.
- 1 8. A method of treating an epileptic condition, the method comprising
2 administering to the mammal a therapeutically effective amount of an agent that increases
3 activity of ST3Gal-III in the mammal.
- 1 9. The method according to claim 8, wherein the agent that increases
2 activity of ST3Gal-III in the mammal is a ST3Gal-III polypeptide.
- 1 10. The method according to claim 8, wherein the agent that increases
2 activity of ST3Gal-III in the mammal is a nucleic acid encoding ST3Gal-III.
- 1 11. The method according to claim 8, wherein the agent that increases
2 activity of ST3Gal-III increases the level of ST3Gal-III protein expression.
- 1 12. The method according to claim 8, wherein the agent that increases
2 activity of ST3Gal-III increases the level of ST3Gal-III mRNA expression.

- 1 13. A method of increasing the levels of one or more Sia α 2-3Gal β 1-
2 3/4GlcNAc moieties in a central nervous system (CNS) cell, the method comprising,
3 introducing into a CNS cell an expression vector comprising a nucleic acid
4 that encodes a ST3Gal-III polypeptide or enzymatically active fragment thereof.
- 1 14. The method of claim 13, wherein the expression vector is introduced in
2 the CNS cell *in vitro*.
- 1 15. The method of claim 13, wherein the expression vector is introduced in
2 the CNS cell *in vivo*.
- 1 16. A method of identifying an agent for the treatment of an epileptic
2 condition in an individual, the method comprising identifying a candidate agent that increases
3 the activity of ST3Gal-III.
- 1 17. The method of claim 16, wherein the step of identifying the agent
2 comprises contacting the candidate agent with a ST3Gal-III polypeptide or enzymatically
3 active fragment thereof.
- 1 18. The method of claim 16, wherein the candidate agent increases the
2 amount of a Sia α 2-3Gal β 1-3/4GlcNAc in a CNS cell.

ST3Gal-III Activity

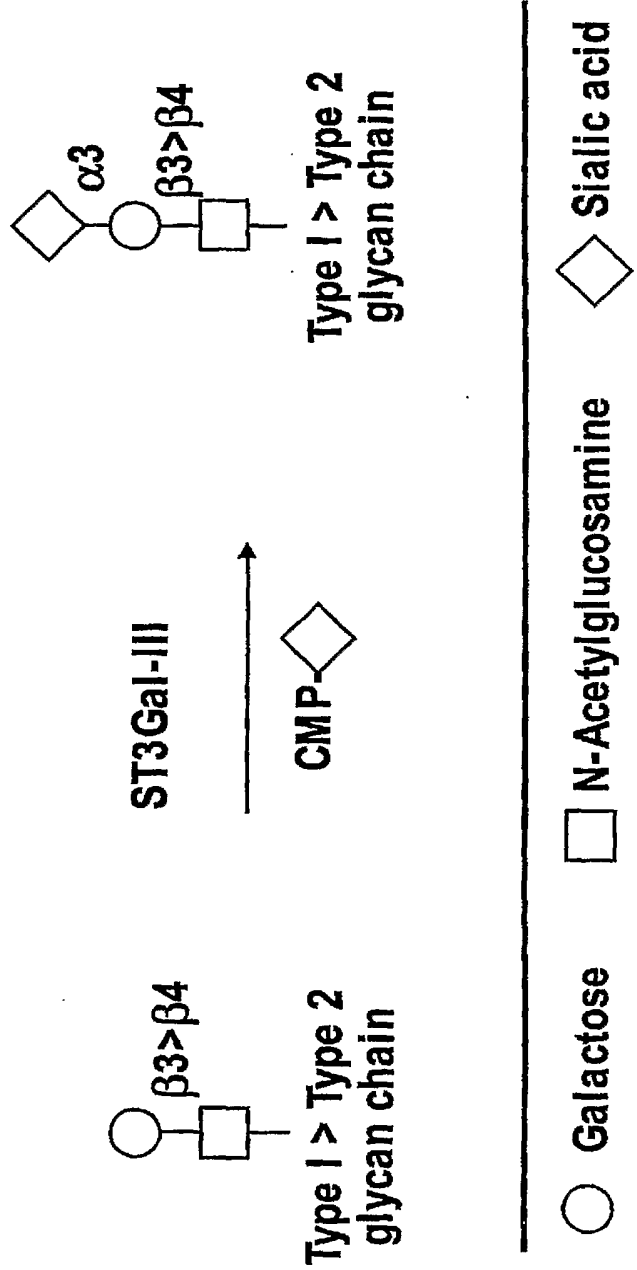


FIG. 1

ST3Gal-III Deficiency Alters Locomotor Activity
and the Contextual Fear Response

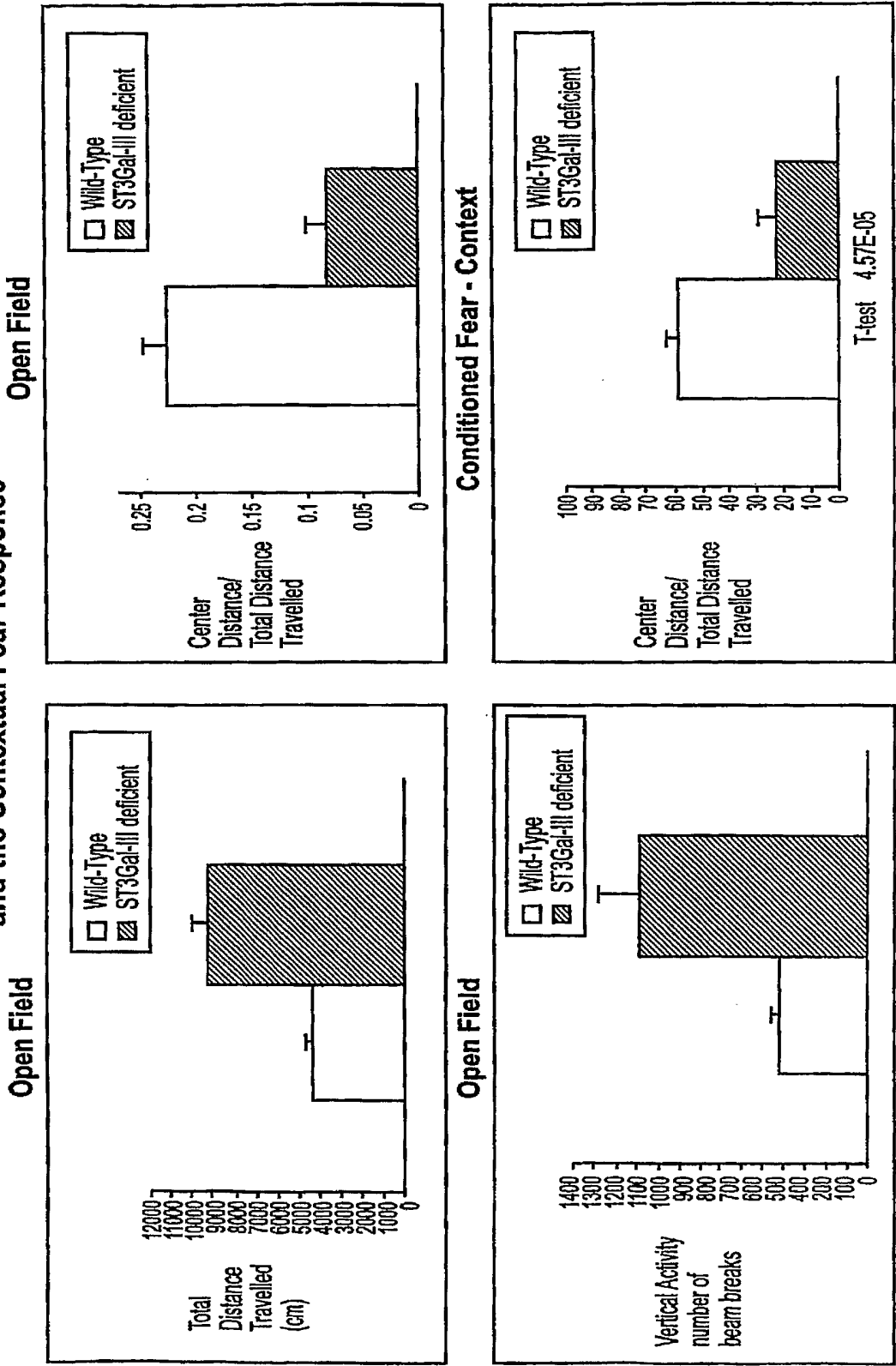


FIG. 2

Impairments in Muscular Strength and Coordination
Among ST3Gal-III Deficient Mice

