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(54) Title: METHODS FOR MODULATING RNA ALTERNATIVE SPLICING IN A SUBJECT IN NEED THEREOF

(57) Abstract: The present invention relates to methods for modulating RNA alternative splicing in a subject. In particular, the present invention relates to a method for modulating RNA alternative splicing in a subject in need thereof comprising administering the subject with a therapeutically amount of an inhibitor of mitochondrial complex I activity.

METHODS FOR MODULATING RNA ALTERNATIVE SPLICING IN A SUBJECT IN NEED THEREOF

FIELD OF THE INVENTION:

The present invention relates to methods for modulating RNA alternative splicing in a subject.

BACKGROUND OF THE INVENTION:

The human genome consists of 20,000 to 25,000 protein coding genes, but the repertoire of mRNA sequences and encoded proteins is far greater as a result of multiple RNA isoforms generated from each gene. RNA transcript diversity evolves from several mechanisms, but RNA alternative splicing represents a major factor driving phenotypic diversity in higher eukaryotes. Indeed splicing events are highly prevalent, estimated to occur for 95% of all multiexon genes. There are numerous modes of RNA alternative splicing observed, of which the most common is exon skipping. In this mode, a particular exon may be included in mRNAs under some conditions or in particular tissues, and omitted from the mRNA in others. The majority of splicing events alter the encoded protein, more than half causing a shift in the mRNA reading frame. Common genetic variants can afford changes in alternative splicing within a "normal" physiological range. However, abnormal variations in splicing are implicated in a large proportion of human genetic disorders result from splicing variants, since more up to 50% of diseases with genetic components involve splicing mutations. Mutations causing aberrant splicing typically result in nonfunctional protein or nonsense-mediated RNA decay, if a codon phase shift introduces premature termination signals. Abnormal splicing variants are also thought to contribute to the development of cancer; although such aberrant splicing products are, under normal conditions, usually safeguarded and eliminated by a posttranscriptional quality control mechanism. Accordingly, major physiological changes are governed by RNA alternative splicing. Large families of splice regulators have been identified that are, each, responsible for finely tuned effects on discrete sets of target proteins (Mukherjee et al.,2011 ; Ule et al, 2003). Activity of those splice regulators is highly controlled by a variety of signaling pathways that are dependent upon homeostatic conditions and cellular environment (Fagnani et al, 2007; Kalsotra et al, 2008; Tomczak et al, 2004; Ip et al., 2007; Zacharias et al, 1996). Consequently, the identification of drugs that are able to modulate RNA alternative splicing is highly desirable

for therapeutic purposes, especially for reduce formation of disease-associated aberrant RNA isoforms.

SUMMARY OF THE INVENTION:

The present invention relates to methods for modulating RNA alternative splicing in a subject. In particular, the present invention relates to a method for modulating RNA alternative splicing in a subject in need thereof comprising administering the subject with a therapeutically amount of an inhibitor of mitochondrial complex I activity.

DETAILED DESCRIPTION OF THE INVENTION:

The inventors show that RNA alternative splicing system can be druggable, with therapeutic potentials, as demonstrated by the effects of the biguanide metformin on embryonic stem cells derivatives affected by myotonic dystrophy type I (Marteyn et al., 2011). The mechanism of action depends upon changes induced by the drug in the expression of a specific subset of splice regulators, downstream of the inhibition of mitochondrial complex I. Biological effects of metformin were shown compatible with usual therapeutic dosage in a clinical investigation that involved diabetic patients. As underscored by those latter results, as well as with cells derived from healthy embryos, metformin effect was not dependent of the myotonic dystrophy pathology. The drug, instead, appears altogether as a modifier of alternative splicing of a subset of genes, with new therapeutic potentials that may concern many more diseases besides those directly linked to defective alternative splicing. Metformin also reveals only one among many drugs that, affecting cell oxidation and possibly other homeostatic equilibriums, are also impacting RNA alternative splicing in ways that deserve to be explored further as a new pharmacological approach to many diseases.

Accordingly an aspect of the present invention relates to a method for modulating RNA alternative splicing in a subject in need thereof comprising administering the subject with a therapeutically amount of an inhibitor of mitochondrial complex I activity.

As used herein, the term “RNA alternative splicing” has its general meaning in the art and refers to the regulated process during gene expression for which a single gene can encode multiple proteins. As will be understood by those skilled in the art, in the cell nucleus, eukaryotic genes are transcribed into pre-messenger RNA (pre-mRNA) which contains both exons and introns. To form mature mRNA, splicing occurs at specific sequences at the

borders of exons and introns (splice sites) thereby removing introns and connecting exons to one another to form mRNA, which is translated into protein. Consequently the proteins translated from alternatively spliced mRNAs will contain differences in their amino acid sequence and, often, in their biological functions. The production of alternatively spliced mRNAs is regulated by a system of trans-acting proteins (i.e. "splice regulators") that bind to cis-acting sites on the pre-mRNA itself. Such proteins include splicing activators that promote the usage of a particular splice site, and splicing repressors that reduce the usage of a particular site. Large families of splice regulators have been identified that are, each, responsible for finely tuned effects on discrete sets of target proteins (Mukherjee et al.,2011 ; Ule et al, 2003). Typically, splice regulators include but are not limited to SRSF1, SRSF6, SFPQ, RBM3, RBM4B, RBM5 and RBM45. According to the invention, the inhibitor of mitochondrial complex I activity provides a modulation of RNA alternative splicing by modulating the expression of the splice regulators. In particular, the inhibitor is able to down regulate the expression of RBM3.

As used herein, the term "mitochondrial complex I" has its general meaning in the art and refers to the first enzymatic complex involved in the mitochondrial respiratory chain. Mitochondrial complex I indeed accomplishes the transfer of electrons from metabolic fuels like glycolysis products and fatty acids to ubiquinone (Coenzyme Q), converting it to ubiquinol. Mitochondrial complex I is an L-shaped assembly of 45 different subunits. Fourteen of them are the 'core subunits' which are found in all complexes I, including the simpler bacterial enzymes. The remainin 31 are 'supernumerary subunits'. Some of the supernumerary subunits have had specific roles ascribed to them (e.g. SDAP is an acyl carrier protein), but most of them do not have specific known roles at present, but they may be involved in assembly, or required for structural stability. Of the fourteen core subunits, seven of are hydrophilic and encoded by the nuclear genome, and seven are highly hydrophobic and encoded by the mitochondrial genome. Table A provides a list of proteins involved in mitochondrial complex I. Typically, the "mitochondrial complex I activity" is defined by its NADH dehydrogenase activity. Said activity can be measured using any assay well-known in the art. These assays can measure the diaphorase-type activity of Complex I such as the "Complex I Enzyme Activity Microplate Assay Kit" from MitoSciences or alternatively measure the production of Reactive Oxygen Species through the use of the cell permeant reagent 2',7' –dichlorofluorescein diacetate (DCFDA), a fluorogenic dye that measures hydroxyl, peroxyl and other reactive oxygen species (ROS) activity within the cell (Cellular

Reactive Oxygen Species Detection Assay Kit from ABCAM). Briefly, NADH dehydrogenase activity is measured using an electron acceptor. For example a biological electron acceptor can be ubiquinone, and an artificial electron acceptor can be ferricyanide (e.g. potassium ferricyanide). The assays typically comprise incubating a cell with NADH and the electron acceptor, and measuring the change in absorbance of NADH at 340 nm over time.

Accordingly, the term "inhibitor of mitochondrial complex I activity" refers to any compound (natural or not) that is able to disrupt the functionality of the complex, especially, by the ability of the compound to inhibit the NADH ferricyanide reductase activity or the NADH ubiquinone reductase activity. Typically, the inhibitor can provide directly its effect on the complex for example by interacting directly with a protein, in particular an enzyme involved in the complex activity or can provide indirectly its effect by limiting the availability of the substrates, cofactors or proteins involved in the complex. The inhibitor thus be selected from the group consisting of compounds acting as true enzymatic inhibitors (i.e. inhibitor of an enzyme activity by competing for example with the substrate or cofactor to the catalytic site of the enzyme), compounds capable of disrupting the organization of the complex (i.e. disrupting the interaction between the proteins involved in the a complex), compounds capable of limiting the availability of the substrates or cofactors , compounds capable of inhibiting the availability of a key protein involved in the complex (i.e. by inhibiting the expression of a protein of the complex). Inhibitors include any type of compounds and typically include small organic molecule, polypeptide, nucleic acid molecules, or any other biomolecule (e.g. a lipid).

In some embodiment, the inhibitor of mitochondrial complex I activity is selected from catechols, such as for example dopamine, 6-hydroxydopamine, L-DOPA and norepinephrine.

In some embodiments, the inhibitor of mitochondrial complex I activity is metformin. The term "metformin" as employed herein refers to metformin or a pharmaceutically acceptable salt thereof such as the hydrochloride salt, the metformin (2:1) fumarate salt, and the metformin (2:1) succinate salt as disclosed in U.S. application Ser. No. 09/262,526 filed Mar. 4, 1999, the hydrobromide salt, the p-chlorophenoxy acetate or the embonate, and other known metformin salts of mono and dibasic carboxylic acids including those disclosed in U.S. Pat. No. 3,174,901, all of which salts are collectively referred to as metformin. The

metformin employed herein may be the metformin hydrochloride salt, namely, that marketed as Glucophage.RTM. (trademark of Bristol-Myers Squibb Company).Metformin is the international nonproprietary name of 1,1-dimethylbiguanide (CAS Number 657-24-9).

In some embodiments, the inhibitor of mitochondrial complex I activity is rotenone. The term “rotenone” as used herein is a common name for the compound having the IUPAC name 2R,6aS, 12aS)-1,2,6,6a,12,12a-hexahydro-2-isopropenyl-8,9dimethoxychromeno [3 ,4 -b] furo (2 , 3 -h)cl1romen-6 -one. Altemative names for this compound include Tubatoxin and Paraderil.

In some embodiments, the inhibitor of mitochondrial complex I activity is troglitazone. Troglitazone can be prepared by the process as described in Japanese Patent Application Kokai No. Sho 61-51189.

In some embodiments, the inhibitor of mitochondrial complex I activity is selected from statins. As used herein the term "statin" refers to HMG-CoA reductase inhibitors, such as pravastatin, simvastatin, lovastatin, fluvastatin, atorvastatin and rosuvastatin and their pharmaceutically acceptable salts thereof. The statins are reversible inhibitors of the microsomal enzyme HMG-CoA reductase, which converts HMG-CoA to mevalonate. This is an early rate-limiting step in cholesterol biosynthesis.

In some embodiments, the inhibitor of mitochondrial complex I activity is resveratrol.

In some embodiment, the inhibitor of mitochondrial complex I activity is an inhibitor of expression of a protein of TABLE A.

An “inhibitor of expression” refers to a natural or synthetic compound that has a biological effect to inhibit the expression of a gene.

In a preferred embodiment of the invention, said inhibitor of gene expression is a siRNA, an antisense oligonucleotide or a ribozyme.

Inhibitors of gene expression for use in the present invention may be based on antisense oligonucleotide constructs. Anti-sense oligonucleotides, including anti-sense RNA molecules and anti-sense DNA molecules, would act to directly block the translation of the

protein mRNA by binding thereto and thus preventing protein translation or increasing mRNA degradation, thus decreasing the level of the protein, and thus activity, in a cell. For example, antisense oligonucleotides of at least about 15 bases and complementary to unique regions of the mRNA transcript sequence encoding the protein can be synthesized, e.g., by conventional phosphodiester techniques and administered by e.g., intravenous injection or infusion. Methods for using antisense techniques for specifically inhibiting gene expression of genes whose sequence is known are well known in the art (e.g. see U.S. Pat. Nos. 6,566,135; 6,566,131; 6,365,354; 6,410,323; 6,107,091; 6,046,321; and 5,981,732).

Small inhibitory RNAs (siRNAs) can also function as inhibitors of gene expression for use in the present invention. Gene expression can be reduced by contacting the tumor, subject or cell with a small double stranded RNA (dsRNA), or a vector or construct causing the production of a small double stranded RNA, such that gene expression is specifically inhibited (i.e. RNA interference or RNAi). Methods for selecting an appropriate dsRNA or dsRNA-encoding vector are well known in the art for genes whose sequence is known (e.g. U.S. Pat. Nos. 6,573,099 and 6,506,559; and International Patent Publication Nos. WO 01/36646, WO 99/32619, and WO 01/68836).

Ribozymes can also function as inhibitors of gene expression for use in the present invention. Ribozymes are enzymatic RNA molecules capable of catalyzing the specific cleavage of RNA. The mechanism of ribozyme action involves sequence specific hybridization of the ribozyme molecule to complementary target RNA, followed by endonucleolytic cleavage. Engineered hairpin or hammerhead motif ribozyme molecules that specifically and efficiently catalyze endonucleolytic cleavage of the protein mRNA sequences are thereby useful within the scope of the present invention. Specific ribozyme cleavage sites within any potential RNA target are initially identified by scanning the target molecule for ribozyme cleavage sites, which typically include the following sequences, GUA, GUU, and GUC. Once identified, short RNA sequences of between about 15 and 20 ribonucleotides corresponding to the region of the target gene containing the cleavage site can be evaluated for predicted structural features, such as secondary structure, that can render the oligonucleotide sequence unsuitable. The suitability of candidate targets can also be evaluated by testing their accessibility to hybridization with complementary oligonucleotides, using, e.g., ribonuclease protection assays.

Both antisense oligonucleotides and ribozymes useful as inhibitors of gene expression can be prepared by known methods. These include techniques for chemical synthesis such as, e.g., by solid phase phosphoramadite chemical synthesis. Alternatively, anti-sense RNA

molecules can be generated by in vitro or in vivo transcription of DNA sequences encoding the RNA molecule. Such DNA sequences can be incorporated into a wide variety of vectors that incorporate suitable RNA polymerase promoters such as the T7 or SP6 polymerase promoters. Various modifications to the oligonucleotides of the invention can be introduced as a means of increasing intracellular stability and half-life. Possible modifications include but are not limited to the addition of flanking sequences of ribonucleotides or deoxyribonucleotides to the 5' and/or 3' ends of the molecule, or the use of phosphorothioate or 2'-O-methyl rather than phosphodiesterase linkages within the oligonucleotide backbone.

Antisense oligonucleotides siRNAs and ribozymes of the invention may be delivered in vivo alone or in association with a vector. In its broadest sense, a "vector" is any vehicle capable of facilitating the transfer of the antisense oligonucleotide siRNA or ribozyme nucleic acid to the cells. Preferably, the vector transports the nucleic acid to cells with reduced degradation relative to the extent of degradation that would result in the absence of the vector. In general, the vectors useful in the invention include, but are not limited to, plasmids, phagemids, viruses, other vehicles derived from viral or bacterial sources that have been manipulated by the insertion or incorporation of the the antisense oligonucleotide siRNA or ribozyme nucleic acid sequences. Viral vectors are a preferred type of vector and include, but are not limited to nucleic acid sequences from the following viruses: retrovirus, such as moloney murine leukemia virus, harvey murine sarcoma virus, murine mammary tumor virus, and rouse sarcoma virus; adenovirus, adeno-associated virus; SV40-type viruses; polyoma viruses; Epstein-Barr viruses; papilloma viruses; herpes virus; vaccinia virus; polio virus; and RNA virus such as a retrovirus. One can readily employ other vectors not named but known to the art.

Preferred viral vectors are based on non-cytopathic eukaryotic viruses in which non-essential genes have been replaced with the gene of interest. Non-cytopathic viruses include retroviruses (e.g., lentivirus), the life cycle of which involves reverse transcription of genomic viral RNA into DNA with subsequent proviral integration into host cellular DNA. Retroviruses have been approved for human gene therapy trials. Most useful are those retroviruses that are replication-deficient (i.e., capable of directing synthesis of the desired proteins, but incapable of manufacturing an infectious particle). Such genetically altered retroviral expression vectors have general utility for the high-efficiency transduction of genes in vivo. Standard protocols for producing replication-deficient retroviruses (including the steps of incorporation of exogenous genetic material into a plasmid, transfection of a packaging cell lined with plasmid, production of recombinant retroviruses by the packaging

cell line, collection of viral particles from tissue culture media, and infection of the target cells with viral particles) are provided in KRIEGLER (A Laboratory Manual," W.H. Freeman C.O., New York, 1990) and in MURRY ("Methods in Molecular Biology," vol.7, Humana Press, Inc., Cliffton, N.J., 1991).

Preferred viruses for certain applications are the adeno-viruses and adeno-associated viruses, which are double-stranded DNA viruses that have already been approved for human use in gene therapy. The adeno-associated virus can be engineered to be replication deficient and is capable of infecting a wide range of cell types and species. It further has advantages such as, heat and lipid solvent stability; high transduction frequencies in cells of diverse lineages, including hematopoietic cells; and lack of superinfection inhibition thus allowing multiple series of transductions. Reportedly, the adeno-associated virus can integrate into human cellular DNA in a site-specific manner, thereby minimizing the possibility of insertional mutagenesis and variability of inserted gene expression characteristic of retroviral infection. In addition, wild-type adeno-associated virus infections have been followed in tissue culture for greater than 100 passages in the absence of selective pressure, implying that the adeno-associated virus genomic integration is a relatively stable event. The adeno-associated virus can also function in an extrachromosomal fashion.

Other vectors include plasmid vectors. Plasmid vectors have been extensively described in the art and are well known to those of skill in the art. See e.g., SANBROOK et al., "Molecular Cloning: A Laboratory Manual," Second Edition, Cold Spring Harbor Laboratory Press, 1989. In the last few years, plasmid vectors have been used as DNA vaccines for delivering antigen-encoding genes to cells in vivo. They are particularly advantageous for this because they do not have the same safety concerns as with many of the viral vectors. These plasmids, however, having a promoter compatible with the host cell, can express a peptide from a gene operatively encoded within the plasmid. Some commonly used plasmids include pBR322, pUC18, pUCl9, pRC/CMV, SV40, and pBlueScript. Other plasmids are well known to those of ordinary skill in the art. Additionally, plasmids may be custom designed using restriction enzymes and ligation reactions to remove and add specific fragments of DNA. Plasmids may be delivered by a variety of parenteral, mucosal and topical routes. For example, the DNA plasmid can be injected by intramuscular, intradermal, subcutaneous, or other routes. It may also be administered by intranasal sprays or drops, rectal suppository and orally. It may also be administered into the epidermis or a mucosal surface using a gene-gun. The plasmids may be given in an aqueous solution, dried onto gold

particles or in association with another DNA delivery system including but not limited to liposomes, dendrimers, cochleate and microencapsulation.

In some embodiment, the subject suffers from a disease characterized by the presence of abnormally spliced mRNAs. In particular, the method of the invention is particularly suitable for treating disorders involving aberrant isoforms. Typically, the method of the invention may be suitable for suppressing or limiting pathogenic RNA Transcripts.

The method of the invention is also particularly suitable for restoring a functionality of a protein. In particular, when a gene is mutated and said mutation causes the expression of an aberrant protein, or is responsible for the fact the protein is not expressed (e.g. the mutation introduces a premature stop codon resulting in nonsense-mediated RNA decay), the method of the invention may be suitable for expressing a functional isoform, It may be particularly suitable to prevent inclusion of exons bearing the mutation. By modulating RNA alternative splicing it is possible as demonstrated by the inventors to "skip" the targeted exons that will thus not be included in the mature mRNA. The mRNA thus no longer contains the information of the skipped exon(s) and the protein it encodes does not contain an amino acid sequence corresponding to the skipped exon(s). Accordingly, in the present specification, the expression "preventing splicing of one (or more) exon(s)" refers to the induction of a targeted deletion of said exon(s) in mature mRNA by a modification of splicing using the method of the invention.

TABLE B provides a list of targets and diseases that may benefit of the method of the invention for restoring functional proteins. In particular, the method of the present invention is useful for the treatment of a genetic disease (e.g. a monogenic disease) selected from the group consisting of myotonic dystrophy type I and progeria.

In a particular embodiment, when the subject suffers from myotonic dystrophy type I, the subject is administerd with an inhibitor of mitochondrial complex I activity that is not metformin.

In a particular, the method of the present invention is useful for the treatment of a angiogenic disease.

An "angiogenic disease" is a disease associated with unregulated angiogenesis. Angiogenic diseases include but are not limited to primary and metastatic solid tumors, including carcinomas of breast, colon, rectum, lung, oropharynx, hypopharynx, esophagus, stomach, pancreas, liver, gallbladder and bile ducts, small intestine, kidney, bladder, urothelium, female genital tract, (including cervix, uterus, and ovaries as well as choriocarcinoma and gestational trophoblastic disease), male genital tract (including prostate, seminal vesicles, testes and germ cell tumors), endocrine glands (including the thyroid, adrenal, and pituitary glands), and skin, as well as hemangiomas, melanomas, sarcomas (including those arising from bone and soft tissues as well as Kaposi's sarcoma) and tumors of the brain, nerves, eyes, such as astrocytomas, gliomas, glioblastomas, retinoblastomas, neuromas, neuroblastomas, Schwannomas, and meningiomas. Angiogenic diseases also relate to tumors arising from hematopoietic malignancies such as leukemias as well both Hodgkin's and non-Hodgkin's lymphomas. Angiogenic diseases also pertain to rheumatoid, immune and degenerative arthritis; various ocular diseases such as diabetic retinopathy, retinopathy of prematurity, corneal graft rejection, retrolental fibroplasia, neovascular glaucoma, rubeosis, retinal neovascularization due to macular degeneration (e.g. age-related macular degeneration), hypoxia, angiogenesis in the eye associated with infection or surgical intervention, and other abnormal neovascularization conditions of the eye. Angiogenic diseases further include skin diseases such as psoriasis; blood vessel diseases such as hemagiomas, and capillary proliferation within atherosclerotic plaques; Osler-Webber Syndrome; myocardial angiogenesis; plaque neovascularization; telangiectasia; hemophiliacjoints'; angiofibroma; and wound granulation. Other angiogenic diseases include diseases characterized by excessive or abnormal stimulation of endothelial cells, including but not limited to intestinal adhesions, Crohn's disease, atherosclerosis, scleroderma, and hypertrophic scars, i.e. keloids, diseases that have angiogenesis as a pathologic consequence such as cat scratch disease (Rochele ninalia quintosa) and ulcers (Helicobacter pylori).

In particular, the method of the invention is useful for the treatment of cancer. Abnormally spliced mRNAs are indeed found in a high proportion of cancerous cells. Accordingly, the method of the invention may be performed for any type of cancers selected from the group consisting of adrenal cortical cancer, anal cancer, bile duct cancer (e.g. periphilar cancer, distal bile duct cancer, intrahepatic bile duct cancer), bladder cancer, bone cancer (e.g. osteoblastoma, osteochrondroma, hemangioma, chondromyxoid fibroma, osteosarcoma, chondrosarcoma, fibrosarcoma, malignant fibrous histiocytoma, giant cell

tumor of the bone, chordoma, lymphoma, multiple myeloma), brain and central nervous system cancer (e.g. meningioma, astocytoma, oligodendrogliomas, ependymoma, gliomas, medulloblastoma, ganglioglioma, Schwannoma, germinoma, craniopharyngioma), breast cancer (e.g. ductal carcinoma in situ, infiltrating ductal carcinoma, infiltrating, lobular carcinoma, lobular carcinoma in, situ, gynecomastia), Castleman disease (e.g. giant lymph node hyperplasia, angiofollicular lymph node hyperplasia), cervical cancer, colorectal cancer, endometrial cancer (e.g. endometrial adenocarcinoma, adenocanthoma, papillary serous adnocarcinroma, clear cell), esophagus cancer, gallbladder cancer (mucinous adenocarcinoma, small cell carcinoma), gastrointestinal carcinoid tumors (e.g. choriocarcinoma, chorioadenoma destruens), Hodgkin's disease, non-Hodgkin's lymphoma, Kaposi's sarcoma, kidney cancer (e.g. renal cell cancer), laryngeal and hypopharyngeal cancer, liver cancer (e.g. hemangioma, hepatic adenoma, focal nodular hyperplasia, hepatocellular carcinoma), lung cancer (e.g. small cell lung cancer, non-small cell lung cancer), mesothelioma, plasmacytoma, nasal cavity and paranasal sinus cancer (e.g. esthesioneuroblastoma, midline granuloma), nasopharyngeal cancer, neuroblastoma, oral cavity and oropharyngeal cancer, ovarian cancer, pancreatic cancer, penile cancer, pituitary cancer, prostate cancer, retinoblastoma, rhabdomyosarcoma (e.g. embryonal rhabdomyosarcoma, alveolar rhabdomyosarcoma, pleomorphic rhabdomyosarcoma), salivary gland cancer, skin cancer (e.g. melanoma, nonmelanoma skin cancer), stomach cancer, testicular cancer (e.g. seminoma, nonseminoma germ cell cancer), thymus cancer, thyroid cancer (e.g. follicular carcinoma, anaplastic carcinoma, poorly differentiated carcinoma, medullary thyroid carcinoma, thyroid lymphoma), vaginal cancer, vulvar cancer, and uterine cancer (e.g. uterine leiomyosarcoma).

