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(57) **Abrégé/Abstract:**

Sequences and protocols for treatment of eye conditions by use of RNA interference are disclosed. Target genes are selected from those responsible for aqueous flow or aqueous outflow, while particularly preferred conditions to be treated include glaucoma and uveitis.



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JUMBO APPLICATIONS / PATENTS

**THIS SECTION OF THE APPLICATION / PATENT CONTAINS MORE
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Treatment Of Eye Disorders Characterized By An
Elevated Intraocular Pressure By Sirnas

5 **FIELD OF THE INVENTION**

The present invention relates to methods and compositions for the treatment of eye disorders; in particular but not exclusively to the treatment of glaucoma. In preferred embodiments, the invention relates to the use of RNAi technology to downregulate the expression of aqueous formation genes and aqueous outflow
10 genes. Methods and compositions for the treatment of eye disorders are also provided.

BACKGROUND OF THE INVENTION

RNAi as a tool to downregulate gene expression

15 Gene targeting by homologous recombination is commonly used to determine gene function in mammals, but this is a costly and time-consuming process. Alternatively, the functions of many genes can be determined after mRNA inhibition with ribozyme or antisense technologies. Although successful in some situations these technologies have been difficult to apply universally. The
20 advent of siRNA-directed "knockdown" has sparked a revolution in somatic cell genetics, allowing the inexpensive and rapid analysis of gene function in mammals.

Establishing a convenient and reliable method to knock-out gene expression at
25 the mRNA level has been a recurrent theme in molecular biology over the last 15 years. In efforts to generate loss-of function cells or organisms, various molecules that included, for example, antisense sequences, ribozymes, and chimeric oligonucleotides have been tested, but the design of such molecules was based on trial and error, depending on the properties of the target gene.

Moreover, the desired effects were difficult to predict, and often only weak suppression achieved (Braasch & Corey, 2002).

After the discovery of the phenomenon in plants in the early 1990s, in 1998
5 Andy Fire and Craig Mello for the first time demonstrated with the worm
Caenorhabditis elegans that dsRNA (double-stranded RNA) may specifically and
selectively inhibit gene expression in an extremely efficient manner (Fire *et al.*,
1998). In their experiment, the sequence of the first strand (the so-called *sense*
RNA) coincides with that of the corresponding region of the target messenger
10 RNA (mRNA). The second strand (*antisense* RNA) is complementary to this
mRNA. The resulting dsRNA turned out to be far more (several orders of
magnitude) efficient than the corresponding single-stranded RNA molecules (in
particular, *antisense* RNA). Fire *et al.*, 1998 named the phenomenon RNAi for
RNA *interference*. This powerful gene silencing mechanism has been shown to
15 operate in several species among most phylogenetic phyla.

RNAi begins when an enzyme named DICER encounters dsRNA and chops it
into pieces called small-interfering RNAs or siRNAs. This protein belongs to the
RNase III nuclease family. A complex of proteins gathers up these RNA remains
20 and uses their code as a guide to search out and destroy any RNAs in the cell
with a matching sequence, such as target mRNA (for review see Bosher &
Labouesse, 2000).

The RNAi phenomenon (Akashi *et al.*, 2001) might be summarized as follows:
25 • Step 1: dsRNA recognition and scanning process.
• Step 2: dsRNA cleavage through RNase III activity and production of siRNAs.
• Step 3: association of the siRNAs and associated factors in RISC complexes.
• Step 4: recognition of the complementary target mRNA.
• Step 5: cleavage of the target mRNA in the centre of the region
30 complementary to the siRNA.
• Step 6: degradation of the target mRNA and recycling of the RISC complex.

In trying to apply the RNAi phenomenon as a technology for gene knockdown, it was soon realized that mammalian cells have developed various protective phenomena against viral infections that could impede the use of this approach. Indeed, the presence of extremely low levels of viral dsRNA triggers an
5 interferon response, resulting in a global non-specific suppression of translation, which in turn triggers apoptosis (Williams, 1997, Gil & Esteban, 2000).

In 2000, a first attempt with dsRNA resulted in the specific inhibition of 3 genes
10 (MmGFP under the control of the Elongation Factor 1a, E-cadherin, and c-mos) in the mouse oocyte and early embryo. Translational arrest, and thus a PKR response, was not observed as the embryos continued to develop (Wlanny & Zernicka-Goetz, 2000). One year later, research at *Ribopharma AG* (Kulmbach, Germany) first demonstrated the functionality of RNAi in mammalian cells.
15 Using short (20-24 base pairs) dsRNAs - which are called *SIRPLEXTM* - they specifically switched off genes even in human cells without initiating the acute-phase response. Similar experiments carried out later by other research groups (Elbashir *et al.*, 2001; Caplen *et al.*, 2001) further confirmed these results.

20 A year later, Paddison *et al.* (Paddison *et al.*, 2002) tried to use small RNAs folded in hairpin structures to inhibit the function of specific genes. This work was inspired by previous studies showing that some genes in *Caenorhabditis elegans* naturally regulate other genes through RNAi by coding for hairpin-structured RNAs. Tested in a variety of normal and cancer human and mouse
25 cell lines, short hairpin RNAs (shRNAs) are able to silence genes as efficiently as their siRNA counterparts. Moreover, shRNAs exhibit better reassociation kinetics *in vivo* than equivalent duplexes. Even more important, these authors generated transgenic cell lines engineered to synthesize shRNAs that exhibit a long-lasting suppressing effect throughout cell divisions (Eurogentec). Recently,
30 another group of small RNAs (also comprised in the range of 21-25 nt) was shown to mediate downregulation of gene expression. These RNAs, known as

small temporally regulated RNAs (stRNAs), have been described in *Caenorhabditis elegans* where they regulate timing of gene expression during development. It should be noted that stRNAs and siRNAs, despite obvious similarities, proceed through different modes of action (for review see Banerjee & Slack, 2002). In contrast with siRNAs, 22 nt long stRNAs downregulate expression of target mRNA after translational initiation without affecting mRNA integrity. Recent studies indicate that the two stRNAs first described in nematodes are the members of a huge family with hundreds of additional micro-RNAs (miRNAs) existing in metazoans (Grosshans & Slack, 2002).

10

Scientists have initially used RNAi in several systems, including *Caenorhabditis elegans*, *Drosophila*, trypanosomes, and various other invertebrates. Moreover, using this approach, several groups have recently presented the specific suppression of protein biosynthesis in different mammalian cell lines — specifically in HeLa cells - showing that RNAi is a broadly applicable method for gene silencing in vitro. Based on these results, RNAi has rapidly become a well recognized tool for validating (identifying and assigning) gene functions. RNA interference employing short dsRNA oligonucleotides will, moreover, permit to decipher the function of genes being only partially sequenced. RNAi will therefore become inevitable in studies such as:

- Inhibition of gene expression at the post-transcriptional level in eukaryotic cells. In this context, RNAi is a straight-forward tool to rapidly assess gene function and reveal null phenotypes.
- Development of the RNAi technology for use in post-implantation embryos.
- The predominant economic significance of RNA interference is established by its application as a therapeutic principle. As so, RNAi may yield RNA-based drugs to treat human diseases.

25

Glaucoma

Glaucoma is one of the leading causes of blindness. Approximately 15% of cases of blindness world-wide result from glaucoma. The most common type,

30

primary open-angle glaucoma, has a prevalence of 1/200 in the general population over 40 years of age.

Glaucoma has been simply defined as the process of ocular tissue destruction caused by a sustained elevation of the Intra Ocular Pressure (IOP) above its normal physiological limits.

It is becoming increasingly clear that many forms of glaucoma have a genetic component, and much current research is focused on identifying chromosomal regions and genes that contribute to glaucoma. It is likely that the aetiology of OAG is multifactorial, resulting from a combination of mutations in more than one gene and as yet unidentified environmental factors. With regard to juvenile and adult-onset OAG, several loci have been identified. However, only one gene is known, namely the myocilin / TIGR (trabecular meshwork inducible glucocorticoid response) gene at the GLC1A locus on chromosome 1q21-q31. More than thirty mutations of this gene have been identified in ethnically diverse populations worldwide. Studies have shown that it is responsible for only about 5% of OAG overall (See reviews in Wirtz & Samples, 2003, and Khaw et al, 2004a).

20

Pathogenesis

Most glaucomas are characterised by an elevated IOP, although the level of elevation may vary. In those glaucomas in which the elevation is initially low (i.e., open angle glaucoma, melanocytic glaucoma) and some secondary glaucoma, retinal ganglion cell and optic nerve damage are slow to progress. In angle-closure glaucoma the sudden high rise in IOP often renders the eye blind, undoubtedly primarily due to a cessation of axoplasmic flow at the level of the lamina cribrosa.

In human studies, it has been widely accepted that tissue ischaemia has a part to play in the initiation or progression of the optic disc damage that occurs in

glaucoma. Retinal ganglion cell degeneration may be necrosis, but the possibility that it is apoptosis triggered by the rise in IOP is plausible, and the respective roles of nitric oxide and glutamate are thought to be relevant during progression of the disease (For a recent review on the subject see Osborne et
5 al, 2003).

Treatment

Although several aetiologies are involved in the glaucoma complex, the absolute determinant in therapy selection is the amount of primary and/or induced
10 change in pressure within the iridocorneal angle.

Current therapies include medications or surgeries aimed at lowering this pressure, although the pathophysiological mechanisms by which elevated IOP leads to neuronal damage in glaucoma are unknown.

15

Medical suppression of an elevated IOP can be attempted using four types of drugs: the aqueous formation suppressors (among them, carbonic anhydrase inhibitors, beta-adrenergic blocking agents, or alpha2-adrenoreceptor agonists) miotics (i.e. parasympathomimetics – cholinergics-, or anticholinesterase
20 inhibitors); uveoscleral outflow enhancers; and the hyperosmotic agents (that produce an osmotic pressure gradient across the blood/aqueous barrier within the ciliary epithelium). All four are used in the treatment of glaucoma, the first three commonly as emergency treatment and in long term control while the hyperosmotic agents are invaluable as emergency and preoperative treatment.

25 A fifth category of drugs, the neuroprotection agents, is beginning to emerge as an important possible addition to medical therapy. Indeed, observation that the NOS and glutamate levels are elevated in glaucoma and that they are involved in retinal ganglion cell necrosis or apoptosis has raised the possibility of neuroprotective therapies and even neuroregeneration. Thus NOS inhibitors,
30 exciting amino acid antagonists, glutamate receptor antagonists, apoptosis inhibitors and calcium channel blockers are all potential candidates in the

development of future glaucoma therapies. The calcium channel blockers may reduce the effect of impaired microcirculation to the optic nerve head whilst potentially increasing outflow facility at the level of the trabecular cells.

- 5 Reviews of various eye disorders and their treatments are given in the references, in particular in Bunce (2005), Costagliola (1995, 2000), Cullinane (2002), Sakaguchi (2002), Shah (2000), and Wang (2005).

Currently our existing therapies must fall short of the mark and the practical
10 difficulties associated with the assessment of outflow facility, the accurate monitoring of therapy and the complexity of surgical techniques all combine to confound the prognosis. The overriding factor in all glaucoma is the degeneration of the retinal ganglion cell, thus neuroprotection through effective ocular hypotension is the essential requirement of any therapy we utilise (for a
15 recent review on the subject, see Khaw et al 2004b).

BRIEF SUMMARY OF THE INVENTION

In the present invention we describe a method for the treatment of eye conditions characterised by an altered IOP in animals, including humans. In
20 particular, the eye conditions may include glaucoma, uveitis, and inflammation. The method is based on the downregulation of expression of genes involved in aqueous formation or aqueous outflow in the eye. Downregulation may be effected by the use of double stranded nucleic acid moieties, named siNA or small interfering NA that are directed at interfering with the mRNA expression
25 of various candidate genes. The siNA are preferably siRNA, although modified nucleic acids or similar chemically synthesised entities are also included within the scope of the invention.

Preferred embodiments of the invention relate to topical application of siNA.
30 Embodiments of the invention also provide pharmaceutical compositions for use in the treatment of eye conditions. The invention may be used within the fields

of local eye treatments, of target genes involved in glaucoma pathogenesis, as well as the use of chemically synthesized entities to treat animal (including humans) diseases.

- 5 In addition to the treatment of glaucoma, the present method is also suitable for the treatment of other diseases of the anterior chamber of the eye. In particular, the method may be applied to the treatment of diseases characterised by altered aqueous formation or outflow in the eye. Examples of conditions which may be treated include local conditions such as infections or
10 inflammations, and general conditions such as uveitis or expression of systemic diseases. Further, certain embodiments of the invention provide treatment for diabetic retinopathy.

DETAILED DESCRIPTION OF THE INVENTION

15 Target genes

In the present invention, we define a list of target genes, whose expression levels may alter IOP. These genes can fall within the groups of genes involved in aqueous formation or the group of genes involved in aqueous outflow. Here is a list of our target genes:

20

- Carbonic Anhydrases II, IV and XII
- Adrenergic Receptors: beta1 and 2 and alpha 1A, 1B and 1D
- Acetylcholinesterase
- Cyclooxygenases 1 and 2
- 25 • ATPases: alpha1, alpha2, alpha3, beta1, beta2
- Endothelial Leukocyte Adhesion Molecule I (ELAM-1)
- Angiotensin System: Angiotensin II, Angiotensin II Converting Enzymes (ACE I and ACE II), Angiotensin II Receptors (ATR1 and ATR2) and Renin
- Cochlin

30

Design of siNA

Although the mechanisms for RNAi remain unknown, the steps required to generate the specific dsRNA oligonucleotides are clear. It has been shown that dsRNA duplex strands that are 21-26 nucleotides in length work most effectively in producing RNA interference. Selecting the right homologous region within the gene is also important. Factors such as the distance from start codon, the G/C content and the location of adenosine dimers are important when considering the generation of dsRNA for RNAi. One consequence of this, however, is that one may need to test several different sequences for the most efficient RNAi and this may become costly.

In 1999, Tuschl *et al.* deciphered the silencing effect of siRNAs showing that their efficiency is a function of the length of the duplex, the length of the 3'-end overhangs, and the sequence in these overhangs. Based on this founder work, Eurogentec recommends that the target mRNA region, and hence the sequence of the siRNA duplex, should be chosen using the following guidelines:

Since RNAi relies on the establishment of complex protein interactions, it is obvious that the mRNA target should be devoided of unrelated bound factors. In this context, both the 5' and 3' untranslated regions (UTRs) and regions close to the start codon should be avoided as they may be richer in regulatory protein binding sites. The sequence of the siRNA is therefore selected as follows:

- In the mRNA sequence, a region located 50 to 100 nt downstream of the AUG start codon or upstream of stop codon is selected.
- In this region, the following sequences are searched for: AA(N19), CA(N19).
- The G/C percentage for each identified sequence is calculated. Ideally, the G/C content is 50 % but it must less than 70 % and greater than 30 %.
- Preferably, sequences containing following repetitions are avoided: AAA, CCC, GGG, TTT, AAAA, CCCC, GGGG, TTTT.

- An accessibility prediction according to the secondary structure of the mRNA is carried out as well.
- A BLAST is also performed (i.e. NCBI ESTs database) with the nucleotide sequence fitting best the previous criteria to ensure that only one gene will be inactivated.

In order to maximize the result's interpretation, the following precautions should be taken when using siRNAs:

- Always test the sense and antisense single strands in separate experiments.
- Try a scramble siRNA duplex. This should have the same nucleotide composition as your siRNA but lack significant sequence homology to any other gene (including yours).
- If possible, knock-down the same gene with two independent siRNA duplexes to control the specificity of the silencing process.

15

Practically, each of the selected genes is introduced as a nucleotide sequence in a prediction program that takes into account all the variables described above for the design of optimal oligonucleotides. This program scans any mRNA nucleotide sequence for regions susceptible to be targeted by siRNAs. The output of this analysis is a score of possible siRNA oligonucleotides. The highest scores are used to design double stranded RNA oligonucleotides (typically 21 bp long, although other lengths are also possible) that are typically made by chemical synthesis.

In addition to siRNA, modified nucleotides may also be used. We plan to test several chemical modifications that are well known in the art. These modifications are aimed at increasing stability or availability of the siRNA. Examples of suitable modifications are described in the publications referenced below.

30

Studies show that replacing the 3'-terminal nucleotide overhanging segments of a 21-mer siRNA duplex having two -nucleotide 3'-overhangs with deoxyribonucleotides does not have an adverse effect on RNAi activity. Replacing up to four nucleotides on each end of the siRNA with
5 deoxyribonucleotides has been reported to be well tolerated, whereas complete substitution with deoxyribonucleotides results in no RNAi activity (Elbashir 2001). In addition, Elbashir et al. also report that substitution of siRNA with 2'-O- methyl nucleotides completely abolishes RNAi activity.

10 Affinity modified nucleosides as described in WO2005/044976 may be used. This publication describes oligonucleotides comprising nucleosides modified so as to have increased or decreased affinity for their complementary nucleotide in the target mRNA and/or in the complementary siNA strand.

15 GB2406568 describes alternative modified oligonucleotides chemically modified to provide improved resistance to degradation or improved uptake. Examples of such modifications include phosphorothioate internucleotide linkages, 2'-O-methyl ribonucleotides, 2'-deoxy-fluoro ribonucleotides, 2'-deoxy ribonucleotides, "universal base" nucleotides, 5-C-methyl nucleotides, and
20 inverted deoxyabasic residue incorporation.

WO2004/029212 describes oligonucleotides modified to enhance the stability of the siRNA or to increase targeting efficiency. Modifications include chemical cross linking between the two complementary strands of an siRNA and chemical
25 modification of a 3' terminus of a strand of an siRNA. Preferred modifications are internal modifications, for example, sugar modifications, nucleobase modifications and/or backbone modifications. 2'-fluoro modified ribonucleotides and 2'-deoxy ribonucleotides are described.

30 WO2005/040537 further recites modified oligonucleotides which may be used in the invention.

As well as making use of dsNA and modified dsNA, the present invention may use short hairpin NA (shNA); the two strands of the siNA molecule may be connected by a linker region, which may be a nucleotide linker or a non-
5 nucleotide linker.

In addition to siNA which is perfectly complementary to the target region, degenerate siNA sequences may be used to target homologous regions. WO2005/045037 describes the design of siNA molecules to target such
10 homologous sequences, for example by incorporating non-canonical base pairs, for example mismatches and/or wobble base pairs, that can provide additional target sequences. In instances where mismatches are identified, non-canonical base pairs (for example, mismatches and/or wobble bases) can be used to generate siNA molecules that target more than one gene sequence. In a non-
15 limiting example, non-canonical base pairs such as UU and CC base pairs are used to generate siNA molecules that are capable of targeting sequences for differing targets that share sequence homology. As such, one advantage of using siNAs of the invention is that a single siNA can be designed to include nucleic acid sequence that is complementary to the nucleotide sequence that is
20 conserved between homologous genes. In this approach, a single siNA can be used to inhibit expression of more than one gene instead of using more than one siNA molecule to target different genes.