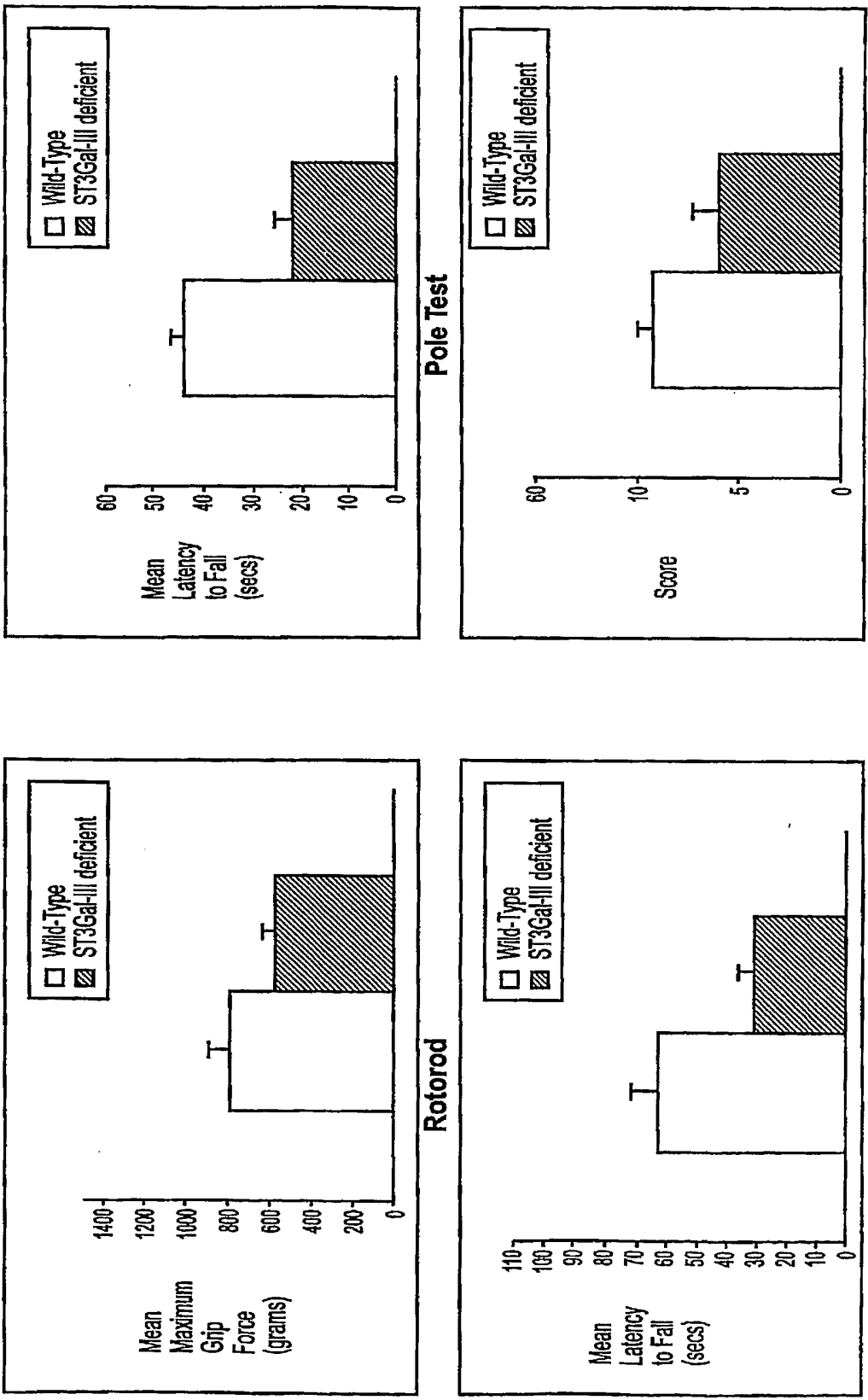


FIG. 3

Increased Metabolism in ST3Gal-III Deficient Mice

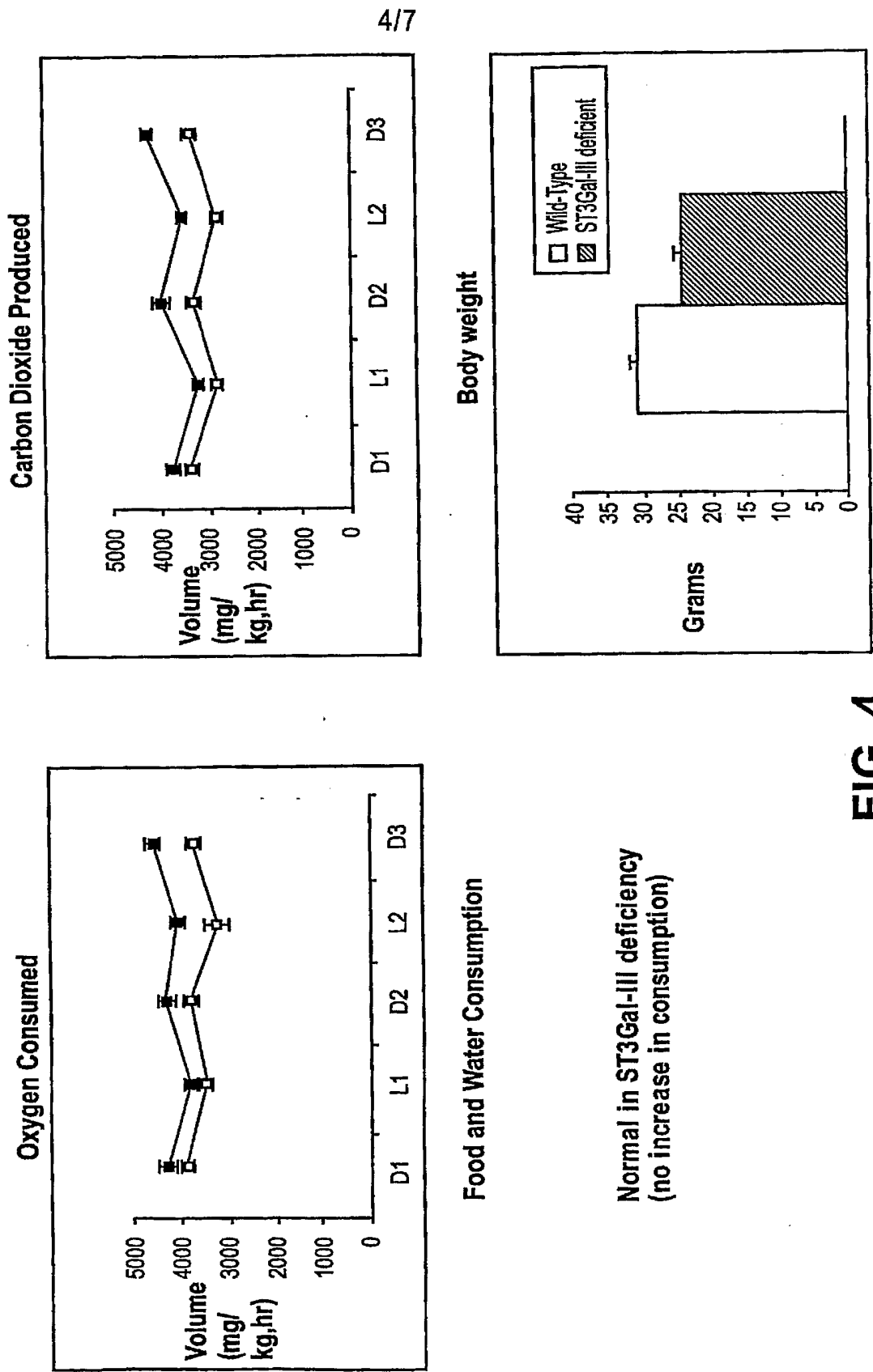
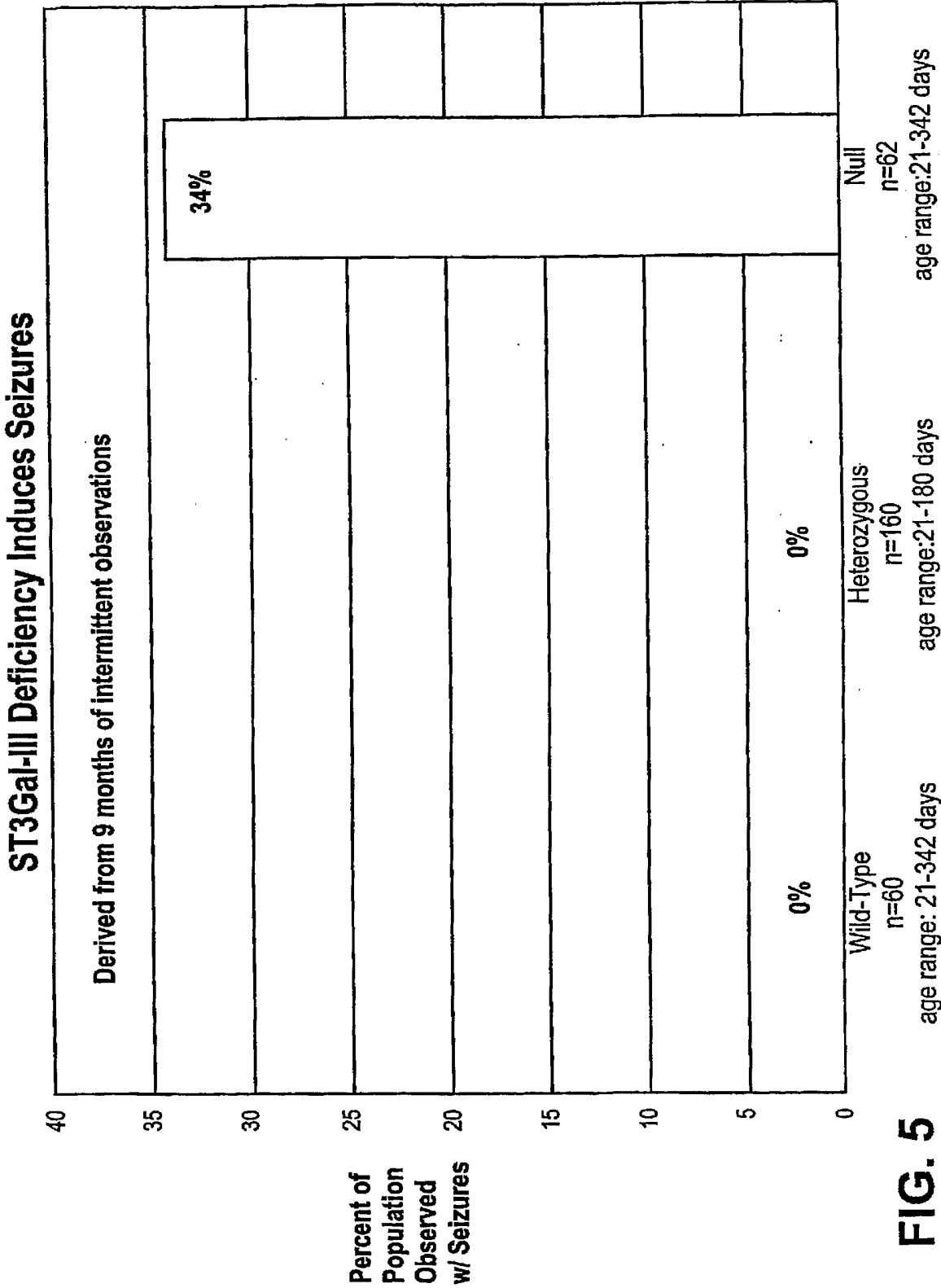