In particular, the method of the present invention is useful for increasing or reducing off-target adverse effects of a drug. Indeed, a drug typically binds to multiple proteins in the body involving many genes. For example, the enzymes that metabolize the drug may be affected by aberrant splicing. Thus by correcting the aberrant splicing the drug will more efficient and/or will not associated with adverse side effects.

By a "therapeutically effective amount" of the inhibitor as above described is meant a sufficient amount of the inhibitor to reach a therapeutical effect. It will be understood, however, that the total daily usage of the compounds and compositions of the present invention will be decided by the attending physician within the scope of sound medical

judgment. The specific therapeutically effective dose level for any particular subject will depend upon a variety of factors including the disorder being treated and the severity of the disorder; activity of the specific compound employed; the specific composition employed, the age, body weight, general health, sex and diet of the subject; the time of administration, route of administration, and rate of excretion of the specific compound employed; the duration of the treatment; drugs used in combination or coincidential with the specific polypeptide employed; and like factors well known in the medical arts. For example, it is well within the skill of the art to start doses of the compound at levels lower than those required to achieve the desired therapeutic effect and to gradually increase the dosage until the desired effect is achieved. However, the daily dosage of the products may be varied over a wide range from 0.01 to 1,000 mg per adult per day. Preferably, the compositions contain 0.01, 0.05, 0.1, 0.5, 1.0, 2.5, 5.0, 10.0, 15.0, 25.0, 50.0, 100, 250 and 500 mg of the active ingredient for the symptomatic adjustment of the dosage to the subject to be treated. A medicament typically contains from about 0.01 mg to about 500 mg of the active ingredient, preferably from 1 mg to about 100 mg of the active ingredient. An effective amount of the drug is ordinarily supplied at a dosage level from 0.0002 mg/kg to about 20 mg/kg of body weight per day, especially from about 0.001 mg/kg to 7 mg/kg of body weight per day.

The Inhibitor of the invention may be combined with pharmaceutically acceptable excipients, and optionally sustained-release matrices, such as biodegradable polymers, to form therapeutic compositions.

"Pharmaceutically" or "pharmaceutically acceptable" refers to molecular entities and compositions that do not produce an adverse, allergic or other untoward reaction when administered to a mammal, especially a human, as appropriate. A pharmaceutically acceptable carrier or excipient refers to a non-toxic solid, semi-solid or liquid filler, diluent, encapsulating material or formulation auxiliary of any type.

In the pharmaceutical compositions of the present invention for oral, sublingual, subcutaneous, intramuscular, intravenous, transdermal, local or rectal administration, the active principle, alone or in combination with another active principle, can be administered in a unit administration form, as a mixture with conventional pharmaceutical supports, to animals and human beings. Suitable unit administration forms comprise oral-route forms such as tablets, gel capsules, powders, granules and oral suspensions or solutions, sublingual and buccal administration forms, aerosols, implants, subcutaneous, transdermal, topical,

intraperitoneal, intramuscular, intravenous, subdermal, transdermal, intrathecal and intranasal administration forms and rectal administration forms.

Preferably, the pharmaceutical compositions contain vehicles which are pharmaceutically acceptable for a formulation capable of being injected. These may be in particular isotonic, sterile, saline solutions (monosodium or disodium phosphate, sodium, potassium, calcium or magnesium chloride and the like or mixtures of such salts), or dry, especially freeze-dried compositions which upon addition, depending on the case, of sterilized water or physiological saline, permit the constitution of injectable solutions.

The pharmaceutical forms suitable for injectable use include sterile aqueous solutions or dispersions; formulations including sesame oil, peanut oil or aqueous propylene glycol ; and sterile powders for the extemporaneous preparation of sterile injectable solutions or dispersions. In all cases, the form must be sterile and must be fluid to the extent that easy syringability exists. It must be stable under the conditions of manufacture and storage and must be preserved against the contaminating action of microorganisms, such as bacteria and fungi.

Solutions comprising compounds of the invention as free base or pharmacologically acceptable salts can be prepared in water suitably mixed with a surfactant, such as hydroxypropylcellulose. Dispersions can also be prepared in glycerol, liquid polyethylene glycols, and mixtures thereof and in oils. Under ordinary conditions of storage and use, these preparations contain a preservative to prevent the growth of microorganisms.

The Inhibitor of the invention can be formulated into a composition in a neutral or salt form. Pharmaceutically acceptable salts include the acid addition salts (formed with the free amino groups of the protein) and which are formed with inorganic acids such as, for example, hydrochloric or phosphoric acids, or such organic acids as acetic, oxalic, tartaric, mandelic, and the like. Salts formed with the free carboxyl groups can also be derived from inorganic bases such as, for example, sodium, potassium, ammonium, calcium, or ferric hydroxides, and such organic bases as isopropylamine, trimethylamine, histidine, procaine and the like.

The carrier can also be a solvent or dispersion medium containing, for example, water, ethanol, polyol (for example, glycerol, propylene glycol, and liquid polyethylene glycol, and the like), suitable mixtures thereof, and vegetables oils. The proper fluidity can be maintained, for example, by the use of a coating, such as lecithin, by the maintenance of the required particle size in the case of dispersion and by the use of surfactants. The prevention of the action of microorganisms can be brought about by various antibacterial and antifusoluble agents, for example, parabens, chlorobutanol, phenol, sorbic acid, thimerosal, and the like. In

many cases, it will be preferable to include isotonic agents, for example, sugars or sodium chloride. Prolonged absorption of the injectable compositions can be brought about by the use in the compositions of agents delaying absorption, for example, aluminium monostearate and gelatin.

Sterile injectable solutions are prepared by incorporating the active polypeptides in the required amount in the appropriate solvent with various of the other ingredients enumerated above, as required, followed by filtered sterilization. Generally, dispersions are prepared by incorporating the various sterilized active ingredients into a sterile vehicle which contains the basic dispersion medium and the required other ingredients from those enumerated above. In the case of sterile powders for the preparation of sterile injectable solutions, the preferred methods of preparation are vacuum-drying and freeze-drying techniques which yield a powder of the active ingredient plus any additional desired ingredient from a previously sterile-filtered solution thereof.

Upon formulation, solutions will be administered in a manner compatible with the dosage formulation and in such amount as is therapeutically effective. The formulations are easily administered in a variety of dosage forms, such as the type of injectable solutions described above, but drug release capsules and the like can also be employed.

For parenteral administration in an aqueous solution, for example, the solution should be suitably buffered if necessary and the liquid diluent first rendered isotonic with sufficient saline or glucose. These particular aqueous solutions are especially suitable for intravenous, intramuscular, subcutaneous and intraperitoneal administration. In this connection, sterile aqueous media which can be employed will be known to those of skill in the art in light of the present disclosure. For example, one dosage could be dissolved in 1 ml of isotonic NaCl solution and either added to 1000 ml of hypodermoclysis fluid or injected at the proposed site of infusion. Some variation in dosage will necessarily occur depending on the condition of the subject being treated. The person responsible for administration will, in any event, determine the appropriate dose for the individual subject.

The Inhibitor of the invention may be formulated within a therapeutic mixture to comprise about 0.0001 to 1.0 milligrams, or about 0.001 to 0.1 milligrams, or about 0.1 to 1.0 or even about 10 milligrams per dose or so. Multiple doses can also be administered.

In addition to the compounds of the invention formulated for parenteral administration, such as intravenous or intramuscular injection, other pharmaceutically acceptable forms include, e.g. tablets or other solids for oral administration; liposomal formulations ; time release capsules ; and any other form currently used.

The present invention also relates to a method for screening a drug for modulating RNA alternative splicing in a subject comprising the steps consisting of i) testing a plurality of test substances fot their ability to inhibit the mitochondrial compex I activity in a test cell, and ii) positeveli selecting the test substances that are able to inhibit the mirochondrial complex I activity.

Inhibition of mitochondrial compex I activity may be evaluated by any method known in the art (see for example methods decribes above).

The term "test cell" refers to any cell that can be used in an in vitro assay. In particularly, the test cell is a human test cell. The test cells may include but are not limited to cells from skin, mammary, lung, intestinal epithelium, brain, heart, eye… In one embodiment the test cell is a malignant cell. In one embodiment the test cell is stem cell (mescenhymal stem cell or pluripotent stem cells such as embryonic stem cells or IPS stem cells). In one embodiment the test celle is a stem cell which harbor a monogenic mutation in a gene of interst (for example genes described in Table B).

The test substances that have been positively selected at the end of any one of the embodiments of the in vitro screening which has been described previously in the present specification may be subjected to further selection steps in view of further assaying its in vivo properties on animal model for a disease of interest or eventually in human in the context of clinical trials. Indeed the test substances that may be selected at the end of any one of the embodiments of the in vitro screening may find various applications.

In one embodiment, the screening method of the invention may further comprise the consisting of testing the tes substances selected at the end of step ii) for their ability to modulate RNA splicing in the test cell, and positively seclecting the test substances that are able to modulate the RNA splicing in the test cell.

Typically, the ability of the test substance to modulate the RNA splicing in the test cell is evaluated for a gene of interest or a plurality of genes of interest. Said genes may be for example selected from Table B. In one embodiment the test cell is a stem cell (e.g. an embryonic stem cell) which harbours a mutation that affect RNA splicing in the cell. For

example, the test cell may be the test cells described in the EXAMPLE, namely VUB03_DM1 cells. Then the splicing of INSR1, SERCA1 and TNNT2 genes may be then studied as described in the EXAMPLE.

In some embodiments, the test substance of may be selected from the group consisting of peptides, peptidomimetics, small organic molecules, or nucleic acids. For example the test substance according to the invention may be selected from a library of compounds previously synthetized, or a library of compounds for which the structure is determined in a database, or from a library of compounds that have been synthetized de novo. In a particular embodiment, the test substance may be selected form small organic molecules. As used herein, the term "small organic molecule" refers to a molecule of size comparable to those organic molecules generally sued in pharmaceuticals. The term excludes biological macromolecules (e.g.; proteins, nucleic acids, etc.); preferred small organic molecules range in size up to 2000da, and most preferably up to about 1000 Da.

The test substances that have been positively selected at the end of any one of the embodiments of the in vitro screening which has been described previously in the present specification may be subjected to further selection steps in view of further assaying its in vivo properties on animal model for a disease of interest or eventually in human in the context of clinical trials. For example, the test substances selected may be evaluated in an in vivo context as described in the EXAMPLE. Brief a DM1 mouse may be adminuistered with the test substances and the recovery in motor skills may be then evaluated. The test substances thar are able to improve the motor skills of the animal model in comparison with the animal not administered with the test substances or administered with a reference molecule (e.g. metformin) may be then selected.

The invention will be further illustrated by the following figures and examples. However, these examples and figures should not be interpreted in any way as limiting the scope of the present invention.

FIGURES:

Example 1: Metformin control of multiple alternative RNA splicing opens new therapeutic potentials

Methods:

The wild type and mutated human embryonic stem cell lines VUB01 and VUB03_DM1 were differentiated in MPCs, transfected with Lipofectamine LTX or not with minigenes allowing the splicing of *TNNT2* and *CLCN1*, and then exposed during 48 hours with various chemical compounds. Total RNA from treated cells was extracted and submitted after reverse transcription to PCR and QPCR analysis to study the expressions of the splicing variant of the *INSR* exon11, *SERCA1* exon22, *TNNT2* exon5, and *CLCN1* exon 7A and the expression of *SRSF1, SRSF6, SFPQ, RBM3, RBM5, RBM4B, RBM45*. Splicing of *INSR* exon11, *SERCA1* exon22, *TNNT2* exon5 after treatment with metformin was also analyzed in human primary myoblasts coming from DM1 patients. Implication of *SRSF1, SFPQ* and *RBM3* in *INSR* exon 11 and SERCA1 exon 22 splicings was investigated through their transient extinction after transfection of siRNA from Qiagen with Lipofectamine RNAiMax in MPCs VUB03_DM1 followed by RT-QPCR and RT-PCR analysis. Quantification of ROS production in treated VUB03_DM1 was performed using the ROS Detection kit from Molecular probes in 96 well plates on an Analyst GT after normalization by the cell number in wells determined on an Arrayscan after nuclei staining with dapi. Wild type and DMSXL mice[20] were treated intraperinoneally for one month with saline or 60 and 180 mg/kg/day of metformin. After one month motor performance was assessed by a grip test and specific force quantified[20]. Mice were sacrified and TA dissected for foci detection by fish and analysis of transgenic DMPK expression and splicing defects analysis by RT-PCR. *INSR* exon11 splicing was analyzed by RT-QPCR in PBLs from patients affected or not with different monogenic diseases after 48 hours of treatment with 25mM metformin and 100µM troglitazone or in PBLs directly collected from diabetic non DM1 patients treated with metformin or with sitagliptin.

Results and discussion:

Myotonic dystrophy type I (DM1) is a monogenic disease characterized by changes in the RNA alternative splicing of a number of genes, leading to abnormal protein isoform ratios and clinical consequences[6-8]. Within the framework of a research program exploring pathological mechanisms in derivatives of stem cell lines derived from embryos carrying

a DM1 defective gene[5], we explored the therapeutic potential of the anti-diabetic biguanide, metformin, because insulin resistance is a hallmark of the disease.

Mesodermal precursor cells (MPCs) derived from the affected embryonic stem cell line VUB03_DM1 and the control cell line VUB01 were exposed for 48 hours to various doses of metformin. This treatment revealed a significant post-transcriptional effect since the inclusion by alternative splicing of exon 11 of *INSR* increased in DM1 cells. A similar shift towards exon 11 inclusion was also observed in control MPCs. In order to determine the overall biological effect of the drug in DM1 cells, the alternative splicing of a series of genes affected by the disease was explored. Reduction of the abnormally high exclusion of exon 22 was observed in MPCs for *SERCA1 (ATP2A1)*[9]. Since some genes were not naturally expressed in MPCs, relevant minigenes were used for hcTNT[6] and *Clcn1*exon7a. Correction of the splicing defects was also observed upon treatment, with decreased inclusion of exon 5 for *TNNT2* and exon 7a for *Clcn1*. Control experiments with the hcTNT minigene mutated in the CUGBP1 response element showed that the normalizing effect of metformin did not depend on the DM1- associated splice factor, CUGBP1. This was consistent with the fact that metformin affected exon 7a of *Clcn1*, which is not controlled by CUGBP1[10]. Similar responses to metformin were observed for the endogenous expression of *INSR1*, *SERCA1* and *TNNT2* in human wild type and DM1 myoblasts.

The pathway by which metformin modulates RNA alternative splicing was explored. A quantitative PCR assay was developed to quantify the relative expression of the *INSR* variants +/- exon11. A vast body of literature points to activation of AMPK[11], inhibition of the mTOR signaling pathway [12], and decreased mitochondrial complex I activity[13, 14] as major molecular targets of the drug. The first two working hypotheses were excluded because neither the specific AMPK agonist, AICAR, nor the specific mTOR inhibitor, rapamycin, elicited changes in the alternative splicing of *INSR* exon11 in spite of activation of the AMPK/mTOR pathway leading to protein synthesis inhibition as measured by eEF2 phosphorylation. The role of AMPK was also excluded because the metformin effect was not altered when the drug was applied to VUB03_DM1 MPCs while the activity of AMPK was blocked with dorsomorphin. Metformin inhibits mitochondrial complex I, as monitored by the accumulation of reactive oxygen species (ROS) in MPC VUB03_DM1 treated with 25mM Metformin. A similar result was obtained when applying 2μM of the specific mitochondrial complex I inhibitor rotenone[15] and this treatment also revealed itself to be instrumental in inducing the inclusion of exon 11 of *INSR* in a dose- dependent manner. Rotenone is a

potent blocker of mitochondrial respiratory chain complex I in contrast to metformin, known to only provoke partial inhibition[16]. Therefore, troglitazone was assayed, as it shares this limited effect with metformin while otherwise influencing very different signaling pathways[16, 17]. Treatment of VUB03_DM1 MPCs with troglitazone confirmed the impact of this more limited mitochondrial complex I effect on *INSR* alternative splicing. The same effect was observed in response to resveratrol used for its ability to inhibit complex I and III of the mitochondrial respiratory chain[18]. Altogether, this series of pharmacological experiments pointed to a metformin mechanism of action on alternative splicing that requires a partial inhibition of mitochondrial complex I, which is known to lead to enhanced levels of reactive oxygen and nitrogen species in the cell.

Molecular mechanisms of action of the drug on alternative splicing was explored on the basis of a recent whole genome transcriptome analysis that revealed down-regulation by metformin, but not rapamycin, of seven potential splice regulators[19]. Among them, RT-qPCR analysis revealed that expressions of *RBM4B, RBM5, RBM45* and *SRSF6* transcripts were not strongly regulated while that of *RBM3, SRSF1* and *SFPQ* decreased with increasing concentrations of metformin. Down-regulation of these three latter genes was also obtained with rotenone, troglitazone and resveratrol. A parallel, decrease in concentration of RBM3, SRSF1 and SFPQ proteins was observed by Western blot analysis in response to metformin. Independent knock-down by RNA interference of the genes encoding these three RNA-binding proteins in VUB03_DM1 MPCs differentially impacted *SERCA1* exon 22 alternative splicing. Knocking down *SRSF1* induced *SERCA1* exon 22 inclusion while *SFPQ* promoted its skipping. RBM3 had no effect. This altered equilibrium in a set of splice regulators governing the same alternative splice with opposite effects likely plays a role in the final protein isoform ratio recorded with the metformin treatment, rather than a specific effect of the drug on a single regulator. Changes observed in *INSR1* splicing of exon 11 were not statistically significant, suggesting additional, yet unrevealed mechanisms.

To determine the biological effects of metformin *in vivo*, a DM1 mouse model having motor performance defects associated with the introduction of a mutant *DMPK* construct was used[20]. DM1 mice were treated for a month with a daily dose of 60 or 180 mg/kg. Metformin induced no changes in either mutant *DMPK* expression or nuclear aggregates. In contrast, the treatment did impact alternative splicing, as shown by exon 5 inclusion being restored in the muscle-associated gene *m-titin* in the diaphragm, a gene that exhibits the greatest splicing alterations in this mouse model. In parallel, a statistically significant recovery in

motor skills was observed in the grip test after treatment. This improvement was observed while the drug had no general metabolic effect on skeletal muscle, as verified by muscle weight and maximal tetanic force normalized to weight of the *tibialis anterior*.

We took the opportunity of patients currently being treated with metformin for type 2 diabetes mellitus, to check whether the drug affected alternative splicing at therapeutic doses in humans. In order to perform a clinical trial in which metformun would be temporarily replaced by another anti-diabetic drug, preliminary experiments were carried out in vitro on peripheral blood lymphocytes (PBLs) and sitagliptin was selected as it did not show any effect on alternative splicing of *INSR1*. Fifteen diabetic patients who had been on a stable dose of metformin between 2.1 and 3g/day for more than a year were then involved in a study where metformin was replaced by sitagliptin for one month (NCT 01349387). It was checked that this change in treatment induced no difference in blood glucose levels. Despite wide physiological variability in *INSR* expression, a statistically significant shift in the transcript ratio towards inclusion of exon 11 was observed with metformin intake. A statistically significant correlation was observed between the decreased *INSR* + exon 11 / - exon 11 ratio with sitagliptin intake and its increase after restarting metformin treatment.

The primary result of this study is that metformin, at doses that are compatible with clinical use, impacts the alternative splicing of many genes having abnormal isoform ratios in cells from DM1 patients. These biological data, along with the motor improvement in a mouse disease model, pave the way for a clinical trial assessing the effects of metformin in patients with DM1 not only on defects in glucose consumption but more broadly on all symptoms associated to the disease.

Potentially as important, the action of metformin on alternative splicing has been shown to not depend on a pre-existing pathology and several other drugs that discretely affect cellular oxidative equilibrium had similar impacts. Central to these biological effects is a subset of members of the vast group of splice regulators[1]. The demonstration that their transcriptional levels can be modulated by drugs opens a path that may have far-reaching clinical applications. Affecting the expression of subsets of splice regulators may reveal itself to be instrumental for therapeutics applied to diseases that would benefit from exon skipping[21]. Even more broadly, altering the isoform ratio of certain proteins may be clinically relevant because the various protein isoforms have clearly differential roles. Along that line, it was interesting to note that alternative splicing of FAS exon 6, which gives rise to either a

pro- or an anti-apoptotic protein[22, 23], was strongly affected by metformin in diabetic patients.

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Throughout this application, various references describe the state of the art to which this invention pertains. The disclosures of these references are hereby incorporated by reference into the present disclosure.

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TABLE A: list of the proteins which are the component of the mitochondrial complex I.