Preferred siNA molecules of the invention are double stranded. A siNA molecule
25 of the invention may comprise blunt ends, that is, ends that do not include any overhanging nucleotides. In one embodiment, an siNA molecule of the invention can comprise one or more blunt ends. In preferred embodiments, the siNA molecules have 3' overhangs. siNA molecules of the invention may comprise duplex nucleic acid molecules with 3' overhangs of n nucleotides
30 ($5 \geq n \geq 1$). Elbashir (2001) shows that 21-nucleotide siRNA duplexes are most active when containing 3'-terminal dinucleotide overhangs.

Candidate oligonucleotides are further filtered for interspecies sequence conservation in order to facilitate the transition from animal to human clinical studies. In preferred embodiments of the invention, conserved oligonucleotides
5 are used; this allows a single oligonucleotide sequence to be used in both animal models and human clinical trials.

GenBank Accession Numbers corresponding to our selected human target genes are shown in Figure 1. In some of these genes, alternative splicing produces a
10 family of transcripts that differ in exon content. The present invention allows individual targeting of each transcript form.

Selected oligonucleotide sequences against which RNAi is directed are shown in Figure 2. Displayed sequences are the DNA sequences targeted by the siNA.
15 Therefore, the invention would make use of NA duplexes with sequences complementary to the indicated DNA sequences.

The sequences shown in Figure 2 are not limiting. As a matter of fact, target DNA need not necessarily be preceded by AA or CA. Further, target DNA could
20 be constituted by sequences included in Figure 2 flanked by any contiguous sequence.

***In vitro* and animal studies.**

Obtaining siRNA duplexes

25 RNAs are preferably chemically synthesized using appropriately protected ribonucleoside phosphoramidites and a conventional DNA/RNA synthesizer. Substitution of one or both strands of a siRNA duplex by 2'-deoxy or 2'-O-methyl oligoribonucleotides abolished silencing in fly extract (Elbashir *et al.* 2001). In mammalian cells, however, it seems possible to substitute the sense
30 siRNA by a 2'-O-methyl oligoribonucleotide (Ge *et al.* 2003).

Most conveniently, siRNAs are obtained from commercial RNA oligo synthesis suppliers, which sell RNA-synthesis products of different quality and costs. In general, 21-nt RNAs are not too difficult to synthesize and are readily provided in a quality suitable for RNAi.

5

Suppliers of RNA synthesis reagents include Proligo (Hamburg, Germany), Dharmacon Research (Lafayette, CO, USA), Glen Research (Sterling, VA, USA), ChemGenes (Ashland, MA, USA), and Cruachem (Glasgow, UK), Qiagen (Germany), Ambion (USA) and Invitrogen (Scotland). The previous custom RNA synthesis companies are entitled to provide siRNAs with a license for target validation. In particular, our siRNA suppliers are Ambion, Dharmacon and
10 Invitrogen, companies that offer the traditional custom chemical synthesis service for siRNA, and supply the siRNA with HPLC purification and delivered in dry form along with RNase-free water. A central web-based resource for RNAi and siRNA methodologies, along with links to additional siRNA related products
15 and services, can be found on the website of above-mentioned suppliers.

An annealing step is necessary when working with single-stranded RNA molecules. It is critical that all handling steps be conducted under sterile, RNase free conditions. To anneal the RNAs, the oligos must first be quantified by UV
20 absorption at 260 nanometres (nm). The following protocol based on Elbashir et al. (2001) is then used for annealing:

- Separately aliquot and dilute each RNA oligo to a concentration of 50 μ M.
- Combine 30 μ l of each RNA oligo solution and 15 μ l of 5X annealing buffer.
- 25 Final buffer concentration is: 100 mM potassium acetate, 30 mM HEPES-KOH pH 7.4, 2 mM magnesium acetate. Final volume is 75 μ l.
- Incubate the solution for 1 minute at 90 °C, centrifuge the tube for 15 seconds, let sit for 1 hour at 37 °C, then use at ambient temperature. The solution can be stored frozen at -20 °C and freeze-thawed up to 5 times. The
30 final concentration of siRNA duplex is usually 20 μ M.

Alternatively, already annealed dsRNAs may be purchased from the suppliers.

Chemically modified nucleic acids may also be used. For example, an overview of the types of modification which may be used is given in WO03/070744. Particular attention is drawn to pages 11 to 21 of this publication. Other possible modifications are as described above. The skilled person will be aware of other types of chemical
5 modification which may be incorporated into RNA molecules.

In vitro system

To check the specificity of the siRNA interference different cell cultures that express the target genes were employed. The cells used for these experiments
10 were: rabbit non-pigmented ciliary epithelium cells NPE, human ciliary epithelium cells OMDC, and human embryonic kidney cells HEK293. The cells are incubated with the corresponding siRNA duplexes, and analysis of the downregulation of expression of the target gene is carried out. For linking siRNA knockdown to specific phenotypes in cultured cells, it is necessary to
15 demonstrate the reduction of targeted protein or at least demonstrate the reduction of the targeted mRNA.

mRNA levels of the target gene can be quantitated by real-time quantitative PCR (RT-PCR). Further, the protein levels can be determined in a variety of
20 ways well known in the art, such as Western blot analysis with specific antibodies to the different target allow direct monitoring of the reduction of targeted protein.

Transfection of siRNA duplexes

25 Several examples of techniques well known in the art are as follows: We can perform a single transfection of siRNA duplex using a cationic lipid, such as RNAiFect Transfection Reagent (Qiagen) and Lipofectamine 2000 Reagent (Invitrogen) and assay for silencing 24, 48 and 72 hours after transfection.

A typical transfection protocol can be performed as follows: For one well of a 6-well plate, we transfect using 100nM as final concentration of siRNA. Following RNAiFect protocol, we seed, the day before transfection, $2-4 \times 10^5$ cells per well in 3ml of an appropriate growth medium, containing DMEM, 10% serum, antibiotics and glutamine, and incubate cells under normal growth conditions (37°C and 5% CO₂). On the day of transfection, cells have to be at 30-50% confluence. We dilute 15ul of 20uM siRNA duplex (corresponding to 100 nM final concentration) in 85ul of Buffer EC-R, to give a final volume of 100ul, and mix by vortexing. For complex formation, we add 19 ul of RNAiFect Transfection Reagent to the diluted siRNA and mix by pipetting or vortexing. After incubating the samples for 10-15 minutes at room temperature to allow formation of transfection complexes, we add the complexes drop-wise onto the cells with 2.9 ml of fresh growth medium low in antibiotics. After swirling the plates to ensure uniform distribution of the transfection complexes, we incubate the cells under their normal growth conditions. The day after, the complexes are removed and fresh and complete growth medium is added. To monitor gene silencing, cells are collected at 24, 48 and 72 hours post-transfection. The Lipofectamine 2000 Reagent protocol is quite similar. The day before transfection, we seed $2-4 \times 10^5$ cells per well in 3ml of an appropriate growth medium, containing DMEM, 10% serum, antibiotics and glutamine, and incubate cells under normal growth conditions (37°C and 5% CO₂). On the day of transfection, cells have to be at 30-50% confluence. We dilute 12.5ul of 20uM siRNA duplex (corresponding to 100 nM final concentration) in 250ul of DMEM, to give a final volume of 262.5ul, and mix. Also, 6ul of Lipofectamine 2000 is diluted in 250ul of DMEM and mixed. After a 5 minutes incubation at room temperature, the diluted oligomer and the diluted Lipofectamine are combined to allow complex formation during a 20 minutes incubation at room temperature. Afterwards, we add the complexes drop-wise onto the cells with 2 ml of fresh growth medium low in antibiotics and mix gently by rocking the plate back and forth, to ensure uniform distribution of the transfection complexes. We incubate the cells under their normal growth conditions and the day after, the complexes are removed

and fresh and complete growth medium is added. To monitor gene silencing, cells are collected at 24, 48 and 72 hours post-transfection.

The efficiency of transfection may depend on the cell type, but also on the passage number and the confluency of the cells. The time and the manner of formation of siRNA-liposome complexes (e.g. inversion versus vortexing) are also critical. Low transfection efficiencies are the most frequent cause of unsuccessful silencing. Good transfection is a non-trivial issue and needs to be carefully examined for each new cell line to be used. Transfection efficiency may be tested transfecting reporter genes, for example a CMV-driven EGFP-expression plasmid (e.g. from Clontech) or a B-Gal expression plasmid, and then assessed by phase contrast and/or fluorescence microscopy the next day.

Testing of siRNA duplexes

Depending on the abundance and the life time (or turnover) of the targeted protein, a knock-down phenotype may become apparent after 1 to 3 days, or even later. In cases where no phenotype is observed, depletion of the protein may be observed by immunofluorescence or Western blotting.

After transfections, total RNA fractions extracted from cells were pre-treated with DNase I and used for reverse transcribed using a random primer. PCR is amplified with a specific primer pair covering at least one exon-exon junction in order to control for amplification of pre-mRNAs. RT/PCR of a non-targeted mRNA is also needed as control. Effective depletion of the mRNA yet undetectable reduction of target protein may indicate that a large reservoir of stable protein may exist in the cell. Alternatively, RealTime PCR amplification can be used to test in a more precise way the mRNA decrease or disappearance. Real-time reverse-transcriptase (RT) PCR quantitates the initial amount of the template most specifically, sensitively and reproducibly. Real-time PCR monitors the fluorescence emitted during the reaction as an indicator of amplicon production during each PCR cycle. This signal increases in direct

proportion to the amount of PCR product in a reaction. By recording the amount of fluorescence emission at each cycle, it is possible to monitor the PCR reaction during exponential phase where the first significant increase in the amount of PCR product correlates to the initial amount of target template.

5

To verify the interference pattern of the differentially expressing genes identified in the cell cultures, qRT-PCR was performed according to the manufacturer protocol.. For quantitative RT-PCR (qRT-PCR), approximately 250 ng of total RNA were used for reverse transcription followed by PCR
10 amplification with specific primers for each gene in reaction mixture containing Master SYBR Green I. Basic PCR conditions comprised an initial step of 30 minutes at 91°C, followed by 40 cycles of 5 s at 95°C, 10 s at 62°C and 15 s at 72°C. Specific primer sequences corresponding to each target gene were used. Quantification of b-actin mRNA was used as a control for data normalization.
15 Relative gene expression comparisons work best when the gene expression of the chosen endogenous/internal control is more abundant and remains constant, in proportion to total RNA, among the samples. By using an invariant endogenous control as an active reference, quantitation of an mRNA target can be normalised for differences in the amount of total RNA added to each
20 reaction.

Pharmaceutical formulations

The present invention may comprise the administration of one or more species of siNA molecule simultaneously. These species may be selected to target one
25 or more target genes.

The siNA molecules of the invention and formulations or compositions thereof may be administered directly or topically (e. g., locally) to the eye as is generally known in the art. For example, a siNA molecule can comprise a
30 delivery vehicle, including liposomes, for administration to a subject. Carriers and diluents and their salts can be present in pharmaceutically acceptable

formulations. Nucleic acid molecules can be administered to cells by a variety of methods known to those of skill in the art, including, but not restricted to, encapsulation in liposomes, by iontophoresis, or by incorporation into other vehicles, such as biodegradable polymers, hydrogels, cyclodextrins poly (lactic-
5 co-glycolic) acid (PLGA) and PLGA microspheres, biodegradable nanocapsules, and bioadhesive microspheres, or by proteinaceous vectors. In another embodiment, the nucleic acid molecules of the invention can also be formulated or complexed with polyethyleneimine and derivatives thereof, such as polyethyleneimine- polyethyleneglycol-N-acetylgalactosamine (PEI-PEG-GAL) or
10 polyethyleneimine- polyethyleneglycol-tri-N-acetylgalactosamine (PEI-PEG-triGAL) derivatives.

A siNA molecule of the invention may be complexed with membrane disruptive agents and/or a cationic lipid or helper lipid molecule.

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Delivery systems which may be used with the invention include, for example, aqueous and non aqueous gels, creams, multiple emulsions, microemulsions, liposomes, ointments, aqueous and non aqueous solutions, lotions, aerosols, hydrocarbon bases and powders, and can contain excipients such as
20 solubilizers, permeation enhancers (e. g., fatty acids, fatty acid esters, fatty alcohols and amino acids), and hydrophilic polymers (e. g. , polycarbophil and polyvinylpyrrolidone). In one embodiment, the pharmaceutically acceptable carrier is a liposome or a transdermal enhancer.

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A pharmaceutical formulation of the invention is in a form suitable for administration, e.g., systemic or local administration, into a cell or subject, including for example a human. Suitable forms, in part, depend upon the use or the route of entry, for example oral, transdermal, or by injection. Other factors are known in the art, and include considerations such as toxicity and forms that
30 prevent the composition or formulation from exerting its effect.

The present invention also includes compositions prepared for storage or administration that include a pharmaceutically effective amount of the desired compounds in a pharmaceutically acceptable carrier or diluent. Acceptable carriers or diluents for therapeutic use are well known in the pharmaceutical art. For example, preservatives, stabilizers, dyes and flavouring agents can be provided. These include sodium benzoate, sorbic acid and esters of p-hydroxybenzoic acid. In addition, antioxidants and suspending agents can be used.

10 A pharmaceutically effective dose is that dose required to prevent, inhibit the occurrence, or treat (alleviate a symptom to some extent, preferably all of the symptoms) of a disease state. The pharmaceutically effective dose depends on the type of disease, the composition used, the route of administration, the type of mammal being treated, the physical characteristics of the specific mammal
15 under consideration, concurrent medication, and other factors that those skilled in the medical arts will recognize.

Generally, an amount between 0.1mg/kg and 100 mg/kg body weight/day of active ingredients is administered.

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The formulations of the invention can be administered in dosage unit formulations containing conventional non-toxic pharmaceutically acceptable carriers, adjuvants and/or vehicles. Formulations can be in a form suitable for oral use, for example, as tablets, troches, lozenges, aqueous or oily
25 suspensions, dispersible powders or granules, emulsion, hard or soft capsules, or syrups or elixirs. Compositions intended for oral use can be prepared according to any method known to the art for the manufacture of pharmaceutical compositions and such compositions can contain one or more such sweetening agents, flavouring agents, colouring agents or preservative
30 agents in order to provide pharmaceutically elegant and palatable preparations. Tablets contain the active ingredient in admixture with non-toxic

pharmaceutically acceptable excipients that are suitable for the manufacture of tablets.

These excipients can be, for example, inert diluents; such as calcium carbonate, sodium carbonate, lactose, calcium phosphate or sodium phosphate; granulating and disintegrating agents, for example, corn starch, or alginic acid; binding agents, for example starch, gelatin or acacia; and lubricating agents, for example magnesium stearate, stearic acid or talc. The tablets can be uncoated or they can be coated by known techniques. In some cases such coatings can be prepared by known techniques to delay disintegration and absorption in the gastrointestinal tract and thereby provide a sustained action over a longer period. For example, a time delay material such as glyceryl monostearate or glyceryl distearate can be employed.

Formulations for oral use can also be presented as hard gelatin capsules wherein the active ingredient is mixed with an inert solid diluent, for example, calcium carbonate, calcium phosphate or kaolin, or as soft gelatin capsules wherein the active ingredient is mixed with water or an oil medium, for example peanut oil, liquid paraffin or olive oil.

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Aqueous suspensions contain the active materials in a mixture with excipients suitable for the manufacture of aqueous suspensions. Such excipients are suspending agents, for example sodium carboxymethylcellulose, methylcellulose, hydropropyl-methylcellulose, sodium alginate, polyvinylpyrrolidone, gum tragacanth and gum acacia; dispersing or wetting agents can be a naturally-occurring phosphatide, for example, lecithin, or condensation products of an alkylene oxide with fatty acids, for example polyoxyethylene stearate, or condensation products of ethylene oxide with long chain aliphatic alcohols, for example heptadecaethyleneoxycetanol, or condensation products of ethylene oxide with partial esters derived from fatty acids and a hexitol such as polyoxyethylene sorbitol monooleate, or

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condensation products of ethylene oxide with partial esters derived from fatty acids and hexitol anhydrides, for example polyethylene sorbitan monooleate. The aqueous suspensions can also contain one or more preservatives, for example ethyl, or n-propyl p-hydroxybenzoate, one or more colouring agents, one or more flavouring agents, and one or more sweetening agents, such as sucrose or saccharin.

Oily suspensions can be formulated by suspending the active ingredients in a vegetable oil, for example arachis oil, olive oil, sesame oil or coconut oil, or in a mineral oil such as liquid paraffin. The oily suspensions can contain a thickening agent, for example beeswax, hard paraffin or cetyl alcohol. Sweetening agents and flavouring agents can be added to provide palatable oral preparations. These compositions can be preserved by the addition of an anti-oxidant such as ascorbic acid.

Dispersible powders and granules suitable for preparation of an aqueous suspension by the addition of water provide the active ingredient in admixture with a dispersing or wetting agent, suspending agent and one or more preservatives. Suitable dispersing or wetting agents or suspending agents are exemplified by those already mentioned above. Additional excipients, for example sweetening, flavouring and colouring agents, can also be present.

Pharmaceutical compositions of the invention can also be in the form of oil-in-water emulsions. The oily phase can be a vegetable oil or a mineral oil or mixtures of these. Suitable emulsifying agents can be naturally-occurring gums, for example gum acacia or gum tragacanth, naturally-occurring phosphatides, for example soy bean, lecithin, and esters or partial esters derived from fatty acids and hexitol, anhydrides, for example sorbitan monooleate, and condensation products of the said partial esters with ethylene oxide, for example polyoxyethylene sorbitan monooleate. The emulsions can also contain sweetening and flavouring agents.

Syrups and elixirs can be formulated with sweetening agents, for example glycerol, propylene glycol, sorbitol, glucose or sucrose. Such formulations can also contain a demulcent, a preservative and flavouring and colouring agents.

5 The pharmaceutical compositions can be in the form of a sterile injectable aqueous or oleaginous suspension.

This suspension can be formulated according to the known art using those suitable dispersing or wetting agents and suspending agents that have been

10 mentioned above.

A sterile injectable preparation can also be a sterile injectable solution or suspension in a non-toxic parentally acceptable diluent or solvent, for example as a solution in 1,3- butanediol. Among the acceptable vehicles and solvents

15 that can be employed are water, Ringer's solution and isotonic sodium chloride solution. In addition, sterile, fixed oils are conventionally employed as a solvent or suspending medium. For this purpose, any bland fixed oil can be employed including synthetic mono-or diglycerides. In addition, fatty acids such as oleic acid find use in the preparation of injectables.

