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(71) Demandeur/Applicant:
UCL BUSINESS LTD, GB

(72) Inventeurs/Inventors:
COX, JAMES JOHN, GB;
SRIVASTAVA, DEVJIT, GB

(74) Agent: NORTON ROSE FULBRIGHT CANADA LLP/S.E.N.C.R.L., S.R.L.

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(54) Title: GENE THERAPY OF THE FAAH PSEUDOGENE

(57) Abrégé/Abstract:
The present invention relates to analgesic treatments to reduce pain through use of an inhibitor of fatty-acid amide hydrolase pseudogene (FAAH-OUT).

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(71) Applicant: **UCL BUSINESS PLC** [GB/GB]; The Network Building, 97 Tottenham Court Road, London W1T 4TP (GB).

(72) Inventor: **COX, James John**; UCL Business PLC, The Network Building, 97 Tottenham Court Road, London, Greater London W1T 4TP (GB).

(74) Agent: **BENTHAM, Andrew**; J A Kemp, 14 South Square, Gray's Inn, London, Greater London WC1R 5JJ (GB).

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(54) Title: GENE THERAPY OF THE FAAH PSEUDOGENE

(57) Abstract: The present invention relates to analgesic treatments to reduce pain through use of an inhibitor of fatty-acid amide hydrolase pseudogene *(FAAH-OUT)*.

GENE THERAPY OF THE FAAH PSEUDOGENE

Field of the Invention

The present invention relates to analgesic treatments to reduce pain.

Background to the Invention

Fatty-acid amide hydrolase (FAAH) is the major catabolic enzyme for a range of bioactive lipids, including the *N*-acyl ethanolamines (such as anandamide (AEA), palmitoylethanolamide (PEA) and oleoylethanolamine (OEA)) and *N*-acyltaurines.[1,2] Anandamide, an endogenous ligand for cannabinoid receptors (i.e. an endocannabinoid), has been shown to have roles in nociception, fear extinction memory, anxiety and depression.[3,4] *Faah* knockout mice have significantly elevated brain tissue levels of anandamide and display an analgesic phenotype in response to acute thermal stimuli and show reduced pain in formalin and carrageenan inflammatory models.[5,6]

The human *FAAH* gene contains a commonly carried hypomorphic SNP (C385A; rs324420) that significantly reduces the activity of the FAAH enzyme.[7] Genetic association studies have investigated the link between this, and other *FAAH* SNPs, and pain sensitivity.[8-10] Notably, homozygous carriers of the hypomorphic SNP in a cohort of women undergoing breast cancer surgery were shown to have significantly lower cold pain sensitivity and less need for postoperative analgesia.[8] Furthermore, a mouse knockin model of the human SNP showed that both the mouse and human SNP carriers display enhanced fear-extinction learning and decreased anxiety-linked behaviours.[11]

Although FAAH is therefore an attractive drug target for treating pain, as well as anxiety and depression, recent clinical trials with FAAH inhibitors have however proven unsuccessful.[12,13] The present invention describes routes to inhibiting FAAH function using gene therapy which are expected to have none of the side effect problems of small molecule FAAH antagonists.

Summary of the Invention

The inventors have discovered a link between a microdeletion in a fatty-acid amide hydrolase pseudogene (*FAAH-OUT*) and an individual's ability to feel pain. In particular, through studying an individual (PFS) with a hypoalgesic phenotype, the inventors

identified a microdeletion in *FAAH-OUT* in the individual that is absent from individuals with a normal pain phenotype. The microdeletion disrupts normal expression of the full-length *FAAH-OUT* transcript (e.g. results in lower or higher *FAAH-OUT* expression) with a consequent diminished FAAH function, and increased levels of endogenous analgesic molecules such as anandamide. It is also possible to directly disrupt the *FAAH* gene using gene therapy.

The invention provides a method of analgesic treatment to reduce pain, comprising administering an effective amount of an inhibitor of fatty-acid amide hydrolase pseudogene (*FAAH-OUT*) to an individual suffering from pain.

The invention also provides an inhibitor of *FAAH-OUT* for use in a method of treating pain, the method comprising administering an effective amount of said inhibitor to a subject.

The invention further provides a method of analgesic treatment to reduce pain, comprising administering an effective amount of an inhibitor of fatty-acid amide hydrolase gene (*FAAH*) to an individual suffering from pain, wherein the inhibitor is a single-stranded or double-stranded DNA or RNA molecule directed against *FAAH*.

The invention also provides an inhibitor of *FAAH* for use in a method of treating pain, the method comprising administering an effective amount of said inhibitor to a subject.

Brief Description of the Figures

Figure 1: (A) Genomic map showing *FAAH*, *FAAH-OUT* and microdeletion in PFS. Human chromosome 1 showing the gene footprints of *FAAH* and *FAAH-OUT*. Exons are denoted by black boxes and direction of transcription shown by arrows. *FAAH* SNP rs324420 maps to exon 3 (shown by asterisk). The 8,131bp microdeletion detected in PFS is shown and is flanked by Alu repeat sequences (grey boxes). The promoter region and exons 1 and 2 of *FAAH-OUT* map to the deleted sequence. (B) Real-time RT-qPCR showing expression profile of *FAAH-OUT* in human tissues. *FAAH-OUT* is expressed in a wide range of human tissues, notably in dorsal root ganglia (DRG) and several brain regions. Expression is shown relative to beta actin.

Figure 2: *FAAH* and *FAAH-OUT* RNA localise differently in human DRG sections. *FAAH* and *FAAH-OUT* RNA expression as detected by fluorescent *in situ* hybridization of RNA (RNAscope® Technology). 5 µm thick FFPE fixed human DRG sections were analysed with probes against *FAAH* and *FAAH-OUT*. DAPI staining was used as a control for cell nuclei. Examples of *FAAH-OUT* (single-tail arrows) and *FAAH* expression (double-tail arrows) are shown. (A) Overall image of human DRG node shows that *FAAH* RNA is readily detected in cytoplasm of neurons whereas *FAAH-OUT* RNA is localised to nuclei. (B) and (C) show areas B and C respectively, which are outlined in the main view (A) to provide a closer view on *FAAH* and *FAAH-OUT* expressing neurons.

Figure 3: Circulating AEA, PEA and OEA levels are significantly increased in PFS. Levels of AEA, PEA, OEA and 2-AG were measured by mass spectrometry from blood samples taken from PFS and 4 unrelated normal controls. AEA, PEA and OEA are substrates for FAAH; 2-AG is not. Controls A and B are homozygous WT for the hypomorphic SNP, controls C and D are heterozygous carriers. Average values for the 4 controls are AEA (1.15 pmol/ml), PEA (43.4 pmol/ml), OEA (5.06 pmol/ml) and 2-AG (42.2 pmol/ml), which is consistent with previous data using a similar measurement protocol.[14] Average values for PFS (2 readings) were AEA (1.99 pmol/ml), PEA (113.07 pmol/ml), OEA (17.26 pmol/ml) and 2-AG (45 pmol/ml).

Figure 4: Quantitative sensory testing in patient PFS. Quantitative Sensory Testing (QST) was performed according to the protocol of the German Research Network on Neuropathic Pain. QST is a measurement of sensory perception to a given stimulus. This test can show abnormalities in sensory function but does not localize abnormalities to specific structures of the nervous system. Comparisons of evaluated sites are done against a Caucasian control population for each one of the evaluated sites. Gain of sensory function is presented as a z score >2, and loss of sensory function as <2. *Control Site*: hand, *Test site*: foot. The test revealed pathological hyposensitivity in the warm detection thresholds and thermal sensory limen for both hand and foot and some hyposensitivity in the foot for thermal pain thresholds. Mechanical detection thresholds were abnormal in the foot. There was no evidence of paradoxical heat sensations and/or dynamic mechanical

allodynia. CDT, cold detection thresholds; WDT, warm detection thresholds; TSL, thermal sensory limen; CPT, cold pain thresholds; HPT, heat pain thresholds; PPT, pressure pain thresholds; MPT, mechanical pain thresholds; MPS, mechanical pain sensitivity; WUR, wind up ratio; MDT, mechanical detection thresholds; VDT, vibration detection thresholds; DMA, dynamic mechanical allodynia; PHS, paradoxical heat sensations.

Figure 5: Identification of microdeletion using the Cytoscan HD array. Chromosome Analysis Suite (Affymetrix) screenshot showing the heterozygous ~ 8kb microdeletion identified on chromosome 1 in PFS. Eight consecutive probes (denoted by spots along the -1 dotted line) show a -1 allele copy number and span chromosome 1p33:46,882,936-46,890,857 (build hg19). At the time of analysis, this microdeletion (filled rectangle) was not annotated in the Database of Genomic Variants (see empty track in Database of genomic variants (DGV) in figure. A similar deletion has subsequently been reported in 1 out of 5008 alleles in phase 3 of the 1000 Genomes Project (this individual, HG10353, is homozygous WT for *FAAH* SNP rs324420). The microdeletion is located ~4.7kb downstream of the *FAAH* 3'UTR. Non-annotated exons are shown next to the *FAAH* gene at the bottom of the figure. We subsequently extended this novel gene footprint into the microdeletion region using 5'RACE.

Figure 6: Validating microdeletion in PFS. (A) PCR primers located outside of the microdeleted region amplified a 2,259 bp region from PFS and her son (i.e. the allele containing the microdeletion), as indicated by the white arrow. The wild-type allele product from the same reaction is 10,390bp (beyond the capability of the DNA polymerase). A 1kb ladder is in lane 1. (B) Sanger sequencing of the mutant allele identified the microdeletion breakpoint (the 8,131bp deleted sequence on the wild-type allele is normally located at the asterisk between the highlighted bases). (C) AluSp sequences (human genome build 38/human; chr1:46418719-46419015 and chr1:46426839-46427143) flank the microdeleted region. Alignment of these sequences shows 89% identity over 298bp, likely predisposing the region to a genomic rearrangement.

Figure 7: Comparison of *FAAH* and *FAAH-OUT* cDNA sequences. (A) Alignment between *FAAH* and *FAAH-OUT* exonic sequences identify an 800 bp region with ~70% nucleotide identity. The high sequence homology means that the genes potentially share microRNA seed sites, with 2 examples shown in bold and underlined text (miR-125a-5p/125b-5p/351/670/4319; CAGGGG and miR-128/128ab; CTGTGC), as predicted by miRcode. (B) Most likely peptide generated from *FAAH-OUT* cDNA, as predicted by ATG^{pr}. (C) The putative FAAH-OUT protein shares 69% homology (50% identity) over a 139 amino acid segment of the FAAH enzyme.

Figure 8: Real-time RT-qPCR in patient PFS fibroblast cell line and 4 unrelated female fibroblast controls. (A) Relative *FAAH* expression to *β-actin*. *FAAH* expression was significantly reduced in PFS fibroblasts compared to four control cell lines. Data were normalized with the mean *FAAH* level of control fibroblast cells taken as 100% (n=4, control fibroblast cells). (B) Relative *BDNF* expression to *β-actin*. *BDNF* expression was significantly increased in PFS fibroblasts compared to four control cell lines. The average expression level of *BDNF* in four control fibroblast lines was normalized with the *BDNF* expression level in the PFS fibroblast sample taken as 100% (n=4, control fibroblast cells). *P* values were generated by t-test, $^{**}p<0.01$, $^{***}p<0.001$. Error bars= SEM

Figure 9: Gene editing in HEK293 cells. (A) Microdeletion in *FAAH-OUT* induced by transiently transfecting SaCas9 plasmids (HMa and HMb) each bearing 2 guide sequences that flank the microdeletion identified in patient PFS. Genomic DNA was used as template to PCR-amplify edited DNA from HMa transfected cells (~463 bp) and from HMb transfected cells (~598 bp). No corresponding edited fragment was amplified from cells transfected with a vector containing no guide sequences. (B) RT-qPCR analysis of *FAAH* mRNA levels following transient transfection with HMa or HMb. The microdeletion in *FAAH-OUT* results in a significant reduction in *FAAH* expression. *P* values were generated by t-test, $^{**}p<0.01$, $^{***}p<0.001$. Error bars= SEM

Figure 10: CRISPRi in HEK293 cells. dSaCas9-KRAB directed to the promoter of *FAAH-OUT* by guide 'FOP1' results in a significant reduction in *FAAH* expression. *P* values were generated by t-test, $^{**}p<0.01$. Error bars= SEM

Brief Description of the Sequences

SEQ ID NO: 1 is the cDNA sequence of wild-type human *FAAH* that does not contain the hypomorphic rs324420 SNP.

SEQ ID NO: 2 is the cDNA sequence of human *FAAH* that contains the hypomorphic SNP rs324420 (C385A).

SEQ ID NO: 3 is the cDNA sequence of wild-type human *FAAH-OUT.*

SEQ ID NO: 4 *is* cDNA sequence of human *FAAH-OUT* comprising the microdeletion.

SEQ ID NO: 5 is the genomic DNA sequence of wild-type human *FAAH-OUT.*

SEQ ID NO: 6 is the genomic DNA sequence of *FAAH-OUT* comprising the microdeletion.

SEQ ID NO: 7 is the genomic DNA sequence corresponding to the microdeletion.

SEQ ID NOs: 8 to 23 are primer sequences.

SEQ ID NOs: 24 to 28 are guide sequences.

SEQ ID NOs: 29 to 38 correspond to the sequences from Figures 6 and 7.

SEQ ID NO: 39 is the genomic DNA sequence of wild-type human *FAAH*, including 5kb either side of *FAAH.*

SEQ ID NO: 40 is the amino acid sequence of wild-type human FAAH that does not contain the hypomorphic rs324420 SNP.

SEQ ID NO: 41 is the amino acid sequence of human FAAH that contains the hypomorphic SNP rs324420.

Detailed Description of the Invention

It is to be understood that different applications of the disclosed products and methods may be tailored to the specific needs in the art. It is also to be understood that the terminology used herein is for the purpose of describing particular embodiments of the invention only, and is not intended to be limiting. All publications, patents and patent applications cited herein, whether supra or infra, are hereby incorporated by reference in their entirety.

As used in this specification and the appended claims, the singular forms "a", "an", and "the" include plural referents unless the content clearly dictates otherwise. Thus, for example, reference to "a peptide" includes "peptides", and the like.

Fatty-acid amide hydrolase pseudogene (FAAH-OUT)

Fatty-acid amide hydrolase pseudogene (*FAAH-OUT*) may also be referred to herein as *FAAHP1* or *FAAHP*. *FAAH-OUT* is expressed in fetal and adult brain and in dorsal root ganglia tissue. *FAAH-OUT* may also be expressed in other parts of the nervous system, such as in the spinal cord. Wildtype *FAAH-OUT* has a genomic DNA sequence of SEQ ID NO: 5. Sequence alignments show that there is nucleotide identity of about 70% within an 800 bp region between *FAAH* and *FAAH-OUT*. The footprint of *FAAH-OUT* gene in genomic DNA is 26960 bp. *FAAH-OUT* transcript (cDNA) is 2845 nucleotides. The FAAH-OUT protein may be about 166 amino acids in length. *FAAH-OUT* may function as a long non-coding RNA. *FAAH-OUT* may include a microdeletion. Typically, the microdeletion is around 8kb in length. For example, using Sanger sequencing, the microdeletion in genomic DNA may be around 8,131bp in length. The microdeletion is located around 4.7kb downstream of the *FAAH* 3' UTR. The microdeletion removes the promoter and first two exons of *FAAH-OUT*. In some instances, a regulatory element or an enhancer element of *FAAH* is located within the microdeletion. The disruption of *FAAH-OUT* by the microdeletion therefore affects expression of *FAAH*.

In some instances, *FAAH-OUT* may be targeted in the treatments described herein.

Fatty-acid amide hydrolase (FAAH) and a SNP located within FAAH gene

Fatty-acid amide hydrolase (FAAH) is a member of the serine hydrolase family of enzymes and is the major catabolic enzyme for a range of bioactive lipids, including the *N*-acyl ethanolamines (e.g. anandamide (AEA), palmitoylethanolamide (PEA) and oleoylethanolamine (OEA)) and *N*-acyltaurines. *FAAH* knockout mice have significantly elevated brain tissue levels of anandamide and display an analgesic phenotype. The human *FAAH* gene contains a commonly carried hypomorphic SNP (C385A; rs324420) that significantly reduces the activity of the FAAH enzyme.

Methods of Treatment/Medical Uses

Analgesic treatment

The present invention relates to a method of analgesic treatment to reduce pain using gene therapy. The method comprises administering an effective amount of an inhibitor of *FAAH-OUT* expression to an individual suffering from pain. The present invention also relates to an inhibitor of *FAAH-OUT* for use in a method of treating pain, the method comprising administering an effective amount of said inhibitor to a subject. The present invention also relates to the use of an inhibitor of *FAAH-OUT* expression in the manufacture of a medicament for treating pain. The method also comprises administering an effective amount of an inhibitor of *FAAH* expression to an individual suffering from pain, wherein the inhibitor is a single-stranded or double-stranded DNA or RNA molecule directed against *FAAH*. The present invention also relates to an inhibitor of *FAAH* for use in a method of treating pain, the method comprising administering an effective amount of said inhibitor to a subject, where the inhibitor is a single-stranded or double-stranded DNA or RNA molecule directed against *FAAH*. The present invention also relates to the use of an inhibitor of *FAAH* expression in the manufacture of a medicament for treating pain.