Approved Symbol	Approved Name	Previous Symbols	Synonyms	Chromosome
MT-ND1	mitochondrially encoded NADH dehydrogenase 1	MTND1	ND1, NAD1	mitochondria
MT-ND2	mitochondrially encoded NADH dehydrogenase 2	MTND2	ND2, NAD2	mitochondria
MT-ND3	mitochondrially encoded NADH dehydrogenase 3	MTND3	ND3, NAD3	mitochondria
MT-ND4	mitochondrially encoded NADH dehydrogenase 4	MTND4	ND4, NAD4	mitochondria
MT-ND4L	mitochondrially encoded NADH dehydrogenase 4L	MTND4L	ND4L, NAD4L	mitochondria
MT-ND5	mitochondrially encoded NADH dehydrogenase 5	MTND5	ND5, NAD5	mitochondria
MT-ND6	mitochondrially encoded NADH dehydrogenase 6	MTND6	NAD6, ND6	mitochondria
NDUFA1	NADH dehydrogenase (ubiquinone) 1 alpha subcomplex, 1, 7.5kDa		MWFE, CI-MWFE	Xq24
NDUFA2	NADH dehydrogenase (ubiquinone) 1 alpha subcomplex, 2, 8kDa		B8	5q31.2
NDUFA3	NADH dehydrogenase (ubiquinone) 1 alpha subcomplex, 3, 9kDa		B9	19q13.42
NDUFA4	NADH dehydrogenase (ubiquinone) 1 alpha subcomplex, 4, 9kDa		MLRQ, CI-9k	7p21.3
NDUFA5	NADH dehydrogenase (ubiquinone) 1 alpha subcomplex, 5, 13kDa		B13, NUFM, CI-13KD-B, UQOR13, CI-13kB	7q31.33

NDUFA6	NADH dehydrogenase (ubiquinone) 1 alpha subcomplex, 6, 14kDa		B14, LYRM6, CI-B14, NADHB14	22q13.2
NDUFA7	NADH dehydrogenase (ubiquinone) 1 alpha subcomplex, 7, 14.5kDa		B14.5a	19p13.2
NDUFA8	NADH dehydrogenase (ubiquinone) 1 alpha subcomplex, 8, 19kDa		PGIV, MGC793	9q33.2
NDUFA9	NADH dehydrogenase (ubiquinone) 1 alpha subcomplex, 9, 39kDa	NDUFS2L	SDR22E1, CI-39k	12p13.3
NDUFA10	NADH dehydrogenase (ubiquinone) 1 alpha subcomplex, 10, 42kDa		CI-42k	2q37.3
NDUFA11	NADH dehydrogenase (ubiquinone) 1 alpha subcomplex, 11, 14.7kDa		B14.7	19p13.3
NDUFA12	NADH dehydrogenase (ubiquinone) 1 alpha subcomplex, 12		DAP13, B17.2	12q22
NDUFA13	NADH dehydrogenase (ubiquinone) 1 alpha subcomplex, 13		CGI-39, CDA016, GRIM-19, GRIM19, B16.6	19p13.11
NDUFAB1	NADH dehydrogenase (ubiquinone) 1, alpha/beta subcomplex, 1, 8kDa		SDAP, FASN2A, ACP	16p12.3
NDUFB1	NADH dehydrogenase (ubiquinone) 1 beta subcomplex, 1, 7kDa		MNLL, CI-MNLL	14q31.3
NDUFB2	NADH dehydrogenase (ubiquinone) 1 beta		AGGG, CI-AGGG	7q34

	subcomplex, 2, 8kDa			
NDUFB3	NADH dehydrogenase (ubiquinone) 1 beta subcomplex, 3, 12kDa		B12	2q33.1
NDUFB4	NADH dehydrogenase (ubiquinone) 1 beta subcomplex, 4, 15kDa		B15	3q13.33
NDUFB5	NADH dehydrogenase (ubiquinone) 1 beta subcomplex, 5, 16kDa		SGDH, CI-SGDH, MGC12314	3q27.1
NDUFB6	NADH dehydrogenase (ubiquinone) 1 beta subcomplex, 6, 17kDa		B17, CI	9p13.2
NDUFB7	NADH dehydrogenase (ubiquinone) 1 beta subcomplex, 7, 18kDa		B18, CI-B18, MGC2480	19p13.12
NDUFB8	NADH dehydrogenase (ubiquinone) 1 beta subcomplex, 8, 19kDa		ASHI, CI-ASHI	10q24.31
NDUFB9	NADH dehydrogenase (ubiquinone) 1 beta subcomplex, 9, 22kDa		B22, UQOR22, LYRM3	8q24.13
NDUFB10	NADH dehydrogenase (ubiquinone) 1 beta subcomplex, 10, 22kDa		PDSW	16p13.3
NDUFB11	NADH dehydrogenase (ubiquinone) 1 beta subcomplex, 11, 17.3kDa		ESSS, NP17.3, Np15	Xp11.3
NDUFC1	NADH dehydrogenase (ubiquinone) 1, subcomplex unknown, 1, 6kDa		KFYI	4q31.1
NDUFC2	NADH dehydrogenase (ubiquinone) 1, subcomplex		B14.5b, HLC-1	11q14.1

	unknown, 2, 14.5kDa			
NDUFS1	NADH dehydrogenase (ubiquinone) Fe-S protein 1, 75kDa (NADH-coenzyme Q reductase)		CI-75k	2q33-q34
NDUFS2	NADH dehydrogenase (ubiquinone) Fe-S protein 2, 49kDa (NADH-coenzyme Q reductase)		CI-49	1q23.3
NDUFS3	NADH dehydrogenase (ubiquinone) Fe-S protein 3, 30kDa (NADH-coenzyme Q reductase)		CI-30	11p11.11
NDUFS4	NADH dehydrogenase (ubiquinone) Fe-S protein 4, 18kDa (NADH-coenzyme Q reductase)		AQDQ, CI-18	5q11.1
NDUFS5	NADH dehydrogenase (ubiquinone) Fe-S protein 5, 15kDa (NADH-coenzyme Q reductase)		CI-15k	1p34.2-p33
NDUFS6	NADH dehydrogenase (ubiquinone) Fe-S protein 6, 13kDa (NADH-coenzyme Q reductase)		CI-13kA	5p15.33
NDUFS7	NADH dehydrogenase (ubiquinone) Fe-S protein 7, 20kDa (NADH-coenzyme Q reductase)		PSST, FLJ46880, FLJ45860, CI-20	19p13
NDUFS8	NADH dehydrogenase (ubiquinone) Fe-S protein 8, 23kDa (NADH-coenzyme Q reductase)		TYKY, CI-23k	11q13.2

NDUFV1	NADH dehydrogenase (ubiquinone) flavoprotein 1, 51kDa		CI-51K	11q13
NDUFV2	NADH dehydrogenase (ubiquinone) flavoprotein 2, 24kDa		CI-24k	18p11.22
NDUFV3	NADH dehydrogenase (ubiquinone) flavoprotein 3, 10kDa		CI-10k	21q22.3

TABLE B: Selection of monogenic pathologies for which a modulation of alternate splicing, leading to a shift in ratio of isoforms, may bear therapeutic consequences.

Gene	Nb exons	Phéno	Name	Category
ABCA1	50			
		HDLD	familial HDL deficiency (hypoalphalipoproteinemia),autosomal dominant,without proven predisposition to coronary artery disease	metabolism/lipoprotein-lipid
		HDLDT1	Tangier disease,autosomal recessive,characterized by orange tonsils enlarged liver,spleen,lymph nodes,associated with very low HDL cholesterol level (analphalipoproteinemia),raised triglycerides,peripheral neuropathy and accumulation of cholesterol esters in macrophages	metabolism/lipoprotein-lipid
ABCA4	50			
		ARMD2	age related macular dystrophy 2 (heterozygous ABCA4 defect), see also STGD1	eye
		CORD4	cone-rod dystrophy 4, characterized by initial loss of visual acuity and macular chorioretinal atrophy, followed by a constriction of the peripheral visual field	eye
		RP19	retinitis pigmentosa 19,retinal rod-cone dystrophy,autosomal recessive characterized by initial night blindness in the first decade,followed by a decrease of visual acuity in the 2nd decade with	eye

			distinctive features of choriocapillaris atrophy	
		STGD1	Stargardt disease, juvenile, macular dystrophy 1, autosomal recessive, characterized by decreased central vision, atrophy of the macula and underlying retinal pigment epithelium and frequent yellow "flavimaculatus flecks" in the posterior pole of the retina, including late onset fundus flavimaculatus	eye
ABCC8	39			
		PHHID1	persistent hyperinsulinemia and hypoglycemia of infancy with pancreatic nesidioblastosis,diffuse 1	metabolism/carbohydrates
		PHHIF	persistent hyperinsulinemia and hypoglycemia of infancy with focal adenomatous hyperplasia of islet cells of pancreas and loss of heterozygosity of the 11p15.5 maternally imprinted region or paternal mutation of SUR1 and maternal loss of 11p15 imprinted genes,paternally mutated in focal adenomatous hyperplasia with hyperinsulinism	metabolism/carbohydrates, endocrinology
ACSL4	16			
		MRX63	mental retardation, X-linked 63	mental retardation
		MRX68	mental retardation, X-linked 68	mental retardation
ADAMTS13	20			

		TTPF	thrombotic thrombocytopenic purpura,familial,autosomal semidominant,characterized by anemia and thrombocytopenia due to intravascular destruction of erythrocytes and blood platelets,diffuse platelet-rich microthrombi in small vessels of mutiple organs with the major complications including renal failure and neurologic dysfunction including true hemolytic and uremic syndrome (HUS)	hematology, kidney and urinary tract
		USS	Schulman-Upshaw syndrome with congenital microangiopathic hemolytic anemia,thrombocytopenia	hematology
AIPL1	6			
		CORD3	retinal cone-rod dystrophy 3	eye
		LCA4	Leber congenital amaurosis type 4, autosomal recessive, characterized by congenital non evolutive blindness, with pendular nystagmus, anterior keratoconus, roving eye movements, absent ocular pursuit and eye poking, severe photophobia, hypermetropia, normal fundus at birth followed by salt and pepper aspect of retina and typical RP, non recordable ERG	eye
ALS2	34			
		ALS2	familial amyotrophic lateral sclerosis, juvenile type, autosomal recessive	neurology
		IAHSP	spastic paralysis ,infantile onset,ascending	neurology
		PLSJ	primary lateral sclerosis juvenile	neurology
ANKH	12			

		CCAL2	chondrocalcinosis 2 (calcium pyrophosphate-dihydrate deposition disease) with early-onset osteoarthritis,calcium pyrophosphate dihydrate deposition disease	osteo-articular
		CMDJ	craniometaphyseal dysplasia,characterized by hypertelorism,hyperostosis and abnormal modeling,increased density of tubular bones and metaphyseal widening,especially of the lower limbs,dominant type,Jackson type	osteo-articular
APC	15			
		APC	adenomatous polyposis coli,also included : attenuated form (mutation codons 1595 to 2844),Gardner syndrome,some cases of Turcot syndrome,congenital hypertrophy of retinal pigment epithelium with mutations codons 463-1387,desmoid tumors (mutations codons 1444-1598 and 1924) and other extracolonic manifestations	digestive tract/gastrointestinal
		CHRPE	retinal pigment epithelium,congenital hypertrophy,Gardner syndrome including Turcot's syndrome (with association to malignant tumor of the CNS)	digestive tract/gastrointestinal, eye
		FIF	fibromatosis familial infiltrative,desmoid,hereditary	digestive tract/gastrointestinal
APOA1	4			

		APOA1	autosomal dominant systemic amyloidosis non neuropathic with widely deposition of amyloid and a great clinical variation among and between families with major clinical problems related to renal,hepatic or cardiac involvement (APOA1 defect with a single extrapositive charge)	cardiovascular, kidney and urinary tract, digestive tract/liver and annex
		CCLD	corneal opacities with HDL deficiency, including analphalipoproteinemia (corneal clouding)	*metabolism/lipoprotein-lipid, eye*
		FAP3	familial amyloid polyneuropathy III,Iowa type (ApoA1 variant,deposit) including Van Allen type	*connective tissue*
APOB	29			
		APOB	abetalipoproteinemia,normotriglyceridemic (ApoB-100 absence),Steinberg type, including familial hypobeta lipoproteinemia	metabolism/lipoprotein-lipid
		AHLP	acanthocytosis, hypobetalipoproteinemia	metabolism/lipoprotein-lipid
		HPCHB	primary hypercholesterolemia with peripheral vascular disease, familial ligand defective APO-B (receptor binding defective LDL) and/or myocardial infarction susceptibility with an insertion/deletion polymorphism in the signal peptide	metabolism/lipoprotein-lipid
ATP2A2	21			
		AKV	acrokeratosis verruciformis, Hopf disease with warty hyperkeratotic lesions on the dorsal aspect of the hands and feet and on the knees and elbows ,without evidence of dyskeratosis	dermatology

		DAR	keratosis follicularis, Darier-White disease, characterized by warty papules and plaques in seborrheic areas, palmoplantar pits and distinctive nail abnormalities	dermatology
ATP7A	23			
		MNK	Menkes syndrome,X-linked recessive disorder of copper metabolism,lethal in childhood	*metabolism/mental*
		OHS	occipital horn syndrome, allelic to MNK, previously known as Ehlers-Danlos syndrome type IX, characterized by skin laxity, hyperextensible joints, bladder diverticula, caracteristic occipital exostoses	connective tissue, metabolism/mental
ATP8B1	27			
		BRIC	benign recurrent intrahepatic cholestasis,Summerskill syndrome ,allelic to PFIC1	digestive tract/liver and annex
		PFIC1	progressive (fatal) familial intrahepatic cholestasis,Byler disease,characterized by high serum bile concentration with intermittent jaundice,normal serum gamma-glutamyl transferase and low biliary salt concentrations,and extrahepatic features such as pancreatitis and marked intestinal malabsorption,allelic to BRIC	digestive tract/liver and annex
ATRX	34			
		ATRX	thalassemia alpha (Hb H), mental retardation syndrome, with facial dysmorphism and epilepsy absent speech, non deletion type, X linked, including	*metabolism/porphyrin and heme*

			mild or moderate mental retardation without characteristic facial features	
		CHLS	Chudley-Lowry syndrome, with moderate to severe mental retardation, short stature, mild obesity, hypogonadism, anteverted nares, inverted -V-shaped upper-lip and macrostomia, allelic to ATRX	mental retardation
		CWS	mental retardation X-linked syndrome, Carpenter Waziri type including coarse facies, brachydactyly and short stature, allelic to ATRX	osteo-articular, mental retardation
		JMS	Juberg-Marsidi syndrome of mental retardation,with growth retardation,deafness,microgenitalism,allelic to ATRX	*congenital malformation, ear, mental retardation, sex-genitalia*
		SFMS	Smith-Fineman-Myers syndrome,characterized by a severe mental retardation,microcephaly,growth failure,facial anomalies and bilateral cryptorchidism overlapping with the ATRX syndrome	congenital malformation, mental retardation
		SHS	mental retardation, X-linked, syndromic, with spastic diplegia (Sutherland-Haan syndrome) and microcephaly, lean body habitus, short stature, striking facial appearance with long narrow faces, upward slant of the eyes, malar hypoplasia, prognathism, high-arched palate and nasal speech. In addition, small testes and midline defects as anal atresia or imperforate anus, clefting of palate	neurology, mental retardation

			and/or uvula, iris coloboma and Tetralogy of Fallot	
BCS1L	7			
		GRACILE	growth retardation,aminoaciduria,cholestasis,iron overload,lactic acidosis and early death,finnish people ,Fellman syndrome	metabolism/lipoprotein-lipid, metabolism/metal
		TELF	complex 3 deficiency with tubulopathy,encephalopathy and liver failure	metabolism/lipoprotein-lipid
BTK	19			
		AGMGHX	agammaglobulinemia and isolated growth hormone deficiency,X-linked ,with short stature, retarded bone age and delayed onset of puberty and immunodeficiency characterized by absent specific antibody production ,Fleisher syndrome	defense and immunity, endocrinology
		AGMX1	agammaglobulinemia, X-linked 1, Bruton type	defense and immunity
		AGMX2	agammaglobulinemia,X-linked 2,with isolated growth hormone deficiency,same as AGMX1	defense and immunity
CACNA1A	48			
		BPTI	benign paroxysmal torticollis of infancy characterized by recurrent episodes of head tilt secondary to cervical dystonia,often accompanied by vomiting, pallor, and ataxia, settling spontaneously	neurology

			within hours or days,between 1and 5 years	
		EA2	episodic (paroxysmal) vestibular cerebellar ataxia, autosomal dominant, beginning in the first or second decade, with long lasting dysarthria and interictal nystagmus, atrophy of the cerebellar vermis, acetazolamide responsive, without myokymia, may be associated to primary generalized epilepsy, allelic to SCA6	neurology
		MHP1	migraine, familial, hemiplegic, with/without aura, associated with a permanent cerebellar ataxia	neurology
		SCA6	ataxia, spinal cerebellar 6, (autosomal dominant cebellar ataxia type I) characterized by a predominant cerebellar phenotype without retinal degeneration, progressive, with anticipation and triplet CAG repeat amplification in the intracellular C-terminus region of CACNA1A calcium channel, allelic to EA2, most frequently sporadic, with numerous oval or rod shaped aggregates in the Purkinje cells leading to their degeneration,and atrophy of the cerebellar vermis	neurology
CASQ2	11			
		VIST	ventricular tadrycardio,stress-induced (and catecholamine induced)	cardiovascular
		VTSIP1	ventricular tachycardia, stress-induced, catecholaminergic, with syncope seizures or sudden death	cardiovascular

CASR	7			
		HHC1	hypercalcemia hypocalciuric,familial,benign 1,autosomal dominant with neuromuscular symptoms hyperphosphatemia and inappropriately low levels of parathyroid hormone,including any cases of wild hypocalcemia with hyperphosphatemia and normal PTH	endocrinology
		HPT2	hypoparathyroidism,autosomal dominant	endocrinology
		HYPOCA	mild hypocalcemia with hyperphosphatemia and normal PTH levels	endocrinology
		HYPOCA B	hypocalcemia severe,autosomal dominant ,with Barrter-like syndrome , nephrocalcinosis, impaired renal function , clinical features of Bartter syndrome (see 241200): decrease in distal tubular fractional chloride reabsorption rate and negative NaCl balance , hypomagnesemia, hypokalemia with metabolic alkalosis, hyperreninemia, and hyperaldosteronemia	kidney and urinary tract
		NSHPT	neonatal severe hyperparathyroidism,heterozygous or homozygous mutation of HHC1	endocrinology
CDH23	13			
		DFNB12	neurosensory recessive deafness 12,non syndromic,prelingual,stable,profound	ear
		USH1D	Usher syndrome type ID, characterized by profound congenital neurosensory deafness, constant vestibular dysfunction and retinitis pigmentosa of prepubertal	ear, eye

			onset, leading to blindness	
CLCN1	23			
		MCR	myotonia, generalized, Becker disease	neuromuscular
		MCT	myotonia congenita,autosomal dominant (Thomsen disease),including myotonia levior	neuromuscular
CLCN5	12			
		FILWP	familial idiopathic low molecular weight proteinuria,proximal tubulopathy with relatively conserved renal function in young patients,without rickets	kidney and urinary tract
		NPHL1	nephrolithiasis,recessive,X linked,with renal failure,same gene as Dent syndrome and X-linked hypophosphatemic rickets	metabolism/membrane transport
		NPHL2	X-linked recessive hypophosphatemic rickets,proximal renal tubular syndrome with low molecular weight proteinuria,hypercalciuria,nephrocalcinosis and progressive renal failure,including Dent syndrome,(same gene as XRN/NPHL1,OMIM 300009) and the Japan variant	metabolism/membrane transport
CLCNKB	20			
		BSNDL	Bartter syndrome type IV like with sensorineural deafness and salt wasting, hypokalemic metabolic alkalosis, autosomal recessive, with polyhydramnios, premature birth, postnatal polyuria and hypokalemic hypochloremic metabolic alkalosis, and a typical appearance, a prominent forehead,	*kidney and urinary tract, ear*

			triangular facies with drooping mouth, and large eyes and pinnae	
		CLCNKB	Bartter syndrome,type III,characterized by hypokalemic metabolic acidosis and renal salt wasting,and a highly variable phenotype ranging from episodes of severe dehydratation in neonatal period to almost asymptomatic patients during adolescence	kidney and urinary tract
		GTMS2	Gitelman syndrome 2, hypokalemic alkalosis in conjunction with hypocalciuria and hypomagnesemia, hypermagnesiuria, late age of presentation (>15 years) and normal growth	kidney and urinary tract
COL11 A1	66			
		AOM2	Stickler syndrome 2, autosomal dominant, characterized by a membranous or type 1 vitreous phenotype associated with congenital myopia, midline clefting, a flattened mid-facial appearance, neurosensory deafness and joint hypermobility and a degenerative arthropathy, later in life (arthroophthalmopathy,)	ear, eye, osteo-articular
		MRSH	Marshall syndrome characterized by midface hypoplasia,saddle nose,myopia,early-onset cataract,neurosensory deafness progressive,predominantly cochlear without defective morphogenesis of the osseous labyrinthe,short stature	ear, eye
COL11	66			

A2				
		DFNA13	neurosensory dominant deafness 13,non syndromic,postlingual,non progressive and predominantly affecting middle frequencies	*ear*
		OCDD	osteochondrodysplasia with neurosensory deafness, cleft palate, without eye involvement, including dominant Stickler-like syndrome	connective tissue
		OSMED	otospondylomegaepiphyseal dysplasia (chondrodystrophy with neurosensory deafness), Nance-Insley syndrome, including flat face, severe neurosensory deafness, cleft palate and short limbs without ocular involvment, including Weissenbacher-Zweymüller syndrome (OMIM 277610)	connective tissue
COL1A 1	51			
		EDS1C	Ehlers-Danlos syndrome,type I ,gravis,classical type,characterized by joint hyperextensibility,joint hypermobility,widened atrophic scars	connective tissue
		EDS7A1	Ehlers-Danlos syndrome, arthrochalasia type VIIA, characterized by severe generalized joint hypermobility, with recurrent subluxations, congenital bilateral hips dislocations	connective tissue
		OI1A	osteogenesis imperfecta,types I & IA with dentinogenesis imperfecta	connective tissue
		OI2A	osteogenesis imperfecta,type II,congenital,lethal	connective tissue

		OI3A	osteogenesis imperfecta,type III,severe,non lethal,dominant and recessive	connective tissue
		OI4A	osteogenesis imperfecta,type IV moderately severe	connective tissue
COL1A2	52			
		EDS11	Ehlers-Danlos syndrome 11, autosomal recessive , characterized by joint hypermobility, skin hyperextensibility, and cardiac valvular defects	osteo-articular, dermatology
		EDS7A2	Ehlers-Danlos syndrome, arthrochalasia type VIIA2, characterized by severe generalized joint hypermobility, with recurrent subluxations, congenital bilateral hip dislocations	connective tissue
		MFSV	Marfan syndrome variant (R618Q substitution in COL1A2)	connective tissue
		OI1B	osteogenesis imperfecta,types I and IA with dentinogenesis imperfecta	connective tissue
		OI2B	osteogenesis imperfecta,type II,congenital,lethal	connective tissue
		OI3B	osteogenesis imperfecta,type III,severe,non lethal,dominant and recessive	connective tissue
		OI4B	osteogenesis imperfecta,type IV,moderately severe	connective tissue
		OPM	osteoporosis,postmenopausal	connective tissue, osteo-articular
COL2A1	53			
		ACG2	achondrogenesis II,Langer Saldino	osteo-articular

			type,including hypochondrogenesis,lethal dwarfism	
		AOM	Stickler syndrome, autosomal dominant, characterized by a vitreous degeneration, Wagner type, associated with congenital myopia (any cases with extreme myopia and bilateral retinal detachment), midline clefting, a flattened mid-facial appearance, neurosensory deafness joint hypermobility and a degenerative arthropathy, later in life (arthroophthalmopathy), including variant predominantly ocular with high risk of retinal detachment and with a few extraocular signs	osteo-articular, ear, eye
		KND	Kniest spondyloepiphyseal dysplasia,myopia and dwarfism	osteo-articular
		NSED	spondyloepiphyseal dysplasia,mild,Namaqualand type	osteo-articular
		OAP	osteoarthrosis,precocious,autosomal dominant,with mild spinal chondrodysplasia,presenting usually young adults but also in children,characterized by pain,stiffness,limp and varying degrees of limitation of passive joint movement,affecting hips,knees,hands and elbows	osteo-articular
		PLSDT	lethal short-limbed platyspondylic dwarfism, Torrance type	osteo-articular
		SEDC	spondyloepiphyseal dysplasia,congenital,	osteo-articular

			autosomal dominant chondrodysplasia, characterized by disproportionate short stature (short trunk), abnormal epiphyses, and flattened vertebral bodies	
		SEMD1	spondyloepimetaphyseal dysplasia congenita,Strudwick type	osteo-articular
		SPPD	spondyloperipheral dysplasia with short ulna, platyspondyly, brachydactyly, epihyseal dyspalsia, midface hypolpasia, early onset grade myopia	osteo-articular
COL3A1	51			
		ACRG	acrogeria,see Ehlers-Danlos syndrome,type IV (EDS4A)	connective tissue
		EDS3	Ehlers-Danlos syndrome,type III,with generalized joint hypermobility,minor hyperextensibility and softness of the skin	connective tissue
		EDS4A	Ehlers-Danlos syndrome,vascular,type IV,autosomal dominant,arterial-ecchymotic,characterized by fragile thin,translucent skin,leading to premature death,extensive bruising,characteristic facial appearance,arterial/intestinal/uterine fragility or rupture	connective tissue
		EIPV1	elastoma intrapapillare perforans verruciformis 1,Miescher elastoma	connective tissue
		FAN	aneurysms,familial,rare	connective tissue
COL4A3	52?			