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The nucleic acid molecules of the invention can also be administered in the form of suppositories, e. g. , for rectal administration of the drug. These compositions can be prepared by mixing the drug with a suitable non-irritating excipient that is solid at ordinary temperatures but liquid at the rectal

25 temperature and will therefore melt in the rectum to release the drug. Such materials include cocoa butter and polyethylene glycols.

Nucleic acid molecules of the invention can be administered parenterally in a sterile medium. The drug, depending on the vehicle and concentration used,

30 can either be suspended or dissolved in the vehicle. Advantageously, adjuvants

such as local anaesthetics, preservatives and buffering agents can be dissolved in the vehicle.

It is understood that the specific dose level for any particular subject depends upon a variety of factors including the activity of the specific compound employed, the age, body weight, general health, sex, diet, time of administration, route of administration, and rate of excretion, drug combination and the severity of the particular disease undergoing therapy.

For administration to non-human animals, the composition can also be added to the animal feed or drinking water. It can be convenient to formulate the animal feed and drinking water compositions so that the animal takes in a therapeutically appropriate quantity of the composition along with its diet. It can also be convenient to present the composition as a premix for addition to the feed or drinking water.

The nucleic acid molecules of the present invention can also be administered to a subject in combination with other therapeutic compounds to increase the overall therapeutic effect. The use of multiple compounds to treat an indication can increase the beneficial effects while reducing the presence of side effects.

Alternatively, certain siNA molecules of the invention can be expressed within cells from eukaryotic promoters. Recombinant vectors capable of expressing the siNA molecules can be delivered and persist in target cells. Alternatively, vectors can be used that provide for transient expression of nucleic acid molecules. Such vectors can be repeatedly administered as necessary. Once expressed, the siNA molecule interacts with the target mRNA and generates an RNAi response. Delivery of siNA molecule expressing vectors can be systemic, such as by intravenous or intra-muscular administration, by administration to target cells ex-planted from a subject followed by reintroduction into the subject, or by any other means that would allow for introduction into the desired target cell.

Animal studies

The New Zealand rabbit is the gold standard in experimental platforms designed to study IOP. It is easy to handle and it has a big eye, similar in size
5 to the human organ. In addition, present equipment to measure IOP is not suited to use in animals with small eyes such as mice or rats. Finally, rabbits have an IOP (around 23 mm Hg) that can be brought down to up to 40% its value using local commercial hypotensive medication. Thus, although it is possible to generate rabbit glaucoma models (for example, surgically blocking
10 episclerotic veins or artificially occluding the trabecular meshwork), we have used normotensive rabbits since, in our hands, the pharmacological decrease in IOP can be easily and reproducibly measured.

Experimental protocol

15 Normotensive New Zealand White rabbits (males, 2–3 kg) were used. The animals were kept in individual cages with free access to food and water. They were submitted to artificial 12 hours light/darkness cycles, to avoid uncontrolled circadian oscillations of IOP. Animal handling and treatment were carried out in accordance with the European Communities Council Directive (86/609/EEC) and
20 the statement of the Association for Research in Vision and Ophthalmology on the Use of Animals in Ophthalmic and Vision Research.

The drugs were typically administered by instilling a small volume (typically 40 μ L) on the corneal surface. Contralateral eyes were treated with the vehicle
25 alone and could be used as controls in each experiment lest there is a sympathy phenomenon with the other eye. Multiple experiments in the same animal should be abolished.

IOP measurements were done using a contact tonometer (TONOPEN XL,
30 Mentor, Norwell, Massachusetts). The TonoPen tonometer is very convenient due to its reliability and small size. Measurements with this instrument were

performed delicately applying the tonometer's sensor to the corneal surface. This device has been shown to be the tonometer of choice for measuring intraocular pressures within the range of 3 to 30 mm Hg in rabbits (Abrams et al., 1996). All measurements fell within this interval: the mean baseline value of
5 intraocular pressure was 17.0 ± 0.39 mm Hg ($n = 100$). Because IOP changes from the night to day, all the experiments were performed at the same time to allow IOP more stable and permit an objective comparison with vehicle treatment. In order to avoid distress to the animal, rabbits were topically anesthetized (oxibuprocaine/tetracaine, 0.4%/1%, in a saline solution (1/4 v:v).
10 The solution was applied (10 μ l) to the cornea before each measurement of intraocular pressure was made. siRNA or saline was applied topically to the cornea in volumes of 40 μ l.

The standard protocol for the siRNA application in rabbit was as follows. Doses
15 of siRNA in saline solution (0.9% w/v) to a final volume of 40ul, were applied to one eye each day during four consecutive days. The opposite eye was taken as a control and 40ul of sterile saline (0.9% w/v) were instilled on it, at the same time points. The IOP was measured before each application and at 2h, 4h and 6h following the instillation, during 10 days. Maximum responses were observed
20 between second and third day. To compare the effect of siRNA with other hypotensive compounds, Xalatan (latanoprost 0.005%) and Trustop (Dorzolamide 2%) were assayed and IOP measured in the same conditions.

Results

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Example 1 In vitro assays.

To determine the inhibition of the different targets involved in glaucoma using RNAi technology, the first step was to perform experiments in cell cultures. For each target, several siRNAs were designed using a specific software according
30 to the rules described before. Those with the best characteristics were selected to be tested. The siRNAs were applied to cell cultures, such as NPE, OMDC and

HEK293. The effect of siRNAs over the target gene was analyzed by real time PCR and semi-quantitative PCR according to standard protocols. The gene target transcript levels were normalized using actin as housekeeping gene. Table I below shows representative results of real time PCR experiments for
5 some of the target genes described previously. The values represent the mean of the percentage of siRNA interference over each gene expression once normalized with the control cells and their standard deviations. Compared to the control cells, the level of the different transcripts at both 24 and 48h time points was significantly reduced after the siRNA treatment. In the Table are
10 included some of the different siRNAs that were tested and their different efficacies in the interference of the target gene. The siRNAs used in the Table
correspond to the listed human siRNA targets given in Figure 2 as follows.

AC2: siRNA1: rabbit sequence homologous to human SEQ. ID. 73
siRNA2: rabbit sequence identical to human SEQ. ID. 54
15 siRNA3: rabbit sequence identical to human SEQ. ID. 66
PTGS1 siRNA1: rabbit sequence homologous to human SEQ. ID. 353
siRNA2: rabbit sequence homologous to human SEQ. ID. 369
PTGS2 siRNA1: rabbit sequence identical to human SEQ. ID. 426
siRNA2: rabbit sequence homologous to human SEQ. ID. 421
20 siRNA3: rabbit sequence homologous to human SEQ. ID. 477

Target		% of gene transcript level	
		24h	48h
AC2	siRNA1	76.25±12.60	84.57±14.70
	siRNA2	37.97±9.78	61.45±9.62
	siRNA3	35.30±9.73	51.14±16.49
PTGS1	siRNA1	42.25±13.76	42.68±17.00
	siRNA2	34.98±14.33	26.30±10.91
PTGS2	siRNA1	68.68±12.48	70.17±19.21
	siRNA2	81.00±13.54	66.85±18.67
	siRNA3	75.45±14.71	61.83±16.96

5 Table I: siRNA treatment reduces the levels of target gene transcripts. RNA was prepared from cells treated with different siRNAs for 24 and 48h. The samples were analyzed by real time PCR using specific primers. The values show the mean expression levels of different transcripts normalized to actin relative to cell control.

Figure 3 shows some representative semi-quantitative gels for some of the targets described above. The decrease of the gene expression for each target gene depends on the efficiency in siRNA silencing. For each target, the most effective siRNA obtained by in vitro studies was administered to the animal model. RNA was prepared from cells treated with different siRNAs. The samples were analyzed by semi-quantitative PCR using specific primers. The figure shows a representative semi-quantitative gel for Beta Adrenergic Receptor 2 expression (A) and other for Acetylcholinesterase expression (B). M: MW
 10 Marker; C: Control cells; TC: Transfection Control; 1: siRNA1; 2: siRNA2; 3: siRNA3; NC: Negative Control. The expression levels for each target depends on the efficiency in siRNA silencing. The siRNAs used in the Figure correspond to the human targets given in Figure 2 as follows:

20 Panel A (Beta Adrenergic Receptor 2)

1: rabbit sequence homologous to human SEQ. ID. 122

2: rabbit sequence identical to human SEQ. ID. 125

3: rabbit sequence homologous to human SEQ. ID. 139

Panel B (Acetylcholinesterase)

1: rabbit sequence homologous to human SEQ. ID. 162

2: rabbit sequence homologous to human SEQ. ID. 177

Example 2 In vivo assays.

5 Previously to the siRNA therapeutical application, the in vivo assays were validated to determine the proper siRNA delivery.

Those siRNAs selected by the in vitro assays were applied to the animal model, following the protocol previously described. To avoid the effect of IOP
10 fluctuations due to circadian cycles, all the applications were performed at the same time. To determine the siRNA effect, intraocular pressures (IOPs) were measured as previously mentioned.

Since glaucoma pathology presents an increase in the intraocular pressure, the
15 aim was to obtain a decrease in its levels following siRNA application.

Most of the results for the different targets showed a significant decrease in IOP levels comparing with controls and also with commercial drugs (Latanoprost and Dorzolamide) and the animals treated with vehicle alone
20 (negative control) didn't present any significant change in their IOP baseline. The data are summarized in table II where values represent the mean of the maximum percentage of IOP reduction after siRNA treatment once normalized and their standard deviations. The decrease in IOP was statistically significant for all the treated targets. These results indicate that siRNAs and commercial
25 drugs act in a similar way, reducing IOP levels around 20%, although siRNAs present a more maintained effect. No secondary effects were observed in the animals along the experimental protocols. The siRNAs used in these experiments correspond to the human targets given in Figure 2 as follows:

AC2: rabbit sequence homologous to human SEQ. ID. 73

30 AC4: rabbit sequence identical to human SEQ. ID. 5

AC12: rabbit sequence identical to human SEQ. ID. 522

- ADRB1: rabbit sequence identical to human SEQ. ID. 105
 ADRB2: rabbit sequence homologous to human SEQ. ID. 139
 ADRA1A: rabbit sequence homologous to human SEQ. ID. 546
 ADRA1B: rabbit sequence homologous to human SEQ. ID. 619
 5 ACHE: rabbit sequence homologous to human SEQ. ID. 189
 PTGS1: rabbit sequence homologous to human SEQ. ID. 322
 PTGS2: rabbit sequence identical to human SEQ. ID. 426
 SELE: rabbit sequence homologous to human SEQ. ID. 262
 ACE1: rabbit sequence homologous to human SEQ. ID. 866
 10 AGTR1: rabbit sequence homologous to human SEQ. ID. 705
 AGTR2: rabbit sequence identical to human SEQ. ID. 774
-
- ATP1A1: rabbit sequence identical to human SEQ. ID. 1399
 ATP1B2: rabbit sequence identical to human SEQ. ID. 1820

Target	IOP reduction (% of the control)
AC2	24.84±3.41
AC4	14.47±5.00
AC12	24.30±1.29
ADRB1	28.04±2.98
ADRB2	21.18±1.88
ADRA1A	9.51±1.04
ADRA1B	17.48±1.30
ACHE	25.25±2.70
PTGS1	14.62±1.93
PTGS2	23.78±2.27
SELE	21.80±1.74
ACE1	17.51±1.28
AGTR1	9.72±1.35
AGTR2	11.22±1.53
ATP1A1	18.13±1.39
ATP1B2	16.32±0.91
Latanoprost	25.46±5.24
Dorzolamide	16.41±2.38

- 15 Table II: Effect of siRNAs on the reduction of IOP in normotensive New Zealand rabbit. The values represent the mean of the percentage of IOP reduction over the control (contralateral eye with vehicle alone) and their standard error (SEM).

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DEMANDES OU BREVETS VOLUMINEUX

**LA PRÉSENTE PARTIE DE CETTE DEMANDE OU CE BREVETS
COMPREND PLUS D'UN TOME.**

CECI EST LE TOME __1__ DE __2__

NOTE: Pour les tomes additionels, veuillez contacter le Bureau Canadien des Brevets.

JUMBO APPLICATIONS / PATENTS

**THIS SECTION OF THE APPLICATION / PATENT CONTAINS MORE
THAN ONE VOLUME.**

THIS IS VOLUME __1__ OF __2__

NOTE: For additional volumes please contact the Canadian Patent Office.

The embodiments of the invention in which an exclusive property or privilege is claimed are defined as follows:

1. Use of short interfering ribonucleic acid (siRNA) in the preparation of a medicament for the treatment of an eye condition comprising an increased intraocular pressure (IOP), wherein said medicament is formulated for topical administration on the corneal surface and downregulates the expression of a target gene in the eye which is:

Carbonic Anhydrase II, IV or XII; Adrenergic Receptor: beta1 or 2 or alpha 1A or 1B; Acetylcholinesterase; Cyclooxygenase 1 or 2; ATPase: alpha1 or beta2; Endothelial Leukocyte Adhesion Molecule I (ELAM-1); Angiotensin System: Angiotensin II, Angiotensin II Converting Enzyme I, or Angiotensin II Receptors (ATR1 or ATR2); or any combination thereof;

and wherein said siRNA is targeted to the sequence of SEQ ID 5, 54, 66, 73, 105, 122, 125, 139, 162, 177, 189, 262, 322, 353, 369, 421, 426, 477, 522, 546, 619, 705, 774, 866, 1399, or 1820.

2. The use of claim 1, wherein the eye condition is glaucoma, infection, inflammation, or uveitis.

3. The use of claim 1 or 2, wherein the eye condition is glaucoma.

4. The use of any one of claims 1 to 3, wherein the siRNA is dsRNA.

5. The use of any one of claims 1 to 3, wherein the siRNA is shRNA.

6. The use of any one of claims 1 to 5, wherein the siRNA comprises a modified oligonucleotide.

7. The use of any one of claims 1 to 6, wherein a plurality of species of siRNA are used.

8. The use of claim 7, wherein said plurality of species are targeted to the same mRNA species.
9. The use of claim 7, wherein said plurality of species are targeted to different mRNA species.
10. The use of any one of claims 1 to 9, wherein the target gene is carbonic anhydrase IV, and the siRNA is targeted to the sequence of SEQ ID 5.
11. The use of any one of claims 1 to 9, wherein the target gene is carbonic anhydrase II, and the siRNA is targeted to the sequence of SEQ ID 54, 66, or 73.
12. The use of any one of claims 1 to 9, wherein the target gene is beta adrenergic receptor 1, and the siRNA is targeted to the sequence of SEQ ID 105.
13. The use of any one of claims 1 to 9, wherein the target gene is beta adrenergic receptor 2, and the siRNA is targeted to the sequence of SEQ ID 122, 125, or 134.
14. The use of any one of claims 1 to 9, wherein the target gene is acetylcholinesterase, and the siRNA is targeted to the sequence of SEQ ID 162, 177, or 189.
15. The use of any one of claims 1 to 9, wherein the target gene is ELAM-1 (selectin E), and the siRNA is targeted to the sequence of SEQ ID 262.
16. The use of any one of claims 1 to 9, wherein the target gene is prostaglandin endoperoxide synthase 1, and the siRNA is targeted to the sequence of SEQ ID 322, 353, or 369.
17. The use of any one of claims 1 to 9, wherein the target gene is prostaglandin endoperoxide synthase 2, and the siRNA is targeted to the sequence of SEQ ID 421, 426, or 477.

18. The use of any one of claims 1 to 9, wherein the target gene is carbonic anhydrase XII, and the siRNA is targeted to the sequence of SEQ ID 522.

19. The use of any one of claims 1 to 9, wherein the target gene is alpha adrenergic receptor 1A, and the siRNA is targeted to the sequence of SEQ ID 546.

20. The use of any one of claims 1 to 9, wherein the target gene is alpha adrenergic receptor 1B, and the siRNA is targeted to the sequence of SEQ ID 619.

21. The use of any one of claims 1 to 9, wherein the target gene is angiotensin II receptor type 1, and the siRNA is targeted to the sequence of SEQ ID 705.

22. The use of any one of claims 1 to 9, wherein the target gene is angiotensin II receptor type 2, and the siRNA is targeted to the sequence of SEQ ID 774.

23. The use of any one of claims 1 to 9, wherein the target gene is angiotensin I converting enzyme 1, and the siRNA is targeted to the sequence of SEQ ID 866.

24. The use of claim 10, wherein the target gene is ATPase alpha 1, and the siRNA is targeted to the sequence of SEQ ID 1399.

25. The use of any one of claims 1 to 9, wherein the target gene is ATPase beta 2, and the siRNA is targeted to the sequence of SEQ ID 1820.

26. An isolated siRNA molecule for use in treatment of an eye condition characterised by an increased intraocular pressure (IOP) in the patient, the siRNA being complementary to the nucleotide sequence of SEQ ID 5, 54, 66, 73,

105, 122, 125, 139, 162, 177, 189, 262, 322, 353, 369, 421, 426, 477, 522, 546, 619, 705, 774, 866, 1399, or 1820.

27. Use of an isolated siRNA molecule having a sequence which is complementary to the nucleotide sequence of SEQ ID 5, 54, 66, 73, 105, 122, 125, 139, 162, 177, 189, 262, 322, 353, 369, 421, 426, 477, 522, 546, 619, 705, 774, 866, 1399, or 1820 in the preparation of a medicament for the treatment of an eye condition characterised by an increased intraocular pressure (IOP), wherein said medicament is formulated for topical administration on the corneal surface.

28. A pharmaceutical composition comprising siRNA having a sequence which is complementary to the nucleotide sequence of SEQ ID 5, 54, 66, 73, 105, 122, 125, 139, 162, 177, 189, 262, 322, 353, 369, 421, 426, 477, 522, 546, 619, 705, 774, 866, 1399, or 1820 and a pharmaceutically acceptable diluent or carrier, wherein said composition is formulated for topical administration on the corneal surface.