The method may be for treating pain. In the case of treatment, the patient typically feels pain or has undergone a procedure that is known to be painful. As used herein, the term "treatment" includes any of following: the prevention of pain; a reduction or prevention of the development or progression of pain; and the reduction or elimination of existing pain.

Therapy and prevention includes, but is not limited to preventing, alleviating, reducing, curing or at least partially arresting symptoms and/or complications resulting from or associated with pain. When provided therapeutically, the therapy is typically provided at or shortly after the onset of pain. Such therapeutic administration is typically to prevent or ameliorate pain progression or to reduce the severity of pain. When provided prophylactically, the treatment is typically provided before the onset of pain. Such prophylactic administration is typically to prevent or delay the onset of pain.

Many different types of pain can be treated or prevented, as can pain originating from many different sources. The pain may be acute (e.g. post-operative pain) or chronic

(e.g. painful conditions such as rheumatoid arthritis, peripheral neuropathy, idiopathic pain, cancer). The pain may be nociceptive pain, neuropathic pain or inflammatory pain. Nociceptive pain is the normal response to noxious insult or injury of tissues such as skin, muscles, visceral organs, joints, tendons, or bones. For instance, nociceptive pain may be somatic (e.g. musculoskeletal, cutaneous) or visceral. Neuropathic pain is caused by damage or disease affecting the somatosensory nervous system. Neuropathic pain may involve peripheral sensitisation or central sensitisation. It may lead to sensory abnormalities, such as numbness or hypersensitivity (hyperalgesia or allodynia). Examples of neuropathic pain include but are not limited to Carpal tunnel syndrome, central pain syndrome, degenerative disc disease, diabetic neuropathy, phantom limb pain, postherpetic neuralgia (shingles), pudendal neuralgia, sciatica and trigeminal neuralgia. Neuropathic pain may also be caused by Guillain-Barre syndrome, cancer, multiple sclerosis, kidney disorders, alcoholism, HIV, nerve damage from spinal cord injury, post-mastectomy pain (PMPS), postoperative hernia repair pain, phantom limb pain (post-amputation) and other types of post-surgical pain. Inflammatory pain is caused by activation and sensitisation of the nociceptive pathway by mediators released at a site of tissue inflammation, which alters the activity of ion channels within affected sensory fibres. Inflammatory pain is typically caused by osteoarthritis, rheumatoid arthritis, Crohn's disease or fibromyalgia.

Treatment or prevention of pain is understood to be effective if pain is either reduced or eliminated. Reduction or elimination of pain can be measured by any suitable technique known in the art, for example via the techniques known as the McGill pain questionnaire or McGill pain index. The McGill Questionnaire consists primarily of three major classes of world descriptors-sensory, affective and evaluative, which are used by patients to specify pain experience. The three major measures are the pain rating index, the number of words chosen and the present pain intensity based on a 1-5 intensity scale.

General

An individual to be treated by the administration of a substance (i.e. inhibitor) may be a human or non-human animal. The term "non-human animal" includes all vertebrates, e.g., mammals and non-mammals, such as non-human primates, sheep, dogs,

cats, horses, cows, chickens, amphibians, reptiles, etc. Administration to humans is preferred.

Specific routes, dosages and methods of administration of the therapeutic agents described herein may be routinely determined by the medical practitioner. These are discussed in more detail below.

The measurement of the levels of chemicals having roles in nociception can be carried out by analysing blood samples or tissue samples. Such chemicals may include, but are not limited to *N*-acyl ethanolamines (e.g. anandamide (AEA), palmitoylethanolamide (PEA) and oleoylethanolamine (OEA)) and *N*-acyltaurines. As an example, significant increases in blood tissue levels of AEA are observed in a subject having an analgesic phenotype.

Exemplary assays for measuring pain-related chemicals are also described in the Examples.

Other treatments

The methods of the present invention may also be used to treat anxiety, depression or post-traumatic stress disorder (PTSD), to reduce fear levels and for rapid wound healing.

FAAH-OUT inhibitors

A *FAAH-OUT* inhibitor is any compound, agent or substance that can reduce the effect of *FAAH-OUT* or suppress *FAAH-OUT* expression. The suppression is preferably selective for *FAAH-OUT* over *FAAH*. Such inhibitors include but are not limited to oligonucleotides, antibodies, small molecules. A particularly preferred agent are oligonucleotides. For example, siRNA or shRNA knockdown may be employed, or antisense oligonucleotides and the Crispr/Cas9 system may be employed for reducing the effect of or suppressing *FAAH-OUT*. CRISPR interference (CRISPRi) may also be employed, for instance using a catalytically dead/inactive Cas9 (e.g. dCas9) optionally via an effector (e.g. repressor) domain such as a KRAB domain. In some embodiments, the inhibitor modifies the DNA sequence encoding *FAAH-OUT*. In some instances, the

modification is made by gene editing. In some instances, the inhibitor targets *FAAH-OUT* but affects expression of *FAAH*. For instance, the inhibitor may disrupt or lead to the removal of a regulatory element or an enhancer element of *FAAH* that is located in *FAAH-OUT*.

A *FAAH-OUT* inhibitor may target a sequence encoding the *FAAH-OUT* gene having SEQ ID NO: 5 or an expression product of the *FAAH-OUT* gene. An expression product of the *FAAH-OUT* gene may be RNA or protein. The sequence encoding the *FAAH-OUT* gene may be a sequence having at least 60%, at least 65%, at least 70%, at least 75%, at least 80%, at least 85%, at least 90%, at least 95%, at least 98% or at least 99% identity to the sequence of SEQ ID NO: 5. The identity level is preferably at least 85% or higher. Identity relative to the sequence of SEQ ID NO: 5 can be measured over a region of at least 1000bp, at least 2000bp, at least 3000bp, at least 4000bp, at least 5000bp, at least 6000bp, at least 7000bp, at least 8000bp, at least 9000bp, at least 10000bp, at least 11000bp or more contiguous nucleotides the sequence shown in SEQ ID NO: 5, or more preferably over the full length of SEQ ID NO: 5.

Oligonucleotides

The present invention provides oligonucleotides that are able to suppress or reduce the effect of *FAAH-OUT*. Such oligonucleotides directed against *FAAH-OUT* are inhibitors of *FAAH-OUT* according to the present invention. As noted above, oligonucleotides may alternatively be used to suppress *FAAH* or FAAH.

The terms "oligonucleotide", "nucleic acid molecule" and "polynucleotide" are used interchangeably herein and refer to a polymeric form of nucleotides of any length, either deoxyribonucleotides or ribonucleotides, or analogs thereof. In the context of this invention, the term "oligonucleotide" refers to an oligomer of nucleotide or nucleoside monomers consisting of naturally-occurring bases, sugars and intersugar (backbone) linkages. The term "oligonucleotide" also includes oligomers comprising non-naturally occurring monomers, or portions thereof, which function similarly. Such modified or substituted oligonucleotides are often preferred over native forms because of properties such as, for example, enhanced cellular uptake, reduced immunogenicity, and increased stability in the presence of nucleases.

The oligonucleotides described herein can be single-stranded DNA or RNA, double-stranded DNA or RNA, DNA-RNA hybrids, or chimeric DNA-RNA structures. Examples of double-stranded RNA include, *e.g.,* siRNA, short hairpin RNA (shRNA) and other RNAi agents such as pre-miRNA. Single-stranded oligonucleotides include, *e.g.,* antisense oligonucleotides, ribozymes, mature miRNA, and triplex-forming oligonucleotides.

Using known techniques and based on a knowledge of the sequence of *FAAH-OUT* or *FAAH*, double-stranded RNA (dsRNA) molecules can be designed to suppress *FAAH-OUT* or *FAAH* expression by sequence homology-based targeting of its RNA transcript. Such dsRNAs will typically be siRNAs, usually in a stem-loop ("hairpin") configuration, or micro-RNAs (miRNAs). The sequence of such dsRNAs will comprise a portion that corresponds with that of a portion of the mRNA transcript of *FAAH-OUT* or *FAAH*. This portion will usually be 100% complementary to the target portion within the allele comprising the dominant mutation but lower levels of complementarity (e.g. 60% or more, 65% or more, 70% or more, 75% or more, 80% or more, 85% or more, 90% or more, or 95% or more) may also be used.

In some instances, the total length of the oligonucleotide may be up to 100, 90, 80, 70, 60, 50, 40, 30 or 20 nucleotides. In others, the total length may be 29, 28, 27, 26, 25, 24, 23, 22, 21, 20, 19, 18, 17, 16, 15, 14, 13, 12, 11 or 10 nucleotides.

Using known techniques and based on a knowledge of the sequence of the *FAAH-OUT* (e.g. based on the nucleotide sequences of SEQ ID NO: 5) or *FAAH* (encoded by SEQ ID NO: 1,2 or 39), a single-stranded antisense oligonucleotide (AON) can be designed to suppress *FAAH-OUT* or *FAAH* by sequence homology-based targeting of its RNA transcript. The sequence of such AONs will comprise a portion that corresponds with that of a portion of the mRNA transcript or *FAAH-OUT* or *FAAH*. This portion will usually be 100% complementary to the target portion within the allele but lower levels of complementarity (e.g. 60% or more, 65% or more, 70% or more, 75% or more, 80% or more, 85% or more, 90% or more or 95% or more) may also be used. The AON may act by binding to pre-mRNA or mRNA via Watson-Crick base pairing and induces gene suppression by different mechanisms such as through RNase H-mediated mRNA degradation. The AON may have a base sequence that is complementary to the mRNA of

FAAH-OUT or *FAAH*. They are prone to rapid degradation by intracellular endonucleases and exonucleases.

The AONs may be gapmers or altimers. A gapmer is a chimeric AON that contains a central block of DNA molecules and is flanked by blocks of 2'-O modified ribooligonucleotides or other artificially modified ribooligonucleotide monomers that protect the internal block from nuclease degradation. The oligonucleotides contain DNA bases, wherein some or all of the DNA bases have a phosphorothioated backbone. For example, none, 5 or more, 10 or more, 15 or more, 20 or more, 25 or more, or all of the DNA bases have a phosphorothioated backbone. DNA that contain phosphorothioated backbones provide an increased resistance to nucleases compared to unmodified DNA.

In one embodiment, the oligonucleotide for use in the invention comprises modifications to help enhance its properties. Hence, the oligonucleotide may be modified by the substitution of at least one nucleotide with at least one modified nucleotide, ideally so that the *in vivo* and *in vitro* stability of the oligonucleotide is enhanced as compared to a corresponding unmodified oligonucleotide. The modified nucleotide may, for instance, be a sugar-modified nucleotide or a nucleobase-modified nucleotide. In some instances, two, three, four, five, six or seven modified nucleotides may be included, or at least that number, in others eight, nine, ten, eleven or twelve such modifications, or at least that number, may be included, in other cases, fifteen, twenty, twenty-one, twenty-two, twenty three, twenty-four, twenty-five or at least such numbers may be modified. In still others all of the nucleotides may be modified, or all but one, two, three, four or five nucleotides.

In some instances, the modified nucleotide is a 2'-deoxy ribonucleotide. In certain instances, the 2'-deoxy ribonucleotide is 2'-deoxy guanosine or 2'-deoxy adenosine. In other instances, the modified nucleotide is a 2'-O-methylguanosine, 2'-O-methyl (e.g., 2'-O-methylcytidine, 2'-O-methylpseudouridine, 2'-O-methyluridine, 2'-O-methyladenosine, 2'-O-methyl) ribonucleotide. In some cases, the modified nucleotide is selected from a 2'-amino, 2'-thio and 2'-fluoro modified ribonucleotide. In a further instances, the modified nucleotide is selected from the group consisting of 2'-fluoro-cytidine, 2'-fluoro-uridine, 2'-fluoro-guanosine, 2'-fluoro-adenosine, 2'-amino-cytidine, 2'-amino-uridine, 2'-amino-adenosine, 2'-amino-guanosine, 2'-amino-butyryl-pyrene-uridine and 2'-amino-adenosine. In an additional instances, the modified nucleotide is selected from 5-iodo-uridine, ribo-

thymidine, 5-bromo-uridine, 2-aminopurine, 5-methyl-cytidine , 5-fluoro-cytidine, and 5-fluoro-uridine, 2,6-diaminopurine, 4-thio-uridine, and 5-amino-allyl-uridine.

In some instances, the modified nucleotide includes: derivatization of the 5 position, for instance being selected from 5-(2-amino) propyl uridine, 5-bromo uridine, 5-propyne uridine, 5-propenyl uridine; derivatization of the 6 position, for instance 6-(2-amino)propyl uridine; derivatization of the 8-position for adenosine and/or guanosines, for instance 8-bromo guanosine, 8-chloro guanosine, or 8-fluoroguanosine, Nucleotide analogs which may be employed include deaza nucleotides, e.g., 7-deaza-adenosine; O- and N-modified (for instance alkylated, such as N6-methyl adenosine) nucleotides; and other heterocyclically modified nucleotide analogs. Examples of modifications to the sugar portion of the nucleotides which may be employed include the 2' OH-group being replaced by a group selected from H, OR, R, F, Cl, Br, I, SH, SR, NH2, NHR, NR2, COOR, or OR, wherein R is substituted or unsubstituted C1-C6 alkyl, alkenyl, alkynyl, aryl and so on. The phosphate group of the nucleotide may also be modified, such as by substituting one or more of the oxygens of the phosphate group with sulphur (for instance by employing phosphorothioates). Modifications may decrease the rate of hydrolysis of polynucleotides comprising the modified bases, for example by inhibiting degradation by exonucleases. In one preferred instance, the oligonucleotide is resistant to ribonucleases. Oligonucleotides which may be employed include those with modifications to promote such resistance, for instance an oligonucleotide of the invention may have preferably been modified with a 2'-O-methyl group (e.g., 2'-O-methylcytidine, 2'-O-methylpseudouridine, 2'-O-methylguanosine, 2'-O-methyluridine, 2'-O-methyladenosine, 2'-O-methyl) and additionally comprise a phosphorothioate backbone.

In some instances, oligonucleotides for use in the invention comprise oligonucleotides that contain phosphorothioate and 2'-O-methyl (e.g., 2'-O-methylcytidine, 2'-O-methylpseudouridine, 2'-O-methylguanosine, 2'-O-methyluridine, 2'-O-methyladenosine, 2'-O-methyl) modification. Other forms of oligonucleotide modifications may be employed, for example, locked nucleic acids (oligonucleotides comprising at least one 2'-C,4'-C-oxy-methylene-linked bicyclic ribonucleotide monomer). In some instances the modified nucleotide employed may be 5-fluorouracil, 5-bromouracil, 5-chlorouracil, 5-iodouracil, hypoxanthine, xanthine, 4-acetylcytosine, 5-(carboxyhydroxylmethyl)uracil, 5-carboxymethylaminomethyl-2-thiouridine, 5-

carboxymethylaminomethyluracil, dihydrouracil, beta-D-galactosylqueosine, inosine, N6-isopentenyladenine, 1-methylguanine, 1-methylinosine, 2,2-dimethylguanine, 2-methyladenine, 2-methylguanine, 3-methylcytosine, 5-methylcytosine, N6-adenine, 7-methylguanine, 5-methylaminomethyluracil, 5-methoxyaminomethyl-2-thiouracil, beta-D-mannosylqueosine, 5'-methoxycarboxymethyluraci 1, 5-methoxyuracil, 2-methylthio-N6-isopentenyladenine, uracil-5-oxyacetic acid (v), wybutoxosine, pseudouracil, queosine, 2-thiocytosine, 5-methyl-2-thiouracil, 2-thiouracil, 4-thiouracil, 5-methyluracil, uracil-5-oxyacetic acid methylester, uracil-5-oxyacetic acid (v), 5-methyl-2-thiouracil, 3-(3-amino-3-N-2-carboxypropyl) uracil, (acp3)w, and 2,6-diaminopurine.

In some instances, the modified oligonucleotide may include modifications to the phosphate backbone such as methyl phosphonates, methyl phosphonothioates, phosphoromorpholidates, phosphoropiperazidates and phosphoramidates. In one example, every other one of the internucleotide bridging phosphate residues may be modified as described. In another non-limiting example, such oligonucleotides are oligonucleotides wherein at least one, or all, of the nucleotides contain a 2' loweralkyl moiety (e.g., C1-C4, linear or branched, saturated or unsaturated alkyl, such as methyl, ethyl, ethenyl, propyl, 1-propenyl, 2-propenyl, and isopropyl).