		ATS2	Alport syndrome,autosomal recessive and dominant forms glomerular nephritis with abnormalities of G basement membrane and neurosensory deafness	ear, kidney and urinary tract
		FBH	familial benign hematuria	kidney and urinary tract
COL4A4				
		ATS2	Alport syndrome,autosomal recessive and dominant forms glomerular nephritis with abnormalities of G basement membrane and neurosensory deafness	ear, kidney and urinary tract
		FBH	familial benign hematuria	kidney and urinary tract
COL5A1	66			
		EDS1A	Ehlers-Danlos syndrome,gravis,classical type,characterized by joint hyperextensibility,widened atrophic scars,joint hypermobility	connective tissue
		EDS2	Ehlers-Danlos syndrome,mitis type II,classical type,characterized by joint hyperextensibility,joint hypermobility,widened atrophic scars,velvety skin and mild propensity for bruising	connective tissue
COL5A2	54			
		EDS1B	Ehlers-Danlos syndrome,gravis type I,classical type characterized by joint hyperextensibility fragile skin with widened atrophic scars joint,mitral valve	connective tissue

			prolapse and other symptoms and dislocation	
		EDS2	Ehlers-Danlos syndrome,mitis type II,classical type,characterized by joint hyperextensibility,joint hypermobility,widened atrophic scars,velvety skin and mild propensity for bruising	connective tissue
COL6A1	36			
		BTHM1	limb girdle muscular dystrophy,autosomal dominant,early onset,benign,slowly progressive,with early flexion contractures,Bethlem myopathy 1,with a secundary decrease in LAMB1 expression	neuromuscular
		UCMD3	Ullrich scleroatonic muscular dystrophy with muscle weakness and multiple contractures at birth or in early infancy, autosomal recessive or dominant	neuromuscular, neurology
COL6A2	28			
		BTHM1	limb girdle muscular dystrophy,autosomal dominant,early onset,benign,slowly progressive,with early flexion contractures,Bethlem myopathy 1,with a secundary decrease in LAMB1 expression	neuromuscular
		UCMD1	Ullrich sclerotonic muscular dystrophy 1, autosomal recessive or dominant	neuromuscular

COL7A1	118			
		EBDD	epidermolysis bullosa,dystrophic,dominant,acral form,Bart,type,with congenital localized absence of skin affecting lower limbs,absence/deformity of nails,blistering of skin and mucosa,also including EBDD pruriginosa(OMIM 604129)	dermatology
		EBDDN	epidermolysis bullosa dystrophic,dominant,neonatal form,transient bullous epidermolysis of the newborn including toenail dystrophy,isolated ,by heterozygous carrier (OMIM 607523)	dermatology
		EBDDT	epidermolysis bullosa,dystrophic,dominant,pretibial with lichenoid features,albopapuloid,Pasini type,including recessive pretibial dystrophic epidermalysis bullosa (OMIM 131850)	dermatology
		EBDR	epidermolysis bullosa,dystrophic,recessive,Hallopeau-Siemens type,including cases of EB localisata	dermatology
CRB1	*11*			

		LCA8	Leber congenital amaurosis type 8, autosomal recessive, characterized by congenital non evolutive blindness, with pendular nystagmus, anterior keratoconus, roving eye movements, absent ocular pursuit and eye poking, severe photophobia, hypermetropia, normal fundus at birth followed by salt and pepper aspect of retina and typical RP, non recordable ERG	eye
		RP12	retinitis pigmentosa 12, autosomal recessive, early onset, with para-arteriolar preservation of the RPE	eye
CTNS	12			
		CLOJ	cystinosis, late-onset juvenile or adolescent nephropathic	kidney and urinary tract
		CONP	cystinosis, ocular nonnephropathic characterized by photophobia due to corneal cystine crystals but absence of renal disease.	eye, metabolism/amino acids
		CTNS	cystinosis, infantile, nephropathic type, autosomal recessive, characterized by onset in the first year of live, tubular dysfunction (renal Fanconi syndrome) with glomerular derivation progressing throughout the first decade of life resulting in end stage renal failure including ocular non nephropathic form	*kidney and urinary tract, metabolism/membrane transport*
CYP11B1	9			
		CYP11B1	adrenal hyperplasia IV,hypertensive form,female pseudohermaphroditism,with hypertension (11 beta-hydroxylase	endocrinology

			deficiency)	
		GSH	hereditary hypertension with primary aldosteronism,sensitive to dexamethasone	endocrinology, cardiovascular
CYP19A1	11			
		CYP19	pseudohermaphroditism, female - hypergonadotropic hypogonadism with multicystic ovaries and low urinary estrogen excretion - also virilization of the mother during pregnancy - estrogen deficiency in male	endocrinology
		GCMF	gynecomastia,familial (aromatase overexpression)	endocrinology
DES	9			
		CMD1I	cardiomyopathy dilated 1 autosomal dominant ,without skeletal myopathy	cardiovascular, neurology
		DES	desmin-related myopathy characterized by progressive muscle weakness spreading to truncal neck flexor, facial, bulbar and respiratory muscles, associated with cardiac dilated cardiomyopathy, conduction blocks, arrhythmias restrictive heart failure, intestinal malabsorption and pseudoobstruction, desmin-reactive deposits in cardiac and skeletal muscle cells, at the biopsy, cytoplamic inclusions immunoreactive for desmin, and abnormal granulofilamentous aggregatase among the myofibrils, autosomal dominant or sporadic	neuromuscular
DMD	86			
		BMD	muscular dystrophy,progressive,Becker	*neuromuscular*

			type (dystrophin defect)	
		CMD3B	cardiomyopathy,dilated,X linked (dystrophin deficiency resulting in a loss of alpha dystroglycan membrane binding) not associated with muscular dystrophy	cardiovascular, neuromuscular
		DMD	muscular dystrophy,progressive,Duchenne type (dystrophin,absence)	*neuromuscular*
		OED	blindness,night,congenital,stationary 2,some incomplete forms,with persistence of slight rod function (dystrophin defect)	eye
DSP	24			
		ARVD8	arrhythmogenic right ventricular dysplasia-8	cardiovascular
		DCWHK	palmoplantar hyperkeratoma (hyperkeratosis), striata 2R, autosomal recessive, associated to woolly hair and a dilated left ventricular cardiomyopaphy,l eading to precocious heart failure (family from Ecuador), Carvajal syndrome, including skin fragility wooly -hair syndrome (OMIM 607655)	cardiovascular, connective tissue
		PPKS2	palmoplantar keratoderma (hyperkeratosis) striata,autosomal dominant,characterized by a linear pattern of skin thickening on the palms and flexion aspect of the fingers	connective tissue
DSPP	6			
		DFNA39	deafness autosomal dominant 39,with dentinogenesis imperfecta 1	ear
		DGI1	dentinogenesis imperfecta 1, type II (putative defect of DSPP), Shields type, osteopontin (SPP1), bone sialoprotein	connective tissue

			(IBSP) and dentin sialophosphoprotein DMP1 excluded, associated or not with progressive hearing loss, including dentinogenesis imperfecta type III (DGI3)	
DYSF	55			
		DMAT	myopathy, distal, with anterior tibial onset and a rapidly progressive course, high serum CK levels and absence of vacuoles in the muscular biopsy (heterogeneous)	neuromuscular
		LGMD2B	limb girdle muscular dystrophy 2B, beginning in the late second decade of life, characterized by symmetrical progressive weakness, atrophy of the proximal limb and trunk muscles, allelic to MM (see symbol)	neuromuscular
		MM	distal muscular dystrophy, early adult type II, autosomal recessive (Miyoshi myopathy), characterized by an onset in the late adolescence or early adulthood, early and predominant involvement of posterior calves, marked elevation of serum CK, dystrophic features in muscle biopsy, a slowly progressive course in the majority of patients, allelic to LGMD2B, with the same mutation of dysferlin giving alternatively cases differing by the primary muscle involvement, i.e distal (EDM3) or proximal (LGMD2B)	*?*
EDNRB	7			
		ABCD	albinism,black lock,cell migration disorder of the neurocytes of the gut and deafness ,autosomal recessive inheritance	ear, dermatology, digestive tract/gastrointestinal

		HSCR2	Hirschsprung disease,2,autosomal recessive,sometimes associated with Waardenburg syndrome,type 4,Shah-Waardenburg syndrome,see also WS4A	congenital malformation, digestive tract/gastrointestinal
		WS4A	Waardenburg syndrome,type 4A,autosomal recessive,partial albinism,deafness,without dystopia canthorum,may be associated to Hirschsprung disease,in Shah-Waardenburg syndrome,see also HSCR2,including ABCD syndrome: (OMIM 600155) albinism,black lock, Hirschsprung disease and deafness	congenital malformation, digestive tract/gastrointestinal, ear
ELA2	5			
		ELA2	cyclic neutropenia,autosomal dominant,oscillating with 21 days periodicity and associated with a risk of opportunistic infection during intervals of neutropenia	hematology
		SCNP1	neutropenia congenital ,autosomal dominant or sporadic, ,Kostmann disease	hematology
ELN	33			
		ELN	cutis laxa (elastin reduced expression)	connective tissue, dermatology
		SVAS	supravalvular aortic stenosis . Localized or diffuse narrowing of the ascending aorta resulting from thickening of the aortic media, leading to ventricular hypertrophy, fibrillative and congestive heart failure, affecting other major arteries, occuring as an isolated disease (ELN defect) or as part of the Williams	*cardiovascular*

			syndrome, see WBS	
		WBS	Williams Beuren syndrome, neurodevelopmental disorder, 1/20 000 live births . characteristic facial features : elfin facies, flat nasal bridge with anteverted nares, wide mouth with fleshy lips, periorbital fullness, epicanthal folds, flat malar region, small mandible and prominent cheeks . heart abnormalities, typically supravalvular aortic stenosis (SAVS) and peripheral pulmonary stenosis (PPS), hyperacusis, infantile hypercalcemia, short stature and abnormal gait . mental retardation . behavioral phenotype : hypersociability, deficits in visual-spatial and global processing, preserved language and face processing	*cardiovascular, mental retardation, multisystem*
ENPP1	25			
		IIAC	idiopathic infantile arterial calcification with calcification occuring particularly in the internal elastic lamina. of muscular arteries and stenosis due to myointimal proliferation, and death from myocardial infarction usually in the first 6 months	cardiovascular, connective tissue, neuromuscular
		OPLL1	ossification of the posterior longitudinal ligament of spine,leading to myelopathy among Japanase patients,locus close to D6S276,likely located in the region between RXRB and COL11A2,homolog to the ttw (tiptoe walking) in mouse which is caused by a nonsense mutation of Npps. In human an association of some	osteo-articular, connective tissue

			alleles of NPPS1 and OPLLS in Japanese population,suggests an etiologic role of NPPS in OPLLS	
EVC	23			
		EVC	Ellis-van Creveld syndrome,chondroectodermal dysplasia,with short ribs,hypotrichosis,polydactyly,nails dystrophia,and dental abnormalities	osteo-articular, congenital malformation, limbs, dermatology
		WAD	Weyers acrofacial dysostosis autosomal dominant condition of hypotelorism,dental abnormalities,postaxial polydactyly,nail dystrophy	osteo-articular, congenital malformation
EXT1	11			
		CDSM	chondrosarcoma	osteo-articular
		EXT1	exostoses,multiple,1,also associated with trichorhinophalangeal syndrome in Langer-Giedion syndrome (see LGCR)	osteo-articular
EXT2	16			
		DEF11S	proximal interstitial deletion of the short arm of chr 11, Potocki-Shaffer syndrome . main features : skull ossification defect (foramina parietalis permagna, FPP) and multiple exostoses (EXT) . others: mental retardation, facial asymetry, asymmetric calcifications of coronary structures, defective vision (severe myopia, nystagmus, strabismus), skeletal anomalies (small hands and feet, tapering fingers), heart defects and anal stenosis	osteo-articular
		EXT2	exostoses,multiple,congenital,2,also associated with foramina parietalia	osteo-articular, multisystem

			permagma,craniosynostosis,micropenis,mental retardation in a contiguous gene syndrome with 11p-deletion (DEF11S)	
EYA1	*16*			
		ASMD4	ocular anterior segment mesenchymal dysgenesis 4, including Peters anomaly and congenital cataract, autosomal dominant	eye
		BOR	branchio-oto-renal syndrome of deafness, preauricular pits, cervical fistulae, kidney dysplasia, including some cases without (BO) renal involvement, excluding the branchio-oculo-facial syndrome (BOFS), allelic to OTFC (see also DURS1) including Melnick-Fraser syndrome	congenital malformation, eye
FBN1	65			
		ECTL	ectopia lentis, allelic to MFS1, with or without minor skeletal changes, autosomal dominant	connective tissue, eye
		KPSI	kyphoscoliosis, isolated, progressive, of variable severity	*osteo-articular*
		MFS1	Marfan syndrome 1, characterized by disproportionate tall stature with long bone overgrowth (dolichostenomelia), arachnodactyly, scoliosis, pectus deformities, bilateral ectopia lentis, aortic dilatation or dissection, . including the severe neonatal sporadic form with crumpled ears, flexion contractures, pulmonary emphysema and loose skin leading to a senile appearance and a fetal outcome by congenital heart failure within the first year of life . including	connective tissue, cardiovascular, eye

			isolated cases of thoracic aortic aneurysm and Marfan-like syndrome (MASS, OMIM 604308)	
		SGS	Shprintzen-Goldberg syndrome of marfanoid habitus craniosynostosis, arachnodactyly, abdominal hernias	*congenital malformation, mental retardation*
		TAA	thoracic aortic aneurysm	cardiovascular
		WMSAD	Weill-Marchesani syndrome, characterized by short stature, brachydactyly, joint stiffness and characteristic eye abnormalities (ectopia lentis, glaucoma, microspherophakia)	eye, congenital malformation
FGA	5			
		AFGC	congenital afibrinogenemia ,including dysfibrogenemia alpha type,causing bleeding diathesis or dysfibrogenemia alpha type causing recurrent thrombosis (OMIM 134820)	hematology
		CAFG	congenital afibrinogenemia, autosomal recessive, characterized by uncontrolled bleeding after birth from umbilical cord and high risk of spontaneous intracerebral bleeding and splenic rupture throughout life	hematology
		FAR1	familial amyloidosis,renal,Ostertag type (FGA deposit)	*connective tissue*
FGFR1	15			
		CRS7A	craniosynostosis syndromatic 7,with characteristic broad thumbs and big toes,Pfeiffer syndrome,including a case of Jackson-Weiss syndrome manifesting only mild craniofacial anomalies with a	*congenital malformation, osteo-articular*

			Pro 252Arg mutation observed in Pfeiffer syndrome	
		KAL2	Kallmann syndrome 2, hypogonadotropic hypogonadism and anosmia	*endocrinology, multisystem*
		OGD	osteoglophonic dysplasia with craniosynostosis, prominent supraorbital ridge, and depressed nasal bridge, as well as the rhizomelic dwarfism and nonossifying bone lesions	connective, osteo-articular
		SCLLS	atypical myeloproliferative disorder with peripheral blood eosoniphilia and stem-cell leukemia-lymphoma syndrome with a translocation t(8;13)(p11;q11-q12),involving FGFR1 and ZNF198 or with a translocation t(6;8)(q27;p11),involving FGFR1 and FOP	*hematology*
FGFR2	7			
		ACS1	acrocephalosyndactyly type 1,Apert syndrome with craniosynostosis,and syndactyly midfacial hypoplasia,brachycephaly,ocular proptosis,beaked nose,high arched cleft palate,mental retardation and severe syndactyly hands/feets	*osteo-articular*
		ANBXL1	Antley-Bixler syndrome 1, craniosynostosis,midface hypoplasia,radiohumeral synostosis,femoral bowing with neonatal femoral fractures. fusion of carpal and tarsal bones,Antley- Bixler-like syndrome,autosomal dominant,associated in any cases with genital abnormalities	osteo-articular

			especially in females	
		CR39	craniosynostosis,syndromatic 9,with cutis gyrata,acanthosis nigricans,digital anomalies,urogenital abnormalities,early death,Beare-Stevenson syndrome	*dermatology*
		CRS11	craniosynostosis, syndromic, associated with ocular anterior chamber dysgenesis hydrocephalus, cleverleaf skull deformity and elbow contractures, autosomal dominant	osteo-articular, congenital malformation, eye
		CRS5A	craniosynostosis, syndromatic 5, Crouzon syndrome with craniofacial dysostosis	osteo-articular, congenital malformation
		CRS6	craniosynostosis,syndromatic 6,Jackson-Weiss syndrome midfacial hypoplasia and hands/feet anomalies,and great phenotypic variability	osteo-articular, congenital malformation
		CRS7B	craniosynostosis, syndromatic 7, with characteristic broad thumbs and big toes, Pfeiffer syndrome	osteo-articular, congenital malformation
FLNA	48			
		BPNH	bilateral periventricular nodular heterotopia in females,with epilepsy ductus arteriosus and coagulopathy,also associated with cerebellar hypoplasia,mental retardation,lethal in boys	*congenital malformation, mental retardation*
		FMTD	frontometaphyseal dysplasia with frontal hyperostosis giving great prominence to the supraciliary ridges, underdeveloped mandible, cryptorchidism, subluxated radial heads, and metaphyseal dysplasia	osteo-articular

			resembling that in Pyle disease (metaphyseal dysplasia)	
		MLNS	Melnick-Needles osteodysplasty with typical facies (exophthalmos, full cheeks, micrognathia and malalignment of teeth), flaring of the metaphyses of long bones, s-like curvature of bones of legs, irregular constrictions in the ribs, and sclerosis of base of skull	osteo-articular, connective tissue
		OPD1	otopalatodigital syndrome,type 1,with deafness,cleft palate,enlarged thumbs and great toes,including diaphyseal incurvation	osteo-articular, congenital malformation
		OPD2	otopalatodigital type 2 with deafness, cleft palate, enlarged thumbs and great toes, visceral and brain anomalies	*congenital malformation*
GABRG 2	9			
		CAE2	chilhood absence epilepsy 2	neurology
		GEFSP3	generalized epilepsy with febrile seizures plus,type 3	neurology
		SMEI1	severe myoclonic epilepsy of infancy, Dravet syndrome	neurology
GCK	11			
		GCK	familial hyperinsulinism autosomal dominant,characterized by hypoglycemia during fasting normal glucose tolerance and reactive hypoglycemia after the ingestion of glucose	metabolism/carbohydrates
		MODY2	diabetes,non insulin-dependent,juvenile type;maturity onset diabetes of the young,2,onset in childhood mild	metabolism/carbohydrates

		PNDM	permanent neonatal diabetes mellitus with complete glucokinase deficiency,autosomal recessive,in kindreds with diverse forms of diabetes in heterozygotes	metabolism/carbohydrates
GDAP1	6			
		CMT2K	Charcot-Marie-Tooth disease type 2K ,autosomal recessive,onset in early childhood (younger than 3 years), characterized by hypotonia at birth and delayed development of early motor milestones, in infancy difficulty walking, foot deformities, kyphoscoliosis, distal limb muscle weakness and atrophy, areflexia including axonal form of CMT with vocal cord paresis,leading to disability by the end of the first decade and on the sural nerve biopsy marked loss of myelinated fibers, axonal degeneration and regeneration, and occasional onion bulb formations.(OMIM 607706)	neurology
		CMT4A	Charcot-Marie-Tooth neuropathy type 4A,demyelinating,recessive,characterized by distal muscle weakness and amyotrophy,sensory loss,decreased or absent tendon reflexes,with decreased nerve conduction velocity,hypomyelination and basal laminal onion bulb including axonal neuropathy CMT2G with vocal cord paresis ,and CMT2K	neurology
GHR	10?			
		GHIS1	dwarfism,Laron type,growth hormone	endocrinology

			insensitivity syndrome 1	
		GHIS2	idiopathic short stature with insensitivity to growth hormone	endocrinology
GJB2	2			
		DFNA3	neurosensory dominant deafness 3,non syndromic,prelingual,slowly progressive (GJB2 defect),(French kindred),same locus as DFNB1,including sudden sensorineural hearing loss	*ear*
		DFNB1	neurosensory recessive deafness 1,DFNB1,non syndromic,prelingual,mild to profound with a large variation among families and a loss of hearing in the high frequency range characteristic in children with connexin 26 impairment,stable associated with sloping of flat audiometric curves and a radiologically normal inner ear,responsible of a majority of non syndromic deafness in a number of populations	ear
		HID	ichthyosis ,hystrix-like, with deafness	ear, dermatology
		KHM2	neurosensory deafness with palmoplantar keratoderma (hyperkeratosis),mutilans,Vohwinkel syndrome,autosomal dominant, with ectodermal dysplasia,constricting bands on the fifth digits of hands and feet (pseudoainhum),including cases of isolated neurosensory deafness and palmar keratoderma	*dermatology*
		KID	keratitis-ichthyosis-deafness syndrome ,including keratoderma palmo-plantar with deafness (OMIM 148350)	ear, dermatology

GLB1	16			
		GLB1	GM1 gangliosidosis,generalized,Landing disease, type 3 (adult) and type1and 2 (infantile and juvenile)	metabolism/lysosomal
		MPS4B	mucopolysaccharidosis,type IVB,Morquio disease B,severe connective tissue and skeletal deformities without neurologic involvment	metabolism/lysosomal
GLI3	14			
		ACLS1	acrocallosal syndrome 1	congenital malformation, mental retardation, neurology
		GCPS	Greig cephalopolysyndactyly syndrome including preaxial and postaxial polysyndactyly, hypertelorism craniosynostosis and broad forehead	multisystem
		PAPA1	polydactyly,postaxial,type A1,with a well-formed,functional ext	osteo-articular, limbs
		PHS1	Pallister-Hall syndrome 1, with hypothalamic hamartoma, central polydactyly, unperforated anus and other malformations, including the PIV (polydactyly, imperforate anus and vertebral malformation)	congenital malformation
		PPA4	polydactyly preaxial IV	osteo-articular
GNAS	12			
		MCAS	McCune-Albright polyostotic fibrous dysplasia with café au lait spots and endocrine dysfunction pituitary adenocarcinomas,including isolated bone fibrous dysplasia,associated or not with early cholestasis	osteo-articular, endocrinology

		PHPIA	pseudo-hypoparathyroidism, type IA, characterized by Albright hereditary osteodystrophy, parathyroid resistant hypocalcemia, hyperphosphatemia and other endocrine abnormalities, including cases without endocrine anomalies (pseudo-pseudohypoparathyroidism) even in a same family, parathyroid resistance is paternally imprinted, and PHPIA is inherited from a female affected by either form, maybe also due to a potential isodisomy of chromosome 20q	osteo-articular, endocrinology
		POH	progressive osseous heteroplasia characterized by extensive dermal ossification during childhood	osteo-articular, dermatology
GUCY2D	*20*			
		CORD6	retinal cone rod dystrophy 6, characterized by initial loss of visual acuity and abnormal color vision, followed by night blindness and peripheral visual field loss	eye
		LCA1	Leber congenital amaurosis type 1,autosomal recessive, characterized by congenital non evolutive blindness, with pendular nystagmus, roving eye movements, absent ocular pursuit and eye poking, severe photophobia and hypermetropia , normal fundus at birth followed by salt and pepper aspect of retina and typical RP, non recordable ERG	eye
GUSB	12			

		GUSB	hydrops fetalis	metabolism/lysosomal
		MPS7	mucopolysaccharidosis,type VII,Sly disease	metabolism/lysosomal
HFE	7			
		HFE	hemochromatosis, adult form, autosomal recessive, characterized by increased iron absorption of dietary iron leading to iron accumulation and cirrhosis of the liver, diabetes mellitus, skin pigmentation, cardiac arrhythmia, failure and arthropathy, excluding juvenile form, with increased risk of acute myocardial infarction in carriers of the Cys282 Tyr mutation, but not increased risk hepatocellular carcinoma	digestive tract/liver and annex, metabolism metal
		VGP	porphyria variegata,severe phenotype	metabolism metal
HPRT1	9			
		GHPR	gout, HPRT-related, Kelley-Seegmiller syndrome, HPRT1 partial deficiency	metabolism/purine or pyrimidine
		HPRT1	Lesch Nyhan syndrome	metabolism/purine or pyrimidine
HR	18			
		ALUNC	alopecia universalis,characterized by complete absence of scalp and body hair	dermatology
		APL	atrichia with papular lesions,characterized by early onset alopecia followed years later by a diffuse papular eruption,autosomal recessive	dermatology
HSPG2	96			
		DDSH	dyssegmental dysplasia,Silverman handmarker type,with anisospondyly and micromelia,severe,lethal	osteo-articular