1/20

Figure 1

Gene name	Transcript accession numbers
Carbonic anhydrase IV (CA4)	NM_000717
Carbonic anhydrase II (CA2)	NM_000067
Adrenergic, beta-1-, receptor (ADRB1)	NM_000684
Adrenergic, beta-2-, receptor (ADRB2)	NM_000024
Acetylcholinesterase (ACHE)	NM_000665, NM_015831
Selectin E (endothelial adhesion molecule 1) (SELE)	NM_000450
Prostaglandin-endoperoxide synthase 1 (prostaglandin G/H synthase and cyclooxygenase) (PTGS1)	NM_000962, NM_080591
Prostaglandin-endoperoxide synthase 2 (prostaglandin G/H synthase and cyclooxygenase) (PTGS2)	NM_000963
Carbonic anhydrase XII (CA12)	NM_001218, NM_206925
Adrenergic, alpha-1A-, receptor (ADRA1A)	NM_033302, NM_033303, NM_033304, NM_000680
Adrenergic, alpha-1B-, receptor (ADRA1B)	NM_000679
Adrenergic, alpha-1D-, receptor (ADRA1D)	NM_000678
Angiotensinogen (AGT)	NM_000029
Angiotensin II receptor, type 1 (AGTR1)	NM_000685, NM_009585, NM_004835, NM_031850, NM_032049
Angiotensin II receptor, type 2 (AGTR2)	NM_000686
Angiotensin I converting enzyme 1 (ACE1)	NM_000789, NM_152830, NM_152831
Angiotensin I converting enzyme 2 (ACE2)	NM_021804
Renin (REN)	NM_000537
Coagulation factor C homolog, cochlin (COCH)	NM_004086
ATPase, Na ⁺ /K ⁺ transporting, alpha 1 polypeptide (ATP1A1)	NM_000701, NM_001001586
ATPase, Na ⁺ /K ⁺ transporting, alpha 2 (+) polypeptide (ATP1A2)	NM_000702
ATPase, Na ⁺ /K ⁺ transporting, alpha 3 polypeptide (ATP1A3)	NM_152296
ATPase, Na ⁺ /K ⁺ transporting, beta 1 polypeptide (ATP1B1)	NM_001677, NM_001001787
ATPase, Na ⁺ /K ⁺ transporting, beta 2 polypeptide (ATP1B2)	NM_001678

Figure 2

CA4			
SEQ ID 1	GCCGAGTCCTCCAACCTACC	SEQ ID 48	CACAACGGACCTGAGCACT
SEQ ID 2	CTACCCCTGCTTGGTGCCA	SEQ ID 49	CGGACCTGAGCACTGGCAT
SEQ ID 3	GTGGGGGTGGAACTGCCAG	SEQ ID 50	GGACTTCCCCATTGCCAAG
SEQ ID 4	ACTGCCAGAAGGACCGCCA	SEQ ID 51	GTATGACCCTTCCCTGAAG
SEQ ID 5	CATCGTCACCACCAAGGCA	SEQ ID 52	GCCCCTGTCTGTTTCCTAT
SEQ ID 6	GGCAAAGGTGGACAAAAAA	SEQ ID 53	GCAACTTCCCTGAGGATCC
SEQ ID 7	AGGTGGACAAAAAACTGGG	SEQ ID 54	CTTCCCTGAGGATCCTCAA
SEQ ID 8	GGTGGACAAAAAACTGGGA	SEQ ID 55	CAATGGTCATGCTTTCAAC
SEQ ID 9	AAAACCTGGGACGCTTCTTC	SEQ ID 56	TGGTCATGCTTTCAACGTG
SEQ ID 10	AAACTGGGACGCTTCTTCT	SEQ ID 57	CGTGGAGTTTGATGACTCT
SEQ ID 11	AACTGGGACGCTTCTTCTT	SEQ ID 58	AGCAGTGCTCAAGGGAGGA
SEQ ID 12	ACTGGGACGCTTCTTCTTC	SEQ ID 59	GCAGTGCTCAAGGGAGGAC
SEQ ID 13	CTGGGACGCTTCTTCTTCT	SEQ ID 60	GGTTCAGAGCATACTGTGG
SEQ ID 14	GAAGCAAACGTGGACTGTC	SEQ ID 61	AAGAAATATGCTGCAGAAC
SEQ ID 15	GCAAACGTGGACTGTCCAA	SEQ ID 62	AGAAATATGCTGCAGAACT
SEQ ID 16	ACGTGGACTGTCCAAAATA	SEQ ID 63	GAAATATGCTGCAGAACTT
SEQ ID 17	CGTGGACTGTCCAAAATAA	SEQ ID 64	ATATGCTGCAGAACTTCAC
SEQ ID 18	AATAACGGGGCACTCAGTGA	SEQ ID 65	TATGCTGCAGAACTTCACT
SEQ ID 19	ATAACGGGGCACTCAGTGAT	SEQ ID 66	CTTCACTTGGTTCACTGGA
SEQ ID 20	TAACGGGGCACTCAGTGATG	SEQ ID 67	CACCAAATATGGGGATTTT
SEQ ID 21	CGGGCACTCAGTGATGATG	SEQ ID 68	ATATGGGGATTTTGGGAAA
SEQ ID 22	CAAGGCCAGCATTTCTGGA	SEQ ID 69	TATGGGGATTTTGGGAAAG
SEQ ID 23	GGCCAGCATTTCTGGAGGA	SEQ ID 70	AGCTGTGCAGCAACCTGAT
SEQ ID 24	ACAGTTGCACCTGCACTGG	SEQ ID 71	GCTGTGCAGCAACCTGATG
SEQ ID 25	CAGTTGCACCTGCACTGGT	SEQ ID 72	CCTGATGGACTGGCCGTTT
SEQ ID 26	AGAGAAGGGGACATCGAGG	SEQ ID 73	GGTTGGCAGCGCTAAACCG
SEQ ID 27	GAGAAGGGGACATCGAGGA	SEQ ID 74	ACCGGGCCTTCAGAAAGTT
SEQ ID 28	GGGGACATCGAGGAATGTG	SEQ ID 75	CCGGGCCTTCAGAAAGTTG
SEQ ID 29	TGTGAAAGAGGCCAGGAC	SEQ ID 76	AGTTGTTGATGTGCTGGAT
SEQ ID 30	AGAGGCCAGGACCCTGAA	SEQ ID 77	GTTGTTGATGTGCTGGATT
SEQ ID 31	GACGAAATTGCGGTGCTGG	SEQ ID 78	AACAAAGGGCAAGAGTGCT
SEQ ID 32	ATTGCGGTGCTGGCCTTTC	SEQ ID 79	ACAAAGGGCAAGAGTGCTG
SEQ ID 33	TTGCGGTGCTGGCCTTTC	SEQ ID 80	CAAAGGGCAAGAGTGCTGA
SEQ ID 34	CCCAGGTGAACGAGGGCTT	SEQ ID 81	AGGGCAAGAGTGCTGACTT
SEQ ID 35	TATCCCCAAACCTGAGATG	SEQ ID 82	GGGCAAGAGTGCTGACTTC
SEQ ID 36	ACCTGAGATGAGCACTACG	SEQ ID 83	GAGTGCTGACTTCACTAAC
SEQ ID 37	CCTGAGATGAGCACTACGA	SEQ ID 84	GAGTGCTGACTTCACAAAC
SEQ ID 38	GGAGGAGAACTGAGGCAC	SEQ ID 85	ACTTTGCAGCTCGTGGCCT
SEQ ID 39	ACTGAGGCACTACTTCCGC	SEQ ID 86	CTTCGATCCTCGTGGCCTC
SEQ ID 40	CTGAGGCACTACTTCCGCT	SEQ ID 87	TCCCTGGATTACTGGACCT
SEQ ID 41	GGTCGTCTGGACTGTGTTC	SEQ ID 88	TGTGTGACCTGGATTGTGC
SEQ ID 42	CAGATCCTGGCATTCTCTC	SEQ ID 89	GGAACCCATCAGCGTCAGC
SEQ ID 43	GCTGTACTACGACAAGGAA	SEQ ID 90	ACTTAACTTCAATGGGGAG
SEQ ID 44	GGAACAGACAGTGAGCATG	SEQ ID 91	CTTAACTTCAATGGGGAGG
SEQ ID 45	CAGACAGTGAGCATGAAGG	SEQ ID 92	CTTCAATGGGGAGGGTGAA
SEQ ID 46	GGACAATGTCAGGCCCTG	SEQ ID 93	TGGGGAGGGTGAACCCGAA
		SEQ ID 94	CCCGAAGAACTGATGGTGG
		SEQ ID 95	GAACTGATGGTGGACAACCT
		SEQ ID 96	CTGATGGTGGACAACCTGGC
		SEQ ID 97	GAACAGGCAAATCAAAGCT
CA2			
SEQ ID 47	ACACAACGGACCTGAGCAC		

SEQ ID 98	CAGGCAAATCAAAGCTTCC
ADRB1	
SEQ ID 99	TGTGCTGGTGATCGTGGCC
SEQ ID 100	CCTCTTCATCATGTCCCTG
SEQ ID 101	GTGCTGCGACTTCGTCACC
SEQ ID 102	GCAGGTGAAGAAGATCGAC
SEQ ID 103	GAAGATCGACAGCTGCGAG
SEQ ID 104	GACGCTGGGCATCATCATG
SEQ ID 105	CGACCCCAAGTGCTGCGAC
SEQ ID 106	CGTGGTGAAGGCCTTCCAC
SEQ ID 107	CTCGGCCTTCAACCCCATC
SEQ ID 108	CCCCATCATCTACTGCCGC
SEQ ID 109	GAAGATCGACAGCTGTGAG

ADRB2	
SEQ ID 110	TAGAAGCCATGCGCCGGAC
SEQ ID 111	TGTGCTGGTCATCACAGCC
SEQ ID 112	GTTGAGCGTCTGCAGACG
SEQ ID 113	CTACTTCATCACTTCACTG
SEQ ID 114	AATGTGGACTTTTGGCAAC
SEQ ID 115	ATGTGGACTTTTGGCAACT
SEQ ID 116	TGTGGACTTTTGGCAACTT
SEQ ID 117	CTTCTGGTGCGAGTTTGG
SEQ ID 118	GTACCAGAGCCTGCTGACC
SEQ ID 119	GAATAAGGCCCGGGTGATC
SEQ ID 120	TAAGGCCCGGGTGATCATT
SEQ ID 121	GGCCCGGGTGATCATTCTG
SEQ ID 122	GCCATCAACTGCTATGCCA
SEQ ID 123	CTGCTATGCCAATGAGACC
SEQ ID 124	TGAGACCTGCTGTGACTTC
SEQ ID 125	CCAAGCCTATGCCATTGCC
SEQ ID 126	GCCTATGCCATTGCCTCTT
SEQ ID 127	AAGGCAGCTCCAGAAGATT
SEQ ID 128	AGGCAGCTCCAGAAGATTG
SEQ ID 129	GGCAGCTCCAGAAGATTGA
SEQ ID 130	GATTGACAAATCTGAGGGC
SEQ ID 131	ATCTGAGGGCCGCTTCCAT
SEQ ID 132	TCTGAGGGCCGCTTCCATG
SEQ ID 133	CCTTAGCCAGGTGGAGCAG
SEQ ID 134	GTTCTGCTTGAAGGAGCAC
SEQ ID 135	GGAGCACAAAGCCCTCAAG
SEQ ID 136	AGCCCTCAAGACGTTAGGC
SEQ ID 137	GCCCTCAAGACGTTAGGCA
SEQ ID 138	GACGTTAGGCATCATCATG
SEQ ID 139	CATTGTGCATGTGATCCAG
SEQ ID 140	CCTCATCCGTAAGGAAGTT
SEQ ID 141	GGAAGTTTACATCCTCCTA
SEQ ID 142	ATTGGATAGGCTATGTCAA
SEQ ID 143	TTGGATAGGCTATGTCAAT
SEQ ID 144	TTCTGGTTTCAATCCCCTT
SEQ ID 145	TCCCCTTATCTACTGCCGG
SEQ ID 146	GGCCTATGGGAATGGCTAC

SEQ ID 147	TGGCTACTCCAGCAACGGC
SEQ ID 148	CACAGGGGAGCAGAGTGGA
SEQ ID 149	GAAAATAAACTGCTGTGTG
SEQ ID 150	AATAAACTGCTGTGTGAAG
SEQ ID 151	ATAAACTGCTGTGTGAAGA
SEQ ID 152	TAAACTGCTGTGTGAAGAC
SEQ ID 153	ACTGCTGTGTGAAGACCTC
SEQ ID 154	CTGCTGTGTGAAGACCTCC
SEQ ID 155	GACTTTGTGGGCCATCAAG
SEQ ID 156	GGTACTGTGCCTAGCGATA
SEQ ID 157	CATTGATTCACAAGGGAGG
SEQ ID 158	GGGAGGAATTGTAGTACAA
SEQ ID 159	GCCATCAACTGCTACGCCA
SEQ ID 160	CATCGTGCACGTGATCCAG

ACHE	
SEQ ID 161	CCTTCCAGAGTGTCTGCTA
SEQ ID 162	TATGTGGACACCCTATACC
SEQ ID 163	CGTGTGGACACCATACCCC
SEQ ID 164	CTACCGGGTGGGAGCCTTT
SEQ ID 165	TGTGGGTCTCCTGGATCAG
SEQ ID 166	TGACACAGAGCTGGTAGCC
SEQ ID 167	CCACGAATGGCACGTGCTG
SEQ ID 168	TGGCACGTGCTGCCTCAAG
SEQ ID 169	GAAAGCGTCTTCCGGTTCT
SEQ ID 170	AGCGTCTTCCGGTTCTCCT
SEQ ID 171	GCGTCTTCCGGTTCTCCTT
SEQ ID 172	GGATGAGGGCTCGTATTTT
SEQ ID 173	AGACAACGAGTCTCTCATC
SEQ ID 174	GACAACGAGTCTCTCATCA
SEQ ID 175	CGAGTCTCTCATCAGCCGG
SEQ ID 176	CACCGTGCTTCCACGCTCT
SEQ ID 177	ACTACACGGCAGAGGAGAA
SEQ ID 178	CTACACGGCAGAGGAGAAA
SEQ ID 179	AATCTTCGCCCAGCGACTG
SEQ ID 180	ATCTTCGCCCAGCGACTGA
SEQ ID 181	TCTTCGCCCAGCGACTGAT
SEQ ID 182	CTTTGCCCGCACAGGGGAT
SEQ ID 183	CCGCTTCCTCCCCAAATTG
SEQ ID 184	ATTGCTCAGCGCCACCGAC
SEQ ID 185	TTGCTCAGCGCCACCGACA
SEQ ID 186	GAACCAGTTCGACCACTAC
SEQ ID 187	CCAGTTCGACCACTACAGC
SEQ ID 188	GCAGGATCGCTGCTCAGAC
SEQ ID 189	CCGTGAGCTGAGCGAGGAC
SEQ ID 190	GAGAGGATCTTTGCCCAGA

SELE	
SEQ ID 191	AGAGAGTGGAGCCTGGTCT
SEQ ID 192	GAGAGTGGAGCCTGGTCTT
SEQ ID 193	CACCTCCACGGAAGCTATG
SEQ ID 194	GCTATGACTTATGATGAGG
SEQ ID 195	AGGTACACACACCTGGTTG

SEQ ID 196	GGTACACACACCTGGTTGC
SEQ ID 197	CAAAGAAGAGATTGAGTAC
SEQ ID 198	AGAAGAGATTGAGTACCTA
SEQ ID 199	GAAGAGATTGAGTACCTAA
SEQ ID 200	GAGATTGAGTACCTAAACT
SEQ ID 201	ACTCCATATTGAGCTATTG
SEQ ID 202	CTCCATATTGAGCTATTCA
SEQ ID 203	AAGTCAACAATGTGTGGGT
SEQ ID 204	AGTCAACAATGTGTGGGTC
SEQ ID 205	GTCAACAATGTGTGGGTCT
SEQ ID 206	CAATGTGTGGGTCTGGGTA
SEQ ID 207	TGTGTGGGTCTGGGTAGGA
SEQ ID 208	CCCAGAAACCTCTGACAGA
SEQ ID 209	ACCTCTGACAGAAGAAGCC
SEQ ID 210	CCTCTGACAGAAGAAGCCA
SEQ ID 211	GAAGCCAAGAACTGGGCTC
SEQ ID 212	GCCAAGAACTGGGCTCCAG
SEQ ID 213	GAAGTGGGCTCCAGGTGAA
SEQ ID 214	CCCAACAATAGGCAAAAAG
SEQ ID 215	CAATAGGCAAAAAGATGAG
SEQ ID 216	TAGGCAAAAAGATGAGGAC
SEQ ID 217	AAAGATGAGGACTGCGTGG
SEQ ID 218	AAGATGAGGACTGCGTGGA
SEQ ID 219	AGATGAGGACTGCGTGGAG
SEQ ID 220	GATGAGGACTGCGTGGAGA
SEQ ID 221	GAGAGAAAAAGATGTGGGC
SEQ ID 222	AAAGATGTGGGCATGTGGA
SEQ ID 223	AAGATGTGGGCATGTGGAA
SEQ ID 224	AGATGTGGGCATGTGGAAT
SEQ ID 225	GATGTGGGCATGTGGAATG
SEQ ID 226	TGATGAGAGGTGCAGCAAG
SEQ ID 227	GAAGAAGCTTGCCCTATGC
SEQ ID 228	GAAGCTTGCCCTATGCTAC
SEQ ID 229	GCTTGCCCTATGCTACACA
SEQ ID 230	TACATCCTGCAGTGGCCAC
SEQ ID 231	TGTGTAGAGACCATCAATA
SEQ ID 232	TTACACTTGCAAGTGTGAC
SEQ ID 233	GTGTGACCCTGGCTTCAGT
SEQ ID 234	GTGTGAGCAAATTGTGAAC
SEQ ID 235	ATTGTGAACTGTACAGCCC
SEQ ID 236	TTGTGAACTGTACAGCCCT
SEQ ID 237	CTGTACAGCCCTGGAATCC
SEQ ID 238	TCCCCTGAGCATGGAAGCC
SEQ ID 239	GCCTGGTTTGCAAGTCACCC
SEQ ID 240	ACTTCAGCTACAATTCTTC
SEQ ID 241	CTTCAGCTACAATTCTTCC
SEQ ID 242	TTCTTCCTGCTCTATCAGC
SEQ ID 243	GCAGCATGGAGACCATGCA
SEQ ID 244	TGGAGTGCTCCTATTCCAG
SEQ ID 245	TGTGGTTGAGTGTGATGCT
SEQ ID 246	ATCCAGCCAATGGGTTCGT
SEQ ID 247	TCCAGCCAATGGGTTCGTG
SEQ ID 248	TGGGTTCGTGGAATGTTTC