In one embodiment, the oligonucleotide for use in the invention is a small interfering RNA (siRNA). An siRNA acts by activating the RNAi-induced suppression complex (also known as the RISC complex). The siRNA molecules can be unmodified or modified and are capable of suppressing (i.e. partially or completely preventing) expression of FAAH-OUT (e.g. having SEQ ID NO: 36) or FAAH protein (e.g. having SEQ ID NOs: 40 or 41). The siRNA may prevent expression of *FAAH-OUT* or *FAAH*. The siRNA may prevent expression of mRNA encoding FAAH-OUT or FAAH protein. The siRNA may prevent translation of an mRNA encoding FAAH-OUT or FAAH protein. The siRNA may reduce or prevent FAAH-OUT or FAAH protein expression by affecting the post translational modification of FAAH-OUT or FAAH protein. An siRNA is typically about 5 to 60 nucleotides in length, about 5 to 55 nucleotides in length, about 5 to 50 nucleotides in length, about 5 to 45 nucleotides in length, about 5 to 40 nucleotides in length, about 5 to 35 nucleotides in length, about 5 to 30 nucleotides in length, about 5 to 25 nucleotides in length, about 5 to 20 nucleotides in length, about 5 to 15 nucleotides in length, or about 5 to 10 nucleotides in length.

In some embodiments, the modified siRNA contains at least one 2'O-Me purine or pyrimidine nucleotide such as a 2'O-Me-guanosine, 2'O-Me-uridine, 2'O-Me-adenosine, and/or 2'O-Me-cytosine nucleotide. The modified nucleotides can be present in one strand (*i.e.,* sense or antisense) or both strands of the siRNA. The siRNA sequences may have overhangs or blunt ends.

The modified siRNA may comprises from about 1% to about 100% (*e.g.,* about 1%, 2%, 3%, 4%, 5%, 6%, 7%, 8%, 9%, 10%, 11%, 12%, 13%, 14%, 15%, 16%, 17%, 18%, 19%, 20%, 21%, 22%, 23%, 24%, 25%, 26%, 27%, 28%, 29%, 30%, 35%, 40%, 45%, 50%, 55%, 60%, 65%, 70%, 75%, 80%, 85%, 90%, 95%, or 100%) modified nucleotides in the double-stranded region of the siRNA duplex. In certain embodiments, one, two, three, four, five, six, seven, eight, nine, ten, or more of the nucleotides in the double-stranded region of the siRNA comprise modified nucleotides.

Suitable siRNA sequences can be identified using any means known in the art. Typically, the methods described in Elbashir *et al.*, *Nature,* 411:494-498 (2001) and Elbashir *et al.*, *EMBO J.,* 20:6877-6888 (2001) are combined with rational design rules set forth in Reynolds *et al.*, *Nature Biotech.,* 22(3):326-330 (2004).

Preferably, siRNA are chemically synthesized. The oligonucleotides that comprise the siRNA molecules of the invention can be synthesized using any of a variety of techniques known in the art, such as those described in Usman *et al.*, *J. Am. Chem. Soc.*, 109:7845 (1987); Scaringe *et al.*, *Nucl. Acids Res.*, 18:5433 (1990); Wincott *et al.*, *Nucl. Acids Res.*, 23:2677-2684 (1995); and Wincott *et al., Methods Mol. Bio.*, 74:59 (1997). The synthesis of oligonucleotides makes use of common nucleic acid protecting and coupling groups, such as dimethoxytrityl at the 5'-end and phosphoramidites at the 3'-end. Alternatively, siRNA molecules can be assembled from two distinct oligonucleotides, wherein one oligonucleotide comprises the sense strand and the other comprises the antisense strand of the siRNA. For example, each strand can be synthesized separately and joined together by hybridization or ligation following synthesis and/or deprotection. In certain other instances, siRNA molecules can be synthesized as a single continuous oligonucleotide fragment, where the self-complementary sense and antisense regions hybridize to form an siRNA duplex having hairpin secondary structure.

In one embodiment, the oligonucleotide for use in the invention is a guide RNA comprising a guide RNA sequence and a tracr RNA. The guide RNA sequence is capable

of hybridizing to a target sequence in the DNA of an allele. The tracr RNA is coupled to the guide RNA sequence. The guide RNA hybridises to the site of the allele carrying a dominant mutation and targets a CRISPR-Cas enzyme to said site. In some embodiments, the guide sequence is between 10-30, or between 15-25, or between 15-20 nucleotides in length. Preferably the CRISPR-Cas enzyme is a Type II CRISPR enzyme, for example Cas-9. The enzyme complexes with the guide RNA. In one embodiment, the complex is targeted to the DNA sequence of *FAAH-OUT* or *FAAH* and will bind by hybridization. In another embodiment, the complex is targeted to the DNA sequence of the regulatory region, e.g. the promoter, of *FAAH-OUT* or *FAAH*. In another embodiment, the complex is targeted to the DNA sequence of the first two exons of *FAAH-OUT* or *FAAH*. In some embodiments, any region of *FAAH-OUT* or *FAAH* may be targeted which leads to deletion of *FAAH-OUT* or *FAAH* and/or disruption of its function. In one embodiment, the enzyme is active and acts as an endonuclease to cleave the DNA either via activation of the non-homologous end-joining or homologous DNA repair pathway, resulting in a blunt end cut or a nick. A repair template sequence can be supplied and be introduced into the allele by homologous recombination, thereby replacing the sequence that it targeted, such as a mutation in the DNA of an allele. In another embodiment, the enzyme is targeted to the DNA of *FAAH-OUT* or *FAAH* but the enzyme comprises one or more mutations that reduce or eliminate its endonuclease activity such that it does not edit *FAAH-OUT* or *FAAH* but does prevent or reduce its transcription. In another embodiment, the enzyme can be engineered such that it is fused to a transcriptional repressor to reduce or disable its endonuclease function. The enzyme will be able to bind the guide RNA and be targeted to the DNA sequence, but no cleavage of the DNA takes place. *FAAH-OUT* or *FAAH* may be suppressed, for example, by the shutting down of the promoter or blockage of RNA polymerase. In another embodiment, the transcription repressor may be bound to the tracr sequence. Functional domains can be attached to the tracr sequence by incorporating protein-binding RNA aptamer sequences, as described in Konermann *et al* (Genome-scale transcriptional activation by an engineered CRISPR-Cas9 complex, Nature, 517, 583-588, 2015). The transcription repressor-tracr sequence complex may be used to target other moieties to a precise gene location as desired.

Other gene editing methods well known in the art may be employed in the invention. Such methods include but are not limited to zinc finger nuclease gene editing

methods, recombinant adeno-associated virus (rAAV) genome editing methods, non-Cas9 CRISPR systems using Cpf1 for gene editing, and methods using transposons. Exemplary nucleases used in these methods include but are not limited to zinc finger nucleases (ZFN), meganucleases and transcription activator-like effector-based nucleases (TALEN).

An oligonucleotide for use in the invention may be conjugated with a peptide or receptor. To assist with delivery of the oligonucleotide, the peptide may for example be a cell penetrating peptide. This technique is described in, for example, WO2009/147368, WO2013/030569, WO2012/150960 and WO2004/097017. The oligonucleotides may also be conjugated to a carrier or encapsulated within a liposome.

The oligonucleotides for use in the invention may be complementary to a region of the RNA transcript from *FAAH-OUT* or *FAAH*. In one instance, the oligonucleotide will be complementary to 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, or 30 nucleotides of that sequence, preferably complementary to 13-25 or 16-21 nucleotides of that sequence.

In one instance, the oligonucleotide is at least 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26 or 27 nucleotides in length, preferably at least 19, 20, 21, 22, 23, 24, 25 or 26 nucleotides in length, for example 13-25 or 16-21 nucleotides in length. In one embodiment, the oligonucleotide is between 10 and 35 nucleotides in length, for example, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, 30, 31, 32, 33, 34, 35 nucleotides in length. In one embodiment, the oligonucleotide is between 18 and 30 nucleotides in length, for example, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29 30 nucleotides in length. It may be that the region of the oligonucleotide capable of hybridisation to is that length, or at least that length, but there are also additional nucleotides at the 5' and/or 3' ends of the oligonucleotide, though in other instances the overall length of the oligonucleotide is that number of nucleotides.

In general, oligonucleotide sequences which are perfectly complementary to a portion of the target RNA may preferably be employed. In some instances though sequence variations that might be expected due to genetic mutation, strain polymorphism, or evolutionary divergence may be present. For example, oligonucleotide sequences with insertions, deletions, and single point mutations relative to the target sequence may also be effective for inhibition. Greater than 70% sequence identity (or complementarity), e.g., 70%, 71%, 72%, 73%, 74%, 75%, 76%, 77%, 78%, 79%, 80%, 81%, 82%, 83%, 84%,

85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99% or even 100% sequence identity, between the oligonucleotide sequence and the target RNA, e.g., target pre-mRNA, is preferred.

Sequence identity, including determination of sequence complementarity for nucleic acid sequences, may be determined by sequence comparison and alignment algorithms known in the field. To determine the percent identity of two nucleic acid sequences (or of two amino acid sequences), the sequences are aligned for optimal comparison purposes (e.g., gaps can be introduced in the first sequence or second sequence for optimal alignment). The nucleotides (or amino acid residues) at corresponding nucleotide (or amino acid) positions are then compared. When a position in the first sequence is occupied by the same residue as the corresponding position in the second sequence, then the molecules are identical at that position. The percent identity between the two sequences is a function of the number of identical positions shared by the sequences (i.e., % homology=# of identical positions/total # of positions*100), optionally penalizing the score for the number of gaps introduced and/or length of gaps introduced.

The comparison of sequences and determination of percent identity between two sequences can be accomplished using a mathematical algorithm. In one embodiment, the alignment generated over a certain portion of the sequence aligned having sufficient identity but not over portions having low degree of identity (i.e., a local alignment). A preferred, non-limiting example of a local alignment algorithm utilized for the comparison of sequences is the algorithm of Karlin and Altschul (1990) *Proc. Natl. Acad. Sci. USA* 87:2264-68, modified as in Karlin and Altschul (1993) *Proc. Natl. Acad. Sci. USA* 90:5873-77. Such an algorithm is incorporated into the BLAST programs (version 2.0) of Altschul, *et al.* (1990) *J. Mol. Biol.* 215:403-10.

In another embodiment, the alignment is optimized by introducing appropriate gaps and percent identity is determined over the length of the aligned sequences (i.e., a gapped alignment). To obtain gapped alignments for comparison purposes, Gapped BLAST can be utilized as described in Altschul *et al.*, (1997) *Nucleic Acids Res.* 25(17):3389-3402. In another embodiment, the alignment is optimized by introducing appropriate gaps and percent identity is determined over the entire length of the sequences aligned (i.e., a global alignment). A preferred, non-limiting example of a mathematical algorithm utilized for the global comparison of sequences is the algorithm of Myers and Miller, *CABIOS* (1989).

Such an algorithm is incorporated into the ALIGN program (version 2.0) which is part of the GCG sequence alignment software package. When utilizing the ALIGN program for comparing amino acid sequences, a PAM120 weight residue table, a gap length penalty of 12, and a gap penalty of 4 can be used.

The oligonucleotide for use in the invention may also hybridise to a site within the *FAAH-OUT* or *FAAH* that may be a site with a polymorphism, such as a Single Nucleotide Polymorphism (SNP), microsatellite polymorphism, insertion polymorphism and deletion polymorphism. Preferably the polymorphism is a SNP. Such polymorphisms may be identified by genotyping the subject and sequencing the mutant allele present in their genome, or they may be known or suspected to be present *a priori*. Targeting an oligonucleotide to such a mutation in the allele will suppress the allele and effect treatment of pain, even if the mutation targeted is non-causative of the disease. Further, both the causative mutation and one or more non-causative ones can be targeted with different oligonucleotides.

Suppression of the expression of an allele can be measured by any suitable technique known in the art. For example, reverse transcription, Sanger sequencing and quantitative real-time PCR is a frequently used technique. The oligonucleotides of the invention can suppress the expression of the allele by any amount, preferably up to 95%, 90%, 85%, 80%, 75%, 70%, 65%, 60%, 55%, 50%, 45%, 40%, 30%, 20% or 10%.

Oligonucleotide delivery

The oligonucleotides for use in the present invention may be introduced into cells using any suitable method. For instance transfection, electroporation, fusion, liposomes, extracellular vesicles (e.g. exosomes or microvesicles), colloidal polymeric particles, dendrimers and viral and non-viral vectors as well as other means known in the art may be used to deliver the oligonucleotide sequences to cells.

In some instances, the oligonucleotide is delivered using methods involving liposome-mediated uptake. Lipofectins and cytofectins are lipid-based positive ions that bind to negatively charged nucleic acid and form a complex that can ferry the nucleic acid across a cell membrane and may be employed. In one instance a lipofectin is used in the delivery of the oligonucleotide, particularly Lipofectamine 2000. In one instance the

oligonucleotide may be delivered using a jetPRIME® reagent. For example, the oligonucleotide may be delivered to cells in vitro using a method involving jetPRIME® reagent. In some instances, no transfection reagents may be required and oligonucleotide may be taken up by target cells directly via gymnosis.

In one embodiment, the oligonucleotides may be delivered using a composition comprising a dendrimer. Dendrimers are nano-sized, radially symmetric molecules with well-defined, homogeneous, and monodisperse structure that has a typically symmetric core, an inner shell, and an outer shell (Madaan et al. (2014) J Pharm Bioallied Sci. 2014 Jul-Sep; 6(3): 139–150). Any dendrimer may be suitable for delivery of oligonucleotides. The dendrimer for use with the oligonucleotides may comprise of consist of polyamidoamine (PAMAM), a poly(propylene imine) (PPI, poly-L-lysine, melamine, poly(etherhydroxylamine) (PEHAM), poly(esteramine) (PEA) and/or polyglycerol. Delivery may be direct to the subject, or for instance to cells or tissues, for instance with the cells or tissues subsequently being reintroduced. Oligonucleotides may be directly introduced into a target cell or introduced extracellular into a cavity, interstitial space, into the circulation of a subject, introduced orally, or may be solution containing the RNA using methods for introducing nucleic acid into cells in vivo.

The oligonucleotides may be delivered by any suitable route of administration. In some instances, administration may be systemic, in others it may be localised. For instance, the oligonucleotides may be administered by direct injection at a tissue site or infusion into a body fluid. Vascular or extravascular circulation, the blood or lymph system, and the cerebrospinal fluid are examples of locations where the RNA may be introduced.

The oligonucleotide may be, for instance, delivered to the nervous system of a subject by any suitable method. For example, injection and in particular intravenous injection of the oligonucleotide reagents of the invention can be used for delivery to peripheral neurons via diffusive and/or active means. Alternatively, the oligonucleotides can be modified to promote crossing of the blood-brain-barrier (BBB) to achieve delivery of said reagents to neuronal cells of the central nervous system (CNS). In certain instances, the oligonucleotides can be delivered by transdermal methods. The oligonucleotide may also be delivered via an implantable device.

Physical methods of introducing an oligonucleotide include injection of a solution containing the oligonucleotide, bombardment by particles covered by the oligonucleotide, soaking the cell or organism in a solution of the oligonucleotide, or electroporation of cell membranes in the presence of the oligonucleotide. A viral vector packaged into a viral particle can be used to achieve efficient introduction of the oligonucleotide into a cell and transcription of oligonucleotide encoded by the expression construct. Other methods known in the art for introducing nucleic acids to cells may be used, such as lipid-mediated carrier transport, chemical-mediated transport, such as calcium phosphate, and the like. The oligonucleotide may be introduced along with components that perform one or more of the following activities: enhance uptake of the oligonucleotide of the invention by a cell, inhibit annealing of single strands of oligonucleotide of the invention, stabilise single strands of oligonucleotide, prevent degradation of the oligonucleotide or otherwise increase inhibition of the target gene.

The oligonucleotides may be modified so that they target specific cells, for instance by binding to receptors found on a particular cell type. The oligonucleotides may be delivered to cells using a vector.

This is also described further in the "Administration route, formulations and dosages" section below.

Vectors

A vector that can be used in the invention may be of any type, for example it may be a plasmid vector or a minicircle DNA.

Typically, vectors that can be used in the invention are viral vectors. The viral vector may for example be based on the herpes simplex virus, adenovirus or lentivirus. The viral vector may be an adeno-associated virus (AAV) vector or a derivative thereof. The viral vector derivative may be a chimeric, shuffled or capsid modified derivative. The viral vector may comprise an AAV genome from a naturally derived serotype, isolate or clade of AAV. The serotype may for example be AAV2, AAV5, AAV8 or AAV9. Preferably, the serotype may be AAV9.

The efficacy of gene therapy is, in general, dependent upon adequate and efficient delivery of the donated DNA. This process is usually mediated by viral vectors. Adeno-associated viruses (AAV), a member of the parvovirus family, are commonly used in gene

therapy. Wild-type AAV, containing viral genes, insert their genomic material into the chromosome of the host cell. The AAV single-stranded DNA genome comprises two inverted terminal repeats (ITRs) and two open reading frames, containing structural (cap) and packaging (rep) genes.