		SJS1	chondrodystrophic myotonia,Schwartz-Jampel syndrome	osteo-articular, congenital malformation, neuromuscular
IFNGR1	7			
		AMYF	atypical mycobacteriosis,familial,disseminated	defense and immunity
		HPIS	H. pylori infection susceptibility	defense and immunity
		IFNGR1	susceptibility to BCG and tuberculosis mycobacterial infections (interferon gamma,receptor 1 deficiency),severe form,associated with a defect in mature granulomas in patients with complete deficiency,familial or sporadic	defense and immunity
IKBKG	10			
		EDAID	ectodermal dysplasia, anhidrotic, with severe immunodeficiency and deficient natural killer cell cytotoxicity	defense and immunity, dermatology
		IP2	incontinentia pigmenti 2, Bloch-Sulzberger syndrome, familial, male-lethal type, X-linked dominant, rare neuro-cutaneous disorder involving skin, teeth, eyes and central nervous system characterized in females by prominent skin signs occuring in four stages : perinatal inflammatory vesicles, verrucous patches of hyperpigmentation and dermal scarring associated with alopecia, invertis/keratitis, hypodontia, the CNS manifestations include seizures, spastic paralysis, microcephaly and mental retardation, eye abnormalities lead	dermatology, eye, neurology

			to blindness due to retinal detachment. Most IP females exhibit severely skewed X-inactivation resulting from loss of cells expressing the mutated X-chromosome around birth. The variability in IP phenotypes result from a combination of the type of mutation, the functional domain affected and X-inactivation	
		OLEDAID	ectodermal dysplasia,anhidrotic,with lymphoedema,osteopetrosis and immunodeficiency resulting from impaired cell responses to liposaccharide,interleukins IL1B,ILI8,TNF/TNFSF5 (CD40)	defense and immunity, dermatology
INSR	22			
		INSR	diabetes mellitus,non insulin-dependent,insulin resistant,,acanthosis nigricans,Rabson-Mendenhall syndrome, with pineal hyperplasia and polycystic ovarian syndrome	metabolism/carbohydrates
		LPCN	leprechaunism,Donohue syndrome,with insulin resistance	metabolism/carbohydrates
ITGB4	40			
		EBHF	epidemolysis bullosa of hands and feet,Weber-Cockayne type epidermolysis bullosa simplex	dermatology
		EBJPAB	epidermolysis bullosa severe,junctional,characterized by blisters within the lamina lucida of the basement membrane zone (BMZ),associated with pyloric atresia,autosomal recessive	dermatology
JAG1	26			

		ALGS	Alagille syndrome, characterized by an hepatic ductular hypoplasia, with cholestasis, anomalies of vertebral segmentation and valvular pulmonar stenosis, eye posterior embryotoxon and retinal pigmentary changes	congenital malformation, digestive tract/liver and annex, eye
		MCAVS	multiple congenital anomalies with a defect of vertebral segmentation (butterfly shaped vertebrae),likely the same as AGS,including familial deafness congenital heart defects and posterior embryotoxon	*congenital malformation*
		TTGF	tetralogy of Fallot,familial with particular facies	*cardiovascular*
KCNQ1	16			
		FAF2	familial atrial fibrillation 2	cardiovascular
		JLNS1	Jervell Lange-Nielsen cardioauditory syndrome 1 of congenital neurosensory deafness, with a long QT, syncopal attacks and a high risk of sudden death, autosomal recessive	cardiovascular, ear
		LQT1	long QT syndrome with ventricular tachyarrhythmia,type 1,characterized by syncopes,seizures predisposing to torsades de pointes and ventricular fibrillation,accounting for 50p100 of cases of the Romano-Ward syndrome,potentially decreasing the outward K+ currents,leading to a high level of membrane depolarization,autosomal dominant with an autosomal recessive form associated with compound heterozygosity for two	cardiovascular

			mutations of KCNQ1	
KIT	21			
		KIT	mastocytosis with associated hematologic conditions or urticaria pigmentosa (somatic mutations of KIT in peripheral blood mononuclear cells)	dermatology
		PBT1	piebald trait 1,piebaldism,with/without neurosensory deafness,homolog to dominant spotting in mouse	dermatology
KRT1	9			
		EHK1	epidermolytic hyperkeratosis 1	dermatology
		ICHM	Curth-Macklin type ichthyosis hystrix with abnormality of tonofibrils and abnormalities in supramolecular keratin intermediate filament organization	dermatology
		PPK1A	palmoplantar keratoderma (hyperkeratosis),diffuse,non epidermolytic or epidermolytic£Unna-Thost disease, including keratosis palmoplantar striata I (OMIM 148700) and keratosis palmoplantar striata 3 (OMIM 607654)	dermatology
KRT14	8			
		EBS2B	epidermolysis bullosa,simplex,Koebner type,autosomal dominant	dermatology
		EBS3B	epidermolysis bullosa,simplex,Weber-Cockayne type,autosomal dominant including epidermolysis bullosa of hands and feet	dermatology
		EBS5B	epidermolysis	dermatology

			bullosa,simplex,herpetiformis,Dowling-Meara type,autosomal dominant	
KRT5	9			
		EBS2A	epidermolysis bullosa,simplex,Koebner type,autosomal dominant	dermatology
		EBS3A	epidermolysis bullosa,simplex,Weber-Cockayne type,autosomal dominant including epidermolysis bullosa, of hand and feet	dermatology
		EBS5A	epidermolysis bullosa,simplex,herpetiformis,Dowling-Meara type,autosomal dominant	dermatology
		EBSMP	epidermolysis bullosa,simplex,with mottled pigmentation,autosomal dominant	dermatology
L1CAM	27			
		CRASH	corpus callosum agenesis,mental retardation,adducted thumbs,spastic paraparesis,hydrocephalus X-linked,mental retardation with clasped thumbs,agenesis or dysgenesis of corpus callosum	mental retardation
		HSAS	hydrocephalus 1,stenosis of the aqueduct of Sylvius;Bicker-Adams syndrome,see CRASH	neurology
		MASA	MASA syndrome : mental retardation,aphasia,shuffling gait,adducted thumbs,see CRASH	congenital malformation, mental retardation
		SPG1	spastic paraplegia,complicated,X-linked,see CRASH	congenital malformation, neurology
LAMA3	76?			
		EBJ1C	epidermolysis bullosa,junctional,Herlitz type,autosomal recessive	dermatology

		GABEB3	epidermolysis bullosa ,generalized atrophic, benign 3,with dystrophy of the nails, nonscarring blistering of skin, mild skin atrophy, hypodontia	dermatology
		LOCS	laryngo-onycho-cutaneous syndrome ,autosomal recessive ,with hoarseness (which was not associated with any obvious laryngeal lesion), dystrophic changes in the nails, and chronic bleeding, crusted lesions of the skin of the face.,Pakistani kindreds	respiratory, dermatology
LAMB3	23			
		EBJ1B1	epidermolysis bullosa, junctional, Herlitz lethal type with a case resulting from uniparental maternal isodisomy	dermatology
		EBJ2B	epidermolysis bullosa,junctional atrophic,generalized benign,non lethal rare form,autosomal recessive	dermatology
LBR	14			
		HEMSK	chondrodystrophy ,hydropic and prenatally lethal,type Moth-Eaten skeletal dysplasia,Greenberg syndrome	osteo-articular, metabolism/lipoprotein lipid
		PHA	Pelger-Huet anomaly characterized by hypolobulated neutrophil nuclei with coarse,skeletal abnormalities (chondrodystrophy)	osteo-articular, hematology
LCAT	*6*			
		FED	dyslipoproteinemic corneal dystrophy, Fish-Eye disease	eye, metabolism/lipoprotein lipid
		LCAT	hypercholesterolemia, unesterified, characterized by corneal opacities, target	eye, metabolism/lipopr

			cell hemolytic anemia, proteinuria with renal failure, Norum disease including susceptibility to familial combined hyperlipemia and premature coronary artery disease	otein lipid
LMNA	12			
		CMD1A	cardiomyopathy, dilated 1A, autosomal dominant, characterized by a progressive disturbance in atrioventricular conduction and a depression of cardiac contractility, including atrial fibrrillation, early-onset (OMIM 607554)	neuromuscular, cardiovascular
		CMT2B1	Charcot-Marie-Tooth neuropathy type 2,axonal,autosomal recessive, characterized by an onset in the second decade, involving upper limbs and proximal muscles, with normal motor-nerve conduction velocity, leading to a severe condition in less than four years	*neurology*
		EMD2	Emery-Dreifuss muscular dystrophy 2, characterized by early contractures of elbows and Achille tendons, slowly progressive, wasting and weakness in humeroperoneal muscles and a dilated cardiomyopathy with life-threatening conduction blocks. also including asymptomatic cases, rare autosomal recessive cases (OMIM 604929) and rares cases associated with partial lipodystrophy	*neuromuscular*
		EMD3	Emery-Dreifuss muscular dystrophy, autosomal recessive, characterized by early onset contractures, a progressive	neuromuscular

			course, a dilated cardiomyopathy with life threatening conduction blocks	
		FPLD1	familial partial lipodystrophy autosomal dominant ,with gradual dystrophy of subcutaneous adipose tissue in the extremities during puberty and adolescence associated to insulin resistance ,hyperinsulinemia,hypertension,dyslipidemia,diabetes (Dunnigan-Kobberling variety) and including any cases of SEIP syndrome	*metabolism/lipoprotein lipid*
		LDHCP	lipoatrophy with diabetes, hepatic steatosis, hypertrophic cardiomyopathy and leukomelanodermic papules, with square jaw, thin lips, high forehead, marked thinning of the eyebrows, pectus excavatum, and narrow shoulders, generalized atrophy of subcutaneous fat , concentric hypertrophy of the left ventricle without cavity dilatation, associated with thickened and regurgitant valves, aortic fibrotic nodules, and calcification of the posterior annulus	connective tissue, dermatology, cardiovascular
		LGMD1B	limb girdle muscular dystrophy 1B, Dutch family, characterized by a slowly progressive, proximal arm weakness, absent ankle deep-tendon reflexes and elevated creatine-kinase values, without early contractures, with early onset cardiac conduction defect	*neuromuscular*

		MADYS1	mandibuloacral dysplasia autosomal recessive with post-natal growth retardation onset at age 5, mandibular and clavicular hypoplasia, acro-osteolysis, delayed closure of the cranial suture, joint contractures, mottled cutaneous pigmentation, types A and B pattern of lipodystrophy, marked basal and post-load hyperinsulinemia indicating insulin resistance, partially overlapping familial partial dystrophy of Dunnigan type (AD), but heterozygotes in MAD clinically asymptomatic	dermatology, osteo-articular
		PRO1	progeria, Hutchinson-Gilford syndrome, autosomal dominant, characterized by precocious senility and premature death, including post natal growth retardation, micrognathia, absence of subcutaneous fat, alopecia, acro-osteolysis and premature atherosclerosis including any atypical cases with generalized wasting, thinned skin and survival to relatively older age	*dermatology, osteo-articular, neuromuscular*
		RDMP2	restrictive dermopathy, lethal 2, tight skin contracture syndrome, autosomal recessive with severe intrauterine growth retardation, congenital contractures, and tense skin that was easily eroded	congenital malformation, dermatology
		WRN2	Werner syndrome 2,atypical ,early onset	connective tissue, dermatology
MAPT	15			

		DDPAC	frontotemporal dementia (OMIM 600274) with obsessive-compulsive behaviour and parkinsonism with variable phenotypes including hereditary Pick disease : . pallido-ponto-nigral degeneration (OMIM 168610) . dysphasic disinhibition, dystonia, muscular atrophy . amyotrophic lateral sclerosis- parkinsonism (OMIM 601104) . progressive subcortical gliosis and pathological features comprising neuronal loss, spongy change in multiple areas of neocortex, presence of prions or double PHF-tau, neurofibrillar tangles or ubiquitin-positive inclusions	neurology, psychiatric disorder
		PSRP	progressive supranuclear palsy, onset in the sixties, characterized by supranuclear vertical gaze palsy, postural instability, predominant frontal cognitive disturbance, erect or opisthotonic posture, spastic or ataxic dysarthria dysphagia, with a fatal outcome with double PHF (paired helical filaments) -tau, neurofibrillar tangles, neuronal and glial tau accumulation in the cortex, basal ganglia, brainstem nuclei and white matter	neurology
MECP2	4			
		MRX16	mental retardation,X-linked 16,moderate,hyperactive deep tendon reflexes,variable short stature,microcephaly,in the same interval than MRX3,MRX25,MRX28,MRX41,MRX48	mental retardation

			but not mutated in GDI1	
		MRX28	mental retardation,X-linked 28,in the same interval than MRX3,MRX16,MRX25 but not mutated in GDI1	mental retardation
		MRX79	mental retardation X-linked,nonspecific	?
		PPMX	mental retardation,with manic-depressive psychosis,pyramidal signs,parkinsonian features and macroorchidism	mental retardation
		RTT	Rett syndrome affecting almost exclusively the females,characterized by a period of normal development for the first 6 to 18 months followed by a progressive deterioration leading to dementia,autism,loss of purposeful use of hands,jerky truncal ataxia,growth retardation and cardiac dysfunction,including some mild forms in females with motor coordination problems,mild learning disability and skewed X inactivation and in males a congenital encephalopathy,severe mental retardation and progressive spasticity,also including cases presenting with the main features of Angelman syndrome,. including cases of non fetal,non progressive severe encephalopathy in males and females	neurology, psychiatric disorder
MITF	8?			
		ADFNS	albinism-deafness syndrome,autosomal dominant,Tietz syndrome,characterized by generalized hypopigmentation and	ear, dermatology

			congenital (prelingual) profound deafness	
		WS2A	Waardenburg syndrome, type 2A, autosomal dominant, including partial albinism, deafness without dystopia canthorum, associated with ocular albinism (TYR defect) in a case of apparent digenism	ear, dermatology, congenital malformation
MLH1	19			
		HNPCC2	non polyposis colorectal cancer 2,replication error tumor (RER)+,mutator phenotype,including cases of Turcot syndrome characterized by primary brain tumor (glioblastoma) and NPCC	digestive tract/gastrointestinal
		MTS2	Muir-Torre syndrome (non polyposis colorectal cancer with multiple cutaneous sebaceous neoplasms or keratoacanthomas)	digestive tract/gastrointestinal
MPZ	6?			
		CMT1B	Charcot-Marie-Tooth neuropathy 2 (HMSN Ib),hypertrophic form,demyelinating,characterized by distal muscle weakness and amyotrophy,sensory loss,decreased or absent tendon reflexes,with decreased nerve conduction velocity,including Dejerine-Sottas syndrome, neuropathy with focally folded myelin sheathes (see also CMT3A),and CMT2I	neurology
		CMT2I	axonal Charcot-Marie-Tooth disease, type 2 I, with prominent sensory involvement, very late onset, progressive, leading to marked disability	neurology

		CMT2J	Charcot-Marie-Tooth neuropathy,type 2J,with hearing loss and pupillary abnormalities£characterized by relatively late onset (37 to 61 years), marked sensory impairment, and distal muscle atrophy and weakness	neurology
		CMT3A	hypomyelination neuropathy,congenital,characterized by onset in infancy of hypotonia,areflexia,distal muscle weakness,very slow nerve conduction velocity,with joint contractures or arthrogryposis multiplex congenita ,including CMT4E	neurology
MSH2	15			
		HNPCC1	non polyposis colorectal cancer 1,endometrial carcinoma,including Lynch syndrome II,replication error tumor (RER)+,mutator phenotype (see MSH2),also including sporadic colorectal carcinoma with somatic mutations of MSH2,also including cases of Turcot syndrome characterized by primary brain tumor (glioblastoma) and NPCC	digestive tract/gastrointestinal
		MTS	Muir-Torre syndrome (non polyposis colorectal cancer with multiple cutaneous sebaceous neoplasms or keratoacanthomas)	digestive tract/gastrointestinal
MYH7	39			
		CMH1	cardiomyopathy,familial,hypertrophic and dilated,1,with a potential severe course,autosomal dominant	cardiovascular, neuromuscular

		MPD1	myopathy, autosomal dominant , distal 1, infantile onset, Laing-type with slow progression, involving proximal muscles in the fourth decade	neuromuscular
MYO7A	49			
		DFNA11	neurosensory dominant deafness 11, non syndromic, postlingual, progressive, Japanese kindred, (allelic to DFNB2)	ear
		DFNB2	neurosensory recessive deafness 2,non syndromic,pre or postlingual,with variable expression,maybe associated in some patients with a mild retinal degeneration (atypical Usher form)	*ear*
		USH1B	Usher syndrome, type IB, autosomal recessive, characterized by profound congenital neurosensory deafness, constant vestibular dysfunction and retinitis pigmentosa of prepubertal onset leading to blindness (see DFNB2)	ear, eye
NDP	3			
		COATS	Coats syndrome, characterized by abnormal retinal development (retinal telangiectasia) which results in massive subretinal lipid accumulation (exudative retinal detachment), almost invariably isolated, unilateral and seen in males, a female with a variant giving birth to a son affected with Norrie disease	eye
		EVR2	vitreoretinopathy,exudative,rare X-linked form (allelic to NDP,may be involving a linked gene in rare cases)	eye

		NDP	Norrie disease (pseudoglioma), characterized by congenital retinal dysplasia, mental retardation and deafness	eye
NDUFV1	10			
		ALXD2	Alexander disease with development of megalencephaly in infancy accompanied by progressive spasticity and dementia	neurology
		NDUFV1	necrotizing encephalopathy ,infantile subacute of Leigh, hypotonia,leukodystrophy mitochondrial with myoclonic epilepsy,complex 1 deficiency	neurology
NF1	57			
		NF1	neurofibromatosis 1 (von Recklinghausen disease), characterized by café au lait spots, axillary freckling, Lisch nodules of the iris, multiple neurofibromas, presumably arising from NF1 inactivation in Schwann cells, tibial pseudarthrosis and a predisposition to certain benign and malignant tumors of the central and peripheral nervous system, with a variable expression even among relatives, bearing with the same mutation and apparently an earlier onset or a more severe form associated with deletions, including neurofibrosarcoma (see TSG17C) allelic loss, only in plexiform tumor in malignant tumors	neurology
		NFFS	neurofibriomatosis,familial,spinal,without cafe-au-lait macules	neurology
		NFNS	Noonan-neurofibromatosis syndrome	cardiovascular,

				neurology, dermatology
		WATS	cafe-au-lait spots with pulmonic stenosis	neurology, dermatology
NF2	18			
		NF2	neurofibromatosis 2,autosomal dominant disorder characterized by tumors of neural-crest origin cells,with biallelic inactivation in schwannomas,meningiomas,mesotheliomas,and testicular anomalies such as presenile lens opacities,and retinal hamartomas,(merlin/Schwannomin defect)	neurology
		SCWT	schwannomatosis,neurilemmomatosis,congenital,cutaneous	neurology
NPC1	25			
		NPC1	Niemann-Pick disease,type C 1,autosomal recessive,a fatal neurovisceral disorder,characterized by ataxic gait,hepato splenomegaly progression to dementia,dysarthria,dystonia,seizures and death at teenage,due to an error in cellular trafficking of exogenous cholesterol with lysosomal accumulation of unesterified cholesterol,accounting for 95% of NPC	neurology, metabolism/lysosomal
		NPD	Niemann-Pick disease,type D,characterized by ataxic gait,hepatosplenomegaly,eventual progression to dementia,dysarthria,dystonia,seizures but distinguished of type C by its less severe	neurology, metabolism/lysosomal

			phenotype and by the Acadian ancestry type,due to an error in cellular trafficking of exogenous cholesterol with lysosomal accumulation of unesterified cholesterol	
NPHP1	4?2 0?			
		NPHP1	nephronophthisis, juvenile, characterized by progressive insidious polyuria due to reduced urinary concentrating ability preceding the decline of renal function and associated with an irregularly thickened tubular basement membrane (TBM), focal interstitial fibrosis, later diffuse tubular-intersitial changes and medullary cystis, leading to renal failure and death in childhood unless treated with dialysis or renal transplantation, including cases associated with oculomotor apraxia type COGAN and with cerebellar malformations without classic symptoms of Joubert	*kidney and urinary tract*
		SLSN1	Senior-Loken syndrome 1, juvenile nephronophtisis with retinal dystrophy different from Leber congenital amaurosis	kidney and urinary tract, eye
NSD1	23			
		STO	Sotos syndrome, overgrowth syndrome . facial gestalt : long, thin face, broad forehead, fronto-temporal hair sparcity, downslanting palpebral fissures, malar flushing. . adults : prominence of the chin, high hairline . macrocephaly, overgrowth in infancy . variable learning difficulties	congenital malformation, mental retardation

		WVSS	Weaver-Smith syndrome of accelerated growth and osseous maturation, unusual craniofacial appearance, hoarse and low-pitched cry, and hypertonia with camptodactyly associated with developmental delay	osteo-articular, mental retardation
OCA2	22			
		AS	Angelman syndrome, with a frequency of ~1/15000, resulting from defects in the maternally imprinted domain located on 15q11q13 . severe developmental delay/mental retardation, profound speech impairment, gait ataxia and/or movement disorder, characteristic behavioural profile including unprovoked prolonged paroxysms of laughther and excitability . other common features include seizures, abnormal EEG patterns, microcephaly, evocative facial features and hypopigmentation . distinct phenotypes distinguish the molecular classes of AS	*multisystem*
		OCA2	albinism, oculocutaneous 2, tyrosinase positive, most common form of OCA worldwide, especially frequent among southern African Blacks also including a milder hypopigmentation phenotype known as the brown oculocutaneous albinism (BOCA), associated to red hair in any cases (when associated mutation of MC1R)	eye, dermatology
		PWS	Prader-Willi contiguous gene syndrome, characterized by hypotonia and feeding difficulties in early infancy, followed in	*multisystem*

			early childhood by excessive eating and obesity, distinctive facial features, acromicria, short stature, hypogonadism, developmental delay, mild to moderate mental retardation, distinctive behavioral phenotype with temper tantrum and obsessive compulsive mannerisms . patients with deletion have more often seizures than patients with UPD	
OTOF	48?			
		DFNB9	neurosensory recessive deafness 9,non syndromic,prelingual,stable	ear
		NSRAN	non-syndromic recessive auditory neuropathy	ear
PAFAH 1B1	11			
		LIS1	lissencephaly,isolated with mutation or deletion of PAFAH1B1,including isolated subcortical laminar heterotopia	congenital malformation, neurology
		MDS	Miller-Dieker contiguous gene syndrome, characterized by lissencephaly, severe to profound mental retardation and a characteristic facial appearance and other anomalies, including a risk of abnormal pregnancy outcome in carriers of balanced translocations involving the Miller Dieker critical region	neurology, multisystem
PANK2	8			
		HARP	hypoprebetalipoproteinemia, acanthocytosis, retinitis pigmentosa and pallidal degeneration	eye, neurology, metabolism/lipoprotein lipid
		PANK2	Hallervorden-Spatz disease, with progressive rigidity dystonia,retinitis	eye, neurology

			pigmentosa, brain iron accumulation, including forms with extensive accumulation of both tau and alpha-synuclein . HARP syndrome characterized by hypoprebetalipoproteinemia, acanthocytosis, retinitis pigmentosa, and pallidal degeneration	
PAX3	10			
		CDHS	craniofacial-deafness-hand syndrome	ear, congenital malformation
		WS1	Waardenburg syndrome,type 1, autosomal dominant, partial albinism and deafness, with dystopia canthorum, leading to failure of MITF regulation	ear, eye, congenital malformation
		WS3	Waardenburg syndrome type 3, characterized by dystopia canthorum, partial albinism and severe upper limb defect (finger contractures and fusion of carpal bones), allelic to WS1	ear, limbs, congenital malformation
PAX6	*14*			
		AN	aniridia, homologous to mouse small eye, Drosophila eyeless, also including atypical phenotypes such as ocular coloboma as well as anophthalmia, foveal hypoplasia and central nervous system defect in compound heterozygotes	eye
		ASMD3	ocular anterior segment mesenchymal dysgenesis 3, including Peters anomaly, Axenfeld anomaly, corneal dystrophy associated with congenital cataract, autosomal dominant	eye
		ECTP	ectopia pupillae	eye