FIG. 4



Early Adult Age of Seizure Onset

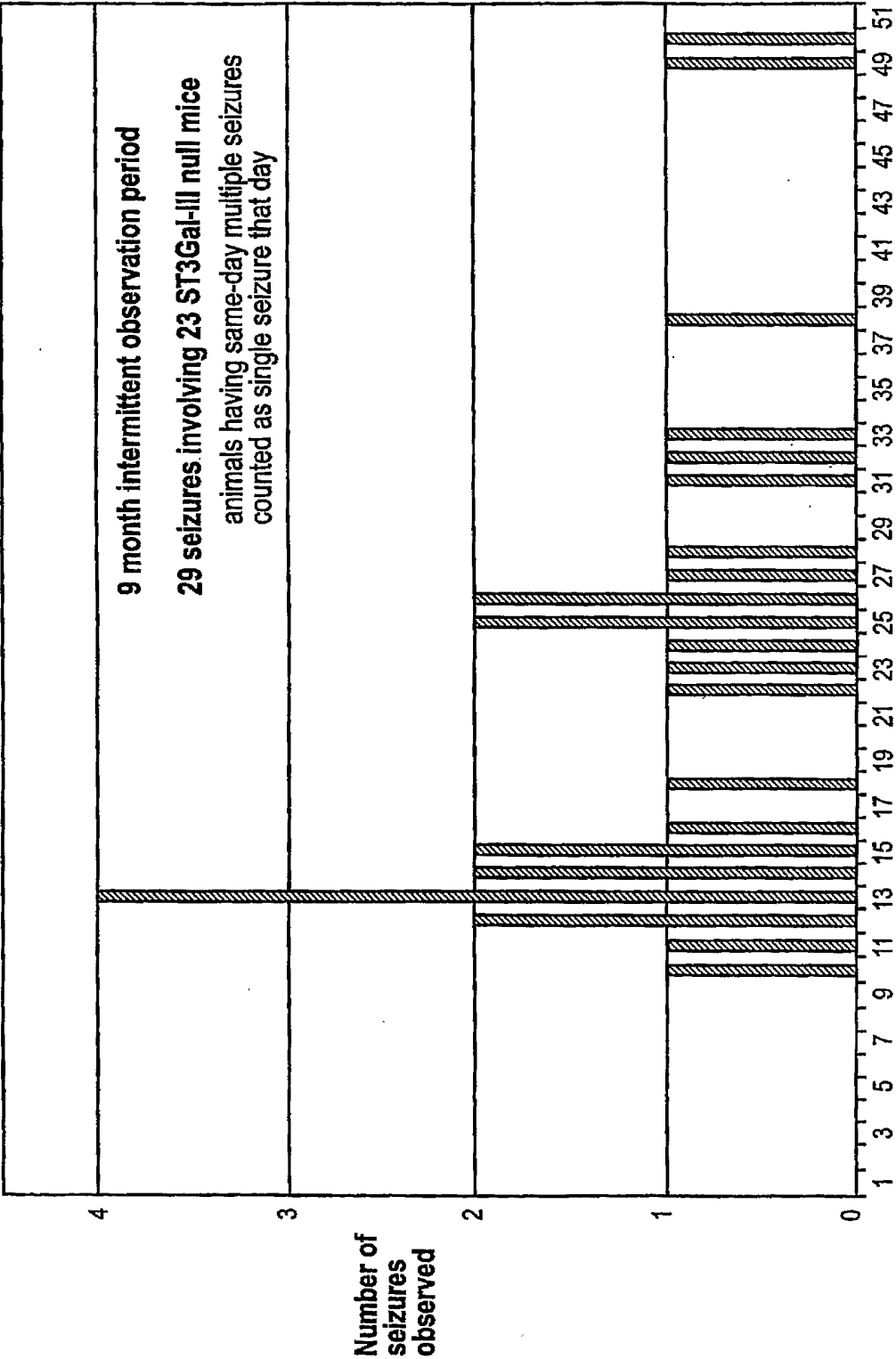


FIG. 6

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Non-Lethal Spontaneous Epileptic Seizure Appearance

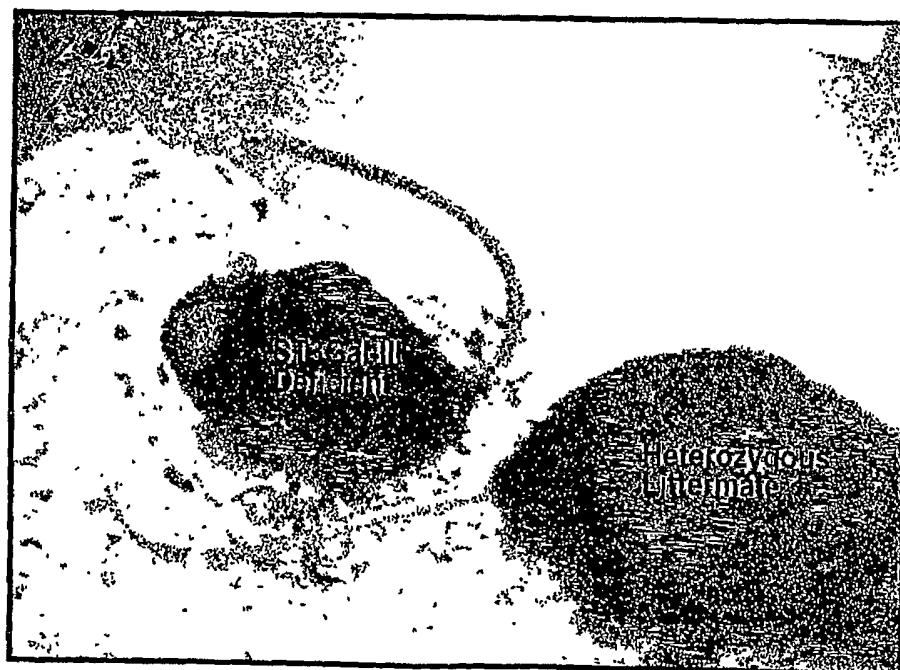


FIG. 7

SEQUENCE LISTING

SEQ ID NO:1 Human ST3Gal-III cDNA sequence (accession number NM_174963)

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1561 agccagcacc acctacacag gagtcttcag acccagagaa ggacgggtgc aagggcccca
1621 ggggcagcaa ggcttgggtg gaggagccag agctgtgcct gctcagcagc cagtctcaga
1681 gaccagcact cagcctcatt cagcatgggt ccttgatgcc agagggccag caggctcctg
1741 gctgtgcccc gcaggcccag catgcagggt gtgggacact gggcagcaag gctgctgccg
1801 gaatcacttc tccaatcagt gtttgggtga ttatcatttt gtgaattttg gtagggggga
1861 gggtagggat aattttattt taaataaggt tggagatgtc aagtggggtt cacttgccat
1921 gcaggaagag gccactaga gggcccatca ggcagtgtta cctgttagct cctgtgggg
1981 caggagtgcc aggaccagcc tgtaccttgc tgtggggcta caggatgggt ggaggatct
2041 caagccagcc cctccagct catgacactg tttggccttt cttggggaga aggcggggta
2101 ttcccactca ccagccctag ctgtcccatg gggaaaccct ggagccatcc cttcgagcc
2161 aacaagaocg cccagggtct atagcagaaa gaactttaaa gctcaggagg gtgacgcca
2221 gctccgcctg ctgggaagag ctcccctcca cagctgcagc tgatccatag gactaccgca
2281 ggcccggaact caccacttg ccacatgttc taggtttcag caacaagact gccagggtgt
2341 tgggttctgc ctttagcctg gaccaaaggg aagtgaggcc caaggagctt acccaagctg
2401 tggcagccgt cccaggccac ccccatggaa gcaataaagc tcttcctga aaaaaaaaaa
2461 aaaaaaaaaa aaaaaaaaaa

```

SEQ ID NO:2 Human ST3Gal-III amino sequence (accession number NP_777623.1)

```

MGLLVFVRNLLLALCLFLVLGFLYSAWKLHLLQWEEDSSKYS
SSSPQEKPVADSVVLSFDSAGQTLGSEYDRLGFLNLDKLS
SPGEPKKLIMPASHPLEILKSLSEDAAFALGFLKLPRPAELATKYANFSEGACKPGYA
SALMTAIFPRFSKPAPMFLDDSFRRKWARIREFVPPFGIKQDNLIKAILSVTKEYRLT
PALDSLRCRRCIIVGNGGVLANKSLGSRIDDYDIVRLNSAPVKGFEKDVGSKTTLRI
TYPEGAMQRPEQYERDSLFLVLAGFKWQDFKWLKYIVYKERSASDGFWKSVATRPKE
PPEIRILNPYFIQEAFTLIGLPFNNGLMGRGNIPTLGSVAVTMALHGCDEVAVAGFG
YDMSTPNAPLHYETVRMAAIKESWTHNIQREKEFLRKLVKARVITDLSSGI