For therapeutic purposes, the only sequences required *in cis,* in addition to the therapeutic gene, are the ITRs. The AAV virus is therefore modified: the viral genes are removed from the genome, producing recombinant AAV (rAAV). This contains only the therapeutic gene, the two ITRs. The removal of the viral genes renders rAAV incapable of actively inserting its genome into the host cell DNA. Instead, the rAAV genomes fuse via the ITRs, forming circular, episomal structures, or insert into pre-existing chromosomal breaks. For viral production, the structural and packaging genes, now removed from the rAAV, are supplied *in trans*, in the form of a helper plasmid. AAV is a particularly attractive vector as it is generally non-pathogenic; the majority people have been infected with this virus during their life with no adverse effects.

rAAV transduces cells via serotype specific receptor-mediated endocytosis. A major factor influencing the kinetics of rAAV transgene expression is the rate of virus particle uncoating within the endosome. This, in turn, depends upon the type of capsid enclosing the genetic material (Ibid.). After uncoating the linear single-stranded rAAV genome is stabilised by forming a double-stranded molecule via *de novo* synthesis of a complementary strand. The use of self-complementary DNA may bypass this stage by producing double-stranded transgene DNA. Natkunarajah et al (2008) found that self-complementary AAV2/8 gene expression was of faster onset and higher amplitude, compared to single-stranded AAV2/8. Thus, by circumventing the time lag associated with second-strand synthesis, gene expression levels are increased, when compared to transgene expression from standard single-stranded constructs. Subsequent studies investigating the effect of self-complementary DNA in other AAV pseudotypes (e.g. AAV2/5) have produced similar results. One caveat to this technique is that, as AAV has a packaging capacity of approximately 4.8kb, the self-complementary recombinant genome must be appropriately sized (i.e. 2.3kb or less).

An AAV genome is a polynucleotide sequence which encodes functions needed for production of an AAV viral particle. These functions include those operating in the replication and packaging cycle for AAV in a host cell, including encapsidation of the

AAV genome into an AAV viral particle. Naturally occurring AAV viruses are replication-deficient and rely on the provision of helper functions in *trans* for completion of a replication and packaging cycle. Accordingly and with the additional removal of the AAV *rep* and *cap* genes, the AAV genome of the vector of the invention is replication-deficient.

The AAV genome may be in single-stranded form, either positive or negative-sense, or alternatively in double-stranded form. The use of a double-stranded form allows bypass of the DNA replication step in the target cell and so can accelerate transgene expression.

The AAV genome may be from any naturally derived serotype or isolate or clade of AAV. As is known to the skilled person, AAV viruses occurring in nature may be classified according to various biological systems.

Commonly, AAV viruses are referred to in terms of their serotype. A serotype corresponds to a variant subspecies of AAV which owing to its profile of expression of capsid surface antigens has a distinctive reactivity which can be used to distinguish it from other variant subspecies. Typically, a virus having a particular AAV serotype does not efficiently cross-react with neutralising antibodies specific for any other AAV serotype. AAV serotypes include AAV1, AAV2, AAV3, AAV4, AAV5, AAV6, AAV7, AAV8, AAV9, AAV10 and AAV11, also recombinant serotypes, such as Rec2 and Rec3, recently identified from primate brain. In vectors used in the invention, the genome may be derived from any AAV serotype. The capsid may also be derived from any AAV serotype. The genome and the capsid may be derived from the same serotype or different serotypes. Reviews of AAV serotypes may be found in Choi et al (*Curr Gene Ther*. 2005; 5(3); 299-310) and Wu et al (*Molecular Therapy*. 2006; 14(3), 316-327).

The AAV serotype determines the tissue specificity of infection (or tropism) of an AAV virus. Accordingly, preferred AAV serotypes for use in AAV viruses administered to patients in accordance with the invention are those which have natural tropism for or a high efficiency of infection of brain tissue or dorsal root ganglia tissue.

Effects of inhibitor administration

Administration of an inhibitor may lead to an increase in the level of N-acyl ethanolamines and N-acyl taurines in the individual. For instance, the administration of an

inhibitor leads to an increase in the levels of anandamide (AEA), palmitoylethanolamide (PEA) and/or oleoylethanolamine (OEA). The administration of an inhibitor may also lead to an increase in N-acyl-taurines *e.g.* *N*-tetracosanoyl-taurine [NAT(24:0)] and *N*-eicosanoyl-taurine [NAT(20:0)].

Combination therapies

An inhibitor may be used in combination with one or more other therapies or agents intended to treat or ameliorate pain in the same individual. The therapies or agents may be administered simultaneously, in a combined or separate form, to an individual. The therapies or agents may be administered separately or sequentially to an individual as part of the same therapeutic regimen.

Exemplary agents include, but are not limited to, non-steroidal anti-inflammatory drugs (NSAIDS) such as ibuprofen, aspirin, naproxen, fenoprofen, flurbiprofen, ketoprofen, oxaprozin, diclofenac sodium, etodolac, indomethacin, ketorolac, sulindac, tolmetin, meclofenamate, mefenamic acid, nabumetone, piroxicam, COX-2 inhibitors such as celecoxib, opioids such as morphine, codeine, oxycodone, hydrocodone, dihydromorphine, pethidine, fentanyl, oxymorphone, methadone, cannabinoids. Anaesthetics, anticonvulsants, antidepressants, neuromodulators, pain-relief injections and psychological therapy, for example, and any other therapy or pain management, may also be used.

Administration routes, formulations and dosages

Specific routes, dosages and methods of administration of the substance (including inhibitors of *FAAH-OUT* or *FAAH* expression) for use in the invention may be routinely determined by the medical practitioner. Typically, a therapeutically effective amount of the substance is administered to the patient. A therapeutically effective amount of the substance is an amount effective to reduce pain in the context of analgesic treatment. A therapeutically effective amount of the substance is administered. The dose may be determined according to various parameters, especially according to the compound used; the age, weight and condition of the patient to be treated; the route of administration; and the required regimen. Again, a physician will be able to determine the required route of administration and dosage for any particular patient.

The substance can be administered to the patient by any suitable means. The substance can be administered by enteral or parenteral routes such as via oral (e.g. inhalation), buccal, anal, pulmonary, intravenous, intra-arterial, intramuscular, intraosseous, intraspinal, intracranial, intraperitoneal, intradermal, subcutaneous, intrathecal, intra-articular, topical or other appropriate administration routes. Intrathecal administration is particularly preferred.

The substance may be administered in a variety of dosage forms. It may be administered orally (e.g. as tablets, troches, lozenges, aqueous or oily suspensions, dispersible powders or granules), parenterally, subcutaneously, intravenously, intramuscularly, intraosseously, intrasternally, intraspinally, intracranially, transdermally or by infusion techniques. The substance may also be administered as a suppository. A physician will be able to determine the required route of administration for each particular patient.

The inhibitor, e.g. oligonucleotide, siRNA, vector or isolated cell can be formulated for use with a pharmaceutically acceptable carrier or diluent and this may be carried out using routine methods in the pharmaceutical art. The pharmaceutical carrier or diluent may be, for example, an isotonic solution. Preferred pharmaceutically acceptable carriers comprise aqueous carriers or diluents. Examples of suitable aqueous carriers that may be employed in the pharmaceutical compositions of the invention include water, buffered water and saline. Examples of other carriers include ethanol, polyols (such as glycerol, propylene glycol, polyethylene glycol, and the like), and suitable mixtures thereof, vegetable oils, such as olive oil, and injectable organic esters, such as ethyl oleate. Proper fluidity can be maintained, for example, by the use of coating materials, such as lecithin, by the maintenance of the required particle size in the case of dispersions, and by the use of surfactants. In many cases, it will be preferable to include isotonic agents, for example, sugars, polyalcohols such as mannitol, sorbitol, or sodium chloride in the composition.

Solid oral forms may for example contain, together with the active compound, diluents, e.g. lactose, dextrose, saccharose, cellulose, corn starch or potato starch; lubricants, e.g. silica, talc, stearic acid, magnesium or calcium stearate, and/or polyethylene glycols; binding agents; e.g. starches, arabic gums, gelatin, methylcellulose, carboxymethylcellulose or polyvinyl pyrrolidone; disaggregating agents, e.g. starch, alginic acid, alginates or sodium starch glycolate; effervescing mixtures; dyestuffs;

sweeteners; wetting agents, such as lecithin, polysorbates, laurylsulphates; and, in general, non-toxic and pharmacologically inactive substances used in pharmaceutical formulations. Such pharmaceutical preparations may be manufactured in known manner, for example, by means of mixing, granulating, tabletting, sugar-coating, or film coating processes.

Liquid dispersions for oral administration may be syrups, emulsions and suspensions. The syrups may contain as carriers, for example, saccharose or saccharose with glycerine and/or mannitol and/or sorbitol.

Suspensions and emulsions may contain as carrier, for example a natural gum, agar, sodium alginate, pectin, methylcellulose, carboxymethylcellulose, or polyvinyl alcohol. The suspensions or solutions for intramuscular injections may contain, together with the active compound, a pharmaceutically acceptable carrier, e.g. sterile water, olive oil, ethyl oleate, glycols, e.g. propylene glycol, and if desired, a suitable amount of lidocaine hydrochloride.

Solutions for intravenous or infusions may contain as carrier, for example, sterile water or preferably they may be in the form of sterile, aqueous, isotonic saline solutions. For suppositories, traditional binders and carriers may include, for example, polyalkylene glycols or triglycerides; such suppositories may be formed from mixtures containing the active ingredient in the range of 0.5% to 10%, preferably 1% to 2%.

Oral formulations include such normally employed excipients as, for example, pharmaceutical grades of mannitol, lactose, starch, magnesium stearate, sodium saccharine, cellulose, magnesium carbonate, and the like. These compositions take the form of solutions, suspensions, tablets, pills, capsules, sustained release formulations or powders and contain 10% to 95% of active ingredient, preferably 25% to 70%. Where the pharmaceutical composition is lyophilised, the lyophilised material may be reconstituted prior to administration, e.g. a suspension. Reconstitution is preferably effected in buffer.

Capsules, tablets and pills for oral administration to a patient may be provided with an enteric coating comprising, for example, Eudragit “S”, Eudragit “L”, cellulose acetate, cellulose acetate phthalate or hydroxypropylmethyl cellulose.

Pharmaceutical compositions suitable for delivery by needleless injection, for example, transdermally, may also be used.

Administration may be in single or multiple doses. Multiple doses may be administered via the same or different routes and to the same or different locations.

Alternatively, doses can be via a sustained release formulation, in which case less frequent administration is required. Dosage and frequency may vary depending on the half-life of the substance in the patient and the duration of treatment desired.

The skilled person and particularly an appropriate physician will be able to identify an appropriate dosage, for instance taking factors such as age, sex, weight, conditions of the patient to be treated, the severity of the disease and the frequency and route of administration and so on into account.

The substance may be an oligonucleotide. Preferably, such oligonucleotides are provided in the form of an expression vector, which may be expressed in the cells of the patient to be treated. This is also described in the section above, "Oligonucleotide delivery", and the sections below. The oligonucleotides maybe naked nucleotide sequences or be in combination with cationic lipids, polymers or targeting systems. The oligonucleotides may be delivered by any available technique, such as those described above. For example, the oligonucleotides may be introduced by needle injection, preferably intradermally, subcutaneously or intramuscularly. Alternatively, the oligonucleotides may be delivered directly across the skin using an oligonucleotide delivery device such as particle-mediated gene delivery. The oligonucleotide may be administered topically to the skin, or to mucosal surfaces for example by intranasal, oral, intravaginal or intrarectal administration. A preferred delivery method is intrathecal administration of an AAV vector.

Uptake of oligonucleotide constructs may be enhanced by several known transfection techniques, for example those including the use of transfection agents. Examples of these agents includes cationic agents, for example, calcium phosphate and DEAE-Dextran and lipofectants, for example, lipofectam and transfectam.

Pharmaceutical compositions may comprise one or more inhibitors, oligonucleotides, siRNAs, vectors, or isolated cells as described. Pharmaceutical compositions may comprise additional active ingredients as well one or more inhibitors, oligonucleotides, siRNAs, vectors, or isolated cells as described. They may also comprise additional therapeutic or prophylactic agents. The additional therapeutic agents or prophylactic agents may be useful for treating or preventing pain.

Administration may be, for instance, by inhalation. Systemic administration may be, for instance, by transmucosal or transdermal means. Transmucosal administration can

be accomplished through the use of nasal sprays or suppositories. For transdermal administration, the oligonucleotides may be, for instance, formulated into a transdermal patches or plasters, ointments, salves, gels, or creams. The oligonucleotides may be, for instance, prepared in the form of suppositories or retention enemas. In some instances, the oligonucleotides may be formulated with carriers that protect the compound against rapid elimination from the body, such as a controlled release formulation, including implants and microencapsulated delivery systems. Biodegradable, biocompatible polymers may be used, such as ethylene vinyl acetate, polyanhydrides, polyglycolic acid, collagen, polyorthoesters, and polylactic acid.

In one embodiment, the pharmaceutical compositions may be formulated in unit dosage forms. In some embodiments the compositions may be formulated in ampoules. The pharmaceutical compositions may be included in a container, pack, or dispenser together with instructions for administration.

The dosage of the oligonucleotide administered will depend upon the particular method being carried out, and when it is being administered to a subject, the nature of disease, the condition of the subject, the particular formulation, and the route of administration. Examples of intracellular concentrations of the oligonucleotide include those in the range from about 0.005 to 50 μM, or more preferably 0.02 to 5 μM. For administration to a subject such as a human, a daily dosage ranging from about 0.001 to 50 mg/kg, preferably 0.01 to 10 mg/kg, and more preferably from 0.1 to 5 mg/kg may be employed. The skilled person and particularly an appropriate physician will be able to identify an appropriate dosage, for instance taking factors such as age, sex, weight and so on into account.

Dosage regimens may be adjusted to provide the optimum desired response (*e.g.*, a therapeutic response). For example, a single dose may be administered, several divided doses may be administered over time or the dose may be proportionally reduced or increased as indicated by the exigencies of the therapeutic situation. Dosage unit form as used herein refers to physically discrete units suited as unitary dosages for the subjects to be treated; each unit contains a predetermined quantity of active compound calculated to produce the desired therapeutic effect in association with the required pharmaceutical carrier.

The invention is illustrated by the following Example:

Example 1

METHODS

German DFNS Protocol for Quantitative Sensory Testing (QST)

QST was performed following informed consent on the dorsum of the foot and the hand according to the German neuropathic pain network (DFNS) protocol by a DFNS trained experimenter.[15] This protocol includes 13 parameters which are designed to detect both gain and loss of function and is summarised below:

Thermal stimuli: Temperature testing was conducted using a TSA-2001-II (Medoc, Israel) with a thermode of contact area 9 cm^2. Thresholds were obtained using ramped stimuli (1°C/s) from 32°C (centre of neutral range) until terminated by subject-control or automated cut-off temperatures whereby the temperature would return to baseline temperature. Thermode temperature was held at 32°C during 10 s inter-stimulus intervals. Sequentially, **cooling and warming detection thresholds (CDT, WDT)** were assessed. The presence of **paradoxical heat sensations (PHS)** was investigated by alternating warming and cooling which were also used to determine **thermal sensory limen (TSL)**. **Cold and heat pain thresholds (CPT, HPT)** were then measured. Tests were performed in triplicate and mean data used for comparison. All subjects were unaware of the timing of initiation of temperature increase and inter-stimuli intervals.

Mechanical stimuli: Mechanical detection threshold (MDT) was assessed using a standardized set of identically round-tipped von Frey hairs (Optihair$_2$-Set, Marstock, Nervtest, Germany) of two-fold incremental bending forces within the range 0.25 – 512 mN. MDT was calculated as a geometric mean of five thresholds ascertained using sequential ascending and descending applications of the hairs by a 'method of limits'. Assessment of **vibration sense (VS)** was performed with a Rydel–Seiffer graded tuning fork (64 Hz, 8/8 scale) that was placed over the processus styloideus ulnae or malleolus internus and left there until the subject could not feel vibration any more and was performed three times. **Mechanical pain threshold (MPT)** were ascertained using a set of seven mechanical probes which exert fixed intensities of 8, 16, 32, 64, 128, 256, 512 mN with a blunt contact area of 0.2 mm diameter. Stimuli were applied in ascending sequence

at a rate of 2 s on, 2 s off until a stimulus was perceived as sharp and subsequent descending until no longer reported as such. Threshold was calculated as the geometric mean of five of these series. **Wind up ratio (WUR)** is a perceptual model of temporal spinal wind up was generated from the perceived intensity of painfulness from a single application of 256 mN pinprick compared to 10 repetitions of the same stimulus applied at a rate of 1/second within a 1 cm^2 area. Pain intensity was reported using a numerical rating scale (NRS) where 0 represents no pain and 100, maximal imaginable pain. The process was repeated five times and WUR calculated by dividing the mean pain report following the ten applications, by the mean intensity reported from single stimuli. **Mechanical pain sensitivity (MPS)** was assessed using the same set of seven weighted pinprick stimuli to obtain a stimulus–response function for pinprick-evoked pain (the strongest pinprick force was about eight times the mean mechanical pain threshold). Subjects were asked to give a pain rating for each stimulus on a '0–100' numerical rating scale ('0' indicating "no pain", and '100' indicating "most intense pain imaginable"). This test was designed to detect pinprick hyperalgesia. **Dynamic mechanical allodynia (DMA)** was assessed as part of this test using a cotton wisp, a cotton wool tip and a standardised brush (Somedic Sweden) exerting a force of 200-400 mN. **Pressure pain threshold (PPT)** was assessed at the thenar eminence and instep using a pressure gauge devise (FDN 200, Wagner instruments, USA) with a probe area of 1 cm^2. Pressure pain threshold was determined using three series of ascending stimulus intensities at an increasing ramp of 50 KPa/s.