SEQ ID 249	TGTTTCCAAAACCCTGGAA
SEQ ID 250	AACCCTGGAAGCTTCCCAT
SEQ ID 251	ACCCTGGAAGCTTCCCATG
SEQ ID 252	CCCTGGAAGCTTCCCATGG
SEQ ID 253	GCTTCCCATGGAACACAAC
SEQ ID 254	CACAACCTGTACATTTGAC
SEQ ID 255	CCTGTACATTTGACTGTGA
SEQ ID 256	GAAGGATTTGAACTAATGG
SEQ ID 257	GGATTTGAACTAATGGGAG
SEQ ID 258	CTAATGGGAGCCCAGAGCC
SEQ ID 259	TGGGAGCCCAGAGCCTTCA
SEQ ID 260	TTGGGACAACGAGAAGCCA
SEQ ID 261	CGAGAAGCCAACGTGTAAA
SEQ ID 262	GCCAACGTGTAAAGCTGTG
SEQ ID 263	CGTGTAAGCTGTGACATG
SEQ ID 264	AGCTGTGACATGCAGGGCC
SEQ ID 265	TGGCTCTGTGAGGTGCAGC
SEQ ID 266	ATCATCCTGCAACTTCACC
SEQ ID 267	TCATCCTGCAACTTCACCT
SEQ ID 268	CTTCACCTGTGAGGAAGGC
SEQ ID 269	GGCTTCATGTTGCAGGGAC
SEQ ID 270	TGCACCACTCAAGGGCAGT
SEQ ID 271	GGGCAGTGGACACAGCAAA
SEQ ID 272	ATCCCAGTTTGTGAAGCTT
SEQ ID 273	TCCCAGTTTGTGAAGCTTT
SEQ ID 274	GCTTTCCAGTGCACAGCCT
SEQ ID 275	TTGTCTTCCTAGTGCTTCT
SEQ ID 276	GGGATCCAAAAGGCTCCAA
SEQ ID 277	AAGGCTCCAATGTGGCCCC
SEQ ID 278	AGGCTCCAATGTGGCCCCA
SEQ ID 279	CGAGAAGCCCACATGTGAA
SEQ ID 280	GCCCACATGTGAAGCTGTG
SEQ ID 281	GCTGTGAGATGCGATGCTG
SEQ ID 282	GGGTTTGGTGAGGTGTGCT
SEQ ID 283	TTACCTACAAGTCCTCTT
SEQ ID 284	GTCCTCTTGTGCCTTCAGC
SEQ ID 285	CTCAACTTGAGTGCACATC
SEQ ID 286	CTTGAGTGCACATCTCAGG
SEQ ID 287	TGGACAGAAGAGGTTTCCTT
SEQ ID 288	GAGGTTTCCTTCCTGCCAAG
SEQ ID 289	GTGGTAAATGTTCAAGCC
SEQ ID 290	AATGTTCAAGCCTGGCAGT
SEQ ID 291	ATGTTCAAGCCTGGCAGTT
SEQ ID 292	TGTTCAAGCCTGGCAGTTC
SEQ ID 293	GCCTGGCAGTTCCGGGAAA
SEQ ID 294	AGATCAACATGAGCTGCAG
SEQ ID 295	GATCAACATGAGCTGCAGT
SEQ ID 296	CATGAGCTGCAGTGGGGAG
SEQ ID 297	GTTGCTGTCTCTGAAGGA
SEQ ID 298	GGATGGACGCTCAATGGCT
SEQ ID 299	TGGCTCTGCAGCTCGGACA
SEQ ID 300	GCTCCCACTGAGTCCAACA
SEQ ID 301	CATTCCTTGGTAGCTGGA

SEQ ID 302	ATGCTTACGGAAAGCAAAG
SEQ ID 303	TGCTTACGGAAAGCAAAGA
SEQ ID 304	GCAAAGAAATTTGTTCTG
SEQ ID 305	AGAAATTTGTTCTGCCAG
SEQ ID 306	GAAATTTGTTCTGCCAGC
SEQ ID 307	ATTTGTTCTGCCAGCAGC
SEQ ID 308	TTTGTTCTGCCAGCAGCT
SEQ ID 309	AGCCTTGAATCAGACGGAA
SEQ ID 310	GCCTTGAATCAGACGGAAG
SEQ ID 311	TCAGACGGAAGCTACCAAA
SEQ ID 312	GCTACCAAAAGCCTTCTTA
SEQ ID 313	AAGCCTTCTTACATCCTTT
SEQ ID 314	AGCCTTCTTACATCCTTTA
SEQ ID 315	GCCTTCTTACATCCTTTAA
SEQ ID 316	AGCCTTGAATCAGATGGAA
SEQ ID 317	GCCTTGAATCAGATGGAAG
SEQ ID 318	TCAGATGGAAGCTACCAAA

PTGS1

SEQ ID 319	TCCCTGTTGTTACTATCCA
SEQ ID 320	TGCCACCTTCATCCGAGAG
SEQ ID 321	CTCAGCACATGACTACATC
SEQ ID 322	CGTGAGCTATTACACTCGT
SEQ ID 323	AGATTGCCCCACACCCATG
SEQ ID 324	GATTGCCCCACACCCATGG
SEQ ID 325	CCAAAGGGAAGAAGCAGTT
SEQ ID 326	AGGGAAGAAGCAGTTGCCA
SEQ ID 327	GGGAAGAAGCAGTTGCCAG
SEQ ID 328	GAAGCAGTTGCCAGATGCC
SEQ ID 329	GCAGTTGCCAGATGCCCAG
SEQ ID 330	GTTCATACCTGACCCCAA
SEQ ID 331	GGCACCAACCTCATGTTTG
SEQ ID 332	CCTCATGTTTGCTTCTTT
SEQ ID 333	CACTTCACCCACCAGTTCT
SEQ ID 334	AACTTCTGGCAAGATGGGT
SEQ ID 335	ACTTCTGGCAAGATGGGTC
SEQ ID 336	CTTCTGGCAAGATGGGTCC
SEQ ID 337	GATGGGTCTGGCTTCACC
SEQ ID 338	TCTGGAGCGTCAGTATCAA
SEQ ID 339	CTGCGGCTCTTTAAGGATG
SEQ ID 340	GGATGGGAACTCAAGTAC
SEQ ID 341	ACTCAAGTACCAGGTGCTG
SEQ ID 342	CTCAAGTACCAGGTGCTGG
SEQ ID 343	GTACCAGGTGCTGGATGGA
SEQ ID 344	ATGTACCCGCCCTCGGTAG
SEQ ID 345	TGTACCCGCCCTCGGTAGA
SEQ ID 346	GAGGCGCCTGTGTTGATGC
SEQ ID 347	CCGTGTGTGTGACCTGCTG
SEQ ID 348	GATTGTCATCGAGGAGTAC
SEQ ID 349	ATTTGACCCAGAGCTGCTG
SEQ ID 350	TTTGACCCAGAGCTGCTGT
SEQ ID 351	TACCGCAACCGCATTGCCA
SEQ ID 352	CCGCATTGCCATGGAGTTC

SEQ ID 353	CCATCTCTACCACTGGCAC
SEQ ID 354	CACCTCCATGTTGGTGGAC
SEQ ID 355	CATGGACCACCACATCCTG
SEQ ID 356	TGAGTACCGCAAGAGGTTT
SEQ ID 357	GAGGTTTGGCATGAAACCC
SEQ ID 358	ACCCTACACCTCCTTCCAG
SEQ ID 359	CCCTACACCTCCTTCCAGG
SEQ ID 360	GGAGATGGCAGCAGAGTTG
SEQ ID 361	TTGTATGGAGACATTGATG
SEQ ID 362	AAGTGCCATCCAAACTCTA
SEQ ID 363	AGTGCCATCCAAACTCTAT
SEQ ID 364	GTGCCATCCAAACTCTATC
SEQ ID 365	ACTCTATCTTTGGGGAGAG
SEQ ID 366	CTCTATCTTTGGGGAGAGT
SEQ ID 367	GGGTCTCCTAGGGAATCCC
SEQ ID 368	TCCCATCTGTTCTCCGGAG
SEQ ID 369	CATTGTCAAGACGGCCACA
SEQ ID 370	GACGGCCACACTGAAGAAG
SEQ ID 371	GAAGCTGGTCTGCCTCAAC
SEQ ID 372	GCTGGTCTGCCTCAACACC
SEQ ID 373	CACCAAGACCTGTCCCTAC
SEQ ID 374	GACCTGTCCCTACGTTTCC

PTGS2

SEQ ID 375	ATCCTTGCTGTTCCCACCC
SEQ ID 376	TCCTTGCTGTTCCCACCCA
SEQ ID 377	AACCGAGGTGTATGTATGA
SEQ ID 378	ACCGAGGTGTATGTATGAG
SEQ ID 379	CCGAGGTGTATGTATGAGT
SEQ ID 380	GTGCGATTGTACCCGGACA
SEQ ID 381	AACTGCTCAACACCGGAAT
SEQ ID 382	ACTGCTCAACACCGGAATT
SEQ ID 383	CTGCTCAACACCGGAATT
SEQ ID 384	CACCGGAATTTTGACAAG
SEQ ID 385	TTATTTCTGAAACCCACTC
SEQ ID 386	ACCCACTCCAAACACAGTG
SEQ ID 387	CCCACTCCAAACACAGTGC
SEQ ID 388	ACACAGTGCACCTACATACT
SEQ ID 389	CACAGTGCACCTACATACTT
SEQ ID 390	GGGATTTTGGAACGTTGTG
SEQ ID 391	CGTTGTGAATAACATTCCC
SEQ ID 392	TAACATTCCCTTCCTTCGA
SEQ ID 393	CATTCCCTTCCTTCGAAAT
SEQ ID 394	CTTACAATGCTGACTATGG
SEQ ID 395	TGCTGACTATGGCTACAAA
SEQ ID 396	AAGCTGGGAAGCCTTCTCT
SEQ ID 397	AGCTGGGAAGCCTTCTCTA
SEQ ID 398	GCTGGGAAGCCTTCTCTAA
SEQ ID 399	GCCTTCTCTAACCTCTCCT
SEQ ID 400	CCTCTCCTATTATACTAGA
SEQ ID 401	AGGTAAAAAGCAGCTTCCT
SEQ ID 402	GGTAAAAAGCAGCTTCCTG
SEQ ID 403	AAAGCAGCTTCCTGATTCA

SEQ ID 404	AAGCAGCTTCCTGATTCAA
SEQ ID 405	AGCAGCTTCCTGATTCAAA
SEQ ID 406	GCAGCTTCCTGATTCAAAT
SEQ ID 407	GAAGAAAGTTCATCCCTGA
SEQ ID 408	GAAAGTTCATCCCTGATCC
SEQ ID 409	AGTTCATCCCTGATCCCCA
SEQ ID 410	GTTTCATCCCTGATCCCCAG
SEQ ID 411	GACAGATCATAAGCGAGGG
SEQ ID 412	ACTCTGGCTAGACAGCGTA
SEQ ID 413	CTCTGGCTAGACAGCGTAA
SEQ ID 414	ACTGCGCCTTTTCAAGGAT
SEQ ID 415	CTGCGCCTTTTCAAGGATG
SEQ ID 416	TTGATGGAGAGATGTATCC
SEQ ID 417	AGATACTCAGGCAGAGATG
SEQ ID 418	GATACTCAGGCAGAGATGA
SEQ ID 419	GTCCCTGAGCATCTACGGT
SEQ ID 420	TCTGGCTGCGGGAACACAA
SEQ ID 421	CACAACAGAGTATGCGATG
SEQ ID 422	CAGAGTATGCGATGTGCTT
SEQ ID 423	ACAGGAGCATCCTGAATGG
SEQ ID 424	CAGGAGCATCCTGAATGGG
SEQ ID 425	TGGGGTGATGAGCAGTTGT
SEQ ID 426	GCAGGCTAATACTGATAGG
SEQ ID 427	TACTGATAGGAGAGACTAT
SEQ ID 428	GATTATGTGCAACACTTGA
SEQ ID 429	CACTTGAGTGGCTATCACT
SEQ ID 430	ACTGAAATTTGACCCAGAA
SEQ ID 431	CTGAAATTTGACCCAGAAC
SEQ ID 432	ATTTGACCCAGAACTACTT
SEQ ID 433	TTTGACCCAGAACTACTTT
SEQ ID 434	CAAACAATTCCAGTACCAA
SEQ ID 435	CAATTCCAGTACCAAATC
SEQ ID 436	TTCCAGTACCAAATCGTA
SEQ ID 437	AATCGTATTGCTGCTGAAT
SEQ ID 438	ATCGTATTGCTGCTGAATT
SEQ ID 439	TCGTATTGCTGCTGAATTT
SEQ ID 440	TTTAACACCCTCTATCACT
SEQ ID 441	CACCCTCTATCACTGGCAT
SEQ ID 442	CAACTCTATATTGCTGGAA
SEQ ID 443	CTCTATATTGCTGGAACAT
SEQ ID 444	CATGGAATTACCCAGTTTG
SEQ ID 445	TTACCCAGTTTGTTGAATC
SEQ ID 446	TCATTCACCAGGCAAATTG
SEQ ID 447	ATTGCTGGCAGGGTTGCTG
SEQ ID 448	TTGCTGGCAGGGTTGCTGG
SEQ ID 449	TGTTCCACCCGCGAGTACAG
SEQ ID 450	AGTATCACAGGCTTCCATT
SEQ ID 451	GTATCACAGGCTTCCATTG
SEQ ID 452	TGAGTACCGCAAACGCTTT
SEQ ID 453	ACGCTTTATGCTGAAGCCC
SEQ ID 454	CGCTTTATGCTGAAGCCCT
SEQ ID 455	GCCCTATGAATCATTTGAA
SEQ ID 456	GAACCTACAGGAGAAAAGG

SEQ ID 457	CTTACAGGAGAAAAGGAAA
SEQ ID 458	AAGGAAATGTCTGCAGAGT
SEQ ID 459	AGGAAATGTCTGCAGAGTT
SEQ ID 460	GGAAATGTCTGCAGAGTTG
SEQ ID 461	ATGTCTGCAGAGTTGGAAG
SEQ ID 462	TGTCTGCAGAGTTGGAAGC
SEQ ID 463	GCACTCTATGGTGACATCG
SEQ ID 464	AAGCCTCGGCCAGATGCCA
SEQ ID 465	AGCCTCGGCCAGATGCCAT
SEQ ID 466	ACCATGGTAGAAGTTGGAG
SEQ ID 467	CCATGGTAGAAGTTGGAGC
SEQ ID 468	GTTGGAGCACCATTCTCCT
SEQ ID 469	AGGACTTATGGGTAATGTT
SEQ ID 470	GGACTTATGGGTAATGTTA
SEQ ID 471	TGTTATATGTTCTCCTGCC
SEQ ID 472	GCCAAGCACTTTTGGTGGA
SEQ ID 473	GCACTTTTGGTGGAAGAAGT
SEQ ID 474	GTGGGTTTTCAAATCATCA
SEQ ID 475	ATCATCAACACTGCCTCAA
SEQ ID 476	TCATCAACACTGCCTCAAT
SEQ ID 477	CACTGCCTCAATTCAGTCT
SEQ ID 478	TTCAGTCTCTCATCTGCAA
SEQ ID 479	TAACGTGAAGGGCTGTCCC
SEQ ID 480	CGTGAAGGGCTGTCCCTTT
SEQ ID 481	GGGCTGTCCCTTTACTTCA
SEQ ID 482	AACAGTCACCATCAATGCA
SEQ ID 483	ACAGTCACCATCAATGCAA
SEQ ID 484	CAGTCACCATCAATGCAAG
SEQ ID 485	TGCAAGTTCTTCCCGCTCC
SEQ ID 486	GTTCTTCCCGCTCCGGACT
SEQ ID 487	TCCCACAGTACTACTAAAA
SEQ ID 488	AAGAACGTTGACTGAACT
SEQ ID 489	AGAACGTTGACTGAACTG
SEQ ID 490	GAACGTTGACTGAACTGT
SEQ ID 491	CACAACAGAGTATGCGACG

CA12

SEQ ID 492	AGGAACAGCCTTCCAGCCC
SEQ ID 493	CGGTTCCAAGTGGACTTAT
SEQ ID 494	GTGGACTTATTTTGGTCCT
SEQ ID 495	TAGCTGGTCCAAGAAGTAC
SEQ ID 496	GAAGTACCCGTCGTGTGGG
SEQ ID 497	GGCTACAATCTGTCTGCCA
SEQ ID 498	TCTGTCTGCCAACAAGCAG
SEQ ID 499	CAAGCAGTTTCTCCTGACC
SEQ ID 500	GCAGTTTCTCCTGACCAAC
SEQ ID 501	CAATGGCCATTCAAGTGAAG
SEQ ID 502	TGGCCATTCAAGTGAAGCTG
SEQ ID 503	CTCAGACCTTTATCCTGAC
SEQ ID 504	CAAGTCAGAAGGCCTCGCT
SEQ ID 505	GTCAGAAGGCCTCGCTGTC
SEQ ID 506	TCCGTCCTATGACAAGATC
SEQ ID 507	GATCTTCAGTCACCTTCAA

SEQ ID 508	CATGTAAAGTACAAAGGCC
SEQ ID 509	AGTACAAAGGCCAGGAAGC
SEQ ID 510	GTACAAAGGCCAGGAAGCA
SEQ ID 511	AGGCCAGGAAGCATTCTGTC
SEQ ID 512	GGCCAGGAAGCATTCTGTCC
SEQ ID 513	GCATTCTGTCCTCGGGATTCA
SEQ ID 514	CATTGAAGAGCTGCTTCCG
SEQ ID 515	GAGCTGCTTCCGGAGAGGA
SEQ ID 516	TATTACCGCTACCGGGGGT
SEQ ID 517	CCCCACTGTGCTCTGGACA
SEQ ID 518	ACCCCGTGCAAATTTCCCA
SEQ ID 519	CCCGGTGCAAATTTCCAG
SEQ ID 520	ATTTCCAGGAGCAGCTGC
SEQ ID 521	TTTCCAGGAGCAGCTGCT
SEQ ID 522	ATGATCAACAACCTCCGGC
SEQ ID 523	TGATCAACAACCTCCGGCA
SEQ ID 524	CAACTTCCGGCAGGTCCAG
SEQ ID 525	CTTCCGGCAGGTCCAGAAG
SEQ ID 526	GTTGATGAGAGGCTGGTA
SEQ ID 527	GTGCAAGTCTGTACTGCGG
SEQ ID 528	GTCTGTACTGCGGCAGGAC
SEQ ID 529	GGAAGAGTATCAAAAAGG
SEQ ID 530	AAAAGGTGATAACAAGGGA
SEQ ID 531	AAAGGTGATAACAAGGGAG
SEQ ID 532	AAGGTGATAACAAGGGAGT
SEQ ID 533	AGGTGATAACAAGGGAGTC
SEQ ID 534	GGTGATAACAAGGGAGTCA
SEQ ID 535	CAAGGGAGTCATTTACAAG
SEQ ID 536	GGGAGTCATTTACAAGCCA
SEQ ID 537	GCCAGCCACCAAGATGGAG
SEQ ID 538	GATGGAGACTGAGGCCAC