		FVH	foveal hypoplasia,isolated	eye
		OPNAB	optic nerve hypoplasia and aplasia, bilateral, including Morning glory disc anomaly	eye
		WAGR	contiguous gene syndrome characterized by predisposition to nephroblastoma (Wilms tumor), aniridia, genitourinary abnormalities, mental retardation	*eye, neoplasia, multisystem*
PDE6B	22			
		ARRP2	retinitis pigmentosa,autosomal recessive 2 (PDE6B),mouse rd homolog	eye
		CSNB3	blindness, night, congenital, stationary 3, autosomal dominant	eye
PEX7	10			
		PBD7	Refsum disease,phytanic acid oxidase deficiency,hereditary motor and sensory neuropathy 4 with ataxia, retinitis pigmentosa,and polyneuropathy ,complementation group 11 or R	eye, mental retardation, neurology
		RCDP1	rhizomelic chondrodysplasia punctata, pseudo-Zellweger syndrome, caracterized by striking shortening of proximal limbs, severely disturbed endochondral bone formation, coronal clefts of vertebrate bodies, associated to cataract, ichthyosis, profound growth and mental retardation and deficiency of all four PTS2 proteins, alkyl-dihydroxyacetone phosphate synthase, phytanyl-CoA hydrolase, 3 ketoacyl-CoA thiolase and mevalonate kinase participating in plasmalogen biosynthesis, phytanic acid catabolism, beta-oxidation of very long straight chain	osteo-articular, metabolism/peroxisomal, eye, dermatology, mental retardation

			fatty acids and isoprenoid biosynthesis respectively	
PITX2	3			
		IHG2	autosomal dominant iris hypoplasia,with goniodysgenesis (iridogoniodysgenesis) elevated intraocular pressure and secundary glaucoma (see RIEG1)	eye
		RIEG1	ocular anterior segment mesenchymal dysgenesis, Axenfeld Rieger syndrome , including posterior embryotoxon, iris stromal hypoplasia and abnormalities of pupil shape (corectopia) and number (polycoria) and secundary glaucoma associated with other anomalies, most frequently anodontia/hypodontia, maxillary hypoplasia, umbilical hernia due a failure of involution of periumbilical skin, see also IHG2	eye
PKD1	46			
		PKD1	polycystic kidney disease 1, adult type, accounting for 85% of cases, occuring by a cellular recessive mechanism supporting a two-hit model for cyst formation (somatic mutation with LOH of PKD1 or in (rare) cases, a somatic mutation in PKD2 generating a heterozygous state with mutations in both genes in the cysts), including some severe forms with intracranial aneurysms (5' mutation	kidney and urinary tract

			commonly associated with vascular disease) and/or a very early onset related to a 2bp deletion in exon 15 of PKD1 gene	
		PKTS	polycystic kidney disease,severe infantile form of the adult type with some features of tuberous sclerosis,contiguous gene syndrome (PkDa1/TSC2 locus)	kidney and urinary tract
PKLR	11			
		PKLR	hemolytic anemia,non spherocytic,chronic,mild to severe forms,autosomal recessive	hematology
		PYKH	high red cell ATP syndrome with pyruvate kinase hyperactivity	hematology
PLP1	7			
		PMDX	Pelizaeus-Merzbacher disease,type 1 characterized by an early onset by anormal eye movements,progressive,mental retardation,bilateral pyramidal signs and evidence of white matter deficit (PLP deficiency or overdosage)	eye, neurology
		SPG2	spastic paraplegia 2,late onset uncomplicated,X-linked	neurology
PMP22	5			
		CMT1A	Charcot-Marie-Tooth neuropathy 1 (HMSN Ia),hypertrophic form,demyelinating,characterized by distal muscle weakness and amyotrophy,sensory loss, decreased or absent tendon reflexes,with decreased nerve conduction velocities,(alteration of PMP22 gene dosage is responsible of	neurology

			abnormal Schwann-cell growth and differentiation),including Dejerine-Sottas syndrome. Charcot-Marie-Tooth 1A is associated in rare cases with deafness (CMT1E)	
		HNPP	neuropathy,hereditary,with liability to pressure palsies,including familial recurrent polyneuropathy (chronic inflammatory demyelinating polyradiculoneuropathy,CIDP),tomaculous neuropathy,and entrappment neuropathies such as carpal tunnel syndrome (brachial plexus neuropathy excluded)	neurology
		RLAD	Roussy-Levy hereditary areflexic dystasia with early onset ,foot deformity, weakness and atrophy of distal limb muscles, especially the peronei, absent tendon reflexes	?
PSAP	14			
		PSAP	sphingolipid activator proteins 1 and 2, combined deficiency, including metachromatic leukodystrophy, atypical Gaucher disease and complex sphingolipidosis with fatal infantile storage disorder (lactosylceramide disorder), mimicking in any cases Krabbe disease	metabolism/lysosomal
		SAPB	leukodystrophy metachromatic,variant with normal ARSA activity	metabolism/lysosomal
		SAPC	Gaucher disease,variant	metabolism/lysosomal
PTEN	9			

		BZS	Bannayan-Zonana syndrome with macrocephaly,lipomas,intestinal hamartomatous polyps,vascular malformations,Hashimoto thyroiditis and speckled penis,including Bannayan-Riley-Ruvalcaba syndrome,characterized by the head of macrocephaly,lipomas and pigmenta macules of the glans penis,could be grouped with Cowden syndrome for clinical purposes and classified as the PTEN hamartomas-tumor syndrome (PHTS)	*congenital malformation*
		JPS2	juvenile polyposis coli presenting with diarrhea,hemorrhage,protein losing enteropathy,characterized by the development throughout the digestive tract of hamartomatous polyps,including Cowden syndrome and/or Bannayan-Riley-Ruvalcaba syndrome	*digestive tract/gastrointestinal*
		MHAM	Cowden syndrome,autosomal dominant,characterized by multiple hamartoma in the breast,thyroid,skin,CNS and gastrointestinal tract associated with trichilemmomas (benign tumors of the hair follicle infundibulum) and mucocutaneous papules which are the hallmark of the syndrome. Including the Lhermitte-Duclos disease with dysplastic gangliocytoma of the cerebellum,manifesting as seizures,tremors and poor coordination. Could be grouped with Bannayan-Zonana-Riley Ruvalcaba syndrome for	*respiratory, dermatology, neurology*

			clinical purposes and classified as the PTEN hamartomas-tumor syndrome (PHTS)	
		PROTLS	Proteus-like syndrome,characterized by hemihypertrophy,lower limb asymmetry,arteriovenous malformation and lipomatosis,not similar to Proteus syndrome	osteo-articular, connective tissue
PTHR1	14			
		BLOD	Blomstrand chondrodysplasia,lethal dwarfism,with advanced endochondral bone formation and increased bone density	osteo-articular
		CDMJ	chondrodysplasia,metaphyseal,Jansen type,with cranial densification,autosomal dominant short-limbed dwarfism , with constitutive activity of PTHR1 in Jansen's form with hypercalcemia	osteo-articular
RDS	3			
		MDBS1	macular dystrophy, autosomal dominant, butterfly shaped pigmentary macular dystrophy 1, including Zermatt macular dystrophy, retinitis pigmentosa with bull's- eye maculopathy and other pattern dystrophies	eye
		RP7	retinitis pigmentosa 7, including retinitis punctata albescens	eye
RECQL 4	20			
		RAPADILINO	RAPADILINO syndrome, including Radial defect, Patellar defect, cleft Palate, Diarrhea, Dislocated joints and Limb	*osteo-articular, congenital malformation*

			deformation, long Nose and Normal intelligence, poikiloderma and Osteosarcoma likely associated, autosomal recessive, more severely expressed in female	
		RTS	Rothmund Thomson syndrome, characterized by skin atrophy and telangiectasia with hyper and hypo pigmentation, congenital skeletal abnormalities, short stature, juvenile cataract, premature ageing, increased risk of mesenchymal tumors linked to abnormal chromatid cohesion and chromosomal instability	dermatology, osteo-articular, eye
RET	20			
		CCHS1	congenital central hypoventilation syndrome,Ondine curse,associated with Hirschsprung disease,Haddad syndrome,(RET defect)	neurology
		HSCR1	Hirschsprung disease1,autosomal dominant form,characterized by intestinal blockage due to a lack of intrinsic ganglion cells in the myenteric and submucosal plexuses of the distal gastrointestinal tract and an increased risk of tumors,with variable expression and reduced penetrance even in multiplex kindreds,including total colonic aganglionosis with small bowel involvement	congenital malformation, digestive tract/gastrointestinal
		MEN2A	endocrine neoplasia,multiple,type IIA, Sipple disease	endocrinology

		MEN2B	endocrine neoplasia,multiple,type IIB,allelic to MEN2A	endocrinology
		MTC1	thyroid carcinoma,medullary 1,mutiple,with/without pheochromocytoma (RET defect),same gene as MEN2A;see also MEN2B,TST1	endocrinology
RHCE	10			
		RH	Rhesus blood group,as determined by RH-D and RH C/c-E/e (RH-CE) loci,including hemolytic disease of the newborn (Rhd phenotype)	*hematology*
		RHECT	blood group red-cell phenotype Rh-Evans (D..), associated with cataract	hematology, eye
		RHNA	blood group RH-null syndrome,amorph type	*hematology*
RHO	5			
		ARRP1	retinitis pigmentosa 1, autosomal recessive 1	eye
		CSNB6	blindness, night, congenital, stationary 6,autosomal dominant	eye
		RP4	retinitis pigmentosa 4, autosomal dominant, type I and others, including some retinitis punctata albescens, the first most common ADRP locus (20-31%)	eye
RLBP1	9			
		ARRP7	retinitis pigmentosa, autosomal recessive 8, early onset, with optic disc atrophy and macular degeneration	eye
		NFRCD	news foundland rod-cone dystrophy,early onset retinal dystrophy,severe,with precoce blindness	eye
		RPALB	retinitis punctata albescens,characterized by congenital stationary night blindness	eye

			and abnormally slow regeneration of visual pigments with uniform white-yellow dots scattered through retina,autosomal recessive,including Bothnia dystrophy (high prevalence in Northern Sweden)	
RPE65	14			
		LCA2	Leber congenital amaurosis type 2, autosomal recessive, characterized by congenital blindness with pendular nystagmus, roving eye movements, absent ocular pursuit and eye poking, night blindness, normal fundus at birth followed by salt and pepper aspect of retina and typical aspect of RP, non recordable ERG, presenting a transient improvement during evolution	eye
		RP20	variable expression retinal dystrophy,childhood-onset,autosomal recessive 8,affecting rod and cone photoreceptors	eye
RPGR	19			
		CORDX1	cone-rod dystrophy, 1 (RP2 and RP3 excluded), progressive retinal degeneration,characterized by progressive photophobia, decreased central vision and dyschromatopsia	eye
		MDXA1	X-linked recessive atrophic macular degeneration	eye
		RP15	retinitis pigmentosa 15,X-linked dominant,characterized by initial loss of visual acuity and color vision followed by	eye

			night blindness and peripheral visual field loss (see OMIM 300029)	
		RP3	retinitis pigmentosa 3, X-linked recessive form of choroidoretinal degeneration which is distinguished from other types by the presence in heterozygous women of a tapetal-like retinal reflex, including retinitis pigmentosa with recurrent respiratory infections	eye
RPS6KA3	22			
		CLS	Coffin-Lowry syndrome characterized by mental retardation,short stature,evolutive coarse facies,everted lips,progressive kyphoscoliosis,soft hands with tapering fingers,a large variety of mutations mostly responsible of loss of function	congenital malformation, mental retardation
		MRX19	mental retardation,X-linked 19	mental retardation
RUNX1	8			
		AML1	acute myeloid leukemia (AML-M2),or Philadelphia positive chronic myelogenous leukemia in the blastic phase,with breakpoint in translocation t(8;21)(q22;q22) (see CBFA2T1,dysregulated by interaction with MEF : myeloid ELF1 like factor) and t(16;21)(q24;q22) (see CBFB), myelodysplasia syndrome with breakpoint in translocation t(3;21)(q26;q22) (see EAP,EVI1,MDS1),acute lymphoblastic leukemia with translocation t(12;21)(p13;q22),most common in childhood leukemia (see ETV6),with low	hematology

			BCL2 expression and with inversions (between D21S65-D21S55-D21S215) in Down syndrome	
		FPDAML	platelet autosomal dominant disorder with prolonged bleeding time thrombocytopenia, aggregation defect and propensity to develop acute myeloid leukemia	hematology
RYR1	106			
		CCO	central core disease of muscle,or nemaline rod myopathy,characterized by hypotonia and proximal muscle weakness in infancy,leading to the delay of motor milestones,with a variable severity of symptoms,a low progressive course,associated skeletal defects and microscopically amorphous-looking areas (cores) in the predominant type I fibers;also presenting as a severe form of multi-minicore myopathy with ophtalmoplegia associated with presence of rods in the muscle fibers and to malignant hyperthermia susceptibility	neuromuscular
		MHS1	hyperthermia susceptibility, malignant 1 (ryanodine receptor defect) including abnormal electrically evoked muscle contraction syndrome in absence of drugs	neuromuscular
SCN1A	26			
		GEFS2	generalized epilepsy with febrile seizures plus,2	neurology
		SMEI2	severe myoclonic epilepsy in infancy 2, a severe form of generalized epilepsy with	neurology

			febrile seizures	
SCN5A	28			
		LQT3	long QT syndrome with ventricular tachyarrhythmia, type 3, characterized by syncopes, seizures, predisposing to torsades de pointes and ventricular fibrillation, potentially increasing the inward Na+ currents leading to a high level of membrane depolarization, also sudden infant death syndrome (frequency unknown)	cardiovascular
		PCCD1	progressive cardiac conduction deficit, characterized by progressive alteration of cardiac conduction through the His-Purkinje system with right or left bundle branch block and large QRS complexes, leading to complete atrioventricular block and causing syncope and sudden death, Lenegre-Lev disease (OMIM 113900), including the sudden unexplained nocturnal death syndrome (SUNDS) and Sick sinus syndrome congenital	cardiovascular
		PCCD2	idiopathic ventricular fibrillation, with sudden death, including form with a right bundle-branch block, and long QT, Brugada syndrome (OMIM 601144)	?
SCNN1B	13			
		PHA1A1	pseudohypoaldosteronism,type 1 (SCNN1B or SCNN1G defect),autosomal recessive,unresponsive to aldosterone	endocrinology
		PSALD	pseudoaldosteronism, hereditary hypertension, salt sensitive, with	endocrinology, cardiovascular

			hypokalemic alkalosis, Liddle syndrome (SCNN1B or SCNN1G defect), autosomal dominant	
SCNN1G	12			
		PHA1A1	pseudohypoaldosteronism,type 1 (SCNN1B or SCNN1G defect),autosomal recessive,unresponsive to aldosterone	endocrinology
		PSALD	pseudoaldosteronism, hereditary hypertension, salt sensitive, with hypokalemic alkalosis, Liddle syndrome (SCNN1B or SCNN1G defect), autosomal dominant	endocrinology, cardiovascular
SFTPC	6			
		FILD	familial interstitial lung disease presenting as chronic pneumonitis in infancy,autosomal dominant	respiratory
		IPAP1	infantile pulmonary alveolar proteinosis 1,with or without fibrosing lung disease	respiratory
SHOX	7			
		DCS	dyschondrosteosis,dominant form of mesomelic dysplasia in pseudoautosomal region characterized by short stature (2 SD below normal) with short forelimbs and distal radioulnar deformity on forearm x rays (Madelung deformity),Leri-Weill syndrome,maybe associated with chondrodysplasia punctata ichthyosis and mental retardation in a putative contiguous gene syndrome,and in any cases isolated Madelung deformity	osteo-articular

		GCX	growth control region,pseudoautosomal,X linked,involved in some idiopatic short stature,linear growth deficiency,maybe also involved in short and dysmorphic skeletal features in Turner syndrome (interaction with oestrogen is responsible of premature fusion of growth plate because of haploinsufficiency of SHOX)	?
		MMDL	mesomelic dwarfism,recessive form,of the hypoplastic ulna,fibula and mandible type,Langer type	osteo-articular
SLC26A 2	2			
		ACG1B	achondrogenesis IB, Fraccaro type, lethal dwarfism	osteo-articular
		ATSG2	atelosteogenesis, type II, lethal dwarfism, de la Chapelle dysplasia, including Mc Alister dysplasia	osteo-articular
		DTD	diastrophic dysplasia	osteo-articular
		EDM4	multiple epiphyseal dysplasia 4, with normal stature, hip dysplasia, double layered patella, including cases of apparently isolated club foot	osteo-articular
SLC26A 4	21			
		DFNB4	neurosensory recessive deafness 4,non syndromic,associated with temporal abnormalities that range from isolated enlarged vestibular acqueduct to developmental abnormalities of cochlea (Mondini	ear

			dysplasia),prelingual,stable,Middle Eastern Druze population	
		PDS	neurosensory deafness, with temporal bone abnormalities that range from isolated enlarged vestibular acqueduct (EVA) to developmental abnormalities of cochlea (Mondini dysplasia) and goiter, with iodine organification defect in the thyroid gland, Pendred syndrome, allelic to DFNB4	ear, endocrinology
SLC37A4	8			
		GSD1B	glycogen storage disease type IB, Von Gierke disease, characterized by hepatomegaly and hypoglycemia, lactic acidemia, hyperuricemia, hyperlipidemia, associated with neutropenia and functional deficiencies of neutrophiles and monocytes resulting in recurrent infections	metabolism/lipoprotein lipid
		GSD1C	glycogen storage disease type IC, von Gierke disease, characterized by hepatomegaly, hypoglycemia, lactic acidemia, hyperuricemia, hyperlipidemia not associated with neutropenia and functional deficiencies of neutrophiles and monocytes, maybe allelic to GSD1B but controversial evidence	metabolism/lipoprotein lipid
SLC4A1	20			
		BGW	blood group- Waldner type	hematology
		DI	Diego blood group	hematology

		DRTAA	renal tubular acidosis,distal,autosomal dominant,characterized by an inadequate urinary secretion resulting in alkaline pH in presence of metabolic acidosis,associated with hypokalemia hypercalciuria and when untreated nephrocalcinosis and usually mild metabolic bone disease and normal red cells,in relation with disorder of epithelial polarity	*kidney and urinary tract*
		EL5	elliptocytosis (ovalocytosis),Malaysian-Melanesian type	hematology
		SPH5	spherocytosis,type V,uncommon	hematology
SOX9	3			
		CMPD1	Campomelic dysplasia characterized by congenital bowing and angulation of long bones, together with other skeletal and extraskeletal defects . genital defects or sex reversal are observed in two-thirds of XY patients . acampomelic dysplasia is observed in some patients . a skeletal dysplasia with Pierre-Robin sequence may represent a mild form of campomelic dysplasia	*osteo-articular, sex-genitalia*
		SRA1	sex reversal,of SOX9,autosomal in XY patients with haplo insufficiency or in XX patients with a duplication of SOX9,allelic to CMPD1	sex-genitalia
SPTA1	52			
		EL2	elliptocytosis,common,type 2	hematology

		HPP	pyropoikilocytosis	hematology
		SPH3	spherocytosis,type III	hematology
TAZ	11			
		CMD3A	cardiomyopathy,dilated,lethal in infancy,allelic to Barth syndrome;see EFE2,recessive X-linked	cardiovascular, neuromuscular
		EFE2	dilated cardiomyopathy associated with skeletal myopathy,neutropenia and abnormal mitochondria (Barth syndrome),including isolated endomyocardial fibroelastosis 2 and 3-methylglutaconic aciduria	cardiovascular, connective tissue
		INVM	isolated noncompaction of the left ventricular myocardium without features of Barth syndrome but allelic to it	cardiovascular
TCF1	10			
		IDDM16	diabetes mellitus,insulin-dependent susceptibility 16	metabolism/carbohydrates
		MODY3	diabetes non insulin dependent, juvenile type, maturity onset diabetes of the young3, excluding NIDDM late onset, post puberal onset, severe form with lower renal threshold for glucose and frequent degenerative complications	metabolism/carbohydrates
TECTA	23			
		DFNA12	neurosensory dominant deafness 12,non syndromic,prelingual,stable in most patients,with mild frequency hearing loss,allelic to DFNA8 may be acting in a digenic mode of inheritance with DFNA2,leading to a severe phenotype or progressive deafness with late onset	ear

		DFNA8	neurosensory dominant deafness 8,non syndromic,prelingual,stable,allelic to DFNA12	ear
		DFNB21	neurosensory recessive deafness 21,non syndromic prelingual,severe to profound	ear
TMPRSS3	13			
		DFNB10	neurosensory recessive deafness 10,non syndromic,prelingual,stable,congenital,allelic to DFNB8	ear
		DFNB8	neurosensory recessive deafness 8,non-syndromic,postlingual,profound,progressive, allelic to DFNB10	ear
TP73L	15			
		ADULT	acro-dermato-ungual-lacrimal-tooth syndrome with ectrodactyly,hypoplastic breasts and nipples primary hypodontia	*congenital malformation*
		AEC	nkyloblepharon-ectodermal dysplasia-clefting syndrome,Hay-Wells syndrome	dermatology, eye
		LMS	limb mammary syndrome,EEC-like,in a Dutch family,characterized by mammary hypoplasia,ectrodactyly,lacrimal-duct-atresia,nail dysplasia, hypohydrosis,hypodontia and cleft palate,maybe allelic to EEC3 but no mutations so far detected in TP63	*congenital malformation*
		RHS	ectodermal dysplasia,anhydrotic with cleft lip,and cleft palate ,Rapp- Hodgkin syndrome,autosomal dominant	*dermatology*
		SHFM4	ectodactyly,ectodermal dysplasia and cleft-lip/palate syndrome 3,including cases of split hand/foot malformation (OMIM 605289)	*congenital malformation*