The findings for each parameter are compared with a control Caucasian population by means of *Z*-scores. The *Z*-score represents the result of a raw score minus the mean of the population and this is further divided by the standard deviation of the population. *Z* scores above or below ±2 standard deviations represent hyper-/hypo-sensitivity and hyper-/hypo-algesia. In the cases when upper limits allowed by the ethics committee for pain testing were reached, the cut-off value expressed is equivalent to the maximum stimulation before it causes any tissue damage (0° to 52°C for temperature, 512mN for mechanical pain, 10Kg for pressure pain).

Skin biopsy

A punch skin biopsy was taken from 10 cm above the lateral malleolus of the leg of the proband and fixed overnight with 2% periodate-lysine-paraformadelhyde and preserved

in sucrose before blocked and processed into 50 μM sections. Nerve fibres were stained using rabbit anti-PGP (protein gene product) 9.5 Ab (1:2000; Ultraclone Ltd, Yarmouth, Isle of Wight, UK) and Cy3 anti-rabbit (1:500; Jackson Immunoresearch, West Grove, PA, USA). By means of a Zeiss LSM 710 confocal microscope, z-stacks (2 μm intervals), maximum intensity projections were generated with a Plan-Apochromat objective at 20× magnification (Carl Zeiss MicroImaging GmbH, Jena, Germany). Analysis was performed as per published guidelines. [16] PGP 9.5-positive nerve fibres crossing the dermal-epidermal junction were counted and IENFD counts are given in number of fibres per millimetres of skin.

Whole exome sequencing

For enrichment of exons and flanking intronic sequences we used the Agilent Human SureSelect V5 kit with UTRs. We performed 100 bp paired-end runs on a Genome Analyzer HiSeq 2000 system (Illumina) generating sequences of 5.2 (PFS), 5.3 (son), 5.4 (mother) and 5.6 (daughter) Gb. This amount of data resulted in the following percentages of targets being covered at greater than or equal to 10x: 95.7 (PFS), 96 (son), 96 (mother) and 96.2 (daughter). Sequence alignment and variant calling was performed against the reference human genome assembly (hg19) by using the Burrows-Wheeler Aligner[17] and the Genome Analysis Toolkit. [18,19] Format conversion and indexing were performed with the Picard software. Single nucleotide variants and small insertions and deletions were checked against established databases (1000 Genomes Project and dbSNP v.142). Variants were further checked using the ExAC browser, dbSNP v.150 and in our in-house database of sequencing data for other diseases (n>2000). The protein coding effects of variants was predicted using SIFT, Polyphen2 and M-CAP. Splicing changes were analysed using the NNSPLICE Splice Site Predictor. Novel variants were verified by Sanger sequencing and checked to see how they segregated within the family (primers available on request).

Genomic copy number analyses

Genomic DNA isolated from a peripheral blood sample from PFS was used for the Cytoscan HD Copy Array (Affymetrix) and run by AROS according to the manufacturer's conditions. Data was analysed using Chromosome Analysis Suite (Affymetrix) software

and novel genomic variants identified by comparison to the Database of Genomic Variants (DGV).

Deletion breakpoint cloning

A range of primers were designed that were predicted to flank the microdeletion identified in the Cytoscan HD Copy Array. A 2,259 bp product was amplified from PFS and the son using LA Taq DNA Polymerase (Clontech) and the primers 5'CCACCAGTGTGCTGGTGGCTAC (SEQ ID NO: 8) and 5'AGCCTCTGGGGCACTTTGACTC (SEQ ID NO: 9) (Fig. 6A). Primers closer to the deletion breakpoints were then designed and used to amplify a 1349 bp product using KAPA HiFi DNA Polymerase and the primers 5'TTAATGTCTGGAGTGATAACATGAC (SEQ ID NO: 10) and 5'ACAACTTCTAATTAGTGTTAATGAC (SEQ ID NO: 11). Sanger sequencing of the gel purified PCR product (Qiagen) using primers 5' TTAATGTCTGGAGTGATAACATGAC (SEQ ID NO: 10) and 5' AAGGCCGGGCGCGGTGACTTAC (SEQ ID NO: 12) enabled identification of the microdeletion breakpoints (Fig. 6B).

PCR amplification and Sanger sequencing of SNP rs324420

Genomic DNA was used as template to amplify a 424 bp product from the region containing SNP rs324420 using primers 5' CTCTGGGCCATGTTGCTGGTTAC (SEQ ID NO: 13) and 5' CAACTGTCACACAGGCCAAAACAG (SEQ ID NO: 14). Purified PCR products were Sanger sequenced by standard methods.

Cloning *FAAH-OUT*

Partial expressed sequence tags (ESTs) were identified downstream of the microdeletion that in Refseq were assembled into a 1267 bp sequence (NR_045483) and annotated as 'fatty acid amide hydrolase pseudogene (*FAAHP1*) non-coding RNA'. To identify further 5'exons, the *FAAHP1* locus from a variety of species was searched using the UCSC genome browser. This led to the identification of EST CN788775 in the cow genome. The nucleotide sequence of this EST was compared to the human genome using the Blat tool and consensus splice donor and acceptor sites identified within the human

genomic DNA sequence. Human adult brain total RNA was reverse transcribed into cDNA using oligo d(T) and the Superscript III first-strand synthesis system (Invitrogen). A forward primer mapping to the most 5' predicted exon (5' CCAGAAGTGGAGGGAGGTAGCAC (SEQ ID NO: 15) and a reverse primer in a downstream predicted exon (5' GCTGTCATAGGTGTCCTTGAGGCTC (SEQ ID NO: 16) were designed and used to amplify a product from human adult brain cDNA. Sanger sequencing confirmed the amplicon to be novel human exons mapping 5' to *FAAHP1*. Next, 5'RACE was carried out using whole human brain Marathon-Ready cDNA (Clontech) using reverse primer (5' CAAAGTGAGACTCCGTCTGCTGC (SEQ ID NO: 17) according to the manufacturer's conditions. The generated amplicon was cloned into the pCR-Blunt II-TOPO (Thermofisher) and sequenced using M13 forward and reverse primers. A forward primer (5' GGCAAAGGCGCCATTCTCCTGGGTACA (SEQ ID NO: 18) was then designed at the most 5' end of the newly identified transcript and a reverse primer (5'GCCAGTCAGAAAATGTTTATTGAGCTC (SEQ ID NO: 19) in the most 3' exon of NR_045483. Human cerebral cortex cDNA was used as template to amplify a 2845 bp product, which was subsequently cloned into pCR-Blunt II-TOPO and fully sequenced. The insert of the sequenced clone (CC2) has been submitted to GenBank under accession number KU950306 and we name the gene *FAAH-OUT*.

Real-time qPCR analysis in human tissues

One μg of total RNA derived from a range of human tissues (Clontech) was reverse transcribed using oligo d(T) and Superscript III first-strand synthesis system (Invitrogen) according to the manufacturer's conditions. Real time PCR was carried out using the Universal SYBR Green Supermix protocol (Bio-Rad) and the following primers: *FAAH-OUT*, 214 bp (5' ACTGACACAGGTGACAGCATCTG (SEQ ID NO: 20) and 5' GTCCAGTCGGTACATGTCTTCAC (SEQ ID NO: 21); and Actin (*ACTB*), 144 bp (5' CCTGGCACCCAGCACAAT (SEQ ID NO: 22) and 5' GGGCCGGACTCGTCATACT (SEQ ID NO: 23). These assays were performed on the BioRad CXF Connect™ real-time thermal cycler. *FAAH-OUT* expression was compared with that of Actin measured on the same sample in parallel on the same plate, giving a CT difference (ΔCT) for *ACTB* minus the test gene. Mean and standard error were performed on the ΔCT data and converted to relative expression levels (2^ΔCT).

RNAscope in adult human dorsal root ganglia tissue

RNAscope fluorescent *in situ* hybridization was performed with the RNAscope® Multiplex Fluorescent V2 Kit according to the manufacturer's experimental protocol for formalin-fixed paraffin-embedded (FFPE) samples. The fluorochromes used to detect target RNA molecules were Opal520 (green) and Opal650 (red) by PerkinElmer at 1:1000 dilution. The specific RNAscope® probes for *FAAH* (#534291-C2) and *FAAH-OUT* (#534301-C3) RNAs were designed and synthesized by ACD company (BioTechne). DAPI staining was used to stain nuclei. Images were collected using Zeiss LSM-880 microscope with Airscan using 4x averaging, exported as uncompressed TIF files and finalised using Adobe Lightroom 7 photoshop.

Assessment of plasma endocannabinoids (EC)

Levels of AEA, PEA, OEA and 2-AG were measured by mass spectrometry from blood samples taken from PFS and 4 unrelated normal controls. Study participants were PFS (index patient, female, post-menopausal (aged 69), *FAAH-OUT* microdeletion and A/C for rs324420); control A (female, post-menopausal (aged 50), CC for rs324420); control B (male, aged 57, CC for rs324420); control C (female, post-menopausal (aged 50), AC for rs324420) and control D (male, aged 49, AC for rs324420). Study participants were free of all medications for at least four weeks. Whole blood, anticoagulated with EDTA, was obtained between 8-9 AM following overnight fasting through venipuncture of a forearm vein. Ex vivo blood was settled on ice for <20 mins and centrifuged at 4°C and plasma stored at -80°C until assayed. Assay of plasma levels of endocannabinoids N-arachidonoylethanolamide (AEA) and 2-arachidonoylglycerol (2-AG) was performed using a previously published method.[20] In brief, 500ul of plasma was directly pipetted into 2ml of acetonitrile, to which the internal standards [$^2H_8$]-AEA (5 pmol) and [$^2H_8$]-2-AG (5 nmol) (Cayman Chemicals, Ann Arbor, MI) had already been added. All samples were sonicated and stored at -20°C overnight to precipitate proteins. The following morning all samples were centrifuged at 1500 x g for 4 minutes, after which the supernatant was transferred to a new vial and centrifuged again under the same parameters. The supernatant from this second centrifugation was then transferred to a clean borosilicate glass tube and dried down under nitrogen gas. All samples were then resuspended in 200ul

of acetonitrile and stored at -80°C until analysis. AEA and 2-AG were quantified using liquid chromatography and tandem mass spectrometry (LC-MS/MS) as described previously[20] and all values were normalized to concentration per ml plasma.

Fibroblast cell lines and microarray analyses

Primary fibroblasts were extracted from a skin biopsy from patient PFS and 4 unrelated female controls (A, D, E and F) and passaged in DMEM containing 20% foetal bovine serum. RNA was isolated using TRIzol Reagent (Life Technologies) and Purelink RNA micro kit (Thermo Fisher) according to the manufacturer's instructions. Microarray analyses were carried out using the Clariom D human transcriptome array (Applied Biosystems) and WT plus kit. Differential gene expression analysis of transcriptome array data was performed using the Transcriptome Analysis Console (TAC Ver 4.0, Thermo Fisher).

CRISPR/Cas9 plasmids

Plasmids 61591[21] and 106219[22] (Addgene) were modified for the gene editing (SaCas9) and transcriptional repression (dSaCas9-KRAB) CRISPR experiments. For gene editing plasmid 61591, the CMV promoter was replaced with a shorter promoter sequence derived from the housekeeping *Eef1a1* gene and the bGH polyadenylation sequence was replaced with a shorter synthetic polyadenylation sequence. gBlocks gene fragments (IDT) were designed to contain a U6 promoter, guide sequence and modified guide scaffold[23] with the design enabling two guide cassettes to be inserted into one plasmid by In-Fusion cloning (Takara). Guide sequences were designed to flank the microdeletion observed in patient PFS. Plasmid HMa contained guides CCCAGTGAGTACGATGGCCAG (SEQ ID NO: 24) and TTAGTGATATTGTTCCGTGGG (SEQ ID NO: 25). Plasmid HMb contained guides TCATGGCCTTTCCCCTTCTCA (SEQ ID NO: 26) and GTCACTTGCAGTCTGATTAAG (SEQ ID NO: 27). The 'empty vector' control contained *Eef1a1*-promoter driven SaCas9 but no guide sequences. For the transcriptional repression CRISPRi experiments the AgeI-EcoRI fragment from plasmid 106219 containing the dSaCas9-KRAB sequence was used to replace the SaCas9 sequence from plasmid 61591, to give a CMV driven dSaCas9-KRAB. Next a gBlocks gene fragment (IDT) was designed to contain a synthetic poly(A) sequence, U6 promoter, guide sequence

and modified guide scaffold[23]. This sequence was cloned into the EcoRI-NotI sites of the modified plasmid 61591 using In-Fusion cloning (Takara). The guide sequence 'FOP1' (AAAAGGTGAGGTCACGAGGCC (SEQ ID NO: 28)) was located within a DNase hypersensitivity site approximately 323 bp upstream of the *FAAH-OUT* transcriptional start site. The 'empty vector' control contained the CMV driven dSaCas9-KRAB but no guide sequence.

Transfection of CRISPR/Cas9 plasmids into HEK293 cells

Lipofectamine 3000 (Invitrogen) was employed as a DNA carrier for transfection into human embryonic kidney 293 cells (ECACC) according to the manufacturer's procedures. The HEK293 cells were cultured in Dulbecco's modified Eagle's medium (Life Technologies, Inc.) with 10% fetal bovine serum (Hyclone). Lipofectamine 3000 was diluted into Opti-MEM I Reduced Serum Medium (Life Technologies, Inc.). 5µg of plasmid DNA was first diluted into Opti-MEM and 10µl of P3000 reagent was added to the mixture. The DNA-liposome complex was prepared by adding diluted DNA into diluted Lipofectamine (ratio 1:1) and incubating the mixture at room temperature for 30 min. DNA-liposome mixture was added to 70% confluent HEK293 cells. After 24 hours of incubation at 37 °C, media was removed and the transfection steps were repeated. The cells were incubated at 37°C in a 5% CO_2 incubator with 92-95% humidity for another 24 hours. To extract total RNA from cultured cells, medium was first aspirated off and cells were rinsed with ice cold PBS. 1ml of Trizol® was added directly to the cells and it was incubated for 5 minutes at room temperature. Cell lysate was passed through a pipet up and down several times. RNA was extracted using PureLink™ RNA Micro Scale Kit (Invitrogen) according to the manufacturer's procedures. Genomic DNA was isolated using the DNeasy Blood and Tissue kit (Qiagen) and used as template to confirm gene editing. Primers 5'TTAATGTCTGGAGTGATAACATGAC (SEQ ID NO: 10) and 5'ACAACTTCTAATTAGTGTTAATGAC (SEQ ID NO: 11) were used to amplify a ~463 bp band from HMa transfected cells and a ~598 bp band from HMb transfected cells. The size of the microdeletion induced by plasmids HMa and HMb was ~9017 bp and ~8882 bp respectively.

Taqman real-time PCR

Primary fibroblast and HEK cell RNA (5 µg) (from the CRISPR/Cas9 experiments) was reverse transcribed using oligo d(T) and Superscript III first-strand synthesis system (Invitrogen) according to the manufacturer's conditions. Taqman real-time PCR was carried out using the following probes: *FAAH* (Hs01038660_m1), *BDNF* (Hs03805848_m1) and *Actin* (Hs01060665_g1). *FAAH* or *BDNF* expression was compared with that of Actin measured on the same sample in parallel on the same plate, giving a CT difference (ΔCT) for *ACTB* minus the test gene. Mean and standard error were performed on the ΔCT data and converted to relative expression levels (2^ΔCT).

RESULTS

Case report

A 66-year-old Caucasian female (herein called PFS) presented to Raigmore Hospital in Inverness, Scotland for orthopaedic surgery, specifically a trapeziectomy with LRTI and EPL realignment following a diagnosis of bilateral pantrapezial osteoarthritis. PFS had a significant deformity and deterioration in the use of the right thumb, but which she reported as painless. The pre-assessment note classed her as ASA I (American Society Anesthesiologist grading) but highlighted that she had a history of vomiting after intake of Morphine. For the surgery she was given general anaesthesia along with an ultrasound guided axillary nerve block. Intra-operatively [between 1530-1630 hours] she received Fentanyl 50 mcg iv, Propofol 200 mg iv, Ondansetron 4 mg iv and 20 ml of 0.25% l-bupivacaine in the axillary nerve block. Post-operatively, her pain intensity score was recorded as 0/10 on the nursing early warning chart (NEWS) consistently till the next day when she was discharged home after the surgery. The only post-operative analgesic she received during her hospital stay was intravenous Paracetamol 1 gm iv in the post anaesthesia care unit [1705 hours] on the day of her surgery. She was also administered Cyclizine 50 mg iv [1655 hours] and Cyclizine 50 mg iv at 1705 hours. PFS did not, extraordinarily, require post-operative pain killers for this known painful surgery (trapeziectomy), and at the bedside was observed to show no pain from pinching or from peripheral iv cannula manipulation, which led to further investigations.