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SEQ ID NO:3 Human ST3Gal-III cDNA sequence (accession number NM_174964)

```

1 actatggcgg cgcccatgca gcccagcgcg ttgtgggctc ccgccgggggt ccccgcgggc
61 tgtcgccgcc gcctacgcgc ctgcctccgc cttcctgccc cgcgtcgggc cgggcgccac
121 ctcccccttg cctccctctc cgctgtggtc atttaggaaa tcgtaaataca tgtgaagatg
181 ggactcttgg tatttgtgcg caatctgctg ctagecctct gcctctttct ggtactggga
241 tttttgtatt attctgcgtg gaagctacac ttactccagt gggaggagga ctccagtaag
301 tatagtcact ctagctcacc ccaggagaag cctgttgcaag attcagtggt tctttccttt
361 gactccgctg gacaaacact aggctcagag tatgatcggg tgggcttcct cctgaatctg
421 gactctaaac tgcttctga attagccacc aagtacgcaa acttttcaga gggagcttgc
481 aagcctgggt atgcttcagc cttgatgacg gccatcttcc cccggttctc caagccagca
541 cccatgttcc tggatgactc ctttcgcaag tgggctagaa tccgggagtt cgtgccgcct
601 tttgggatca aaggtcaaga caatctgac aaagccatct tgtcagtcac caaagagtac
661 cgctgaccc ctgccttgga cagcctccgc tgccgcgcgt gcatcatcgt gggcaatgga
721 ggcgcttctg ccaacaagtc tctgggggtc cgaattgacg actatgacat tgtggtgaga
781 ctgaattcag caccagtgaaggctttgag aaggacgtgg gcagcaaaac gacactgcgc
841 atcacctacc ccgagggcgc catgcagcgg cctgagcagt acgagcgca ttctctcttt
901 gtccctcgcc gcttcaagtg gcaggacttt aagtgggtga aatacatcgt ctacaaggag
961 agagtgagtg catcggtagg cttctggaaa tctgtggcca ctgagtgcc caaggagccc
1021 cctgagattc gaatcctcaa cccatatttc atccaggagg ccgccttcac cctcattggc
1081 ctgcccttca acaatggcct catgggcccgc ggggaacatcc ctacccttgg cagtgtggca
1141 gtgaccatgg cactacacgg ctgtgacgag gtggcagtcg caggatttgg ctatgacatg
1201 agcacaccca acgcacccct gcaactactat gagaccgttc gcatggcagc catcaaagag
1261 tcctggacgc acaatatcca gcgagagaaa gagtttctgc ggaagctcgc gaaagctcgc
1321 gtcactactg atctaagcag tggcatctga gtgggcccag cacatggcca tagaggcca
1381 ggcaccacca ggagcagcag ccagcaccac ctacacagga gtcttcagac ccagagaagg
1441 acggtgcaa gggccccagg ggcagcaagg ccttgggtga gcagccagag ctgtgcctgc
1501 tcagcagcca gtctcagaga ccagcactca gcctcattca gcatgggtcc ttgatgccag
1561 agggccagca ggctcctggc tgtgcccagc agggccagca tgcaggtggt gggacactgg
1621 gcagcaaggc tgctgcggga atcaactctc caatcagtggt ttggtgtatt atcattttgt
1681 gaatttgggt aggggggagg gtagggataa tttattttta aataagggtg gagatgtcaa
1741 gttgggttca cttgccatgc aggaagaggc ccactagagg gcccatcagg cagtgttacc
1801 tgttagctcc ctgtggggca ggagtgcag gaccagcctg taccttgctg tggggctaca
1861 ggatggtggg caggatctca agccagcccc ctccagctca tgacactgtt tggcctttct
1921 tggggagaag gcggggtatt cccactcacc agccctagct gtcccatggg gaaaccctgg
1981 agccatccct tcggagccaa caagacccgc ccagggttat agcagaaaga actttaagc
2041 tcaggagggt gacgcccagc tccgcctgct ggggaagagc cccctccaca gctgcagctg
2101 atccatagga ctaccgcagg cccggactca ccaacttgcc acatgttcta ggtttcagca
2161 acaagactgc caggtggttg ggttctgcct ttagcctgga ccaaagggaa gtgaggcca
2221 aggagcttac ccaagctgtg gcagccgtcc caggccacc ccattggaagc aataaagctc
2281 ttccctgaaa aaaaaaaaaa aaaaaaaaaa aaaaaa

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SEQ ID NO:4 Human ST3Gal-III amino sequence (accession number NP_777624.1)

```

MGLLVFVRNLLLALCLFLVLGFLYSAWKLHLLQWEEDSSKYSH
SSSPQEKPVADSVVLSFDSAGQTLGSEYDRLGFLNLD SKLPAELATKYANFSEGACK
PGYASALMTAIFPRFSKPAPMFLDDSF RKWARIREFVPPFGIKQDNLIKAILSVTKE
YRLTPALDSLRCRCIIVGNGGVLANKSLGSRIDYDIVVRLNSAPVKGF EKDVGSKT
TLRITYPEGAMQRPEQYERDSLFLAGFKWQDFKWLKYIVYKERSASDGF WKSVATR
VPKEPPEIRILNPYFIQEAFTLIGLPFNNGLMGRGNIP TLGSVAVTMALHGCDEVAV
AGFGYDMSTPNAPLHYETVRMAAIKESWTHNIQREKEFLRKL VKARVITDLSSGI

```

SEQ ID NO:5 Human ST3Gal-III cDNA sequence (accession number NM_174965)

```

1 actatggcgg cgcccatgca gcccagcgcg ttgtgggctc ccgccgggggt ccccgcgggc
61 tgtcgccgcc gcctacgcgc ctgcctccgc cttcctgccc cgcgtcgggc cgggcgccac
121 ctcccccttg cctccctctc cgctgtggtc atttaggaaa tcgtaaataca tgtgaagatg
181 ggactcttgg tatttgtgcg caatctgctg ctagecctct gcctctttct ggtactggga
241 tttttgtatt attctgcgtg gaagctacac ttactccagt gggaggagga ctccagtaag

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301 tatagtcaact ctagctcacc ccaggagaag cctgttgagc attcagtggg tcttttcttt
361 gactccgctg gacaaacact aggctcagag tatgatcggg tgggcttcct cctgaatctg
421 gactcctaac tgccctgctga attagccacc aagtacgcaa acttttcaga gggagcttgc
481 aagcctgggt atgcttcagc cttgatgacg gccatcttcc cccggttctc caagccagca
541 cccatgttcc tggatgactc ctttcgcaag tgggctagaa tccgggaggt cgtgccgcct
601 tttgggatca aaggtcaagt cctggacgca caatatccag cgagagaaaag agtttctgcg
661 gaagctgggt aaagctcgcg tcatcactga tctaagcagt ggcactctgag tgggcccagc
721 acatggccat agaggcccag gcaccaccag gagcagcagc cagcaccacc tacacaggag
781 tcttcagacc cagagaagga cggtgccaag ggcccaggg gcagcaaggc cttggtggag
841 cagccagagc tgtgcctgct cagcagccag tctcagagac cagcactcag cctcattcag
901 catgggtcct tgatgccaga gggccagcag gctcctgggt gtgccagca gcccagcat
961 gcaggtgggt ggacactggg cagcaaggct gctgccgaa tcacttctcc aatcagtgtt
1021 tgggtgtatta tcattttgtg aatttgggtg ggggggaggg tagggataat ttatttttaa
1081 ataaggttgg agatgtcaag ttgggttcac ttgccatgca ggaagaggcc cactagaggg
1141 cccatcaggc agtgttacct gttagctccc tgtggggcag gagtgccagg accagcctgt
1201 accttgctgt ggggctacag gatgggtggc aggatctcaa gccagcccc tccagctcat
1261 gacactgttt ggcctttctt ggggagaagg cgggtattc ccactacca gccctagctg
1321 tcccatgggg aaaccctgga gccatccctt cggagccaac aagaccgcc cagggtata
1381 gcagaaagaa ctttaaagct caggaggtg acgccagct ccgctgctg ggaagagctc
1441 cctccacag ctgcagctga tccataggac taccgcaggc ccggactcac caacttgcca
1501 catgttctag gtttcagcaa caagactgcc aggtggttgg gttctgcctt tagcctggac
1561 caaaggggaa tgaggccaa ggagcttacc caagctgtgg cagccgtccc aggccacccc
1621 catggaagca ataaagctct tccctgaaaa aaaaaaaaaa aaaaaaaaaa aaaaa

```

SEQ ID NO:6 Human ST3Gal-III amino sequence (accession number NP_777625.1)

MGLLVFVRNLLLALCLFLVLGFLYSAWKHLHLQWEEDSSKYSH
SSSPQEKPVADSVVLSFDSAGQTLGSEYDRLGFLNLD SKLPAELATKYANFSEGACK
PGYASALMTAIFPRFSKPAPMFLDDSRKWARIREFVPPFGIKQVLD AQYPARERVS
AEAGESSRHH

SEQ ID NO:7 Human ST3Gal-III cDNA sequence (accession number NM_174966)