ADRA1A

SEQ ID 539	ATGCTTCCGACAGCTCCAA
SEQ ID 540	TGCTTCCGACAGCTCCAAC
SEQ ID 541	CATTTCCAAGGCCATTCTG
SEQ ID 542	CATCCTAGTGATCCTCTCC
SEQ ID 543	CATCTGGGCGGCAGTGGAT
SEQ ID 544	CCATCGTCACCCAGAGGAG
SEQ ID 545	GTCTGGCCTCAAGACCGAC
SEQ ID 546	GACCGACAAGTCGGACTCG
SEQ ID 547	GTCGGACTCGGAGCAAGTG
SEQ ID 548	GTGACGCTCCGCATCCATC
SEQ ID 549	GACCAAGACGCACTTCTCA
SEQ ID 550	GACGCACTTCTCAGTGAGG
SEQ ID 551	GTTCTCCCGGGAGAAGAAA
SEQ ID 552	GAAAGCGGCCAAAACGCTG
SEQ ID 553	AACGCTGGGCATCGTGGTC
SEQ ID 554	GCCCTCTGAAACAGTTTTT
SEQ ID 555	AATAGTATTTTGGCTCGGA
SEQ ID 556	ATAGTATTTTGGCTCGGAT
SEQ ID 557	TAGTATTTTGGCTCGGATA
SEQ ID 558	ACAGCTGCATCAACCCCAT

SEQ ID 559	CAGCTGCATCAACCCCATC
SEQ ID 560	CCCCATCATATACCCATGC
SEQ ID 561	GAGTTCAAAAAGGCCTTTC
SEQ ID 562	AAAGGCCTTTCAGAATGTC
SEQ ID 563	AAGGCCTTTCAGAATGTCT
SEQ ID 564	AGGCCTTTCAGAATGTCTT
SEQ ID 565	GGCCTTTCAGAATGTCTTG
SEQ ID 566	TGTCTTGAGAATCCAGTGT
SEQ ID 567	TCCAGTGTCTCTGCAGAAA
SEQ ID 568	TCCAGTGTCTCCGCAGAAA
SEQ ID 569	AGCAGTCTTCCAACATGC
SEQ ID 570	GCAGTCTTCCAACATGCC
SEQ ID 571	ACATGCCCTGGGCTACACC
SEQ ID 572	GGGCAACACAAGGACATGG
SEQ ID 573	CACAAGGACATGGTGCGCA
SEQ ID 574	GAGAGACCTTCTACAGGAT
SEQ ID 575	GACGGATGGCGTTTGTGAA
SEQ ID 576	ATTTTCTCTTCCATGCC
SEQ ID 577	TTTTTCTCTTCCATGCCCC
SEQ ID 578	AGACCAATCCTCCTGTACC
SEQ ID 579	GACCAATCCTCCTGTACCA
SEQ ID 580	TCCTCCTGTACCACAGCCC
SEQ ID 581	GTCTCGCTCTGTCACCAGG
SEQ ID 582	GAGATTCTCCTGCCTCAGC
SEQ ID 583	GAATTGCAGAGAGCATATC
SEQ ID 584	TTGCAGAGAGCATATCAAG
SEQ ID 585	TTTTATGATGCCACCGTGG
SEQ ID 586	AGGGTCTAGAATGCTGATC
SEQ ID 587	GGGTCTAGAATGCTGATCT
SEQ ID 588	GTAAAAGCTTTTTGGAGGT
SEQ ID 589	AAGCTTTTTGGAGGTCTGC
SEQ ID 590	AGCTTTTTGGAGGTCTGCT
SEQ ID 591	GCTTTTTGGAGGTCTGCTG
SEQ ID 592	CCCCCAGCCTTGACAAGAA
SEQ ID 593	GAACCATCAAGTTCCAACC
SEQ ID 594	CCATCAAGTTCCAACCATT
SEQ ID 595	GTTCCAACCATTAAAGGTCC
SEQ ID 596	CCATTAAGGTCCACACCAT
SEQ ID 597	GGTCCACACCATCTCCCTC
SEQ ID 598	CGGGGAGGAAGTCTAGGAC

ADRA1B

SEQ ID 599	GATGAATCCCGACCTGGAC
SEQ ID 600	CACATCAGCACCTGCCAC
SEQ ID 601	AAATGCCAACTTCACTGGC
SEQ ID 602	AATGCCAACTTCACTGGCC
SEQ ID 603	ATGCCAACTTCACTGGCCC
SEQ ID 604	TGCCAACTTCACTGGCCCC
SEQ ID 605	CTTCACTGGCCCCAACCAG
SEQ ID 606	CCAGACCTCGAGCAACTCC
SEQ ID 607	CATCCTAGTCATCTTGTCT
SEQ ID 608	CTACTTCATTGTCAACCTG
SEQ ID 609	CGATGACAAGGAGTGCGGG

SEQ ID 610	GAACCCTTCTATGCCCTCT
SEQ ID 611	CCCTTCTATGCCCTTCT
SEQ ID 612	GAGAACCACCAAGAACCTA
SEQ ID 613	CCACCAAGAACCTAGAGGC
SEQ ID 614	GAACCTAGAGGCAGGAGTC
SEQ ID 615	CCTAGAGGCAGGAGTCATG
SEQ ID 616	GGAGATGTCCAACCTCCAAG
SEQ ID 617	CTCCAAGGAGCTGACCCTG
SEQ ID 618	GGAGCTGACCCTGAGGATC
SEQ ID 619	GAACCTTCACGAGGACACC
SEQ ID 620	CTTTCACGAGGACACCCTT
SEQ ID 621	CCCCAGGAGTTCCATAGCT
SEQ ID 622	ACTTTTAAAGTTCTCCAGG
SEQ ID 623	CTTTTAAAGTTCTCCAGGG
SEQ ID 624	GTTCTCCAGGGAAAAGAAA
SEQ ID 625	AAGAAAGCAGCTAAGACGT
SEQ ID 626	AGAAAGCAGCTAAGACGTT
SEQ ID 627	GAAAGCAGCTAAGACGTTG
SEQ ID 628	AGCAGCTAAGACGTTGGGC
SEQ ID 629	GCAGCTAAGACGTTGGGCA
SEQ ID 630	GACGTTGGGCATTGTGGTC
SEQ ID 631	CAGCTGCCTCAACCCCATC
SEQ ID 632	CCCCATCATCTACCCATGC
SEQ ID 633	GGAGTTCAAGCGCGCTTTC
SEQ ID 634	AAGCAACATGCCCTGGCG

ADRA1D

SEQ ID 635	CCTGCTTGTCATCCTCTCA
SEQ ID 636	CTATTTTCATCGTGAACCTG
SEQ ID 637	GTACCCAGCCATCATGACC
SEQ ID 638	GTTCTCCCGTGAGAAGAAA
SEQ ID 639	GAAAGCGGCCAAGACTCTG
SEQ ID 640	GACTCTGGCCATCGTCGTG
SEQ ID 641	GGTCATCTTCTGGCTCGGC
SEQ ID 642	CCCGCTCATCTACCCCTGT
SEQ ID 643	AGTCTCCAGCCTGTGCGAC
SEQ ID 644	GTCTCCAGCCTGTGCGACA
SEQ ID 645	TTGGCCGACTACAGCAACC
SEQ ID 646	CCTACGGGAGACCGATATT

AGT

SEQ ID 647	TGAGAGTACCTGTGAGCAG
SEQ ID 648	TGCCGGGAAGCCCAAAGAC
SEQ ID 649	GCCCAAAGACCCACCTTC
SEQ ID 650	AGACCCACCTTCATACCT
SEQ ID 651	GACCCACCTTCATACCTG
SEQ ID 652	TTCAGGCCAAGACATCCCC
SEQ ID 653	GACATCCCCTGTGGATGAA
SEQ ID 654	AAGGCCCTACAGGACCAGC
SEQ ID 655	AGGCCCTACAGGACCAGCT
SEQ ID 656	AACTTGACACCGAAGACAA
SEQ ID 657	ACTTGACACCGAAGACAAG
SEQ ID 658	CTTGACACCGAAGACAAGT

SEQ ID 659	GACAAGTTGAGGGCCGCAA
SEQ ID 660	GTTGAGGGCCGCAATGGTC
SEQ ID 661	TGGTCGGGATGCTGGCCAA
SEQ ID 662	CTTCTTGGGCTTCCGTATA
SEQ ID 663	CGGCTGTCTTTGGCACCT
SEQ ID 664	TCCTGGGTGTTCTTGGAA
SEQ ID 665	GGACAAGAACTGCACCTCC
SEQ ID 666	CTGGATGTTGCTGCTGAGA
SEQ ID 667	GATTGACAGGTTTCATGCAG
SEQ ID 668	GACTGGCTGCTCCCTGATG
SEQ ID 669	CACCTACGTCCACTTCCAA
SEQ ID 670	GGGAAGATGAAGGGCTTCT
SEQ ID 671	GATGAAGGGCTTCTCCCTG
SEQ ID 672	CAGCACCTCAGTGTCTGTT
SEQ ID 673	CTTCTCGGTGACTCAAGTG
SEQ ID 674	GTGCCCTTCACTGAGAGCG
SEQ ID 675	GGTGGAGGGTCTCACTTTC
SEQ ID 676	AACTCCCTCAACTGGATGA
SEQ ID 677	ACTCCCTCAACTGGATGAA
SEQ ID 678	CTCCCTCAACTGGATGAAG
SEQ ID 679	CTGGATGAAGAACTGTCT
SEQ ID 680	GAAACTGTCTCCCCGGACC
SEQ ID 681	ACTGTCTCCCCGGACCATC
SEQ ID 682	CTGGTGCTGCAAGGATCTT
SEQ ID 683	GGATCTTATGACCTGCAGG
SEQ ID 684	CCTGCAAAAATTGAGCAAT
SEQ ID 685	AAATTGAGCAATGACCGCA
SEQ ID 686	AATTGAGCAATGACCGCAT
SEQ ID 687	ATTGAGCAATGACCGCATC
SEQ ID 688	TTGAGCAATGACCGCATCA
SEQ ID 689	GCGGATGAGAGAGAGCCCA
SEQ ID 690	CAGCTTAACAAGCCTGAGG
SEQ ID 691	CAAGCCTGAGGTCTTGGAG
SEQ ID 692	GCCTGAGGTCTTGGAGGTG
SEQ ID 693	CCGCCCATTCCTGTTTGCT
SEQ ID 694	CCCGCTGAGCACAGCATGA

AGTR1

SEQ ID 695	CTCTTCTACTGAAGATGGT
SEQ ID 696	AGAATCCAAGATGATTGTC
SEQ ID 697	GAATCCAAGATGATTGTCC
SEQ ID 698	TCCAAGATGATTGTCCCAA
SEQ ID 699	GATGATTGTCCCAAAGCTG
SEQ ID 700	AGCTGGAAGGCATAATTAC
SEQ ID 701	GCTGGAAGGCATAATTACA
SEQ ID 702	TATTTGGAAACAGCTTGGT
SEQ ID 703	ACAGCTTGGTGGTGATAGT
SEQ ID 704	CAGCTTGGTGGTGATAGTC
SEQ ID 705	GCTGAAGACTGTGGCCAGT
SEQ ID 706	GACTGTGGCCAGTGTTTTT
SEQ ID 707	TTAGCACTGGCTGACTTA
SEQ ID 708	TACCGCTGGCCCTTTGGCA
SEQ ID 709	GATTGCTTCAGCCAGCGTC

SEQ ID 710	CCTGTACGCTAGTGTGTTT
SEQ ID 711	TGAAGTCCCGCCTTCGACG
SEQ ID 712	TGCTTGTAGCCAAAGTCAC
SEQ ID 713	AGTCACCTGCATCATCATT
SEQ ID 714	GTCACCTGCATCATCATTT
SEQ ID 715	AATTCAACCCTTCCGATAG
SEQ ID 716	ATTCAACCCTTCCGATAGG
SEQ ID 717	TTCAACCCTTCCGATAGGG
SEQ ID 718	AAATATACTGGGTTTCCTG
SEQ ID 719	AATATACTGGGTTTCCTGT
SEQ ID 720	ATATACTGGGTTTCCTGTT
SEQ ID 721	TATACTGGGTTTCCTGTTT
SEQ ID 722	GGCCCTAAAGAAGGCTTAT
SEQ ID 723	GAAGGCTTATGAAATTCAG
SEQ ID 724	GGCTTATGAAATTCAGAAG
SEQ ID 725	TTCAGAAGAACAAACCAAG
SEQ ID 726	CTAGGCATCATACGTGACT
SEQ ID 727	TTGCAGATATTGTGGACAC
SEQ ID 728	CAATTGCCTGAATCCTCTT
SEQ ID 729	TTGCCTGAATCCTCTTTTT
SEQ ID 730	AGATATTTTCTCCAGCTTC
SEQ ID 731	GATATTTTCTCCAGCTTCT
SEQ ID 732	AATATATTCCCCCAAAGC
SEQ ID 733	ATATATTCCCCCAAAGCC
SEQ ID 734	TATATTCCCCCAAAGCCA
SEQ ID 735	AAGCCAAATCCCACTCAA
SEQ ID 736	AGCCAAATCCCACTCAAAC
SEQ ID 737	GCCAAATCCCACTCAAACC
SEQ ID 738	ATCCCACTCAAACCTTTCA
SEQ ID 739	TCCCACTCAAACCTTTCAA
SEQ ID 740	CCTTTCAACAAAATGAGC
SEQ ID 741	CAAAAATGAGCACGCTTTC
SEQ ID 742	AAATGAGCACGCTTTCCTA
SEQ ID 743	AATGAGCACGCTTTCCTAC
SEQ ID 744	ATGAGCACGCTTTCCTACC
SEQ ID 745	TGAGCACGCTTTCCTACCG
SEQ ID 746	TGTAAGCTCATCCACCAAG
SEQ ID 747	GCTCATCCACCAAGAAGCC
SEQ ID 748	GAAGCCTGCACCATGTTTT
SEQ ID 749	GCCTGCACCATGTTTTGAG

AGTR2

SEQ ID 750	TATGAAGGGCAACTCCACC
SEQ ID 751	CTCCACCCTTGCCACTACT
SEQ ID 752	AAACATTACCAGCGGTCTT
SEQ ID 753	AACATTACCAGCGGTCTTC
SEQ ID 754	ACATTACCAGCGGTCTTCA
SEQ ID 755	CATTACCAGCGGTCTTCAC
SEQ ID 756	CATCTCTGGCAACAATGAG
SEQ ID 757	CAATGAGTCTACCTTGAAC
SEQ ID 758	TGAGTCTACCTTGAAGTGT
SEQ ID 759	CTGTTACAGAAACCATCA
SEQ ID 760	CCATCAGATAAGCATTTAG

SEQ ID 761	GCATTTAGATGCAATTCCT
SEQ ID 762	TATTGTCGTGGTTACACTG
SEQ ID 763	AAGGGTCCTAAAAAGGTTT
SEQ ID 764	AGGGTCCTAAAAAGGTTTC
SEQ ID 765	GGGTCCTAAAAAGGTTTCT
SEQ ID 766	GGTTTCTAGCATATACATC
SEQ ID 767	CCTCGCTGTGGCTGATTTA
SEQ ID 768	TCTGTCATCTACCCCTTTC
SEQ ID 769	AGAAGAAATCCCTGGCAAG
SEQ ID 770	GAAGAAATCCCTGGCAAGC
SEQ ID 771	GAAATCCCTGGCAAGCATC
SEQ ID 772	ATCCCTGGCAAGCATCTTA
SEQ ID 773	TCCCTGGCAAGCATCTTAT
SEQ ID 774	GCATCTTATATAGTTCCCC
SEQ ID 775	CCATTGAATACTTAGGAGT
SEQ ID 776	TACTTAGGAGTGAATGCTT
SEQ ID 777	TGCTTGCATTATGGCTTTC
SEQ ID 778	ATATGCCCAATGGTCAGCT
SEQ ID 779	TATGCCCAATGGTCAGCTG
SEQ ID 780	TGGTCAGCTGGGATTGCCT
SEQ ID 781	AACACTTACTGAAGACGAA
SEQ ID 782	ACACTTACTGAAGACGAAT
SEQ ID 783	CACTTACTGAAGACGAATA
SEQ ID 784	GACGAATAGCTATGGGAAG
SEQ ID 785	TAGCTATGGGAAGAACAGG
SEQ ID 786	GAACAGGATAACCCGTGAC
SEQ ID 787	CAGGATAACCCGTGACCAA
SEQ ID 788	CCCGTGACCAAGTCCTGAA
SEQ ID 789	GTCCTGAAGATGGCAGCTG
SEQ ID 790	GATGGCAGCTGCTGTTGTT
SEQ ID 791	TAGCTGCGAAGTTATAGCA
SEQ ID 792	GTTATAGCAGTCATTGACC
SEQ ID 793	CAGCTGCGTTAATCCGTTT
SEQ ID 794	ACCGGTTCCAACAGAAGCT
SEQ ID 795	CCGGTTCACAGAAGCTC
SEQ ID 796	CAGAAGCTCCGCAGTGTGT
SEQ ID 797	GCTCCGCAGTGTGTTTAGG
SEQ ID 798	TTACTTGGCTCCAAGGGAA
SEQ ID 799	GGGAAAAGAGAGAGTATGT
SEQ ID 800	AAGAGAGAGTATGTCTTGC
SEQ ID 801	AGAGAGAGTATGTCTTGCC
SEQ ID 802	GAGAGAGTATGTCTTGCCG
SEQ ID 803	AAGCAGTTCTCTTAGAGAA
SEQ ID 804	AGCAGTTCTCTTAGAGAAA
SEQ ID 805	GCAGTTCTCTTAGAGAAAT
SEQ ID 806	ATGGAGACCTTTGTGTCTT
SEQ ID 807	TGGAGACCTTTGTGTCTTA

ACE1

SEQ ID 808	CTTTTCTGCTGACGAGGCC
SEQ ID 809	CAGGTGCTGTTCCAGAGCG
SEQ ID 810	CATCACCGCGGAGAATGCA
SEQ ID 811	TGCAAGGCGCCAGGAGGAA