PFS had previously been diagnosed with osteoarthritis of the hip which she reported as painless, which was not consistent with the severe degree of joint degeneration. At 65 years-of-age she received a hip replacement and was administered only two tablets

of Paracetamol 1 gram orally on post-operative day 1 and 2. PFS reports that she was encouraged to take the Paracetamol but that she did not ask for any pain killers. She was also administered a single dose of Morphine (MST Morphine Sulphate 10 mg) on the post-operative evening. This caused severe nausea and vomiting for 2 days. Post-operatively, her pain intensity scores were recorded as 0/10 throughout except for one score of 1/10 at 2200 hours on the post-operative evening. Her past surgical history is notable for multiple varicose vein and dental procedures. PFS states that she has never required analgesia following any of these interventions.

PFS reports a long standing history of painless injuries where she did not use analgesics (e.g. suturing of a cut ear, fractured left wrist). Throughout her life she has had numerous episodes where she has burned and cut herself without any pain being elicited. She often smells the burning flesh before noticing any burning injury and that is the only alerting situation to the injury. She notes these wounds heal very quickly and often leave little or no residual scar. Mosquito bites cause her inflammation (redness and swelling) and nettle stings are noted as pleasant and not painful.

Menstruation began at 11 years-of-age with periods being uncomfortable, causing her bloating, and a general feeling of unpleasantness. She did not complain about pain during her two childbirths at 29 and 42 years of age (although remembers receiving gas analgesia). She recalls labour as causing her a sensation of pressure, felt unpleasant, but not painful. She required stitches for a tear but no painkillers were required.

PFS lives with her husband and has been a teacher before she retired. She has a daughter and son from her previous marriage. Her family history is unremarkable for neuropathy or painful conditions. Her mother and daughter appear to perceive pain normally. Her father (now deceased) had little requirement for pain killers. Her son also reports of having some degree of pain insensitivity but not to the same extent as his mother. He does not feel pain from donating blood or from cuts or bruises and frequently scalds his mouth with hot drinks and food and not realising until skin starts to peel off. He reports never having the need to take pain killers.

PFS is not taking any medication at present and is fit and active. She is awaiting a trapeziectomy in her other hand. She has no other medical conditions apart from arthritis. PFS has a very talkative and happy, non-anxious, disposition with an ever-optimistic outlook. She reports of long-standing memory lapses (e.g. frequently forgetting words

mid-sentence and placement of keys). She reports of never panicking, not even in dangerous situations, such as in a recent road traffic accident.

Following the painless trapeziectomy surgery, at 67 years-of-age, PFS was referred to and further investigated by pain genetics teams from University College London and the University of Oxford. Ethical approval was granted from both Institutions and written consent taken. On clinical examination there were multiple scars around the arms and on the back of hands. Blood pressure was 105/75 mmHg lying with no postural drop. Examination of the cranial nerves was normal and there was no muscle weakness or significant motor abnormalities in the limbs. All deep tendon reflexes were preserved. In the upper limbs light touch, joint position sense and vibration were preserved distally, but temperature sensation was lost to the wrists bilaterally and pin prick sensation was impaired to the shoulder (i.e. it was felt as a touch but did not elicit the sharp pricking painful sensation). In the lower limbs touch, joint position sense and vibration were also preserved distally. Temperature sensation was lost to the base of the toes and pinprick sensation was lost to the knees. Quantitative sensory testing (Fig. 4) demonstrated hyposensitivity to noxious heat both in the hands and the feet. A skin biopsy showed a normal intra-epidermal nerve fibre density.

Additional clinical information

PFS was born in 1947 and reports of no problems with walking or speech and other developmental milestones were achieved without issues. Education was unremarkable and has completed primary school teacher training and has a diploma in special needs education. She has no problems smelling and can tell the difference between coffee, orange, perfume, mint and she enjoys spices and different flavours. PFS has never smoked tobacco and very occasionally consumes alcohol. She has been a vegetarian for 38 years and a vegan for 11 years and there is no clinical history of vitamin deficiencies. Of note, her dental surgeon observed, most unusually, that her saliva dissolves the fixative for a temporary denture after just 90 mins.

Upon examination at 67 years-of-age her height was 170 cm and weight was 63 kg. The intra epidermal nerve fibre density from the distal leg (10 cm above the lateral malleolus) was 5.8 f/mm and within normal range for age and gender.[24] Nerve conduction tests demonstrated normal motor and sensory conduction parameters. She refers to a

burning sensation in her toes due to the hallux valgus which is accompanied by tingling and pins and needles which she describes as being "pleasant". Sweating is normal in warm conditions.

Genetic tests

Genomic DNA was isolated from peripheral blood samples donated from PFS, her two children and her mother. Exome sequencing was performed for all 4 members to identify a pathogenic mutation for this novel disorder. Given the partial phenotype in the son we predicted a dominant inheritance pattern with variable expressivity. We also considered that PFS may be presenting with a full phenotype due to the inheritance of an additional loss of function allele. Given the previously undescribed phenotype, we searched for novel variants in PFS's exome which were absent in her unaffected mother and daughter, but inherited by her son. Following filtering of variants we identified 4 candidate mutations in PFS and her son: *MACF1* (NM_012090:c.C14416T:p.L4806F); *USP24* (NM_015306:c.G6490A:p.V2164M); *KIAA1107* (NM_015237:c.A3359G:p.N1120S) and *NSD1* (NM_022455:c.C6703T:p.H2235Y). The variants in *USP24*, *KIAA1107* and *NSD1* are annotated as benign by the Polyphen2 (HumVar) tool. The *MACF1* variant is annotated as 'probably damaging' and is a neural gene. However, we considered this microtubule-actin crosslinking factor to be a low priority candidate following an analysis of known gene functions in relation to pain.[25] Instead, we broadened our genetic analyses and searched for cytogenetic copy number changes using the Cytoscan HD Array (Affymetrix). This analysis identified an ~8 kb heterozygous microdeletion in PFS on chromosome 1 (Fig. 5) that began ~4.7 kb downstream from the 3' end of *FAAH* (Fig. 1A). One Colombian male (HG01353) out of 5008 alleles screened in the 1000genomes project also carries a similar-sized microdeletion, but is homozygous wild-type for *FAAH* SNP rs324420.

Validating microdeletion and cloning of *FAAH-OUT*

To confirm the existence of the microdeletion, PCR primers flanking the predicted deleted region were designed and used to amplify the mutant PFS allele (Fig. 6A). The deletion breakpoints were identified by Sanger sequencing (Fig. 6B) which showed the size of the microdeletion to be 8,131bp. AluSp repeat sequences (Fig. 1 and 6C) flank the

microdeletion and are likely to predispose this region to genomic rearrangements. PCR analysis (Fig. 6A) showed the partially affected son inherits the microdeletion, but it is not present in the genomes of the unaffected mother and daughter. Furthermore, Sanger sequencing showed PFS to be heterozygous for the FAAH hypomorphic SNP (rs324420) (Table 1).

Table 1: Genotype summary

The proband (PFS) carries both the *FAAH-OUT* microdeletion and the hypomorphic *FAAH* SNP and displays a full hypoalgesic phenotype. Her son carries the *FAAH-OUT* microdeletion and presents a partial hypoalgesic phenotype. Neither the unaffected mother nor daughter carry the microdeletion and have no pain-sensing deficits.

	Hypoalgesic phenotype	***FAAH-OUT* microdeletion**	***FAAH* hypomorphic SNP (rs324420)**
PFS	Full	Het	Het
Mother	Normal	WT	Het
Son	Partial	Het	WT
Daughter	Normal	WT	Het

Given the extraordinary phenotype in PFS and the vicinity of the microdeletion to *FAAH*, we investigated how the microdeletion could be pathogenic. Interestingly, partial human expressed sequence tags (ESTs) were identified downstream of the microdeletion that were annotated as an *FAAH* pseudogene, *FAAHP1* (herein called *FAAH-OUT*), and further analyses using the cow genome identified potential further conserved 5' exons. Using RT-PCR and 5'RACE we cloned a full-length transcript with robust expression in adult brain. Like *FAAH*, this 2.845kb *FAAH-OUT* sequence is expressed in fetal and adult brain and in dorsal root ganglia tissue (Fig. 1B). RNAscope analyses in adult human dorsal root ganglia sections show that the *FAAH-OUT* transcript predominantly localises to the nucleus, which is consistent with a potential role of the RNA regulating the expression of *FAAH* (Fig. 2). Sequence alignments show ~70% nucleotide identity within an 800 bp region between *FAAH* and *FAAH-OUT* (Fig. 7A). Open reading frame and Kozak consensus analyses (ATG^{pr}) indicate that the most likely predicted FAAH-OUT peptide

contains 166 amino acids (Fig. 7B) and shares 69% similarity to a region of FAAH (Fig. 7C), although *FAAH-OUT* is potentially more likely to function as a long non-coding RNA.[26, 37]

To determine the effects of carrying both the microdeletion in *FAAH-OUT* and the hypomorphic *FAAH* SNP, we measured circulating fatty acid amide levels from blood samples from PFS and compared them to four control individuals, 2 of which were heterozygous carriers of the SNP. Strikingly, AEA levels were increased by 70% and circulating levels of OEA and PEA were approximately tripled compared to controls (Fig. 3). The levels of 2-AG, another endocannabinoid but not a substrate for FAAH, were largely unaltered. These results are consistent with FAAH showing a significant loss of function in the patient.

BDNF is upregulated in patient fibroblasts

To further investigate the downstream effects of carrying the *FAAH-OUT* microdeletion and hypomorphic *FAAH* SNP, we isolated fibroblasts from a skin biopsy from patient PFS and 4 unrelated female normal controls. Real-time qPCR showed a ~64% reduction in *FAAH* transcript in the patient fibroblast cell line compared to controls (Fig. 8A). Furthermore, microarray analyses showed that brain-derived neurotrophic factor (*BDNF*) was significantly upregulated in the patient fibroblasts compared to controls, which was verified by real-time qPCR (Fig. 8B). An upregulation of *BDNF* is consistent with previous data showing that inhibition of FAAH results in elevated anandamide and BDNF levels and has been linked to an antidepressant-like effect in a rat model of subchronic mild stress.[27]

Gene editing in HEK293 cells

Next, we used gene editing with CRISPR/Cas9 to introduce a similar sized microdeletion in HEK293 cells to the one identified in patient PFS. Transfection of SaCas9 plasmids 'HMa' and 'HMb' (bearing different guide-pairs that flank the microdeletion) resulted in gene editing and generation of a microdeletion in the HEK293 cells (Fig. 9A). Real-time qPCR showed that following transient transfection, the level of *FAAH* transcript was significantly reduced for both plasmids HMa and HMb compared to transfection with a control vector, indicating that the microdeletion directly affects *FAAH*

expression (Fig. 9B). We then searched for DNase hypersensitivity sites upstream of the *FAAH-OUT* gene and designed a guide sequence 'FOP1' within the promoter region of *FAAH-OUT*. Transient transfection of this CRISPRi plasmid bearing dSaCas9-KRAB and guide FOP1 resulted in a ~25% reduction in *FAAH* expression (Fig. 10). Taken together, this data indicates that expression of the full-length *FAAH-OUT* transcript in cis is needed for normal expression of *FAAH*, and is a potential gene therapy route to inhibit normal *FAAH* function.

DISCUSSION

The endocannabinoid system is an important physiological system that performs a wide array of homeostatic functions and is important for pain perception.[28] FAAH is a critical enzyme for the breakdown of a range of bioactive lipids (including the endocannabinoid AEA and related fatty-acid amides and N-acyl-taurines) with diverse physiological roles. Mouse modelling of FAAH loss of function mutations and pharmacological inhibition studies have shown a range of phenotypes including hypoalgesia, accelerated skin wound healing, enhanced fear-extinction memory, reduced anxiety and short term memory deficits.[6,11,29-32] Furthermore, human hypomorphic *FAAH* SNPs are associated with a reduced need for post-operative analgesia, increased postoperative nausea and vomiting induced by opioids and decreased anxiety-linked behaviours.[8,11,14,33-35]

Here we report a new human genetic disorder in a patient with hypoalgesia, altered fear and memory symptoms and a non-anxious disposition. This disorder is due to the co-inheritance of a microdeletion in a novel pseudogene and a known *FAAH* hypomorphic SNP. The microdeletion is flanked by repeat sequences which likely predispose the region to genomic rearrangements, as seen in other genomic disorders.[36] Consequently there is likely to be additional similar individuals in the general population. The likelihood that this disorder has been under-reported is highlighted by the fact that PFS was diagnosed at 66-years-of-age, despite a recurrent history of painless injuries. Lipid profiling in peripheral blood samples showed significant increases in AEA, OEA and PEA in PFS, which could be further exaggerated in the brain and DRG. Further work is needed to understand which fatty-acid amide is the major contributor to the patient phenotype.

The microdeletion removes the promoter and first two exons of *FAAH-OUT* but how this disrupts the function of *FAAH* is still to be exactly elucidated. One hypothesis is that the *FAAH-OUT* transcript normally functions as a decoy for microRNAs due to the high sequence homology and protects *FAAH* mRNA from degradation (Fig. 6A).[26] Alternatively, *FAAH-OUT* may have an epigenetic role in regulating *FAAH* transcription, or the deletion removes a critical transcriptional regulatory element.[36,37] The RNAscope experiments in adult human dorsal root ganglia suggest a nuclear function for *FAAH-OUT*. The gene editing and CRISPRi experiments in HEK293 cells indicate that transcription of full-length *FAAH-OUT* in cis is needed for normal *FAAH* expression.

This patient provides new insights into the role of the endocannabinoid system in analgesia and more specifically on the *FAAH* genomic locus and highlights the importance of the adjacent, previously uncharacterised *FAAH-OUT* gene to pain sensation. Given the previous failure of FAAH-inhibitor analgesic drug trials, these results have significance as they may provide a new route to developing FAAH-related analgesia through targeting of *FAAH-OUT*.

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Sequences

SEQ ID NO: 1 – cDNA sequence of wild-type human *FAAH* (without hypomorphic rs324420 SNP)

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SEQ ID NO: 2 – cDNA sequence of human *FAAH* with hypomorphic SNP rs324420 (C385A) (bold and underlined)

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SEQ ID NO: 3 – cDNA sequence of wild-type human *FAAH-OUT*

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gctcaataaa cattttctga ctggc

SEQ ID NO: 4 – cDNA sequence of human *FAAH-OUT* comprising the microdeletion

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SEQ ID NO: 5 – genomic DNA sequence of wild-type human *FAAH-OUT*

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SEQ ID NO: 6 – genomic DNA sequence of *FAAH-OUT* comprising the microdeletion

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SEQ ID NO: 7 - genomic DNA sequence corresponding to the microdeletion

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SEQ ID NO: 8 – primer
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SEQ ID NO: 9 – primer
5′AGCCTCTGGGGCACTTTGACTC

SEQ ID NO: 10 – primer
5′TTAATGTCTGGAGTGATAACATGAC

SEQ ID NO: 11 – primer
5′ACAACTTCTAATTAGTGTTAATGAC

SEQ ID NO: 12 – primer
5′AAGGCCGGGCGCGGTGACTTAC

SEQ ID NO: 13 – primer
5′ CTCTGGGCCATGTTGCTGGTTAC

SEQ ID NO: 14 – primer
5′ CAACTGTCACACAGGCCAAAACAG

SEQ ID NO: 15 – forward primer
5′ CCAGAAGTGGAGGGAGGTAGCAC

SEQ ID NO: 16 –reverse primer
5′ GCTGTCATAGGTGTCCTTGAGGCTC

SEQ ID NO: 17 – reverse primer
5′ CAAAGTGAGACTCCGTCTGCTGC

SEQ ID NO: 18 – forward primer
5′ GGCAAAGGCGCCATTCTCCTGGGTACA

SEQ ID NO: 19 – reverse primer
5′GCCAGTCAGAAAATGTTTATTGAGCTC

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SEQ ID NO: 24 – guide
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SEQ ID NO: 25 – guide
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SEQ ID NO: 26 – guide
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SEQ ID NO: 27 – guide
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SEQ ID NO: 28 – guide 'FOP1'
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SEQ ID NO: 39 – genomic DNA sequence of wild-type human *FAAH* (without hypomorphic rs324420 SNP), including 5kb either side of *FAAH* (*FAAH* exons in bold)

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TC

SEQ ID NO: 40 – amino acid sequence of wild-type human FAAH (without hypomorphic rs324420 SNP)

MVQYELWAALPGASGVALACCFVAAAVALRWSGRRTARGAVVRARQRQRAGLENMDRAAQRFRLQNPDLD
SEALLALPLPQLVQKLHSRELAPEAVLFTYVGKAWEVNKGTNCVTSYLADCETQLSQAPRQGLLYGVPVS
LKECFTYKGQDSTLGLSLNEGVPAECDSVVVHVLKLQGAVPFVHTNVPQSMFSYDCSNPLFGQTVNPWKS
SKSPGGSSGGEGALIGSGGSPLGLGTDIGGSIRFPSSFCGICGLKPTGNRLSKSGLKGCVYGQEAVRLSV
GPMARDVESLALCLRALLCEDMFRLDPTVPPLPFREEVYTSSQPLRVGYYETDNYTMPSPAMRRAVLETK
QSLEAAGHTLVPFLPSNIPHALETLSTGGLFSDGGHTFLQNFKGDFVDPCLGDLVSILKLPQWLKGLLAF
LVKPLLPRLSAFLSNMKSRSAGKLWELQHEIEVYRKTVIAQWRALDLDVVLTPMLAPALDLNAPGRATGA
VSYTMLYNCLDFPAGVVPVTTVTAEDEAQMEHYRGYFGDIWDKMLQKGMKKSVGLPVAVQCVALPWQEEL
CLRFMREVERLMTPEKQSS

SEQ ID NO: 41 – amino acid sequence of human FAAH that contains the hypomorphic SNP rs324420 (bold)

MVQYELWAALPGASGVALACCFVAAAVALRWSGRRTARGAVVRARQRQRAGLENMDRAAQRFRLQNPDLD
SEALLALPLPQLVQKLHSRELAPEAVLFTYVGKAWEVNKGTNCVTSYLADCETQLSQA**T**RQGLLYGVPVS
LKECFTYKGQDSTLGLSLNEGVPAECDSVVVHVLKLQGAVPFVHTNVPQSMFSYDCSNPLFGQTVNPWKS
SKSPGGSSGGEGALIGSGGSPLGLGTDIGGSIRFPSSFCGICGLKPTGNRLSKSGLKGCVYGQEAVRLSV
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LVKPLLPRLSAFLSNMKSRSAGKLWELQHEIEVYRKTVIAQWRALDLDVVLTPMLAPALDLNAPGRATGA
VSYTMLYNCLDFPAGVVPVTTVTAEDEAQMEHYRGYFGDIWDKMLQKGMKKSVGLPVAVQCVALPWQEEL
CLRFMREVERLMTPEKQSS

CLAIMS

1. A method of analgesic treatment to reduce pain, comprising administering an effective amount of an inhibitor of fatty-acid amide hydrolase pseudogene (*FAAH-OUT*) to an individual suffering from pain.