```

1 actatggcgg cgcccatgca gccagcgcg ttgtgggctc ccgcgggggt ccccgcgccg
61 tgcgcgccgc gcctacgcgc ctgcctccgc ctctctgccc cgcgtcgggc cgggcgccac
121 cccccccctg cctccctctc cgtgtgggtc atttaggaaa tcgtaaatca tgtgaagatg
181 ggactcttgg tatttgtgcg caatctgctg ctagccctct gcctctttct ggtactggga
241 tttttgtatt attctgcgtg gaagctacac ttactccagt gggaggagga ctccaattca
301 gtgggtcttt cctttgactc cgtggacaa acactaggct cagagtatga tcggttgggc
361 ttctctctga atctggactc taaactgcct gctgaattag ccaccaagta cgcaaatctt
421 tcagagggag cttgcaagcc tggctatgct tcagccttga tgacggccat cttcccccg
481 ttctccaagc cagcaccat gttcctggat gactccttcc gcaagtgggc tagaatccgg
541 gagttcgtgc cgccttttgg gatcaaaggc caagacaatc tgatcaaagc catcttgtca
601 gtcaccaaag agtaccgcct gaccctgccc ttggacagcc tccgctgccg ccgctgcac
661 atcgtgggca atggaggcgt tcttgccaac aagtctctgg ggtcacgaat tgacgactat
721 gacattgtgg tgagactgaa ttacgacca gtgaaaggct ttgagaagga cgtgggcagc
781 aaaacgacac tgcccatcac ctaccccgag ggcgccatgc agcggcctga gcagtacgag
841 cgcgattctc tctttgtcct cgcgggttcc aagtggcagg actttaagtg gttgaaatac
901 atcgtctaca aggagagagt gtcttgagc cacaatatcc agcgagagaa agagtctctg
961 cggaagctgg tgaaagctcg cgtcatcact gatctaagca gtggcatctg agtgggccc
1021 gcacatggcc atagaggccc aggcaccacc aggcagcagc gccagacca cctacacagg
1081 agtcttcaga ccagagaag gacggtgcca agggcccag ggcagcaag gccttgggtg
1141 agcagccaga gctgtgcctg ctacgacgc agtctcagag accagcactc agcctcattc
1201 agcatgggtc cttgatgcca gaggccagc aggtcctgg ctgtgcccag caggcccagc
1261 atgcaggtgg tgggacactg ggcagcaagg ctgctgccg aatcacttct ccaatcagt
1321 tttggtgtat tatcattttg tgaatttggg taggggggag ggtagggata atttattttt
1381 aaataagggt ggagatgtca agttgggttc acttgccatg caggagagg cccactagag
1441 ggcccatcag gcagtgttac ctgttagctc cctgtggggc aggagtgccg ggaccagcct
1501 gtaccttgct gtggggctac aggatgggtg gcaggatctc aagccagccc cctccagctc
1561 atgacactgt ttggcctttc ttggggagaa ggcgggggat tccactcac cagccctagc

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1621 tgtcccatgg ggaaacctg gagccatccc ttcggagcca acaagaccgc cccagggcta
1681 tagcagaaag aacttttaaag ctcaggaggg tgacgcccag ctccgcctgc tgggaagagc
1741 tccccctccac agctgcagct gatccatagg actaccgcag gcccggaact accaacttgc
1801 cacatgttct aggtttcagc aacaagactg ccaggtgggt gggttctgcc tttagcctgg
1861 accaaaggga agtgaggccc aaggagctta cccaagctgt ggcagccgtc ccaggccacc
1921 cccatggaag caataaagct cttccctgaa aaaaaaaaaa aaaaaaaaaa aaaaaaaa

```

SEQ ID NO:8 Human ST3Gal-III amino sequence (accession number NP_777626.1)

MGLLVFVRNLLLALCLFLVLGFLYSAWKLHLLQWEEDSNSVVL
SFDSAGQTLGSEYDRLGFLNLDSKLPaelATKYANFSEGACKPGYASALMTAIFPRF
SKPAPMFLDDSFRRKWARIREFVPPFGIKGQDNLKAILSVTKEYRLTPALDSLRCRR
IIVGNGGVLANKSLGSRIDDYDIVVRLNSAPVKGFEKDVGSKTTLRITYPEGAMQRPE
QYERDSLFLVLAGFKWQDFKWLKYIVYKERVSWTHNIQREKEFLRKLVKARVITDLSSGI

SEQ ID NO:9 Human ST3Gal-III cDNA sequence (accession number NM_174967)

```

1 actatggcgg cgcccatgca gccagcgcg ttgtgggctc ccgcccgggt cccccgggc
61 tgcgcgcgcc gcctacgccg ctgcctccgc ctctctgccc cgcgtcgggc cgggcgccac
121 ctccccctg cctccctctc cgctgtgggtc atttaggaaa tcgtaaatca tgtgaagatg
181 ggactcttgg tatttgtgcg caatctgctg ctagccctct gcctctttct ggtactggga
241 tttttgtatt attctgcgtg gaagctacac ttactccagt gggaggagga ctccaattca
301 gtggttcttt cctttgactc cgctggacaa acactaggct cagagtatga tcggttgggc
361 ttcctcctga atctggactc taaactgcct gctgaattag ccaccaagta cgaaacttt
421 tcagaggag cttgcaagcc tggctatgct tcagccttga tgacggccat cttccccgg
481 ttctccaagc cagcaccat gtctctggat gaactcttgc gcaagtgggc tagaatccgg
541 gagttcgtgc cgcttttgg gatcaaagg caagtcttgc acgcacaata tccagcgaga
601 gaaagagttt ctgcggaagc tggtgaaagc tcgcgtcatc actgatctaa gcagtggcat
661 ctgagtgggc ccagcacatg gccatagagg cccaggcacc accaggagca gcagccagca
721 ccacctacac aggagtcttc agaccagag aaggacggtg ccaagggccc caggggcagc
781 aaggccttgg tggagcagcc agagctgtgc ctgctcagca gccagtctca gagaccagca
841 ctgagcctca ttcagcatgg gtcttctgat ccagagggcc agcaggctcc tggctgtgcc
901 cagcaggccc agcatgcagg tgggtgggaca ctgggcagca aggctgctgc cggaatcact
961 tctccaatca gtgtttggtg tattatcatt ttgtgaattt gggtaggggg gagggtaggg
1021 ataatttatt tttaaataag gttggagatg tcaagttggg ttactttgcc atgcaggaag
1081 agggccacta gagggcccat caggcagtggt tacctgttag ctccctgttg ggcaggagtg
1141 ccaggaccag cctgtacctt gctgtggggc tacaggatgg tgggcaggat ctcaagccag
1201 cccctccag ctcatgacac tgtttggcct ttcttgggga gaaggcgggg tattccact
1261 caccagccct agctgtccca tggggaaacc ctggagccat cccttcggag ccaacaagac
1321 cgccccagg. ctatagcaga aagaacttta aagctcagga gggtagcgc cagctccgcc
1381 tgctgggaag agctcccctc cacagctgca gctgatccat aggactaccg caggcccgga
1441 ctcaccaact tgccacatgt tctaggtttc agcaacaaga ctgccaggtg gttgggttct
1501 gccttttagc tggaccaaag ggaagtgagg cccaaggagc ttaccaagc tgtggcagcc
1561 gtcccaggcc acccccatgg aagcaataaa gctcttcctt gaaaaaaaaa aaaaaaaaaa
1621 aaaaaaaaaa

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SEQ ID NO:10 Human ST3Gal-III amino sequence (accession number NP_777627.1)

MGLLVFVRNLLLALCLFLVLGFLYSAWKLHLLQWEEDSNSVVL
SFDSAGQTLGSEYDRLGFLNLDSKLPaelATKYANFSEGACKPGYASALMTAIFPRF
SKPAPMFLDDSFRRKWARIREFVPPFGIKGQVLDQYPARERVSaeAGESSRHH

SEQ ID NO:11 Human ST3Gal-III cDNA sequence (accession number NM_174968)

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1 actatggcgg cgcccatgca gccagcgcg ttgtgggctc ccgcccgggt cccccgggc
61 tgcgcgcgcc gcctacgccg ctgcctccgc ctctctgccc cgcgtcgggc cgggcgccac
121 ctccccctg cctccctctc cgctgtgggtc atttaggaaa tcgtaaatca tgtgaagatg
181 ggactcttgg tatttgtgcg caatctgctg ctagccctct gcctctttct ggtactggga

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241 tttttgtatt attctgcgtg gaagctacac ttactccagt gggaggagga ctccaattca
301 gtggttcttt cctttgactc cgctggacaa acactaggct cagagtatga tcggttgggc
361 ttccctcctga atctggactc taaactctca ccgaggactc tctgcacggt ggtttttggc
421 cttgactgca tattggaatc acctggagag cctaaaaaat tactgatgcc tgcacccac
481 cctctagaga ttttgaagtc actgagcgag gacgcagcct ttgcattagg atttttaaag
541 ctgcccaggc ctgctgaatt agccaccaag tacgcaaact tttcagaggg agcttgcaag
601 cctggctatg cttcagcctt gatgacggcc atcttccccc ggttctccaa gccagcacc
661 atgttctctg atgactcctt tcgcaagtgg gctagaatcc gggagtctgt gccgcctttt
721 gggatcaaaag gtcaagacaa tctgatcaaa gccatcttgt cagtcaccaa agagtaccgc
781 ctgacccttg ccttggacag cctccgctgc cgccgctgca tcatcgtggg caatggaggc
841 gttcttgcca acaagtctct ggggtcacga attgacgact atgacattgt ggtgagactg
901 aattcagcac cagtgaagg ctttgagaag gacgtgggca gcaaaacgac actgcgcatc
961 acctaccccg agggcgccat gcagcggcct gagcagtagc agcgcgattc tctctttgtc
1021 ctgcgcggct tcaagtggca ggactttaag tgggtgaaat acatcgtcta caaggagaga
1081 gtgagtgcac cggatggctt ctggaaatct gtggccactc gagtgcccaa ggagccccct
1141 gagattcgaa tcctcaaccc atatttcac caggaggccg ccttcaccct cattggcctg
1201 cccttcaaca atggcctcat gggccggggg aacatcccta cccttggcag tgtggcagtg
1261 accatggcac tacacggctg tgacgagggt gcagtcgcag gatttggcta tgacatgagc
1321 acaccaacg caccctgca ctactatgag accgttcgca tggcagccat caaagagctc
1381 tggacgcaca atatccagcg agagaaagag tttctgcgga agctggtaga agctcgcgtc
1441 atcactgata taagcagtgg catctgagtg ggcccagcac atggccatag aggccaggc
1501 accaccagga gcagcagcca gccacccta cacaggagt ttcagacca gagaaggacg
1561 gtgccaaagg ccccaggggc agcaaggcct tgggtggagc gccagagctg tgccctgtca
1621 gcagccagtc tcagagacca gcactcagcc tcattcagca tgggtccttg atgccagagg
1681 gccagcaggc tcctggctgt gccagcagg cccagcatgc aggtggtggg aactgggca
1741 gcaaggctgc tgccggaatc acttctccaa tcagtgtttg gtgtattatc attttgtgaa
1801 tttgggtagg ggggagggtg gggataatth atttttaaat aagggtggag atgtcaagtt
1861 gggttcactt gccatgcagg aagaggccca ctagaggggc catcaggcag tgttacctgt
1921 tagctccctg tggggcagga gtgccaggac cagcctgtac cttgctgtgg ggctacagga
1981 tgggtgggag gatctcaagc cagccccctc cagctcatga cactgttttg ctttctttgg
2041 ggagaaggcg gggatattccc actcaccagc cctagctgtc ccatggggaa accctggagc
2101 catcccttcg gagccaacaa gaccgcccc gggctatagc agaaagaact ttaaagctca
2161 ggagggtgac gccagctcc gctgctggg aagagctccc ctcacagct gcagctgatc
2221 cataggacta ccgcaggccc ggactcacca acttgccaca tgttctaggt ttcagcaaca
2281 agactgccag gtggttgggt tctgccttta gcctggacca aagggaagtg aggcccaagg
2341 agcttaccac agctgtggca gccgtcccag gccaccccca tggaagcaat aaagctcttc
2401 cctgaaaaaa aaaaaaaaaa aaaaaaaaaa aaa