SEQ ID 812	GGCCAAGGAGCTGTATGAA
SEQ ID 813	GGAGCTGTATGAACCGATC
SEQ ID 814	CCGATCTGGCAGAACTTCA
SEQ ID 815	CGCCCTGCTAAGCAACATG
SEQ ID 816	GCAACATGAGCAGGATCTA
SEQ ID 817	CATGAGCAGGATCTACTCC
SEQ ID 818	GGTCTGCCTCCCCAACAAG
SEQ ID 819	CAAGACTGCCACCTGCTGG
SEQ ID 820	CATCCTGGCTTCCTCGCGA
SEQ ID 821	GCTACGCCATGCTCCTGTT
SEQ ID 822	ACCGCTGTACGAGGATTTC
SEQ ID 823	CCGCTGTACGAGGATTTC
SEQ ID 824	TGAAGCCTACAAGCAGGAC
SEQ ID 825	GCCTACAAGCAGGACGGCT
SEQ ID 826	GCAGGACGGCTTCACAGAC
SEQ ID 827	CACCTCTACCAACAGCTAG
SEQ ID 828	CAGCTAGAGCCCCTCTACC
SEQ ID 829	AACATCTACGACATGGTGG
SEQ ID 830	ACATCTACGACATGGTGGT
SEQ ID 831	CATCTACGACATGGTGGTG
SEQ ID 832	GCCCAACCTCGATGTCACC
SEQ ID 833	CCTCGATGTCACCAGTACT
SEQ ID 834	GGGTCGATGCTGGAGAAGC
SEQ ID 835	CAGGAAAGACTTCAGGATC
SEQ ID 836	AGACTTCAGGATCAAGCAG
SEQ ID 837	GACTTCAGGATCAAGCAGT
SEQ ID 838	CATCTGCACAAAATCGGCC
SEQ ID 839	AATCGGCCTGCTGGACCGT
SEQ ID 840	TGACACGGAAAGTGACATC
SEQ ID 841	AGTGACATCAATTACTTGC
SEQ ID 842	GTGACATCAATTACTTGCT
SEQ ID 843	ATGGCACTGGAAAAAATTG
SEQ ID 844	TGGCACTGGAAAAAATTGC
SEQ ID 845	AAAATTGCCTTCCTGCCCT
SEQ ID 846	AAATTGCCTTCCTGCCCTT
SEQ ID 847	AATTGCCTTCCTGCCCTTT
SEQ ID 848	ATTGCCTTCCTGCCCTTTG
SEQ ID 849	TTGCCTTCCTGCCCTTTGG
SEQ ID 850	CTTCGACTGGTGGTATCTT
SEQ ID 851	CCAAGTATCAGGGGATCTG
SEQ ID 852	GTATCAGGGGATCTGTCCT
SEQ ID 853	ACGAAACCCACTTTGATGC
SEQ ID 854	CGAAACCCACTTTGATGCT
SEQ ID 855	ACCCACTTTGATGCTGGAG
SEQ ID 856	CCCACTTTGATGCTGGAGC
SEQ ID 857	GTTTCATGTTCCAAATGTG
SEQ ID 858	ATGTGACACCATACATCAG
SEQ ID 859	TGTGACACCATACATCAGG
SEQ ID 860	GGACATGGTCGGCTTAGAT
SEQ ID 861	GTACTTCCAGCCAGTCACC
SEQ ID 862	CTACCCGGAGGGCATAGAC
SEQ ID 863	GTTTGTGGAGGAATATGAC
SEQ ID 864	TATGACCGGACATCCCAGG

SEQ ID 865	CGAGTATGCCGAGGCCAAC
SEQ ID 866	CTGGAACTACAACACCAAC
SEQ ID 867	CTACAACACCAACATCACC
SEQ ID 868	CACCAACATCACCACAGAG
SEQ ID 869	CATCACCACAGAGACCAGC
SEQ ID 870	GATTCTGCTGCAGAAGAAC
SEQ ID 871	GAACATGCAAATAGCCAAC
SEQ ID 872	CATGCAAATAGCCAACCAC
SEQ ID 873	ATAGCCAACCACACCCTGA
SEQ ID 874	TAGCCAACCACACCCTGAA
SEQ ID 875	CCACACCCTGAAGTACGGC
SEQ ID 876	GTTTGATGTGAACCAGTTG
SEQ ID 877	CCAGTTGCAGAACACCACT
SEQ ID 878	CACCACTATCAAGCGGATC
SEQ ID 879	GCGGATCATAAAGAAGGTT
SEQ ID 880	AGAAGGTTTCAGGACCTAGA
SEQ ID 881	GAAGGTTTCAGGACCTAGAA
SEQ ID 882	GGTTCAGGACCTAGAACGG
SEQ ID 883	CAAGATCCTGTTGGATATG
SEQ ID 884	GATCCTGTTGGATATGGAA
SEQ ID 885	ACCACCTACAGCGTGGCCA
SEQ ID 886	ATATGAAGACCTGTTATGG
SEQ ID 887	TATGAAGACCTGTTATGGG
SEQ ID 888	GACCTGTTATGGGCATGGG
SEQ ID 889	ATACGTGGAACCTCATCAAC
SEQ ID 890	TACGTGGAACCTCATCAACC
SEQ ID 891	CTCATCAACCAGGCTGCCC
SEQ ID 892	TGGCTATGTAGATGCAGGG
SEQ ID 893	CATCTATGACTTGGTGGTG
SEQ ID 894	GGAGGCTGATGATTTCTTC
SEQ ID 895	CAAGTCGATGCTGGAGAAG
SEQ ID 896	GTCGATGCTGGAGAAGCCA
SEQ ID 897	CGGCAAGGACTTCCGGATC
SEQ ID 898	GGACTTCCGGATCAAGCAG
SEQ ID 899	GCAGTGCACCACCGTGAAC
SEQ ID 900	CTTGGAGGACCTGGTGGTG
SEQ ID 901	ATGGGCCACATCCAGTATT
SEQ ID 902	TGGGCCACATCCAGTATTT
SEQ ID 903	AGACTTACCTGTGGCCTTG
SEQ ID 904	GACTTACCTGTGGCCTTGA
SEQ ID 905	GCACCTGCACAGTCTCAAC
SEQ ID 906	CCTGCTGAGCAGTGAGGGT
SEQ ID 907	CTTTCTGATGAAGATGGCC
SEQ ID 908	GATGGCCCTTGACAAGATC
SEQ ID 909	GATCGCCTTTATCCCCTTC
SEQ ID 910	GCATCACCAAGGAGAACTA
SEQ ID 911	GGAGAACTATAACCAGGAG
SEQ ID 912	CTATAACCAGGAGTGGTGG
SEQ ID 913	GGTGACTTTGACCCAGGGG
SEQ ID 914	GTTCCACATTCTTCTAGC
SEQ ID 915	GTGTGACATCTACCAGTCC
SEQ ID 916	GCCATGCAGCTGATCACGG
SEQ ID 917	CGAGCTGCATGGGGAGAAG

SEQ ID 918	CAGGTGACAGTCACCCATG
SEQ ID 919	GCAGCCAGGCAACAACCAG
SEQ ID 920	CAACCAGCAGCCAGACAAC
SEQ ID 921	CCAGCAGCCAGACAACCAC
SEQ ID 922	ACCTGGTGACTGATGAGGC
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SEQ ID 924	CTGGACGCCGAACCTCCGAT
SEQ ID 925	CTCCGATGACTTCTACAAT
SEQ ID 926	TGAGACCGAGACCAAGATC
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SEQ ID 933	GGGAAGCCCCAGTGACAT
SEQ ID 934	GCCCCAGTGACATGTCAA
SEQ ID 935	AGAGGGCTGCAAGCTCTGG
SEQ ID 936	GCCCTAACTTCCTCCAGC
SEQ ID 937	ACTTCCTCCAGCTGCACAA
SEQ ID 938	CTTCCTCCAGCTGCACAAG
SEQ ID 939	GGACATGGAGAGGTCCCAG

ACE2

SEQ ID 940	GCTCTTCCTGGCTCCTTCT
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SEQ ID 942	CAGGCCAAGACATTTTGG
SEQ ID 943	GTTTAACCACGAAGCCGAA
SEQ ID 944	CCACGAAGCCGAAGACCTG
SEQ ID 945	GCCGAAGACCTGTTCTATC
SEQ ID 946	GACCTGTTCTATCAAAGTT
SEQ ID 947	AGTTCACCTTGCTTCTTGGA
SEQ ID 948	GTTCACTTGCTTCTTGGA
SEQ ID 949	CACCAATATTACTGAAGAG
SEQ ID 950	GAGAATGTCCAAAACATGA
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SEQ ID 963	TTCAGAATCTCACAGTCAA
SEQ ID 964	TCTCACAGTCAAGCTTCAG
SEQ ID 965	GCTTCAGCTGCAGGCTCTT
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SEQ ID 1079	CCCTGGACCCTAGCATTGG
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SEQ ID 1082	TGTTGTAGGAGCAAAGAAC
SEQ ID 1083	AGAACATGAATGTAAGGCC
SEQ ID 1084	GAACATGAATGTAAGGCCA
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SEQ ID 1103	GCATATGAATGGAACGACA
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SEQ ID 1105	CGACAATGAAATGTACCTG
SEQ ID 1106	TGAAATGTACCTGTTCCGA
SEQ ID 1107	ATGTACCTGTTCCGATCAT
SEQ ID 1108	TGTACCTGTTCCGATCATC
SEQ ID 1109	TCAGATGATTCTTTTTGGG
SEQ ID 1110	TTTGAAACCAAGAATCTCC
SEQ ID 1111	TTTCTTTGTCACTGCACCT
SEQ ID 1112	ATGTGTCTGATATCATTCC
SEQ ID 1113	TGTGTCTGATATCATTCTT
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SEQ ID 1121	CACTTGGACCTCCTAACCA
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SEQ ID 1124	ATAAAGCAAGAAGTGGAGA
SEQ ID 1125	TAAAGCAAGAAGTGGAGAA
SEQ ID 1126	AGCAAGAAGTGGAGAAAAT
SEQ ID 1127	GCAAGAAGTGGAGAAAATC

SEQ ID 1128	GAAGTGGAGAAAATCCTTA
SEQ ID 1129	GTGGAGAAAATCCTTATGC
SEQ ID 1130	AATCCTTATGCCTCCATCG
SEQ ID 1131	ATCCTTATGCCTCCATCGA
SEQ ID 1132	TCCTTATGCCTCCATCGAT
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SEQ ID 1134	GGAGAAAATAATCCAGGAT
SEQ ID 1135	TAATCCAGGATTCCAAAAC
SEQ ID 1136	TCCAGGATTCCAAAACACT
SEQ ID 1137	AACACTGATGATGTTTCAGA
SEQ ID 1138	ACACTGATGATGTTTCAGAC
SEQ ID 1139	CACTGATGATGTTTCAGACC

REN	
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SEQ ID 1142	CGGATCTTCCTCAAGAGAA
SEQ ID 1143	GAGAATGCCCTCAATCCGA
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SEQ ID 1145	TCCGAGAAAGCCTGAAGGA
SEQ ID 1146	AGCCTGAAGGAACGAGGTG
SEQ ID 1147	GCCTGAAGGAACGAGGTGT
SEQ ID 1148	GGAACGAGGTGTGGACATG
SEQ ID 1149	CGAGGTGTGGACATGGCCA
SEQ ID 1150	CCCATGAAGAGGCTGACAC
SEQ ID 1151	GAGGCTGACACTTGGCAAC
SEQ ID 1152	CACCACCTCCTCCGTGATC
SEQ ID 1153	CTACATGGACACCCAGTAC
SEQ ID 1154	ACCTTCAAAGTCGTCTTTG
SEQ ID 1155	CCTTCAAAGTCGTCTTTGA
SEQ ID 1156	AGTCGTCTTTGACACTGGT
SEQ ID 1157	GTCGTCTTTGACACTGGTT
SEQ ID 1158	TGTTTGGGTGCCCTCCTCC
SEQ ID 1159	GTGCAGCCGTCTCTACACT
SEQ ID 1160	GCTCTTCGATGCTTCGGAT
SEQ ID 1161	GCACAATGGAACAGAACTC
SEQ ID 1162	TGGAACAGAACTCACCTC
SEQ ID 1163	CAGAACTCACCTCCGCTA
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SEQ ID 1173	CAGAGATTCCGAGAATTCC
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SEQ ID 1176	GGGAATTTCCACTATATCA
SEQ ID 1177	TTTCCACTATATCAACCTC
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SEQ ID 1187	GAATACACGCTCACCAGCG
SEQ ID 1188	TCCTACAGTAGTAAAAAGC
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SEQ ID 1190	AAGCTGTGCACACTGGCCA
SEQ ID 1191	AGCTGTGCACACTGGCCAT
SEQ ID 1192	GCTGTGCACACTGGCCATC
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SEQ ID 1194	GTTCTACACAGAGTTTGAT
SEQ ID 1195	CAACCGCATTGGCTTCGCC
SEQ ID 1196	CCGCATTGGCTTCGCCTTG

COCH	
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SEQ ID 1201	TTCTCTGTGTATGGGAACA
SEQ ID 1202	TCAGCAACTCAGGGGGACC
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SEQ ID 1204	AACTATTCCTCAGTAGATG
SEQ ID 1205	ACTATTCCTCAGTAGATGC
SEQ ID 1206	CTATTCCTCAGTAGATGCC
SEQ ID 1207	TGGCATCCAGTCTCAAATG
SEQ ID 1208	ATGCTTTCTAGATGGTCTG
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SEQ ID 1255	AGGGATCCCCAAAGTGGTG
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SEQ ID 1285	GATAGCTGCTGTACAGTTT
SEQ ID 1286	AGAGAATGTCCTAGCTGTC
SEQ ID 1287	GAGAATGTCCTAGCTGTCA
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SEQ ID 1303	GGAGTCTCATGCTTTCTTC
SEQ ID 1304	GAGAGTTCACAGGATTAGA
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ATP1A1

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SEQ ID 1329	CTTAGCCTTGATGAACCTC
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SEQ ID 1336	TGTTACTGTGGATTGGAGC
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SEQ ID 1338	GAGGAACCTCAAAACGATA
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SEQ ID 1343	TCTGTACCTGGGTGTGGTG
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SEQ ID 1348	GATCATGGAATCCTTCAA
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SEQ ID 1352	ACATGGTCCCTCAGCAAGC
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SEQ ID 1355	ATGGTGAGAAAATGAGCAT
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SEQ ID 1373	TCAGAACCCAGACTAGGT
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SEQ ID 1382	GGCACCGCACGTGGTATTG
SEQ ID 1383	GAATTGCCACACTTGCTTC
SEQ ID 1384	TTGCCACACTTGCTTCTGG
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SEQ ID 1389	GGAAAACTGCTTAGTGAA
SEQ ID 1390	AACTGCTTAGTGAAGAAC
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SEQ ID 1394	GAACTTAGAAGCTGTGGAG
SEQ ID 1395	CTTAGAAGCTGTGGAGACC
SEQ ID 1396	GCTGTGGAGACCTTGGGGT
SEQ ID 1397	AACTGGAACCTCTGACTCAG
SEQ ID 1398	ACTGGAACCTCTGACTCAGA
SEQ ID 1399	CTGGAACCTCTGACTCAGAA
SEQ ID 1400	CTCTGACTCAGAACCGGAT
SEQ ID 1401	TCAAATCCATGAAGCTGAT
SEQ ID 1402	ATCCATGAAGCTGATACGA
SEQ ID 1403	TCCATGAAGCTGATACGAC
SEQ ID 1404	GCTGATACGACAGAGAATC
SEQ ID 1405	TCAGAGTGGTGTCTCTTTT
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SEQ ID 1410	AACCTACCTATTCTTAAGC
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SEQ ID 1413	GCGGGCAGTTGCAGGAGAT
SEQ ID 1414	AGTGCATAGAGCTGTGCTG
SEQ ID 1415	GTGCATAGAGCTGTGCTGT
SEQ ID 1416	GGAGATGAGAGAAAGATAC
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SEQ ID 1419	AATCGTCGAGATACCCTTC
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SEQ ID 1436	TTTCCCTATCGATAATCTG
SEQ ID 1437	TCTGTGCTTTGTTGGGCTC
SEQ ID 1438	ATGTCGAAGTGCTGGAATT
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SEQ ID 1442	GGTCATCATGGTCACAGGA
SEQ ID 1443	TCACAGCTAAAGCTATTGC
SEQ ID 1444	AGCTATTGCCAAAGGTGTG
SEQ ID 1445	GCTATTGCCAAAGGTGTGG
SEQ ID 1446	AGGTGTGGGCATCATCTCA
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SEQ ID 1448	GGCAATGAGACCGTGGAAG
SEQ ID 1449	TGAGACCGTGGAAGACATT
SEQ ID 1450	GACATTGCTGCCCGCCTCA
SEQ ID 1451	CATCCCAGTCAGCCAGGTG
SEQ ID 1452	AGGACATGACCTCCGAGCA
SEQ ID 1453	GGACATGACCTCCGAGCAG
SEQ ID 1454	GTACCACACTGAGATAGTG
SEQ ID 1455	GCTCATCATTGTGGAAGGC
SEQ ID 1456	GGCTGCCAAAGACAGGGTG
SEQ ID 1457	AGACAGGGTGCTATCGTGG
SEQ ID 1458	GACAGGGTGCTATCGTGGC
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SEQ ID 1460	GAAAGCAGACATTGGGGTT
SEQ ID 1461	AGCAGACATTGGGGTTGCT
SEQ ID 1462	GCAGACATTGGGGTTGCTA
SEQ ID 1463	GCAAGCTGCTGACATGATT
SEQ ID 1464	GCTGCTGACATGATTCTTC
SEQ ID 1465	CTTTGCCTCAATTGTGACT
SEQ ID 1466	TTGTGACTGGAGTAGAGGA
SEQ ID 1467	GGTCGTCTGATCTTTGATA
SEQ ID 1468	CTTGAAGAAATCCATTGCT
SEQ ID 1469	GAAATCCATTGCTTATACC
SEQ ID 1470	CCAGTAACATTCCCGAGAT
SEQ ID 1471	CATTCCCGAGATCACCCCG
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SEQ ID 1483	TTACCTGTTGGGCCTCCG
SEQ ID 1484	CGATGTGGAAGACAGCTAC
SEQ ID 1485	GACAGCTACGGGCAGCAGT
SEQ ID 1486	AATCGTGGAGTTCACCTGC
SEQ ID 1487	ATCGTGGAGTTCACCTGCC
SEQ ID 1488	TCGTGGAGTTCACCTGCCA
SEQ ID 1489	GACCAGGAGGAATTCGGTC
SEQ ID 1490	TTCGGTCTTCCAGCAGGGG
SEQ ID 1491	CAAGATCTTGATATTTGGC
SEQ ID 1492	GATCTTGATATTTGGCCTC

SEQ ID 1493	GAGACAGCCCTGGCTGCTT
SEQ ID 1494	TGGGTGTTGCTCTTAGGAT
SEQ ID 1495	ACCTACCTGGTGGTTCTGT
SEQ ID 1496	CCTACCTGGTGGTTCTGTG
SEQ ID 1497	GTCAGAAACTCATCATCA
SEQ ID 1498	AACTCATCATCAGGCGACG
SEQ ID 1499	ACTCATCATCAGGCGACGC
SEQ ID 1500	CTCATCATCAGGCGACGCC