2. The method according to claim 1, wherein the inhibitor suppresses *FAAH-OUT* gene expression.

3. The method according to claim 1 or 2, wherein the inhibitor suppresses *FAAH-OUT* transcription or reduces the effect of *FAAH-OUT* to achieve an analgesic effect.

4. The method according to any one of the preceding claims, wherein the administration of the inhibitor leads to an increase in the level of N-acyl ethanolamines in the individual, optionally wherein the N-acyl ethanolamines are selected from at least one of anandamide (AEA), palmitoylethanolamide (PEA) and oleoylethanolamine (OEA).

5. The method according to any one of the preceding claims, wherein the inhibitor modifies the DNA sequence encoding *FAAH-OUT*.

6. The method according to claim 5, wherein the modification is made by gene editing.

7. The method according to any one of the preceding claims, wherein the inhibitor is a guide RNA comprising a guide sequence that hybridises to the site of *FAAH-OUT* and targets a CRISPR-Cas enzyme to *FAAH-OUT*.

8. The method according to claim 7, wherein the guide sequence targets the CRISPR-Cas enzyme to a regulatory region of *FAAH-OUT*.

9. The method according to claim 7, wherein the guide sequence targets the CRISPR-Cas enzyme to a promoter of *FAAH-OUT*.

10. The method according to any one of claims 1 to 4, wherein the inhibitor is a single-stranded or double-stranded DNA or RNA molecule directed against *FAAH-OUT*.

11. The method according to any one of the preceding claims, wherein the inhibitor targets a sequence encoding the *FAAH-OUT* gene having SEQ ID NO: 5 or an expression product of said *FAAH-OUT* gene.

12. The method according to any one of the preceding claims, wherein the inhibitor is administered intrathecally.

13. The method according to any one of the preceding claims, wherein the inhibitor is delivered using an adeno-associated vector (AAV).

14. An inhibitor of *FAAH-OUT* for use in a method of treating pain, the method comprising administering an effective amount of said inhibitor to a subject.

15. The inhibitor of *FAAH-OUT* for use according to claim 14, wherein the inhibitor suppresses *FAAH-OUT* gene expression.

16. The inhibitor of *FAAH-OUT* for use according to claim 14 or 15, wherein the inhibitor suppresses *FAAH-OUT* transcription or reduces the effect of *FAAH-OUT* to achieve an analgesic effect.

17. The inhibitor of *FAAH-OUT* for use according to any one of claims 14 to 16, wherein the inhibitor is a guide RNA comprising a guide sequence that hybridises to the site of the *FAAH-OUT* and targets a CRISPR-Cas enzyme to a promoter of *FAAH-OUT*.

18. The inhibitor of *FAAH-OUT* for use according to claim 17, wherein the guide sequence targets the CRISPR-Cas enzyme to a regulatory region of *FAAH-OUT*.

19. The inhibitor of *FAAH-OUT* for use according to claim 17, wherein the guide sequence targets the CRISPR-Cas enzyme to a promoter of *FAAH-OUT*.

20. The inhibitor of *FAAH-OUT* for use according to any one of claims 14 to 16, wherein the inhibitor is a single-stranded or double-stranded DNA or RNA molecule directed against *FAAH-OUT*.

21. The inhibitor of *FAAH-OUT* for use according to any one of claims 14 to 20, wherein the inhibitor is administered intrathecally.

22. The inhibitor of *FAAH-OUT* for use according to any one of claims 14 to 21, wherein the inhibitor is delivered using an AAV vector.

23. A method of analgesic treatment to reduce pain, comprising administering an effective amount of an inhibitor of fatty-acid amide hydrolase gene (*FAAH*) to an individual suffering from pain, wherein the inhibitor is a single-stranded or double-stranded DNA or RNA molecule directed against *FAAH*.

24. The method according to claim 23, wherein the inhibitor suppresses *FAAH* transcription or reduces the effect of *FAAH* to achieve an analgesic effect.

25. The method according to claim 23 or claim 24, wherein the inhibitor modifies the DNA sequence encoding *FAAH*.

26. The method according to any one of claims 23 to 25, wherein the inhibitor targets a sequence encoding the FAAH protein encoded by SEQ ID NO: 1.

27. The method according to any one of claims 23 to 25, wherein the inhibitor targets a sequence encoding the *FAAH* gene having SEQ ID NO: 39.

28. The method according to any one of claims 23 to 27, wherein the modification is made by gene editing.

29. The method according to any one of claims 23 to 28, wherein the inhibitor is a guide RNA comprising a guide sequence that hybridises to the site of *FAAH* and targets a CRISPR-Cas enzyme to *FAAH*.

30. The method according to claim 23 or 24, wherein the inhibitor targets the amino acid sequence of wild-type FAAH protein having SEQ ID NO: 40.

31. An inhibitor of *FAAH* for use in a method of treating pain, the method comprising administering an effective amount of said inhibitor to a subject, wherein the inhibitor is a single-stranded or double-stranded DNA or RNA molecule directed against *FAAH*.

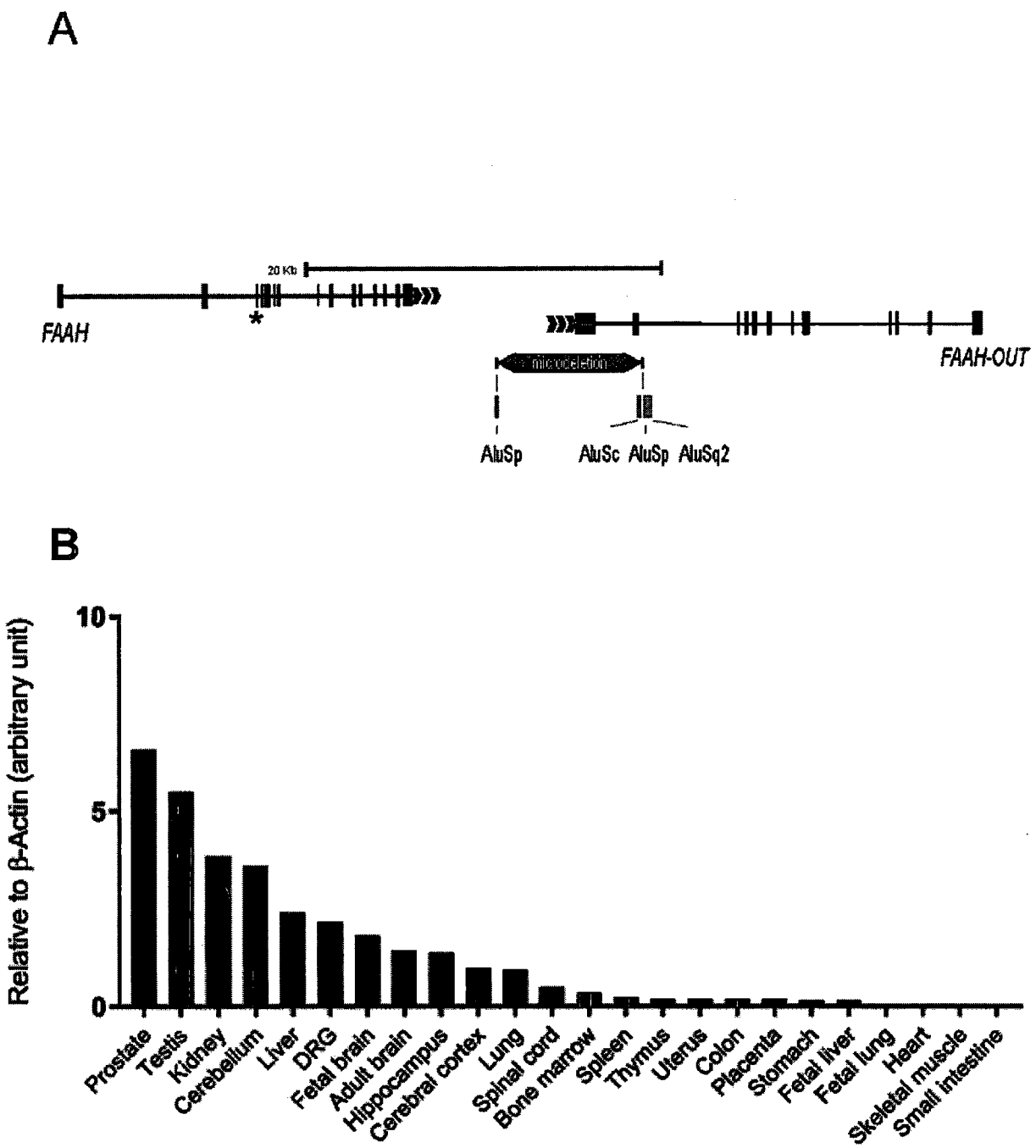
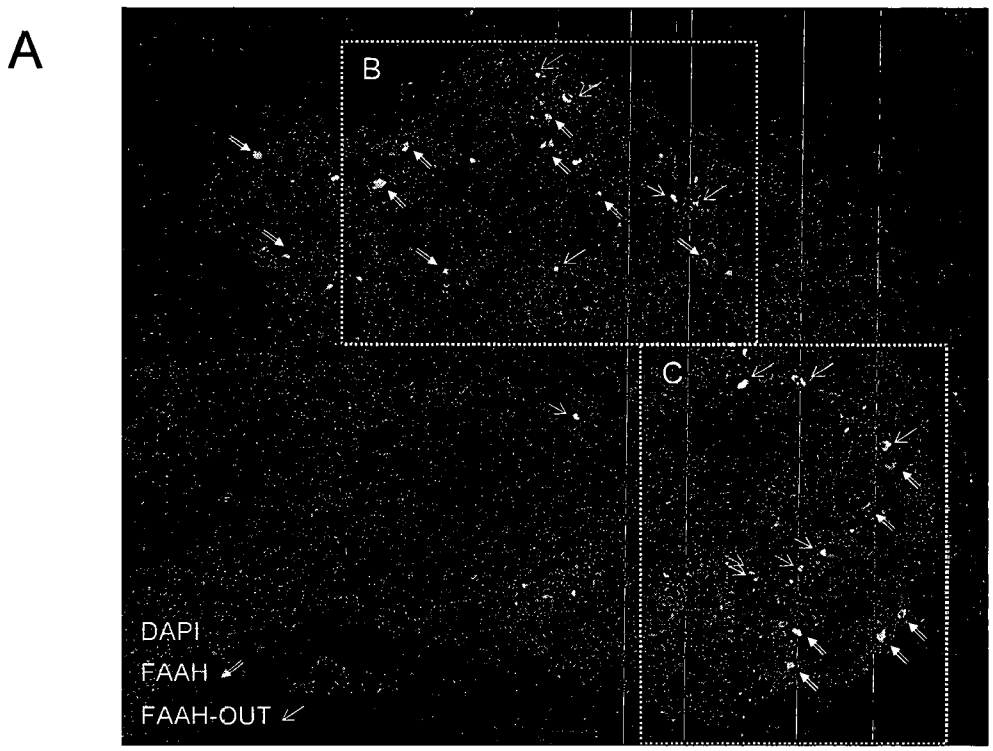

A
20 Kb
FAAH
*
FAAH-OUT
microdeletion
AluSp
AluSc AluSp AluSq2
B
Relative to β-Actin (arbitrary unit)
10
5
0
Prostate
Testis
Kidney
Cerebellum
Liver
DRG
Fetal brain
Adult brain
Hippocampus
Cerebral cortex
Lung
Spinal cord
Bone marrow
Spleen
Thymus
Uterus
Colon
Placenta
Stomach
Fetal liver
Fetal lung
Heart
Skeletal muscle
Small intestine