TRPS1	7			
		TRPS1	trichorhinophalangeal syndrome I,characterized by sparse scalp hair,a bulbous tip of the nose,a long flat philtrum,a thin upper vermilion border and protruding ears,associated with skeletal anomalies including cone-shaped epiphyses at the phalanges,hip malformation and short stature	osteo-articular, congenital malformation, dermatology
		TRPS3	trichorhinophalangeal syndrome 3 with short stature and remarkably short hands without exostoses,mostly allelic to TRPS1,Sugio-Kajii syndrome	osteo-articular
TSC1	21?			
		FCDBC	focal cortical dysplasia of Taylor balloon cell type ,epilepsy-associated without additional features of neurocutaneous phacomatosis	neurology
		TSC1	tuberous sclerosis 1, characterized by the development of hamartomas in cerebral cortex, responsible of seizures, mental retardation and mental disorder including autism, cortical tuber, hamartomas in other organs, including subependymal nodules, facial angiofibromas, subungual fibromas, forehead plaques, shagreen patches, cardiac rhabdomyomas and renal angiomyololipomas	neurology
TSHR	12?			
		GHTF	gestational hyperthyroidism,familial,autosomal dominant,caused by a mutant of	endocrinology

			thyrotropin receptor hypersensitive to human chorionic gonadotropin	
		HFTA	hyperfunctioning thyroid adenoma with somatic mutations of TSHR,hyperthyroidism,non immune,autosomal dominant or sporadic congenital form	endocrinology
		TSHR	hypothyroidism,congenital,with high TSH,TSH unresponsiveness (TSHR defect in few cases),including thyroid hypoplasia	endocrinology
TULP1	*14*			
		LCA10	Leber congenital amaurosis type 10,autosomal recessive, with nystagmus,night blindness ,profound visual deficiency,without hypermetropia,rod cone dystrophy	eye
		RP14	retinitis pigmentosa,autosomal recessive 4,severe,early onset,characterized by nystagmus,diminished visual acuity color vision disturbances,bull's eye maculopathy and peripheral pigmentary retinopathy,associated with an unrecordable ERG	eye
USH1C	28			
		DFNB18	neurosensory recessive deafness 18,non syndromic,Indian kindred,located in the USH1C region	ear
		USH1C	Usher syndrome, type IC, characterized by profound congenital neurosensory deafness, constant vestibular dysfunction and retinitis pigmentosa of prepubertal onset, leading to blindness (British	ear, eye

			kindred -Louisiana Acadian)	
USH2A	21			
		ARRP15	retinitis pigmentosa autosomal recessive 15,non syndromic	eye
		USH2A	Usher syndrome, type IIA, autosomal recessive, congenital, moderate to severe neurosensory deafness, progressive with age,normal vestibular function and retinitis pigmentosa, exhibiting phenotypic variation, including atypical cases with vestibular dysfunction, including cases of non syndromic retinitis pigmentosa	ear, eye
WAS	*12*			
		THC	thrombocytopenia,X-linked (same gene as WASP)	*hematology*
		WASP	Wiskott-Aldrich syndrome,including isolated thrombocytopenia,with increased apoptosis of lymphocytes	*hematology*
		XLN	severe congenital neutropenia,X-linked recessive characterized by recurrent major bacterial infections,associated monocytopenia and at bone marrow examination,arrest at the promyelocyte/myelocyte stage	*defense and immunity*
WFS1	8			
		DFNA14	neurosensory dominant deafness,non syndromic,bilateral and symetrical,only affecting low and mild frequencies up to 2000 Hz	ear
		DFNA38	neurosensory dominant deafness 38, nonsyndromic , progressive, autosomal	*ear*

			dominant	
		DFNA6	neurosensory dominant deafness 6, non syndromic, postlingual, progressive, low frequency hearing loss	ear
		WFS1	Wolfram syndrome,autosomal recessive,progressive neurodegenerative disorder,diabetes insipidus,non autoimmune insulin dependent diabetes mellitus,(optic atrophy,neurosensory deafness,renal-tract abnormalities,late ataxia and myoclonus),peripheral neuropathy psychiatric illness,Dueto-vasopressin neuron loss in the supraoptic nucleus and defect in precursor processing	metabolism/carbohydrates, ear, eye, kidney and urinary tract
WT1	9			
		DDS	Denys Drash syndrome, characterized by urogenital malformation, pseudohermaphroditism, Wilms tumor, nephroblastoma, infantile nephropathy with diffuse mesangial sclerosis evolving towards a renal failure and abnormal expression of PAX2, maybe involved in the pathological mechanisms leading to glomerular dysfunction ; see also GUD, dystomia-deafness syndrome with progressive deafness, severe dysarthria, bizarre posturing of head and neck and hyperactivity	*congenital malformation, ear, neurology, kidney and urinary tract*
		FS	Frasier syndrome, male pseudohermaphroditism with normal female external genitalia, streak gonads, with focal segmental glomerulosclerosis,	kidney and urinary tract, sex-genitalia

			nephrotic syndrome and gonadoblastoma but no Wilms tumor, related to but distinct from Denys-Drash syndrome	
		GUD	genitourinary dysplasia component of WAGR (including partial androgen resistance), overlapping Denys Drash syndrome (see DDS), associated with germline WT1 mutation	*congenital malformation, kidney and urinary tract*
		IDMS	nephrotic syndrome with an isolated diffuse or,rarely,a focal segmental mesangial sclerosis	*kidney and urinary tract*
		WAGR	contiguous gene syndrome characterized by predisposition to nephroblastoma (Wilms tumor), aniridia, genitourinary abnormalities, mental retardation	*eye, neoplasia, multisystem*
		WT1	Wilms tumor susceptibility 1,also involved in translocation t(11;22)(p13;q12) (see DSRCT),and in liver tumor suppression (see TSG11G)	kidney and urinary tract
XK	3			
		MCLDP	McLeod phenotype (acanthocytosis,elevated CK,and neurological defects),chorea,myopathy,areflexia,neuroacanthosis	hematology
		XK	Kell blood group precursor	hematology

CLAIMS:

1. A method for modulating RNA alternative splicing in a subject in need thereof comprising administering the subject with a therapeutically amount of an inhibitor of mitochondrial complex I activity.

2. The method according to claim 1 wherein the subject suffers from a disease selected from the group consisting of the diseases depicted in Table B, angiogenic diseases or and cancers.

3. The method according to claim 1 or 2 wherein the inhibitor of mitochondrial complex I activity is selected from the group consisting of catechols, metformin, statins, rotenone, troglitazone, resveratrol and inhibitors of expression of a protein selected in Table A, providing that when the subject suffers from myotonic dystrophy type I the inhibitor of mitochondrial complex I activity is not metformin.

INTERNATIONAL SEARCH REPORT

International application No
PCT/EP2014/057321

A. CLASSIFICATION OF SUBJECT MATTER
INV. A61K31/05 A61K31/353 A61K31/427 A61K31/55 A61P3/06
ADD.

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
A61K A61P

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)
EPO-Internal, BIOSIS, WPI Data, EMBASE

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 2011/121109 A1 (INST NAT SANTE RECH MED [FR]; BAGHDOYAN SANDRINE [FR]; PESCHANSKI MARC) 6 October 2011 (2011-10-06) claims 1,3,4,5 examples	1-3
X	WO 01/66098 A2 (AVENTIS PHARMA GMBH [DE]; JAYE MICHAEL [US]; DUVERGER NICOLAS [FR]; SE) 13 September 2001 (2001-09-13) claims 12,15	1-3

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[X] Further documents are listed in the continuation of Box C.

[X] See patent family annex.

* Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier application or patent but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
2 May 2014	22/08/2014

Name and mailing address of the ISA/	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Fax: (+31-70) 340-3016	Büttner, Ulf

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Form PCT/ISA/210 (second sheet) (April 2005)

C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	M. ANDREA MARKUS ET AL: "Resveratrol, by Modulating RNA Processing Factor Levels, Can Influence the Alternative Splicing of Pre-mRNAs", PLOS ONE, vol. 6, no. 12, 13 December 2011 (2011-12-13), page e28926, XP055067988, DOI: 10.1371/journal.pone.0028926 page 1119, column 2, paragraph 1	1-3
X	DATABASE BIOSIS [Online] BIOSCIENCES INFORMATION SERVICE, PHILADELPHIA, PA, US; April 2010 (2010-04), PATEL NIKETA A ET AL: "Alternative splicing of key survival genes during adipogenesis", XP002699491, Database accession no. PREV201300073275 abstract & FASEB JOURNAL, vol. 24, April 2010 (2010-04), CONFERENCE ON EXPERIMENTAL BIOLOGY; ANAHEIM, CA, USA; APRIL 24 -28, 2010 ISSN: 0892-6638(print)	1-3
X	MARY S SAKLA ET AL: "Induction of full-length survival motor neuron by polyphenol botanical compounds", HUMAN GENETICS, SPRINGER, BERLIN, DE, vol. 122, no. 6, 26 October 2007 (2007-10-26), pages 635-643, XP019590594, ISSN: 1432-1203 figure 4	1-3
X	ART J ET AL: "Identification of the KH type splicing regulatory protein (KSRP) as a new important mediator of the anti-inflammatory effects of resveratrol", NAUNYN-SCHMIEDEBERG'S ARCHIVES OF PHARMACOLOGY, vol. 385, no. Suppl. 1, March 2012 (2012-03), page 6, XP002699492, & 78TH ANNUAL CONGRESS OF THE GERMAN-SOCIETY-FOR-EXPERIMENTAL-AND-CLINIC AL-PHARMACOLOGY-AND-TOXICOLOGY; DRESDEN, GERMANY; MARCH 19 -22, 2012 abstract	1-3
X	WO 2008/022284 A2 (ASPREVA PHARMACEUTICALS CORP [CA]; HAYDEN MICHAEL [CA]; HALL NOEL [CA]) 21 February 2008 (2008-02-21) claims 25,54	1-3

1 -/--

C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	ALRASADI K ET AL: "Comparison of Treatment of Severe High-Density Lipoprotein Cholesterol Deficiency in Men With Daily Atorvastatin (20 mg) Versus Fenofibrate (200 mg) Versus Extended-Release Niacin (2 g)", AMERICAN JOURNAL OF CARDIOLOGY, CAHNERS PUBLISHING CO., NEWTON, MA, US, vol. 102, no. 10, 15 November 2008 (2008-11-15), pages 1341-1347, XP025627932, ISSN: 0002-9149, DOI: 10.1016/J.AMJCARD.2008.07.010 [retrieved on 2008-09-11] table 3	1-3
X	LUTUCUTA S ET AL: "NOVEL POLYMORPHISMS IN PROMOTER REGION OF ATP BINDING CASSETTE TRANSPORTER GENE AND PLASMA LIPIDS, SEVERITY, PROGRESSION AND REGRESSION OF CORONARY ATHEROSCLEROSIS AND RESPONSE TO THERAPY", CIRCULATION RESEARCH, GRUNE AND STRATTON, BALTIMORE, US, vol. 88, no. 9, 1 January 2001 (2001-01-01), pages 969-973, XP001016375, ISSN: 0009-7330 page 970, column 2	1-3
X	BELA F ASZTALOS ET AL: "High-density lipoprotein subpopulations in pathologic conditions", THE AMERICAN JOURNAL OF CARDIOLOGY, vol. 91, no. 7, 1 April 2003 (2003-04-01), pages 12-17, XP055068013, ISSN: 0002-9149, DOI: 10.1016/S0002-9149(02)03383-0 page 13E, last paragraph page 16E	1-3

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INTERNATIONAL SEARCH REPORT

International application No.
PCT/EP2014/057321

Box No. II Observations where certain claims were found unsearchable (Continuation of item 2 of first sheet)

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☐ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

2. ☒ Claims Nos.: 1-3(partially)
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:

see FURTHER INFORMATION sheet PCT/ISA/210

3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box No. III Observations where unity of invention is lacking (Continuation of item 3 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

see additional sheet

1. ☐ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.

2. ☐ As all searchable claims could be searched without effort justifying an additional fees, this Authority did not invite payment of additional fees.

3. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:

4. ☒ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

1-3(partially)

Remark on Protest

☐ The additional search fees were accompanied by the applicant's protest and, where applicable, the payment of a protest fee.

☐ The additional search fees were accompanied by the applicant's protest but the applicable protest fee was not paid within the time limit specified in the invitation.

☐ No protest accompanied the payment of additional search fees.

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

This International Searching Authority found multiple (groups of) inventions in this international application, as follows:

1. claims: 1-3(partially)

A method for modulating RNA alternative splicing in a subject in need thereof wherein the subject suffers from a disease that affects Gene ABCA4 with a therapeutically amount of an inhibitor of mitochondrial complex I activity.

---

2. claims: 1-3(partially)

A method for modulating RNA alternative splicing in a subject in need thereof wherein the subject suffers from a disease that affects Gene ABCC8 with a therapeutically amount of an inhibitor of mitochondrial complex I activity.

---

3. claims: 1-3(partially)

A method for modulating RNA alternative splicing in a subject in need thereof wherein the subject suffers from a disease that affects Gene ACSL4 with a therapeutically amount of an inhibitor of mitochondrial complex I activity.

---

4. claims: 1-3(partially)

A method for modulating RNA alternative splicing in a subject in need thereof wherein the subject suffers from a disease that affects Gene ADAMTS13 with a therapeutically amount of an inhibitor of mitochondrial complex I activity.

---

5. claims: 1-3(partially)

A method for modulating RNA alternative splicing in a subject in need thereof wherein the subject suffers from a disease that affects Gene AIPL1 with a therapeutically amount of an inhibitor of mitochondrial complex I activity.

---

6. claims: 1-3(partially)

A method for modulating RNA alternative splicing in a subject in need thereof wherein the subject suffers from a disease that affects Gene ALS2 with a therapeutically amount of an inhibitor of mitochondrial complex I activity.

---

7. claims: 1-3(partially)

A method for modulating RNA alternative splicing in a subject in need thereof wherein the subject suffers from a

disease that affects Gene ANKH with a therapeutically amount of an inhibitor of mitochondrial complex I activity.

---

8. claims: 1-3(partially)

A method for modulating RNA alternative splicing in a subject in need thereof wherein the subject suffers from a disease that affects Gene APC with a therapeutically amount of an inhibitor of mitochondrial complex I activity.

---

9. claims: 1-3(partially)

A method for modulating RNA alternative splicing in a subject in need thereof wherein the subject suffers from a disease that affects Gene APOA1 with a therapeutically amount of an inhibitor of mitochondrial complex I activity.

---

10. claims: 1-3(partially)

A method for modulating RNA alternative splicing in a subject in need thereof wherein the subject suffers from a disease that affects Gene APOB with a therapeutically amount of an inhibitor of mitochondrial complex I activity.

---

11. claims: 1-3(partially)

A method for modulating RNA alternative splicing in a subject in need thereof wherein the subject suffers from a disease that affects Gene ATPA2 with a therapeutically amount of an inhibitor of mitochondrial complex I activity.

---

12. claims: 1-3(partially)

A method for modulating RNA alternative splicing in a subject in need thereof wherein the subject suffers from a disease that affects Gene ATP7A with a therapeutically amount of an inhibitor of mitochondrial complex I activity.

---

13. claims: 1-3(partially)

A method for modulating RNA alternative splicing in a subject in need thereof wherein the subject suffers from a disease that affects Gene ATP8B1 with a therapeutically amount of an inhibitor of mitochondrial complex I activity.

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14. claims: 1-3(partially)

A method for modulating RNA alternative splicing in a

subject in need thereof wherein the subject suffers from a disease that affects Gene ATRX with a therapeutically amount of an inhibitor of mitochondrial complex I activity.

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15. claims: 1-3(partially)

A method for modulating RNA alternative splicing in a subject in need thereof wherein the subject suffers from a disease that affects Gene BCS1L with a therapeutically amount of an inhibitor of mitochondrial complex I activity.

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16. claims: 1-3(partially)

A method for modulating RNA alternative splicing in a subject in need thereof wherein the subject suffers from a disease that affects Gene BTK with a therapeutically amount of an inhibitor of mitochondrial complex I activity.

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17. claims: 1-3(partially)

A method for modulating RNA alternative splicing in a subject in need thereof wherein the subject suffers from a disease that affects Gene CACNA1A with a therapeutically amount of an inhibitor of mitochondrial complex I activity.

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18. claims: 1-3(partially)

A method for modulating RNA alternative splicing in a subject in need thereof wherein the subject suffers from a disease that affects Gene CASQ2 with a therapeutically amount of an inhibitor of mitochondrial complex I activity.

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19. claims: 1-3(partially)

A method for modulating RNA alternative splicing in a subject in need thereof wherein the subject suffers from a disease that affects Gene CDH23 with a therapeutically amount of an inhibitor of mitochondrial complex I activity.

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20. claims: 1-3(partially)

A method for modulating RNA alternative splicing in a subject in need thereof wherein the subject suffers from a disease that affects Gene CLCN1 with a therapeutically amount of an inhibitor of mitochondrial complex I activity.

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21. claims: 1-3(partially)

A method for modulating RNA alternative splicing in a subject in need thereof wherein the subject suffers from a disease that affects Gene CLCN5 with a therapeutically amount of an inhibitor of mitochondrial complex I activity.
---

22. claims: 1-3(partially)

A method for modulating RNA alternative splicing in a subject in need thereof wherein the subject suffers from a disease that affects Gene CLCNKB with a therapeutically amount of an inhibitor of mitochondrial complex I activity.
---

23. claims: 1-3(partially)

A method for modulating RNA alternative splicing in a subject in need thereof wherein the subject suffers from a disease that affects Gene COL11A1 with a therapeutically amount of an inhibitor of mitochondrial complex I activity.
---

24. claims: 1-3(partially)

A method for modulating RNA alternative splicing in a subject in need thereof wherein the subject suffers from a disease that affects Gene COL11 with a therapeutically amount of an inhibitor of mitochondrial complex I activity.
---

25. claims: 1-3(partially)

A method for modulating RNA alternative splicing in a subject in need thereof wherein the subject suffers from a disease that affects Gene COL1A1 with a therapeutically amount of an inhibitor of mitochondrial complex I activity.
---

26. claims: 1-3(partially)

A method for modulating RNA alternative splicing in a subject in need thereof wherein the subject suffers from a disease that affects Gene COL1A2 with a therapeutically amount of an inhibitor of mitochondrial complex I activity.
---

27. claims: 1-3(partially)

A method for modulating RNA alternative splicing in a subject in need thereof wherein the subject suffers from a disease that affects Gene COL2A1 with a therapeutically amount of an inhibitor of mitochondrial complex I activity.
---

28. claims: 1-3(partially)

A method for modulating RNA alternative splicing in a subject in need thereof wherein the subject suffers from a disease that affects Gene COL3A1 with a therapeutically amount of an inhibitor of mitochondrial complex I activity.
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29. claims: 1-3(partially)

A method for modulating RNA alternative splicing in a subject in need thereof wherein the subject suffers from a disease that affects Gene COL4A3 with a therapeutically amount of an inhibitor of mitochondrial complex I activity.
---

30. claims: 1-3(partially)

A method for modulating RNA alternative splicing in a subject in need thereof wherein the subject suffers from a disease that affects Gene COL4A4 with a therapeutically amount of an inhibitor of mitochondrial complex I activity.
---

31. claims: 1-3(partially)

A method for modulating RNA alternative splicing in a subject in need thereof wherein the subject suffers from a disease that affects Gene COL5A1 with a therapeutically amount of an inhibitor of mitochondrial complex I activity.
---

32. claims: 1-3(partially)

A method for modulating RNA alternative splicing in a subject in need thereof wherein the subject suffers from a disease that affects Gene COL5A2 with a therapeutically amount of an inhibitor of mitochondrial complex I activity.
---

33. claims: 1-3(partially)

A method for modulating RNA alternative splicing in a subject in need thereof wherein the subject suffers from a disease that affects Gene COL6A1 with a therapeutically amount of an inhibitor of mitochondrial complex I activity.
---

34. claims: 1-3(partially)

A method for modulating RNA alternative splicing in a subject in need thereof wherein the subject suffers from a disease that affects Gene COL6A2 with a therapeutically amount of an inhibitor of mitochondrial complex I activity.

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

35. claims: 1-3(partially)

A method for modulating RNA alternative splicing in a subject in need thereof wherein the subject suffers from a disease that affects Gene COL7A1 with a therapeutically amount of an inhibitor of mitochondrial complex I activity.

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36. claims: 1-3(partially)

A method for modulating RNA alternative splicing in a subject in need thereof wherein the subject suffers from a disease that affects Gene CRB1 with a therapeutically amount of an inhibitor of mitochondrial complex I activity.

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37. claims: 1-3(partially)

A method for modulating RNA alternative splicing in a subject in need thereof wherein the subject suffers from a disease that affects Gene CTNS with a therapeutically amount of an inhibitor of mitochondrial complex I activity.

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38. claims: 1-3(partially)

A method for modulating RNA alternative splicing in a subject in need thereof wherein the subject suffers from a disease that affects Gene CYP11B1 with a therapeutically amount of an inhibitor of mitochondrial complex I activity.

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39. claims: 1-3(partially)

A method for modulating RNA alternative splicing in a subject in need thereof wherein the subject suffers from a disease that affects Gene CYP19A1 with a therapeutically amount of an inhibitor of mitochondrial complex I activity.

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40. claims: 1-3(partially)

A method for modulating RNA alternative splicing in a subject in need thereof wherein the subject suffers from a disease that affects Gene DES with a therapeutically amount of an inhibitor of mitochondrial complex I activity.

---

41. claims: 1-3(partially)

A method for modulating RNA alternative splicing in a subject in need thereof wherein the subject suffers from a disease that affects Gene DMD with a therapeutically amount of an inhibitor of mitochondrial complex I activity.

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42. claims: 1-3(partially)

A method for modulating RNA alternative splicing in a subject in need thereof wherein the subject suffers from a disease that affects Gene DSP with a therapeutically amount of an inhibitor of mitochondrial complex I activity.

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43. claims: 1-3(partially)

A method for modulating RNA alternative splicing in a subject in need thereof wherein the subject suffers from a disease that affects Gene DSPP with a therapeutically amount of an inhibitor of mitochondrial complex I activity.

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44. claims: 1-3(partially)

A method for modulating RNA alternative splicing in a subject in need thereof wherein the subject suffers from a disease that affects Gene DYSF with a therapeutically amount of an inhibitor of mitochondrial complex I activity.

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45. claims: 1-3(partially)

A method for modulating RNA alternative splicing in a subject in need thereof wherein the subject suffers from a disease that affects Gene EDNRB with a therapeutically amount of an inhibitor of mitochondrial complex I activity.

---

46. claims: 1-3(partially)

A method for modulating RNA alternative splicing in a subject in need thereof wherein the subject suffers from a disease that affects Gene ELA2 with a therapeutically amount of an inhibitor of mitochondrial complex I activity.

---

47. claims: 1-3(partially)

A method for modulating RNA alternative splicing in a subject in need thereof wherein the subject suffers from a disease that affects Gene ELN with a therapeutically amount of an inhibitor of mitochondrial complex I activity.

---

48. claims: 1-3(partially)

A method for modulating RNA alternative splicing in a subject in need thereof wherein the subject suffers from a disease that affects Gene ENPP1 with a therapeutically amount of an inhibitor of mitochondrial complex I activity.

---

49. claims: 1-3(partially)

A method for modulating RNA alternative splicing in a subject in need thereof wherein the subject suffers from a disease that affects Gene EVC with a therapeutically amount of an inhibitor of mitochondrial complex I activity.

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50. claims: 1-3(partially)

A method for modulating RNA alternative splicing in a subject in need thereof wherein the subject suffers from a disease that affects Gene EXT1 with a therapeutically amount of an inhibitor of mitochondrial complex I activity.

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51. claims: 1-3(partially)

A method for modulating RNA alternative splicing in a subject in need thereof wherein the subject suffers from a disease that affects Gene EXT2 with a therapeutically amount of an inhibitor of mitochondrial complex I activity.

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52. claims: 1-3(partially)

A method for modulating RNA alternative splicing in a subject in need thereof wherein the subject suffers from a disease that affects Gene EYA1 with a therapeutically amount of an inhibitor of mitochondrial complex I activity.

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53. claims: 1-3(partially)

A method for modulating RNA alternative splicing in a subject in need thereof wherein the subject suffers from a disease that affects Gene FBN1 with a therapeutically amount of an inhibitor of mitochondrial complex I activity.

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54. claims: 1-3(partially)

A method for modulating RNA alternative splicing in a subject in need thereof wherein the subject suffers from a disease that affects Gene FGA with a therapeutically amount of an inhibitor of mitochondrial complex I activity.

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55. claims: 1-3(partially)

A method for modulating RNA alternative splicing in a subject in need thereof wherein the subject suffers from a disease that affects Gene FGFR1 with a therapeutically

amount of an inhibitor of mitochondrial complex I activity.
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56. claims: 1-3(partially)

A method for modulating RNA alternative splicing in a subject in need thereof wherein the subject suffers from a disease that affects Gene FGFR2 with a therapeutically amount of an inhibitor of mitochondrial complex I activity.
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57. claims: 1-3(partially)

A method for modulating RNA alternative splicing in a subject in need thereof wherein the subject suffers from a disease that affects Gene FLNA with a therapeutically amount of an inhibitor of mitochondrial complex I activity.
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58. claims: 1-3(partially)

A method for modulating RNA alternative splicing in a subject in need thereof wherein the subject suffers from a disease that affects Gene GABRG2 with a therapeutically amount of an inhibitor of mitochondrial complex I activity.
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59. claims: 1-3(partially)

A method for modulating RNA alternative splicing in a subject in need thereof wherein the subject suffers from a disease that affects Gene GCKwith a therapeutically amount of an inhibitor of mitochondrial complex I activity.
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60. claims: 1-3(partially)

A method for modulating RNA alternative splicing in a subject in need thereof wherein the subject suffers from a disease that affects Gene GDAP1 with a therapeutically amount of an inhibitor of mitochondrial complex I activity.
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61. claims: 1-3(partially)

A method for modulating RNA alternative splicing in a subject in need thereof wherein the subject suffers from a disease that affects Gene GHR with a therapeutically amount of an inhibitor of mitochondrial complex I activity.
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62. claims: 1-3(partially)

A method for modulating RNA alternative splicing in a subject in need thereof wherein the subject suffers from a

disease that affects Gene GJB2 with a therapeutically amount of an inhibitor of mitochondrial complex I activity.