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SEQ ID NO:12 Human ST3Gal-III amino sequence (accession number NP_777628.1)

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MGLLVFVRNLLLALCLFLVLGFLYYSAWKLHLLQWEEDSNSVVL
SFDSAGQTLGSEYDRLGFLNLD SKLSPRTLCTVVFGLDCILESPGEPK KLLMPASHP
LEILKSLSEDAAFALGFLKLPRPAELATKYANFSEGACKPGYASALMTAIFPRFSKPA
PMFLDDSFWRKWARIREFVPPFGIKGQDNLIKAILSVTKEYRLTPALDSLRCRRCIIVG
NGGVLANKSLGSRIDDYDIVVRLNSAPVKGF EKDVGSKTTLRITYPEGAMQRPEQYER
DSLFVLAGFKWQDFKWLKYIVYKERSASDGF WKSVATRVKPEPPEIRILNPYFIQEA
AFTLIGLPFNNGLMGRGNIPTLGSAVVTMALHGCDEVAVAGFGYDMSTPNAPLHYET
VRMAAIKESWTHNIQREKEFLRKLVKARVITDLSSGI

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SEQ ID NO:13 Human ST3Gal-III cDNA sequence (accession number NM_174969)

```

1 actatggcgg cgcccatgca gccagcgcg ttgtgggctc ccgcgggggt ccccgcggc
61 tgtcgccgcc gcctacgccg ctgcctccgc cttcctgccc cgcgtcgggc cgggcgccac
121 ctcccccttg cctccctctc cgctgtggtc atttaggaaa tcgtaaataca tgtgaagatg
181 ggactcttgg tatttgtgcg caatctgctg ctagccctct gcctctttct ggtactggga
241 tttttgtatt attctgcgtg gaagctacac ttactccagt gggaggagga ctccaagtat
301 gatcggttgg gcttctcctt gaatctggac tctaaactgc ctgctgaatt agccaccaag
361 tacgcaaact tttcagaggg agcttgcaag cctggctatg cttcagcctt gatgacggcc
421 atcttccccc ggttctccaa gccagcacc atgttctctg atgactcctt tcgcaagtgg
481 gctagaatcc gggagtctgt gccgcctttt gggatcaaaag gtcaagacaa tctgatcaaa

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541 gccatcttgt cagtcaccaa agagtaccgc ctgaccctg ccttggacag cctccgctgc
601 cgccgctgca tcatcgtagg caatggaggc gttcttgcca acaagtctct ggggtcacga
661 attgacgact atgacattgt ggtgagactg aattcagcac cagtgaagag ctttgagaag
721 gacgtgggca gcaaaacgac actgcgcata acctaccccg agggcgccat gcagcggcct
781 gagcagtacg agcgcgattc tctctttgtc ctgcgggct tcaagtggca ggactttaag
841 tggttgaaat acatcgctca caaggagaga gtgagtgcac cggatggctt ctggaaatct
901 gtggccactc gagtgcccaa ggagccccc gagattcgaa tcctcaacct atatttcac
961 caggaggccg ccttcaccct cattggcctg cccttcaaca atggcctcat gggccggggg
1021 aacatcccta cccttggcag tgtggcagtg accatggcac tacacggctg tgacgaggtg
1081 gcagtcgcag gatttggcta tgacatgagc acaccaacg caccctgca ctactatgag
1141 accgttcgca tggcagccat caaagagtcc tggacgcaca atatccagcg agagaaagag
1201 tttctgcgga agctggtgaa agctgcgctc atcactgac taagcagtgg catctgagt
1261 ggcccagcac atggccatag agggccaggc accaccagga gcagcagcca gcaccaccta
1321 cacaggagtc ttcagacca gagaaggacg gtgccaaggg ccccgagggc agcaaggcct
1381 tggtaggagca gccagagctg tgcctgctca gcagccagtc tcagagacca gcactcagcc
1441 tcattcagca tgggtccttg atgccagagg gccagcaggc tcctggctgt gcccagcagg
1501 cccagcatgc aggtggtggg acactgggca gcaaggctgc tgccggaatc acttctccaa
1561 tcagtgtttg gtgtattatc attttgtgaa tttgggtagg ggggagggtg gggataattt
1621 atttttaaat aaggttggag atgtcaagtt gggttcactt gccatgcagg aagaggccca
1681 ctagagggcc catcaggcag tgttacctgt tagctccctg tggggcagga gtgccagctc
1741 cagcctgtac cttgctgtgg ggctacagga tggtagggc gatctcaagc cagccccctc
1801 cagctcatga cactgtttgg cctttcttgg ggagaaggcg gggattccc actcaccagc
1861 cctagctgtc ccatggggaa accctggagc catcccttcg gagccaacaa gaccgcccc
1921 gggctatagc agaaagaact ttaaagctca ggagggtgac gccagctcc gcctgctggg
1981 aagagctccc ctccacagct gcagctgac cataggacta ccgcaggccc ggactacca
2041 acttgccaca tgttctaggt ttcagcaaca agactgccag gtggttgggt tctgccttta
2101 gcctggacca aagggaagtg agggccaagg agcttacca agctgtggca gccgtcccag
2161 gccaccccc tgggaagcaat aaagctcttc cctgaaaaa aaaaaaaaa aaaaaaaaa
2221 aaa

```

SEQ ID NO:14 Human ST3Gal-III amino sequence (accession number NP_777629.1)

MGLLVFVRNLLLALCLFLVLGFLYYSAWKLHLLQWEEDSKYDRL
 GFLNLDSKLPALATKYANFSEGACKPGYASALMTAIFPRFSKPAPMFLDDSFWRKA
 RIREFVPPFGIKGQDNLIKAILSVTKEYRLTPALDSLRCRRCIIIVNGGVLANKSLGS
 RIDDYDIVRLNSAPVKGFEDVGSKTTLRITYPEGAMQRPEQYERDSLFLVLAGFKWQ
 DFKWLKYIVYKERSASDGFWKSVATRPKEPPEIRILNPYFIQEAAFTLIGLPFNNG
 LMGRGNIPTLGSVAVTMALHGCDEVAVAGFGYDMSTPNAPLHYETVRMAAIKESWTH
 NIQREKEFLRKLVKARVITDLSSGI

SEQ ID NO:15 Human ST3Gal-III cDNA sequence (accession number NM_174970)

```

1 actatggcgg cgcccatgca gcccagcgcg ttgtgggctc ccgcccgggt cccccgcggc
61 tgtgcgcgcc gcctacgcc ctgcctccgc cttcctgccc cgcgtcgggc cgggcgccac
121 ctccccccctg cctccctctc cgctgtggctc atttaggaaa tcgtaaatca tgtgaagatg
181 ggactcttgg tatttgtgct caatctgctg ctagccctct gcctctttct ggtactggga
241 tttttgtatt attctgcgtg gaagctacac ttactccagt gggaggagga ctccaagtat
301 gatcggttgg gcttcctcct gaatctggac tctaaactgc ctgctgaatt agccaccaag
361 tacgcaaaact tttcagaggg agcttgcaag cctggctatg cttcagcctt gatgacggcc
421 atcttcccc gggtctccaa gccagacccc atgttcctgg atgactcctt tcgcaagtgg
481 gctagaatcc gggagttcgt gccgcctttt gggatcaaaag gtcaagtcc tgcgcacaa
541 tatccagcga gagaaagagt ttctgcggaa gctgggtgaaa gctcgcgtca tcatgatct
601 aagcagtggc atctgagtgg gcccagcaca tggccataga ggcccaggca ccaccaggag
661 cagcagccag caccacctac acaggagtct tcagaccagc agaaggacgg tgccaagggc
721 cccaggggca gcaaggcctt ggtggagcag ccagagctgt gcctgctcag cagccagtct
781 cagagaccag cactcagcct cattcagcat gggctcctga tgccagaggg ccagcaggct
841 cctggctgtg cccagcaggc ccagcatgca ggtggtggga cactgggcag caaggctgct
901 gcgggaatca cttctccaat cagtgtttgg tgtattatca ttttgtgaat ttgggtaggg
961 gggagggtag ggataattta tttttaaata aggttgaga tgtcaagttg ggttcacttg
1021 ccatgcagga agaggccac tagagggcc atcaggcagt gttacctgt agctccctgt

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1081 ggggcaggag tgccaggacc agcctgtacc ttgctgtggg gctacaggat ggtgggcagg
1141 atctcaagcc agccccctcc agctcatgac actgtttggc ctttcttggg gagaaggcgg
1201 ggtattccca ctcaccagcc ctagctgtcc catggggaaa ccctggagcc atcccttcgg
1261 agccaacaag accgccccag ggctatagca gaaagaactt taaagctcag gagggtgacg
1321 ccagctccg cctgctggga agagctcccc tccacagctg cagctgatcc ataggactac
1381 cgcaggcccc gactcaccaa cttgccacat gttctagggt tcagcaacaa gactgccagg
1441 tggttgggtt ctgccttttag cctggaccaa agggaagtga ggcccaagga gcttacccaa
1501 gctgtggcag ccgtcccagg ccacccccat ggaagcaata aagctcttcc ctgaaaaaaa
1561 aaaaaaaaaa aaaaaaaaaa aa