ATP1A2

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SEQ ID 1502	GAAGAAACAGAAGGAGAAG
SEQ ID 1503	GAAACAGAAGGAGAAGGAA
SEQ ID 1504	ACAGAAGGAGAAGGAACTG
SEQ ID 1505	CAGAAGGAGAAGGAACTGG
SEQ ID 1506	GGAGAAGGAACTGGATGAG
SEQ ID 1507	GGAAGTGGATGAGCTGAAG
SEQ ID 1508	CTGGATGAGCTGAAGAAGG
SEQ ID 1509	GAAGGAGGTGGCAATGGAT
SEQ ID 1510	GGAGGTGGCAATGGATGAC
SEQ ID 1511	TGGATGACCACAAGCTGTC
SEQ ID 1512	GCTGTCCTTGGATGAGCTG
SEQ ID 1513	ATACCAAGTGGACCTGTCC
SEQ ID 1514	TACCAAGTGGACCTGTCCA
SEQ ID 1515	CCCCTGAGTGGGTCAAGTT
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SEQ ID 1523	CATGGTACCTCAGCAAGCC
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SEQ ID 1532	GCGCATGGCACGGAAGAAC
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SEQ ID 1534	CTGCCTGGTGAAGAACCTG
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SEQ ID 1536	ATCCATGAGGCTGACACCA
SEQ ID 1537	TCCATGAGGCTGACACCAC
SEQ ID 1538	GATCAGTCTGGGGCCACTT
SEQ ID 1539	ACGATCCCCTACGTGGACG
SEQ ID 1540	TTGCTGGTCTCTGCAACCG
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SEQ ID 1552	CAAGTACCAGCTGTCTATC
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SEQ ID 1554	GGAGATCCCGCTCGACAAG
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SEQ ID 1556	GATGCCTTTCAAATGCCT
SEQ ID 1557	AATGCCTACATGGAGCTGG
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SEQ ID 1598	TGATCTGGAGGACAGCTAT
SEQ ID 1599	GGTGGTGGAGTTCACGTGC
SEQ ID 1600	CTCAGTCTTCCAGCAGGGC
SEQ ID 1601	CAAGATCCTGATTTTTGGG
SEQ ID 1602	GATCCTGATTTTTGGGCTC
SEQ ID 1603	AGTCACCTGGTGGTTCTGC
SEQ ID 1604	GTCACCTGGTGGTTCTGCG
SEQ ID 1605	AGCTCATCCTGCGGCGGTA
SEQ ID 1606	GCTCATCCTGCGGCGGTAT

ATP1A3

SEQ ID 1607	GATGGGGGACAAGAAAGAT
SEQ ID 1608	GAAAGATGACAAGGACTCA
SEQ ID 1609	AGATGACAAGGACTCACCC
SEQ ID 1610	GATGACAAGGACTCACCCA
SEQ ID 1611	GGACTCACCCAAGAAGAAC
SEQ ID 1612	GAAGAACAAGGGCAAGGAG
SEQ ID 1613	GAACAAGGGCAAGGAGCGC
SEQ ID 1614	GAAGGAGGTGGCTATGACA
SEQ ID 1615	GGAGGTGGCTATGACAGAG
SEQ ID 1616	GATGTCAGTGGAAGAGGTC
SEQ ID 1617	GAGGTCTGCCGGAAATACA
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SEQ ID 1636	GAACCTGGAGGCTGTAGAA
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SEQ ID 1638	GACAGGGACCCTCACTCAG
SEQ ID 1639	CCAGATCCACGAGGCTGAC
SEQ ID 1640	GAGTTCGCACACCTGGGTG
SEQ ID 1641	TCGCGCTGTCTTCAAGGGT
SEQ ID 1642	GGGTGGTCAGGACAACATC
SEQ ID 1643	CATCCCTGTGCTCAAGAGG
SEQ ID 1644	GAGGGATGTGGCTGGGGAT
SEQ ID 1645	GTGCATCGAGCTGTCCTCT
SEQ ID 1646	GCTGATGCGTGAACGCAAC
SEQ ID 1647	CGCAACAAGAAAGTGGCTG

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SEQ ID 1649	GAAAGTGGCTGAGATTCCC
SEQ ID 1650	AGTGGCTGAGATTCCCTTC
SEQ ID 1651	GTGGCTGAGATTCCCTTCA
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SEQ ID 1653	CAAATACCAGCTCTCCATC
SEQ ID 1654	ATACCAGCTCTCCATCCAT
SEQ ID 1655	TACCAGCTCTCCATCCATG
SEQ ID 1656	CGACAACCGATACCTGCTG
SEQ ID 1657	CCGATACCTGCTGGTGATG
SEQ ID 1658	ATGAAGGAGGCCTTCCAGA
SEQ ID 1659	TGAAGGAGGCCTTCCAGAA
SEQ ID 1660	GGAGGCCTTCCAGAATGCC
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SEQ ID 1662	GGGCTTTGCCTTCGACTGT
SEQ ID 1663	CTTCACCACGGACAACCTC
SEQ ID 1664	CCTCTGCTTTGTGGGCCTC
SEQ ID 1665	GGTCATCATGGTCACCGGC
SEQ ID 1666	GGCCATTGCCAAGGGTGTG
SEQ ID 1667	GGGTGTGGGCATCATCTCT
SEQ ID 1668	CGAGACTGTGGAGGACATC
SEQ ID 1669	CATTCCCGTCAGCCAGGTT
SEQ ID 1670	GGACTTCACCTCCGAGCAA
SEQ ID 1671	ATCGACGAGATCCTGCAGA
SEQ ID 1672	TCGACGAGATCCTGCAGAA
SEQ ID 1673	TCACACCGAGATCGTCTTC
SEQ ID 1674	GCTCATCATTGTGGAGGGC
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SEQ ID 1678	CTTTGCCTCCATCGTCACA
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SEQ ID 1681	GAAGTCCATTGCCTACACC
SEQ ID 1682	GTCCATTGCCTACACCCTG
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SEQ ID 1685	GCGACATCATGAAGAGACA
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SEQ ID 1696	GGTGGTGGAGTTCACCTGC
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SEQ ID 1698	CAAGATCCTGATCTTCGGG
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SEQ ID 1701	ATCCGCAAACCTCATCCTGC
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SEQ ID 1703	ACTCATCCTGCGCAGGAAC
SEQ ID 1704	CTCATCCTGCGCAGGAACC
SEQ ID 1705	GGAAACCTACTACTGACCT

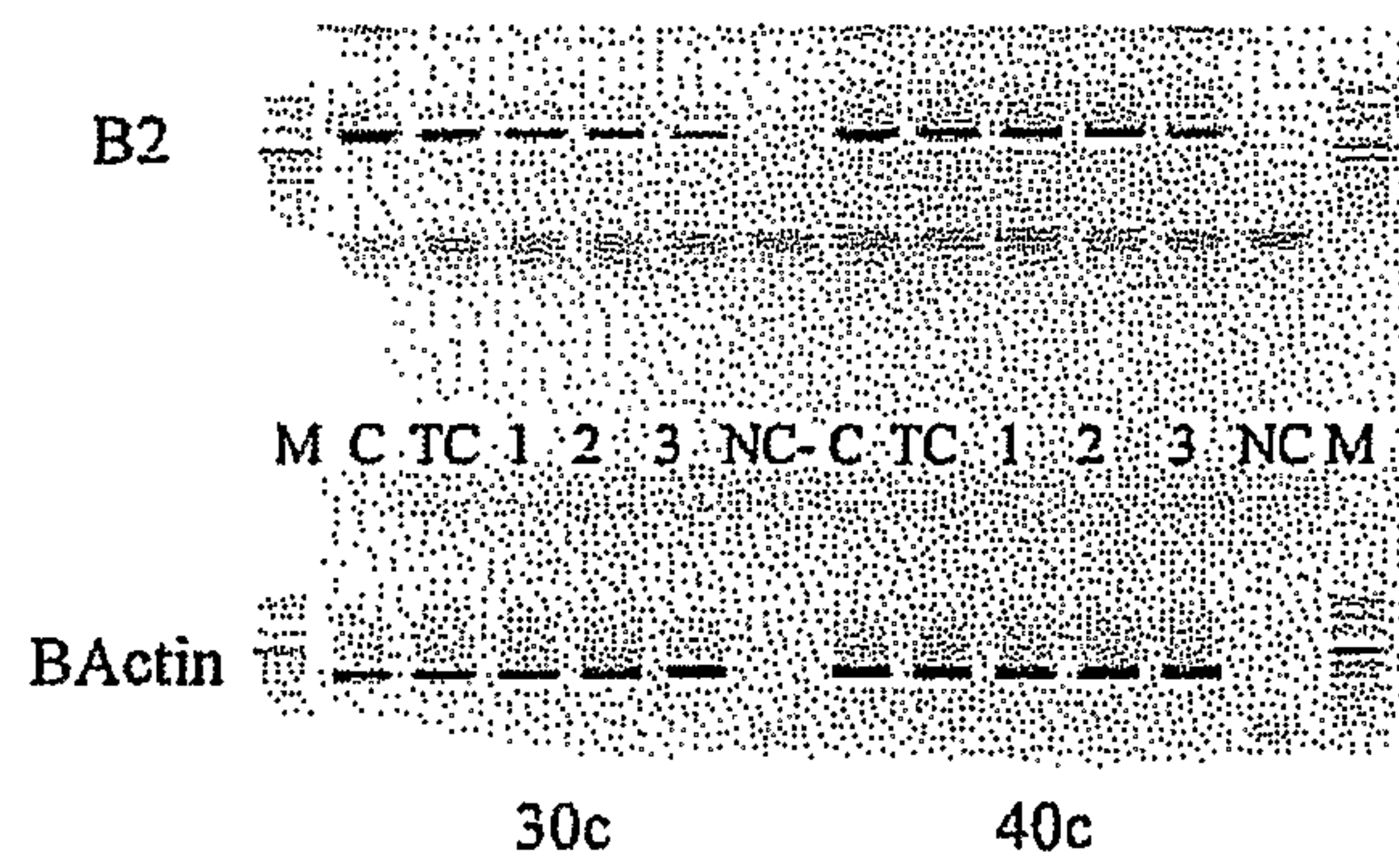
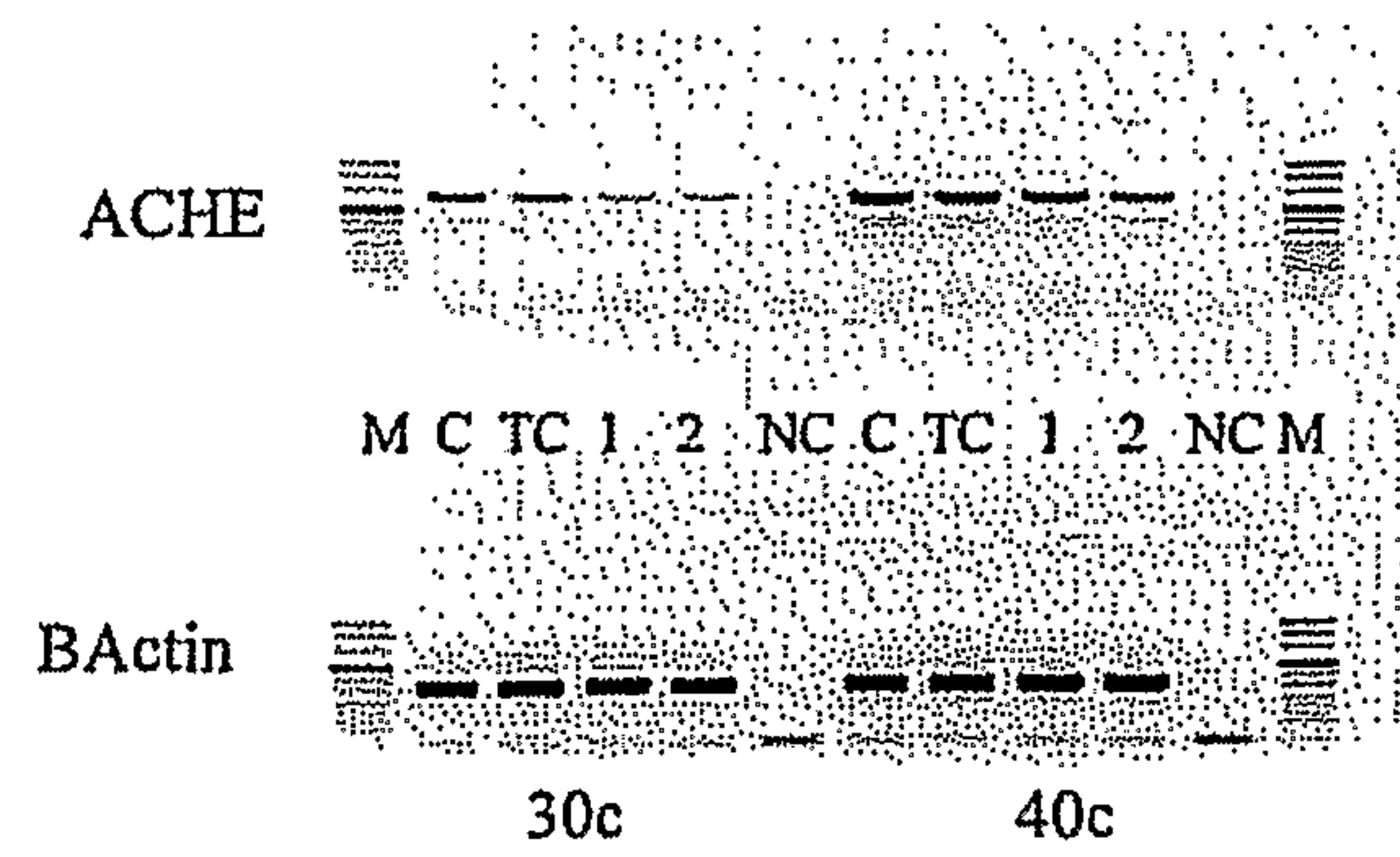
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SEQ ID 1710	GAAATTCATCTGGAACCTCA
SEQ ID 1711	ATTCATCTGGAACCTCAGAG
SEQ ID 1712	TTCATCTGGAACCTCAGAGA
SEQ ID 1713	CTCAGAGAAGAAGGAGTTT
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SEQ ID 1729	AAGTACAAAGATTCAGCCC
SEQ ID 1730	AGTACAAAGATTCAGCCCA
SEQ ID 1731	GTACAAAGATTCAGCCCAG
SEQ ID 1732	AGATTCAGCCCAGAGGGAT
SEQ ID 1733	GATTCAGCCCAGAGGGATG
SEQ ID 1734	GATTGTGGCGATGTGCCCA
SEQ ID 1735	CCGAAAGAACGAGGAGACT
SEQ ID 1736	AGAACGAGGAGACTTTAAT
SEQ ID 1737	GAACGAGGAGACTTTAATC
SEQ ID 1738	CGAGGAGACTTTAATCATG
SEQ ID 1739	TCATGAACGAGGAGAGCGA
SEQ ID 1740	CGAGGAGAGCGAAAGGTCT
SEQ ID 1741	AGGTCTGCAGATTCAAGCT
SEQ ID 1742	GGTCTGCAGATTCAAGCTT
SEQ ID 1743	GCTTGAATGGCTGGGAAAT
SEQ ID 1744	TGGCTGGGAAATTGCTCTG
SEQ ID 1745	TGATGAAACTTATGGCTAC
SEQ ID 1746	ACTTATGGCTACAAAGAGG
SEQ ID 1747	CTTATGGCTACAAAGAGGG
SEQ ID 1748	AGAGGGCAAACCGTGCATT
SEQ ID 1749	GAGGGCAAACCGTGCATTA
SEQ ID 1750	CCGTGCATTATTATAAAGC
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SEQ ID 1752	GCTCAACCGAGTTCTAGGC
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SEQ ID 1754	ACCTAAGCCTCCCAAGAAT
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SEQ ID 1756	GCCTCCCAAGAATGAGTCC
SEQ ID 1757	GAATGAGTCCTTGGAGACT
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SEQ ID 1768	TGTGGAGTATTTTGGACTG
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SEQ ID 1771	CTCCTGCAGCCCAAATACC
SEQ ID 1772	ATACCTGCAGCCCCTGCTG
SEQ ID 1773	TCTTACCATGGACACTGAA
SEQ ID 1774	ATTCGCATAGAGTGTAAGG
SEQ ID 1775	TTCGCATAGAGTGTAAGGC
SEQ ID 1776	GGCGTACGGTGAGAACATT
SEQ ID 1777	CATTGGGTACAGTGAGAAA
SEQ ID 1778	AGACCGTTTTTCAGGGACGT
SEQ ID 1779	GACCGTTTTTCAGGGACGTT
SEQ ID 1780	TTGAAGTTAAGAGCTGATC

SEQ ID 1803	CGTGCCTGCCAATTCAACC
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SEQ ID 1805	GATGAACCGGGTCATCAAC
SEQ ID 1806	CCGGGTCATCAACTTCTAT
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SEQ ID 1809	CCAGAGCATGAATGTTACC
SEQ ID 1810	TGTTACCTGTGCTGGGAAG
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SEQ ID 1818	AAGTTCCACGTGAACTACA
SEQ ID 1819	AGTTCCACGTGAACTACAC
SEQ ID 1820	GTTCCACGTGAACTACACA
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SEQ ID 1822	GTTCTGAATGTGACCCCC
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SEQ ID 1826	TGTCGCATCAACGCCGCCA
SEQ ID 1827	CATCGCCACAGACGATGAG
SEQ ID 1828	ACTCCGCATCAACAAAACC
SEQ ID 1829	CTCCGCATCAACAAAACCT

ATP1B2

SEQ ID 1781	GATGGTCATCCAGAAAGAG
SEQ ID 1782	AGAGAAGAAGAGCTGCGGG
SEQ ID 1783	GAGAAGAAGAGCTGCGGGC
SEQ ID 1784	GGAGTTCGTGTGGAACCCG
SEQ ID 1785	CCCGAGGACGCACCAGTTT
SEQ ID 1786	GACTGAGAACCTTGATGTC
SEQ ID 1787	CCTTGATGTCATTGTCAAT
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SEQ ID 1796	AAGAATGATGTCTGCCGCC
SEQ ID 1797	AGAATGATGTCTGCCGCC
SEQ ID 1798	GAATGATGTCTGCCGCCCT
SEQ ID 1799	CAGCCAGATAATGGAGTCC
SEQ ID 1800	TGGAGTCCTCAACTACCCC
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SEQ ID 1802	ACGTGCCTGCCAATTCAAC

Fig. 3**A****B**