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63. claims: 1-3(partially)

A method for modulating RNA alternative splicing in a subject in need thereof wherein the subject suffers from a disease that affects Gene GLB1 with a therapeutically amount of an inhibitor of mitochondrial complex I activity.

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64. claims: 1-3(partially)

A method for modulating RNA alternative splicing in a subject in need thereof wherein the subject suffers from a disease that affects Gene GLI3 with a therapeutically amount of an inhibitor of mitochondrial complex I activity.

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65. claims: 1-3(partially)

A method for modulating RNA alternative splicing in a subject in need thereof wherein the subject suffers from a disease that affects Gene GNAS with a therapeutically amount of an inhibitor of mitochondrial complex I activity.

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66. claims: 1-3(partially)

A method for modulating RNA alternative splicing in a subject in need thereof wherein the subject suffers from a disease that affects Gene GUCY2D with a therapeutically amount of an inhibitor of mitochondrial complex I activity.

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67. claims: 1-3(partially)

A method for modulating RNA alternative splicing in a subject in need thereof wherein the subject suffers from a disease that affects Gene GUSB with a therapeutically amount of an inhibitor of mitochondrial complex I activity.

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68. claims: 1-3(partially)

A method for modulating RNA alternative splicing in a subject in need thereof wherein the subject suffers from a disease that affects Gene HFE with a therapeutically amount of an inhibitor of mitochondrial complex I activity.

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69. claims: 1-3(partially)

A method for modulating RNA alternative splicing in a

subject in need thereof wherein the subject suffers from a disease that affects Gene HPRT1 with a therapeutically amount of an inhibitor of mitochondrial complex I activity.

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70. claims: 1-3(partially)

A method for modulating RNA alternative splicing in a subject in need thereof wherein the subject suffers from a disease that affects Gene HR with a therapeutically amount of an inhibitor of mitochondrial complex I activity.

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71. claims: 1-3(partially)

A method for modulating RNA alternative splicing in a subject in need thereof wherein the subject suffers from a disease that affects Gene EDNRB with a therapeutically amount of an inhibitor of mitochondrial complex I activity.

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72. claims: 1-3(partially)

A method for modulating RNA alternative splicing in a subject in need thereof wherein the subject suffers from a disease that affects Gene HSPG2 with a therapeutically amount of an inhibitor of mitochondrial complex I activity.

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73. claims: 1-3(partially)

A method for modulating RNA alternative splicing in a subject in need thereof wherein the subject suffers from a disease that affects Gene IFNGR1 with a therapeutically amount of an inhibitor of mitochondrial complex I activity.

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74. claims: 1-3(partially)

A method for modulating RNA alternative splicing in a subject in need thereof wherein the subject suffers from a disease that affects Gene IKBKG with a therapeutically amount of an inhibitor of mitochondrial complex I activity.

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75. claims: 1-3(partially)

A method for modulating RNA alternative splicing in a subject in need thereof wherein the subject suffers from a disease that affects Gene INSR with a therapeutically amount of an inhibitor of mitochondrial complex I activity.

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76. claims: 1-3(partially)

A method for modulating RNA alternative splicing in a subject in need thereof wherein the subject suffers from a disease that affects Gene ITGB4 with a therapeutically amount of an inhibitor of mitochondrial complex I activity.

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77. claims: 1-3(partially)

A method for modulating RNA alternative splicing in a subject in need thereof wherein the subject suffers from a disease that affects Gene JAG1 with a therapeutically amount of an inhibitor of mitochondrial complex I activity.

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78. claims: 1-3(partially)

A method for modulating RNA alternative splicing in a subject in need thereof wherein the subject suffers from a disease that affects Gene KCNG1 with a therapeutically amount of an inhibitor of mitochondrial complex I activity.

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79. claims: 1-3(partially)

A method for modulating RNA alternative splicing in a subject in need thereof wherein the subject suffers from a disease that affects Gene KIT with a therapeutically amount of an inhibitor of mitochondrial complex I activity.

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80. claims: 1-3(partially)

A method for modulating RNA alternative splicing in a subject in need thereof wherein the subject suffers from a disease that affects Gene KRT1 with a therapeutically amount of an inhibitor of mitochondrial complex I activity.

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81. claims: 1-3(partially)

A method for modulating RNA alternative splicing in a subject in need thereof wherein the subject suffers from a disease that affects Gene KRT14 with a therapeutically amount of an inhibitor of mitochondrial complex I activity.

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82. claims: 1-3(partially)

A method for modulating RNA alternative splicing in a subject in need thereof wherein the subject suffers from a disease that affects Gene KRT5 with a therapeutically amount of an inhibitor of mitochondrial complex I activity.

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83. claims: 1-3(partially)

A method for modulating RNA alternative splicing in a subject in need thereof wherein the subject suffers from a disease that affects Gene L1CAM with a therapeutically amount of an inhibitor of mitochondrial complex I activity.

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84. claims: 1-3(partially)

A method for modulating RNA alternative splicing in a subject in need thereof wherein the subject suffers from a disease that affects Gene LAMA3 with a therapeutically amount of an inhibitor of mitochondrial complex I activity.

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85. claims: 1-3(partially)

A method for modulating RNA alternative splicing in a subject in need thereof wherein the subject suffers from a disease that affects Gene LAMB3 with a therapeutically amount of an inhibitor of mitochondrial complex I activity.

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86. claims: 1-3(partially)

A method for modulating RNA alternative splicing in a subject in need thereof wherein the subject suffers from a disease that affects Gene LBR with a therapeutically amount of an inhibitor of mitochondrial complex I activity.

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87. claims: 1-3(partially)

A method for modulating RNA alternative splicing in a subject in need thereof wherein the subject suffers from a disease that affects Gene LCAT with a therapeutically amount of an inhibitor of mitochondrial complex I activity.

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88. claims: 1-3(partially)

A method for modulating RNA alternative splicing in a subject in need thereof wherein the subject suffers from a disease that affects Gene LMNA with a therapeutically amount of an inhibitor of mitochondrial complex I activity.

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89. claims: 1-3(partially)

A method for modulating RNA alternative splicing in a subject in need thereof wherein the subject suffers from a disease that affects Gene MAPT with a therapeutically amount of an inhibitor of mitochondrial complex I activity.

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90. claims: 1-3(partially)

A method for modulating RNA alternative splicing in a subject in need thereof wherein the subject suffers from a disease that affects Gene MECP2 with a therapeutically amount of an inhibitor of mitochondrial complex I activity.

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91. claims: 1-3(partially)

A method for modulating RNA alternative splicing in a subject in need thereof wherein the subject suffers from a disease that affects Gene MITF with a therapeutically amount of an inhibitor of mitochondrial complex I activity.

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92. claims: 1-3(partially)

A method for modulating RNA alternative splicing in a subject in need thereof wherein the subject suffers from a disease that affects Gene MLH1 with a therapeutically amount of an inhibitor of mitochondrial complex I activity.

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93. claims: 1-3(partially)

A method for modulating RNA alternative splicing in a subject in need thereof wherein the subject suffers from a disease that affects Gene MPZ with a therapeutically amount of an inhibitor of mitochondrial complex I activity.

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94. claims: 1-3(partially)

A method for modulating RNA alternative splicing in a subject in need thereof wherein the subject suffers from a disease that affects Gene MSH2 with a therapeutically amount of an inhibitor of mitochondrial complex I activity.

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95. claims: 1-3(partially)

A method for modulating RNA alternative splicing in a subject in need thereof wherein the subject suffers from a disease that affects Gene MYH7 with a therapeutically amount of an inhibitor of mitochondrial complex I activity.

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96. claims: 1-3(partially)

A method for modulating RNA alternative splicing in a subject in need thereof wherein the subject suffers from a disease that affects Gene MYO7A with a therapeutically amount of an inhibitor of mitochondrial complex I activity.

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

97. claims: 1-3(partially)

A method for modulating RNA alternative splicing in a subject in need thereof wherein the subject suffers from a disease that affects Gene NDP with a therapeutically amount of an inhibitor of mitochondrial complex I activity.

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98. claims: 1-3(partially)

A method for modulating RNA alternative splicing in a subject in need thereof wherein the subject suffers from a disease that affects Gene NDUFV1 with a therapeutically amount of an inhibitor of mitochondrial complex I activity.

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99. claims: 1-3(partially)

A method for modulating RNA alternative splicing in a subject in need thereof wherein the subject suffers from a disease that affects Gene NF1 with a therapeutically amount of an inhibitor of mitochondrial complex I activity.

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100. claims: 1-3(partially)

A method for modulating RNA alternative splicing in a subject in need thereof wherein the subject suffers from a disease that affects Gene NF2 with a therapeutically amount of an inhibitor of mitochondrial complex I activity.

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101. claims: 1-3(partially)

A method for modulating RNA alternative splicing in a subject in need thereof wherein the subject suffers from a disease that affects Gene NPC1 with a therapeutically amount of an inhibitor of mitochondrial complex I activity.

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102. claims: 1-3(partially)

A method for modulating RNA alternative splicing in a subject in need thereof wherein the subject suffers from a disease that affects Gene NPHP1 with a therapeutically amount of an inhibitor of mitochondrial complex I activity.

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103. claims: 1-3(partially)

A method for modulating RNA alternative splicing in a subject in need thereof wherein the subject suffers from a disease that affects Gene NSD1 with a therapeutically amount of an inhibitor of mitochondrial complex I activity.

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104. claims: 1-3(partially)

A method for modulating RNA alternative splicing in a subject in need thereof wherein the subject suffers from a disease that affects Gene OCA2 with a therapeutically amount of an inhibitor of mitochondrial complex I activity.

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105. claims: 1-3(partially)

A method for modulating RNA alternative splicing in a subject in need thereof wherein the subject suffers from a disease that affects Gene OTOF with a therapeutically amount of an inhibitor of mitochondrial complex I activity.

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106. claims: 1-3(partially)

A method for modulating RNA alternative splicing in a subject in need thereof wherein the subject suffers from a disease that affects Gene PAFFAH1B1 with a therapeutically amount of an inhibitor of mitochondrial complex I activity.

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107. claims: 1-3(partially)

A method for modulating RNA alternative splicing in a subject in need thereof wherein the subject suffers from a disease that affects Gene PANK2 with a therapeutically amount of an inhibitor of mitochondrial complex I activity.

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108. claims: 1-3(partially)

A method for modulating RNA alternative splicing in a subject in need thereof wherein the subject suffers from a disease that affects Gene PAX3 with a therapeutically amount of an inhibitor of mitochondrial complex I activity.

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109. claims: 1-3(partially)

A method for modulating RNA alternative splicing in a subject in need thereof wherein the subject suffers from a disease that affects Gene PAX6 with a therapeutically amount of an inhibitor of mitochondrial complex I activity.

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110. claims: 1-3(partially)

A method for modulating RNA alternative splicing in a subject in need thereof wherein the subject suffers from a disease that affects Gene PDE6B with a therapeutically

amount of an inhibitor of mitochondrial complex I activity.

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111. claims: 1-3(partially)

A method for modulating RNA alternative splicing in a subject in need thereof wherein the subject suffers from a disease that affects Gene PEX7 with a therapeutically amount of an inhibitor of mitochondrial complex I activity.

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112. claims: 1-3(partially)

A method for modulating RNA alternative splicing in a subject in need thereof wherein the subject suffers from a disease that affects Gene PITX2 with a therapeutically amount of an inhibitor of mitochondrial complex I activity.

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113. claims: 1-3(partially)

A method for modulating RNA alternative splicing in a subject in need thereof wherein the subject suffers from a disease that affects Gene PKD1 with a therapeutically amount of an inhibitor of mitochondrial complex I activity.

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114. claims: 1-3(partially)

A method for modulating RNA alternative splicing in a subject in need thereof wherein the subject suffers from a disease that affects Gene PKLR with a therapeutically amount of an inhibitor of mitochondrial complex I activity.

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115. claims: 1-3(partially)

A method for modulating RNA alternative splicing in a subject in need thereof wherein the subject suffers from a disease that affects Gene PLP1 with a therapeutically amount of an inhibitor of mitochondrial complex I activity.

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116. claims: 1-3(partially)

A method for modulating RNA alternative splicing in a subject in need thereof wherein the subject suffers from a disease that affects Gene PMP22 with a therapeutically amount of an inhibitor of mitochondrial complex I activity.

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117. claims: 1-3(partially)

A method for modulating RNA alternative splicing in a subject in need thereof wherein the subject suffers from a

disease that affects Gene PSAP with a therapeutically amount of an inhibitor of mitochondrial complex I activity.

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118. claims: 1-3(partially)

A method for modulating RNA alternative splicing in a subject in need thereof wherein the subject suffers from a disease that affects Gene PTEN with a therapeutically amount of an inhibitor of mitochondrial complex I activity.

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119. claims: 1-3(partially)

A method for modulating RNA alternative splicing in a subject in need thereof wherein the subject suffers from a disease that affects Gene PTHR1 with a therapeutically amount of an inhibitor of mitochondrial complex I activity.

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120. claims: 1-3(partially)

A method for modulating RNA alternative splicing in a subject in need thereof wherein the subject suffers from a disease that affects Gene RDS with a therapeutically amount of an inhibitor of mitochondrial complex I activity.

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121. claims: 1-3(partially)

A method for modulating RNA alternative splicing in a subject in need thereof wherein the subject suffers from a disease that affects Gene RECQL4 with a therapeutically amount of an inhibitor of mitochondrial complex I activity.

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122. claims: 1-3(partially)

A method for modulating RNA alternative splicing in a subject in need thereof wherein the subject suffers from a disease that affects Gene RET with a therapeutically amount of an inhibitor of mitochondrial complex I activity.

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123. claims: 1-3(partially)

A method for modulating RNA alternative splicing in a subject in need thereof wherein the subject suffers from a disease that affects Gene RHCE with a therapeutically amount of an inhibitor of mitochondrial complex I activity.

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124. claims: 1-3(partially)

A method for modulating RNA alternative splicing in a

subject in need thereof wherein the subject suffers from a disease that affects Gene RHO with a therapeutically amount of an inhibitor of mitochondrial complex I activity.

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125. claims: 1-3(partially)

A method for modulating RNA alternative splicing in a subject in need thereof wherein the subject suffers from a disease that affects Gene RLBP1 with a therapeutically amount of an inhibitor of mitochondrial complex I activity.

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126. claims: 1-3(partially)

A method for modulating RNA alternative splicing in a subject in need thereof wherein the subject suffers from a disease that affects Gene RPE65 with a therapeutically amount of an inhibitor of mitochondrial complex I activity.

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127. claims: 1-3(partially)

A method for modulating RNA alternative splicing in a subject in need thereof wherein the subject suffers from a disease that affects Gene RPGR with a therapeutically amount of an inhibitor of mitochondrial complex I activity.

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128. claims: 1-3(partially)

A method for modulating RNA alternative splicing in a subject in need thereof wherein the subject suffers from a disease that affects Gene RPS6KA3 with a therapeutically amount of an inhibitor of mitochondrial complex I activity.

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129. claims: 1-3(partially)

A method for modulating RNA alternative splicing in a subject in need thereof wherein the subject suffers from a disease that affects Gene RUNX1 with a therapeutically amount of an inhibitor of mitochondrial complex I activity.

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130. claims: 1-3(partially)

A method for modulating RNA alternative splicing in a subject in need thereof wherein the subject suffers from a disease that affects Gene RYR1with a therapeutically amount of an inhibitor of mitochondrial complex I activity.

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131. claims: 1-3(partially)

A method for modulating RNA alternative splicing in a subject in need thereof wherein the subject suffers from a disease that affects Gene SCN1A with a therapeutically amount of an inhibitor of mitochondrial complex I activity.

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132. claims: 1-3(partially)

A method for modulating RNA alternative splicing in a subject in need thereof wherein the subject suffers from a disease that affects Gene SCN5A with a therapeutically amount of an inhibitor of mitochondrial complex I activity.

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133. claims: 1-3(partially)

A method for modulating RNA alternative splicing in a subject in need thereof wherein the subject suffers from a disease that affects Gene SCNN1B with a therapeutically amount of an inhibitor of mitochondrial complex I activity.

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134. claims: 1-3(partially)

A method for modulating RNA alternative splicing in a subject in need thereof wherein the subject suffers from a disease that affects Gene SCNN1G with a therapeutically amount of an inhibitor of mitochondrial complex I activity.

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135. claims: 1-3(partially)

A method for modulating RNA alternative splicing in a subject in need thereof wherein the subject suffers from a disease that affects Gene SFTPC with a therapeutically amount of an inhibitor of mitochondrial complex I activity.

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136. claims: 1-3(partially)

A method for modulating RNA alternative splicing in a subject in need thereof wherein the subject suffers from a disease that affects Gene SHOX with a therapeutically amount of an inhibitor of mitochondrial complex I activity.

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137. claims: 1-3(partially)

A method for modulating RNA alternative splicing in a subject in need thereof wherein the subject suffers from a disease that affects Gene SLC26A2 with a therapeutically amount of an inhibitor of mitochondrial complex I activity.

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138. claims: 1-3(partially)

A method for modulating RNA alternative splicing in a subject in need thereof wherein the subject suffers from a disease that affects Gene SLC26A with a therapeutically amount of an inhibitor of mitochondrial complex I activity.

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139. claims: 1-3(partially)

A method for modulating RNA alternative splicing in a subject in need thereof wherein the subject suffers from a disease that affects Gene SLC37A4 with a therapeutically amount of an inhibitor of mitochondrial complex I activity.

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140. claims: 1-3(partially)

A method for modulating RNA alternative splicing in a subject in need thereof wherein the subject suffers from a disease that affects Gene with a therapeutically amount of an inhibitor of mitochondrial complex I activity.

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141. claims: 1-3(partially)

A method for modulating RNA alternative splicing in a subject in need thereof wherein the subject suffers from a disease that affects Gene SLC4A1 with a therapeutically amount of an inhibitor of mitochondrial complex I activity.

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142. claims: 1-3(partially)

A method for modulating RNA alternative splicing in a subject in need thereof wherein the subject suffers from a disease that affects Gene SOX9 with a therapeutically amount of an inhibitor of mitochondrial complex I activity.

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143. claims: 1-3(partially)

A method for modulating RNA alternative splicing in a subject in need thereof wherein the subject suffers from a disease that affects Gene SPTA1 with a therapeutically amount of an inhibitor of mitochondrial complex I activity.

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144. claims: 1-3(partially)

A method for modulating RNA alternative splicing in a subject in need thereof wherein the subject suffers from a disease that affects Gene TAZ with a therapeutically amount of an inhibitor of mitochondrial complex I activity.

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145. claims: 1-3(partially)

A method for modulating RNA alternative splicing in a subject in need thereof wherein the subject suffers from a disease that affects Gene TCF1 with a therapeutically amount of an inhibitor of mitochondrial complex I activity.

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146. claims: 1-3(partially)

A method for modulating RNA alternative splicing in a subject in need thereof wherein the subject suffers from a disease that affects Gene TECTA with a therapeutically amount of an inhibitor of mitochondrial complex I activity.

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147. claims: 1-3(partially)

A method for modulating RNA alternative splicing in a subject in need thereof wherein the subject suffers from a disease that affects Gene TMPRSS3 with a therapeutically amount of an inhibitor of mitochondrial complex I activity.

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148. claims: 1-3(partially)

A method for modulating RNA alternative splicing in a subject in need thereof wherein the subject suffers from a disease that affects Gene TP73L with a therapeutically amount of an inhibitor of mitochondrial complex I activity.

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149. claims: 1-3(partially)

A method for modulating RNA alternative splicing in a subject in need thereof wherein the subject suffers from a disease that affects Gene TRPS1 with a therapeutically amount of an inhibitor of mitochondrial complex I activity.

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150. claims: 1-3(partially)

A method for modulating RNA alternative splicing in a subject in need thereof wherein the subject suffers from a disease that affects Gene TSC1 with a therapeutically amount of an inhibitor of mitochondrial complex I activity.

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151. claims: 1-3(partially)

A method for modulating RNA alternative splicing in a subject in need thereof wherein the subject suffers from a disease that affects Gene TSHR with a therapeutically amount of an inhibitor of mitochondrial complex I activity.

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152. claims: 1-3(partially)

A method for modulating RNA alternative splicing in a subject in need thereof wherein the subject suffers from a disease that affects Gene TULP1 with a therapeutically amount of an inhibitor of mitochondrial complex I activity.

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153. claims: 1-3(partially)

A method for modulating RNA alternative splicing in a subject in need thereof wherein the subject suffers from a disease that affects Gene USH1C with a therapeutically amount of an inhibitor of mitochondrial complex I activity.

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154. claims: 1-3(partially)

A method for modulating RNA alternative splicing in a subject in need thereof wherein the subject suffers from a disease that affects Gene USH2A with a therapeutically amount of an inhibitor of mitochondrial complex I activity.

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155. claims: 1-3(partially)

A method for modulating RNA alternative splicing in a subject in need thereof wherein the subject suffers from a disease that affects Gene WAS with a therapeutically amount of an inhibitor of mitochondrial complex I activity.

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156. claims: 1-3(partially)

A method for modulating RNA alternative splicing in a subject in need thereof wherein the subject suffers from a disease that affects Gene WFS1 with a therapeutically amount of an inhibitor of mitochondrial complex I activity.

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157. claims: 1-3(partially)

A method for modulating RNA alternative splicing in a subject in need thereof wherein the subject suffers from a disease that affects Gene WT1 with a therapeutically amount of an inhibitor of mitochondrial complex I activity.

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158. claims: 1-3(partially)

A method for modulating RNA alternative splicing in a subject in need thereof wherein the subject suffers from a disease that affects Gene XK with a therapeutically amount of an inhibitor of mitochondrial complex I activity.

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159. claims: 1-3(partially)

A method for modulating RNA alternative splicing in a subject in need thereof wherein the subject suffers from anangiogenic disease with a therapeutically amount of an inhibitor of mitochondrial complex I activity.

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160. claims: 1-3(partially)

A method for modulating RNA alternative splicing in a subject in need thereof wherein the subject suffers from cancer with a therapeutically amount of an inhibitor of mitochondrial complex I activity.

Continuation of Box II.2

Claims Nos.: 1-3(partially)

The compounds of claims 1 are functionally defined. Although the description mentions a limited number of compounds,the compounds fulfilling the functional definition are not part of the common general knowledge. Without technical guidance as to how suitable compounds may be traced out, it is not sufficient with respect to Art. 5 PCT that candidate compounds may be identified by a known screening method or an assay disclosed in the patent application. Art. 5 PCT is only met if the functionally defined class of compounds is available to the skilled person. If the functional class of compounds is not commonly known and the patent application discloses only isolated examples of chemical compounds having such function, Art. 5 PCT is only considered to be met if there is sufficient information in the entire application which enables the skilled person to find alternative compounds with the function without undue effort.
Method claim 1 is not acceptable under Articles 5/6 PCT. The therapeutic application is functionally defined by a mechanism of action which does not allow any practical application in the form of a defined, real treatment of a pathological condition (disease).
The search has been limited to compounds according to the diseases according to claim 2 and compounds according to claim 3.

The applicant's attention is drawn to the fact that claims relating to inventions in respect of which no international search report has been established need not be the subject of an international preliminary examination (Rule 66.1(e) PCT). The applicant is advised that the EPO policy when acting as an International Preliminary Examining Authority is normally not to carry out a preliminary examination on matter which has not been searched. This is the case irrespective of whether or not the claims are amended following receipt of the search report or during any Chapter II procedure. If the application proceeds into the regional phase before the EPO, the applicant is reminded that a search may be carried out during examination before the EPO (see EPO Guidelines C-IV, 7.2), should the problems which led to the Article 17(2) declaration be overcome.

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No
PCT/EP2014/057321

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