```

SEQ ID NO:16 Human ST3Gal-III amino sequence (accession number NP_777630.1)

MGLLVFVRNLLLALCLFLVLGFLYSAWKLHLLQWEEDSKYDRL
 GFLNLDSKLPaelATKYANFSEGACKPGYASALMTAIFPRFSKPAPMFLDDSRKWA
 RIREFVPPFGIKGQVLDAQYPARERVSAEAGESSRHH

SEQ ID NO:17 Human ST3Gal-III cDNA sequence (accession number NM_174971)

```

1 actatggcgg cgcccatgca gccagcgcg ttgtgggctc ccgcccgggt cccccgcggc
61 tgtcgccgcc gcctacgcc ctgcctccgc cttcctgccc cgcgtcgggc cgggcgccac
121 ctccccctg cctccctctc cgctgtggtc atttaggaaa tcgtaaata tgtgaagatg
181 ggactcttgg tatttgtgcg caatctgctg ctagccctct gcctctttct ggtactggga
241 tttttgtatt attctgcgtg gaagctacac ttactccagt gggaggagga ctccaagtat
301 gatcggttgg gcttcctcct gaatctggac tctaaactct caccgaggac tcttgcacg
361 gtgggttttg gccttgactg catattggaa tcacctggag agcctaaaaa attactgatg
421 cctgcatccc accctctaga gattttgaag tctactgagc aggacgcagc ctttgcatta
481 ggatttttaa agctgcccag goctgctgaa ttagccacca agtacgcaaa cttttcagag
541 ggagcttgca agcctggcta tgcttcagcc ttgatgacgg ccattcttccc ccggttctcc
601 aagccagcac ccattgtcct ggatgactcc tttcgcaagt gggctagaat ccgggagttc
661 gtgcgcctt ttgggatcaa aggtcaagac aatctgatca aagccatctt gtcagtcacc
721 aaagagtacc gcctgacccc tgccctggac agcctccgct gccgccgctg catcatcgtg
781 ggcaatggag gcgttcttgc caacaagtct ctgggggtcac gaattgacga ctatgacatt
841 gtggtgagac tgaattcagc accagtgaat ggctttgaga aggacgtggg cagcaaaacg
901 aactgcgca tcacctaccc cgagggcgcc atgcagcggc ctgagcagta cgagcgcgat
961 tctctctttg tcctcgccgg cttcaagtgg caggacttta agtggttgaa atacatcgtc
1021 tacaaggaga gagtgagtgc atcggatggc ttctggaaat ctgtggccac tcgagtgcce
1081 aaggagcccc ctgagattcg aatcctcaac ccattttca tccaggagcg cgccttcacc
1141 ctcatgggcc tgcccttcaa caatggcctc atgggcgggg ggaacatccc tacccttggc
1201 agtgtggcag tgaccatggc actacacggc tgtgacgagg tggcagtcgc aggatttggc
1261 tatgacatga gcacacccaa cgcacccctg cactactatg agaccgttcg catggcagcc
1321 atcaaagagt cctggacgca caatatccag cgagagaaa agtttctgcg gaagctggtg
1381 aaagctcgcg tcatcactga tctaagcagt ggcattctgag tgggcccagc acatggccat
1441 agaggcccag gcaccaccag gacgagcagc cagcaccacc tacacaggag tcttcagacc
1501 cagagaagga cggtgccaag ggccccaggg gcagcaaggc cttggtggag cagccagagc
1561 tgtgcctgct cagcagccag tctcagagac cagcactcag cctcattcag catgggtcct
1621 tgatgccaga gggccagcag gctcctggct gtgccagca ggccagcat gcaggtggtg
1681 ggacactggg cagcaaggct gctgcgggaa tcaacttctc aatcagtggt tgggtgatta
1741 tcattttgtg aatttgggta ggggggaggg tagggataat ttatttttaa ataaggttgg
1801 agatgtcaag ttgggttcac ttgccatgca ggaagaggcc cactagaggg cccatcaggc
1861 agtgttacct gttagctccc tgtggggcag gagtgccagg accagcctgt accttgcgtg
1921 ggggtacag gatggtgggc aggatctcaa gccagcccc tccagctcat gacactgttt
1981 ggcctttctt ggggagaagg cggggtattc ccactacca gccctagctg tcccatgggg
2041 aaaccctgga gccatccctt cggagocaa aagaccgccc cagggtctata gcagaaagaa
2101 ctttaaagct caggagggtg acgccagct cgcctgctg ggaagagctc ccctccacag
2161 ctgcagctga tccataggac taccgcaggc cgggactcac caacttgcca catgttctag
2221 gtttcagcaa caagactgcc aggtggttgg gttctgcctt tagcctggac caaagggag
2281 tgaggcccaa ggagcttacc caagctgtgg cagccgtccc aggccacccc catggaagca
2341 ataaagctct tccctgaaaa aaaaaaaaaa aaaaaaaaaa aaaaa

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SEQ ID NO:18 Human ST3Gal-III amino sequence (accession number NP_777631.1)

MGLLVFVRNLLLALCLFLVLGFLYYSAWKLHLLQWEEDSKYDRL
 GFLNLD SKLSPTLCTVVFGLDCILESPGEPKLLMPASHPLEILKSLSEDAAFALG
 FLKLPRPAELATKYANFSEGACKPGYASALMTAIFPRFSKPAPMFLDDSFRRKWARIRE
 FVPPFGIKGQDNLIKAILSVTKEYRLTPALDSLRCRRCIIVGNGGVLANKSLGSRIDD
 YDIVVRLNSAPVKGFEKDVGSKTTLRITYPEGAMQRPEQYERDSLFLVLAGFKWQDFKW
 LKYIVYKERVSASDGFWKSVATRVKPEPEIRILNPYFIQEAAFTLIGLPFNNGLMGR
 GNIPTLGSVAVTMALHGCDEVAVAGFGYDMSTPNAPLHYYETVRMAAIKESWTHNIQR
 EKEFLRKLVKARVITDLSSGI

SEQ ID NO:19 Human ST3Gal-III cDNA sequence (accession number NM_174972)

```

1 actatggcgg cgcccatgca gcccagcgcg ttgtgggctc ccgccgggggt ccccgcgggc
61 tgtcgccgcc gcctacgcgc ctgcctccgc cttcctgccc cgcgtcgggc cgggcgccac
121 ctcccccttg cctccctctc cgctgtgggc atttaggaaa tcgtaaataca tgtgaagatg
181 ggactcttgg tatttgtgcg caatctgctg ctagccctct gcctctttct ggtactggga
241 tttttgtatt attctgcgtg gaagctacac ttactccagt gggaggagga ctccaattca
301 gtggttcttt cctttgactc cgctggacaa aactaggctc cagagtatga tcggttgggc
361 ttcctcctga atctggactc taaactgcct gctgaattag ccaccaagta cgaaactttt
421 tcagagggag cttgcaagcc tggctatgct tcagccttga tgacggccat cttccccggg
481 ttctccaagc cagcaccatc gttcctggat gactccttcc gcaagtgggc tagaatccgg
541 gagttcgtgc cgcttttgg gatcaaaggt caagacaatc tgatcaaagc catcttgtca
601 gtcaccaaag agtacgcgc gaccctgcc ttggacagcc tccgtgccg ccgctgcac
661 atcgtgggca atggaggcgt tcttgccaac aagtctctgg ggtcacgaat tgacgactat
721 gacattgtgg tgaggccag gctctgagtg ggcctgctct ctgtagactg aattcagcac
781 cagtgaagg ctttgagaag gacgtgggca gcaaacgac actgcgcatc acctaccccg
841 agggcgccat gcagcgccct gagcagtagc agcgcgattc tctctttgtc ctgcgggct
901 tcaagtggca ggactttaag tggttgaaat acatcgtcta caaggagaga gtgagtgcac
961 cggatggctt ctggaaatct gtggccactc gagtgcccaa ggagccccct gagattcgaa
1021 tcctcaaccc atatttcatc caggaggccg ccttcaccct cattggcctg cccttcaaca
1081 atggcctcat gggccggggg aacatcccta cccttggcag tgtggcagtg accatggcac
1141 tacacggctg tgacgaggtg gcagtcgcag gatttggcta tgacatgagc acaccaacg
1201 caccctgca ctactatgag accgttcgca tggcagccat caaagagtcc tggacgcaca
1261 atatccagcg agagaaagag tttctgcgga agctggtgaa agctcgcgtc atcactgatc
1321 taagcagtg catctgagtg gggccagcac atggccatag aggccaggc accaccagga
1381 gcagcagcca gcaccaacta cacaggagtc ttcagacca gagaaggacg gtgccaaggg
1441 cccagggggc agcaaggcct tgggtggagca gccagagctg tgctgtctca gcagccagtc
1501 tcagagacca gcactcagcc tcattcagca tgggtccttg atgccagagg gccagcaggc
1561 tcctggctgt gccagcagg cccagcatgc aggtggtggg aactgggca gcaaggctgc
1621 tgccggaatc acttctccaa tcagtgtttg gtgtattatc attttgtgaa tttgggtagg
1681 ggggagggta gggataattt atttttaaat aagggtggag atgtcaagtt ggggttactt
1741 gccatgcagg aagaggccca ctagagggcc catcaggcag tgttacctgt tagctccctg
1801 tggggcagga gtgccaggac cagcctgtac cttgctgtgg ggctacagga tgggtggcag
1861 gatctcaagc cagccccctc cagctcatga cactgtttgg cctttcttgg ggagaaggcg
1921 gggtatcccc actcaccagc cctagctgtc ccatggggaa accctggagc catcccttcg
1981 gagccaacaa gaccgcccc gggctatagc agaaagaact ttaaagctca ggagggtgac
2041 gccagctcc gcctgctggg aagagctccc ctccacagct gcagctgac cataggacta
2101 ccgagggccc ggactcacca acttgccaca tgttctaggt ttcagcaaca agactgccag
2161 gtggttgggt tctgccttta gcctggacca aagggaagtg aggcccaagg agcttaccga
2221 agctgtggca gccgtcccag gccaccccca tgggaagcaat aaagctcttc cctgaaaaaa
2281 aaaaaaaaaa aaaaaaaaaa aaa

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SEQ ID NO:20 Human ST3Gal-III amino sequence (accession number NP_777632.1)

MGLLVFVRNLLLALCLFLVLGFLYYSAWKLHLLQWEEDSNSVVL
 SFDSAGQTLGSEYDRLGFLNLD SKLPAELATKYANFSEGACKPGYASALMTAIFPRF
 SKPAPMFLDDSFRRKWARIREFVPPFGIKGQDNLIKAILSVTKEYRLTPALDSLRCRRC
 IIVGNGGVLANKSLGSRIDDYDIVVRPL

SEQ ID NO:21 Mouse ST3Gal-III cDNA sequence (accession number NM_009176)

```

1  ggccgctgcg tccccacccat ggccggcgccc gtgcagcttg ccgcgtcctg ggctccctct
61  ggggtccccc eggtgtcccc cgtatttcgc gctgcaattg cctccgcgct ctgctgctgc
121 cctggcgcca cccgcccccg gctccctctc ctgctgctgg aaggcctgcc ctgctgcccc
181 gaagcagctc tcggccgccc cggccctccc ccggccagac cggcccgagc cgcgtgctgg
241 accaaagccc gggcccggtt gggggccagg cctgccagag ggccgcgcga gccgggcccga
301 gcgcgcccag gtcacctgtg tgcagtgtcc caggcgcgcg agtctgagcg caaaggaggg
361 tcacggtcac ccgggacccg ctgtgggaca agcgcaagaa agtccgggga aagcctagcg
421 ggagtcacca agagtagcgg ttgtcatctc tgccttcccc ggggccagat ccttctcgga
481 gcgaccgggt cagtttatca aagtcatgta ggaaattgtg agtcatgtga agatgggact
541 cttggtatct gtgcgcaatc tgctgctagc cctctgcctc ttcttggtcc tgggattttt
601 gtattattct gcctggaagc tacacttact ccaatgggaa gactccaatt cattgcttct
661 ttcccttgac tccgctggac aaaccctagg cacagagtat gataggctgg gcttccctct
721 gaagctggac tctaaactgc ctgccgagct agccaccaag tacgcaaact tttccgaggg
781 agcttgcaaa cccggctacg cttcagccat gatgactgcc atcttcccca ggttctccaa
841 gccagacccc atgttcctgg atgactcctt tcgcaagtgg gctaggatcc gggagtttgt
901 gccacctttt gggatcaaag gtcaagacaa tctgatcaaa gccatcttgt cagtcaccaa
961 agaataccgc ctgacccctg ccttgacag cctccactgc cgcgctgca tcattgtagg
1021 caatggaggg gtccctcgcca acaagtctct ggggtcacgg attgacgact atgacattgt
1081 gatcagactg aactcagcac ctgtgaaggg ctttgagagg gacgtgggca gcaagaccac
1141 cctacgcata acctaccctg agggcgccat gcagcgacct gagcaatatg aacgagactc
1201 tatctttgtc ctgctgggtc tcaagtggca ggacttcaag tggctgaagt acatcgctca
1261 caaggagaga gtgagtgcac ctgatggctt ctggaagtcc gtggccaccc gagtgcccaa
1321 ggagccccct gagatccgca tcctcaaccc atacttcata caggaggctg ccttcaactc
1381 cattggactg cccttcaaca acggcctcat gggcagaggg aacatcccaa cccttggcag
1441 tgtggcagtg accatggcac tacacggctg tgatgaagtg gcagtcgcgg gctttggcta
1501 tgacatgaac acacccaatg cacccttgca ctactatgaa actgtgcgca tggcagccat
1561 caaagagtcc tggacacaca acatccagcg agagaaagag tttctgcgga agctagttaa
1621 ggcaactgtc atcaactgac taagcagcgg tatctgagtg ggccggacac caggccagag
1681 aggtctacgc caggaccaag cagctgccac ctgcacagga gccttcccac ccagagaggg
1741 acagtgccaa gagacccgag ggccagttag gccttggaag ggcaaccaga gctgtgcccc
1801 ctgcaggcca gcttcagaga ccagcaccct gccttgctgc ctgggtccat gaagccagag
1861 ggccaggagg ccaactggctg tggccagcag gccagcatg caggaggtgg gacatttggt
1921 agcaagaatg ctaccagaat catttctcta atcagtgttt ggtgtattat cattttgtga
1981 atttgggtat ggggagggga gggataattt atttttaaat tagatgtcac atttgggtca
2041 cttgtttgtc agaaagaggc ccactagagg gccatcaga cagtgggtacc agtgaactcc
2101 ctgaaggatg gaggtgtggt gaccatgctt cagggaaccg gaggtggata gcattctcat
2161 tcagccatct ccagctcacg acaactcttg gccttccttg gggagaagat gaagtactcc
2221 ctctcaccag ccaccagtgt cccacagggg aaccccagag ccatcccttt aaagccaaca
2281 ggacagctct tggacaagag cagagagaac tcaggaggca aggccagacc cagcctgacg
2341 ggaatgaatg gctccgtcca tagctgtccc taatccatgg ggcagtaatc cttcctgaac
2401 tgtoagatgg tctgggtttc ttgctgggac tgccagctcc atgggtccta cccaggacca
2461 gaggggaagt aggtccagg acctaccca ggctgccgca gccagccggg gcagctctca
2521 cggaagcaat aaagctctcc tctgaatctg

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SEQ ID NO:22 Mouse ST3Gal-III amino sequence (accession number NP_033202.2)

```

MGLLVFVRNLLLALCLFLVLGFLYSAWKLHLLQWEDSNSLLLS
LDSAGQTLGTEYDRLGLLKLDSKLPaelATKYANFSEGACKPGYASAMMTAIFPRFS
KPAPMFLDDSFARKWARIREFVPPFGIKGQDNLIKAILSVTKYRLTPALDSLHCRCI
IVNGGVLANKSLGSRIDDYDIVIRLNSAPVKGFERDVGSKTTLRITYPEGAMQRPQ
YERDSIFVLAGEFKWQDFKWLKIVYKERSASDGFWSVATRVPEPPEIRILNPYFI
QEAAFTLIGLPFNNGLMGRGNIPTLGSVAVTMALHGCDEVAVAGFGYDMNTPNAPLHY
YETVRMAAIKESWTHNIQREKEFLRKLVKARVITDLSSGI

```

SEQ ID NO:23 Mouse ST3Gal-III cDNA sequence (accession number BC006710)

```

1  gcggaccgca  ggattggtgg  tccgcgcgct  gcgtcccccac  catggcggcg  cccgtgcagc
61  ttgccgcgtc  ctgggctccc  tctgggggtcc  cctcggtgtg  ccccgctatt  cgcgtgcaa
121  ttgcctccgc  gctctgcgtg  cgccctggcg  ccacccgccc  ccggcctccc  tctctgctgc
181  ggtcatgtag  gaaattgtga  gtcattgtgaa  gatgggactc  ttggtatttg  tgcgcaatct
241  gctgctagcc  ctctgcctct  tcctggtcct  gggatttttg  tattattctg  cctggaagct
301  acacttactc  caatgggaag  actccaattc  attgcttctt  tcccttgact  ccgctggaca
361  aaccctaggc  acagagtatg  ataggctggg  cttcctcctg  aagctggact  ctaaactgcc
421  tgccgagcta  gccaccaagt  acgcaaactt  ttccgagggg  gcttgcaaac  ccggctacgc
481  ttcagctatg  atgactgcca  tcttccccag  gttctccaag  ccagcaccca  tgttcctgga
541  tgactccttt  cgcaagtggg  ctaggatccg  ggagtttgtg  ccaccttttg  ggatcaaagg
601  tcaagacaat  ctgatcaaag  ccattctgtc  agtcaccaa  gaataccgcc  tgaccctgc
661  cttggacagc  ctccactgcc  gccgctgcac  cattgtaggc  aatggagggg  tcctcgccaa
721  caagtctctg  gggtcacgga  ttgacgacta  tgacattgtg  atcagactga  actcagcacc
781  tgtgaagggc  tttgagaggg  acgtgggcag  caagaccacc  ctacgcatca  cctaccctga
841  gggcgccatg  cagcgacctg  agcaatatga  acgagactct  ctctttgtcc  tcgctggctt
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SEQ ID NO:24 Mouse ST3Gal-III amino sequence (accession number AAH06710.1)

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