Figure 1


A
B
C
DAPI
FAAH
FAAH-OUT

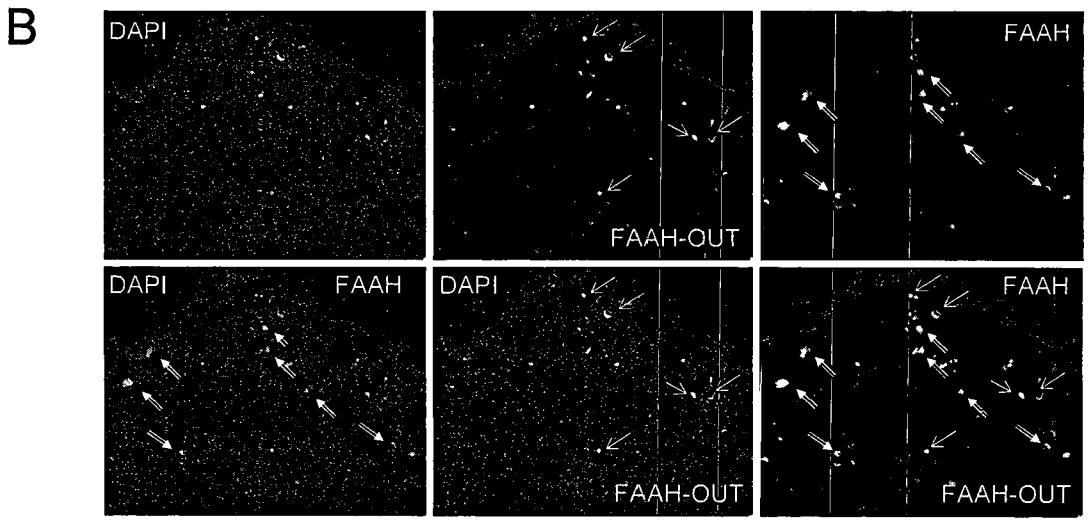

B
DAPI
FAAH-OUT
FAAH
DAPI
FAAH
DAPI
FAAH-OUT
FAAH
FAAH-OUT

Figure 2

C

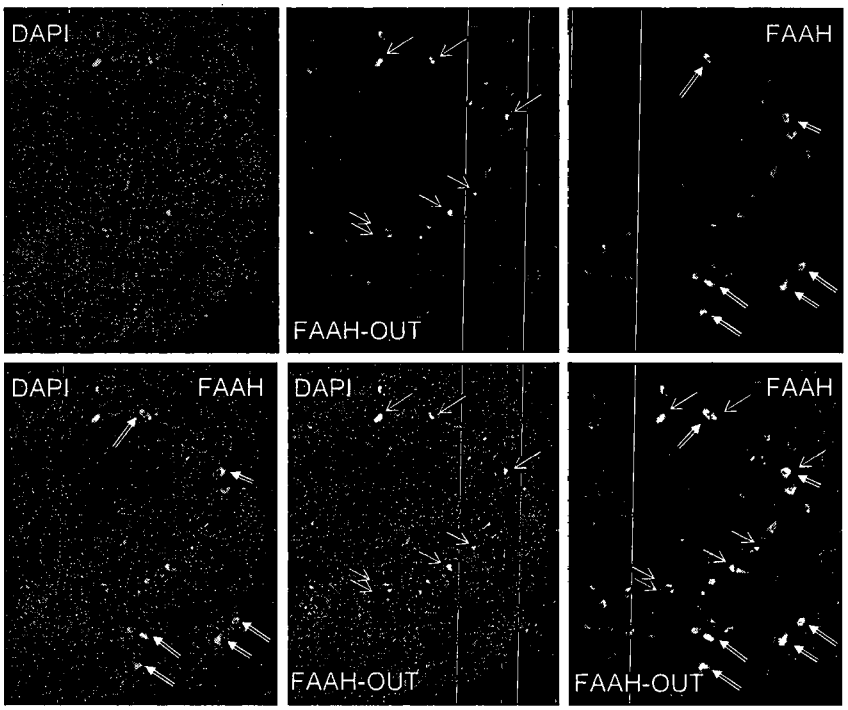
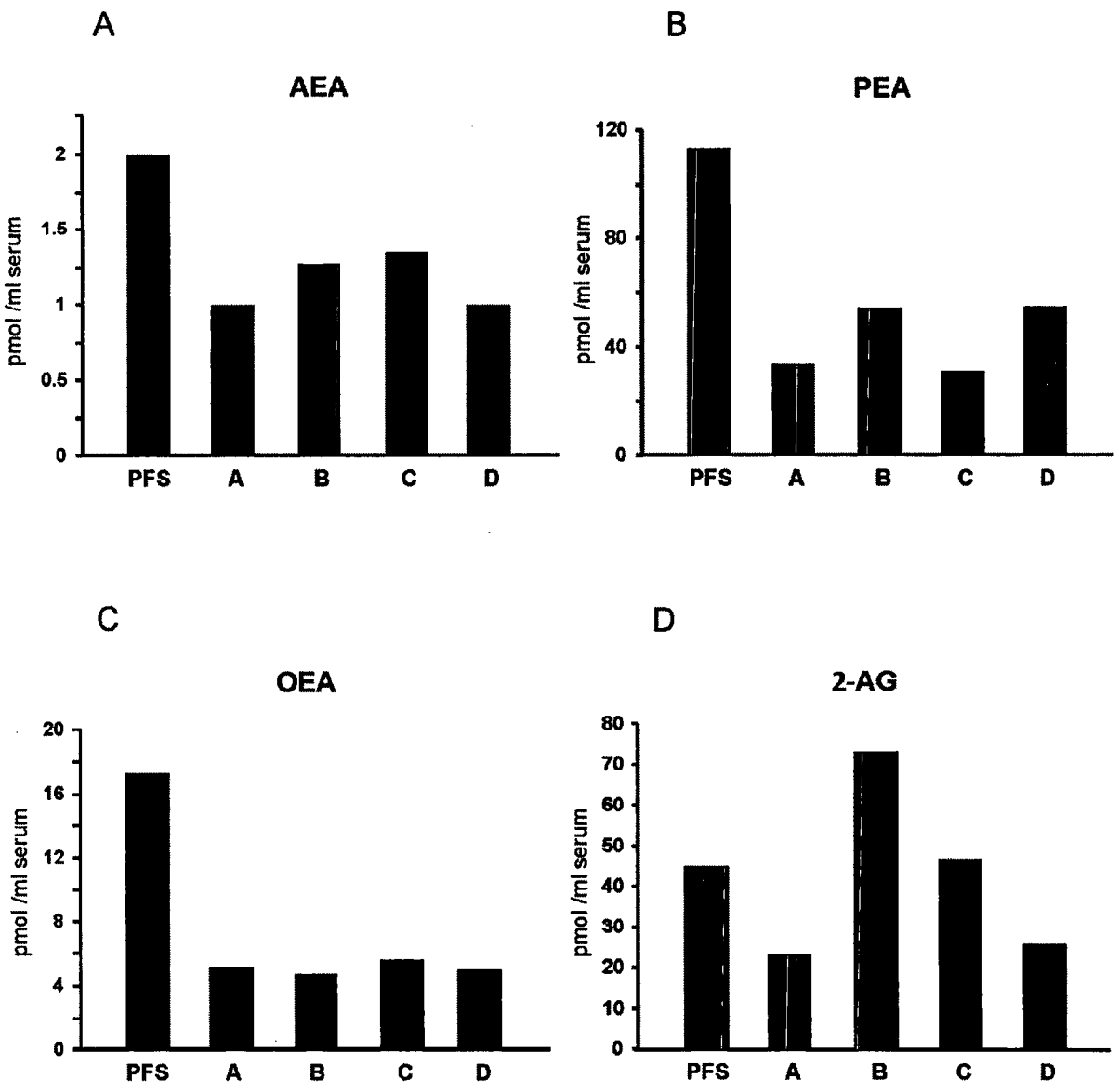


Figure 2 (Cont)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AEA
pmol /ml serum
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1.5
1
0.5
0
PFS
A
B
C
D
B
PEA
pmol /ml serum
120
80
40
0
PFS
A
B
C
D
C
OEA
pmol /ml serum
20
16
12
8
4
0
PFS
A
B
C
D
D
2-AG
pmol /ml serum
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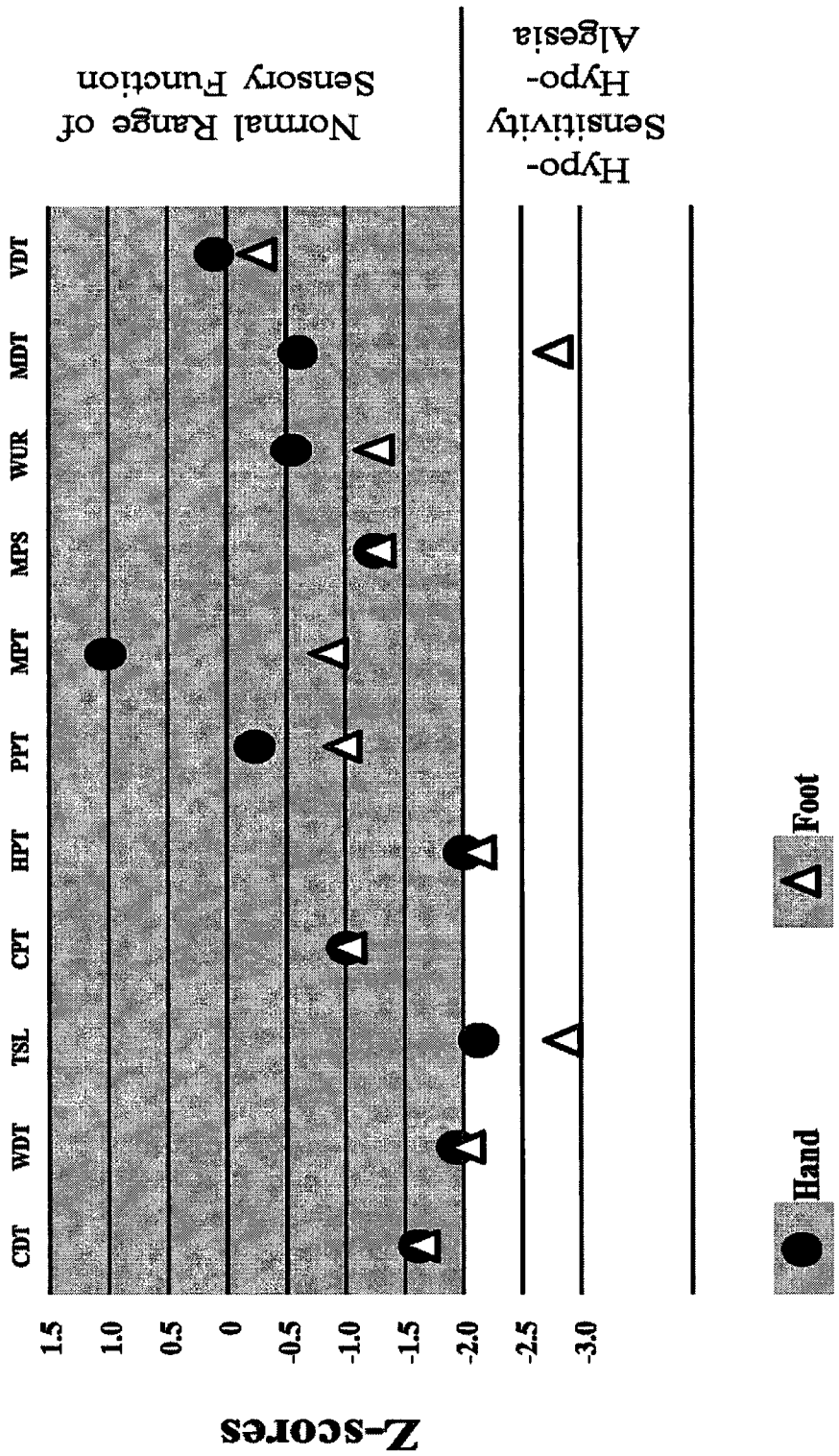
70
60
50
40
30
20
10
0
PFS
A
B
C
D

Figure 3


Hypo-
Sensitivity
Hypo-
Algesia
Normal Range of
Sensory Function
CDT
WDT
TSL
CPT
HPT
PPT
MPT
MPS
WUR
MDT
VDT
1.5
1.0
0.5
0
-0.5
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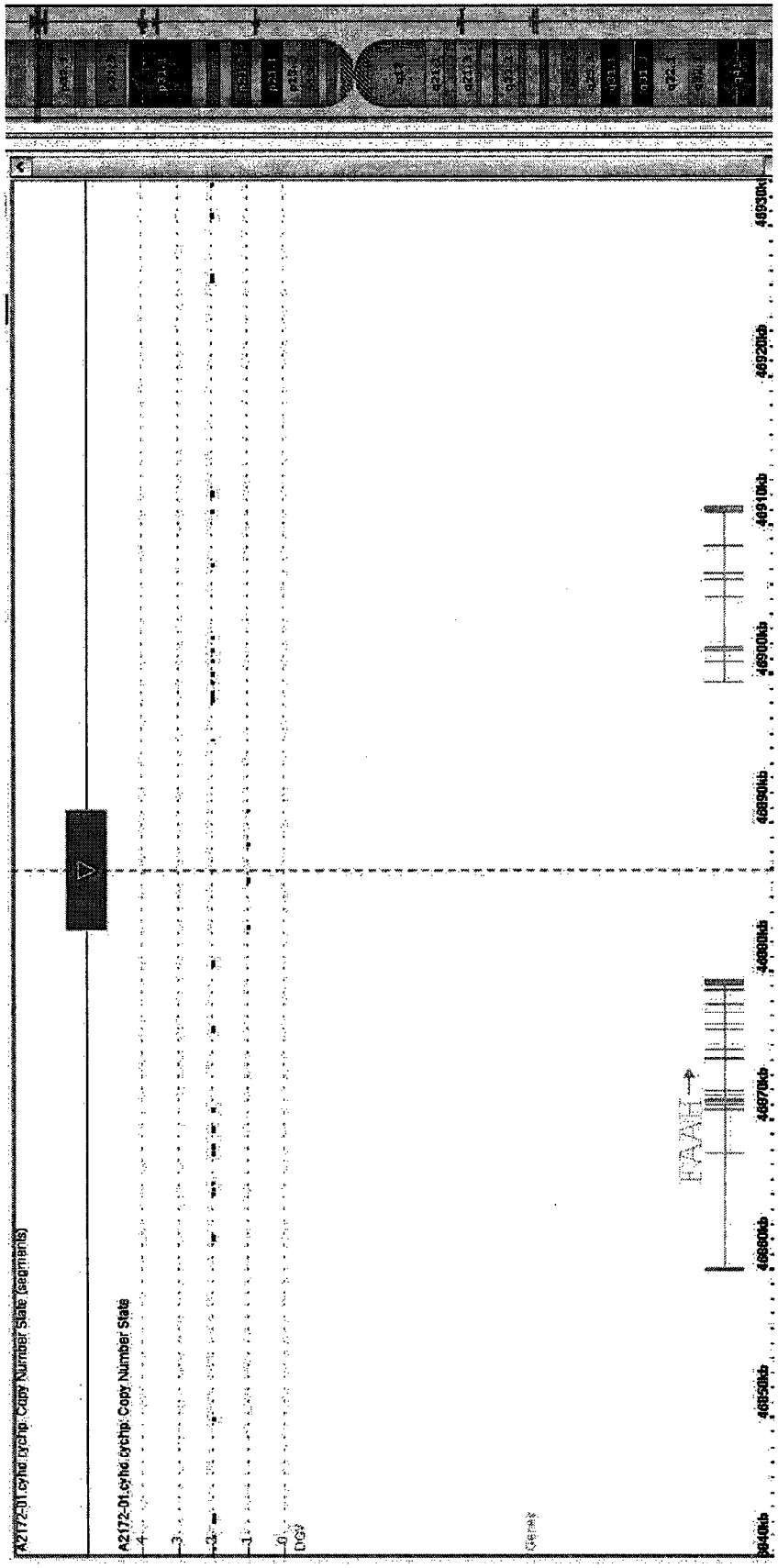
-1.5
-2.0
-2.5
-3.0
Z-scores
Hand
Foot

Figure 4

6/12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4
3
2
1
0
DGV
Genes
RAF1

Figure 5

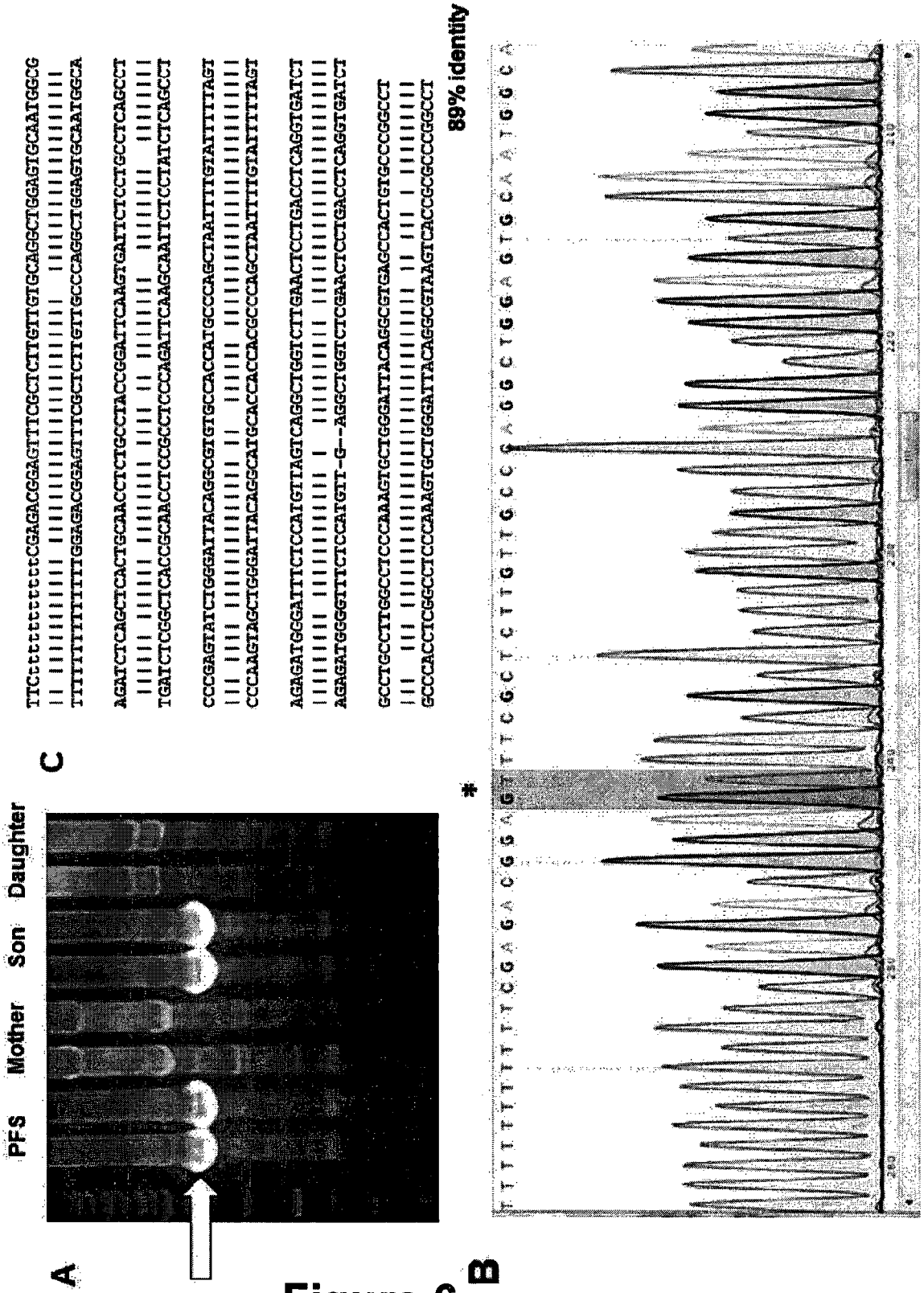

Figure 6

A

```
FAAH       476  GGCCTGCTCTATGGCGTCCCTGTGAGCCTCAAGGAGTGCTTCACCTACAAGGGCCAGGAC
FAAH-OUT  1363  GGCCTTCTCTATGGGGTCCCCATGAGCCTCAAGGACACCTATGACAGCATGGGCCATGAC

FAAH       536  TC--CACGC----TGGGCTTGAGCCTGAATGAAGGGGTGCCGGCGGAGTGCGACAGCGTA
FAAH-OUT  1423  TGTGCATGCCGCCTGGCCTAGTTCCTGGA-GAAGCC-TGC-GACCAAG---GACGGGGTC

FAAH       590  GTGGTGCATGTGCTGAAGCTGCAGGGTGCCGTGCCCTTCGTGCACACCAATGTTCCACAG
FAAH-OUT  1477  ATTATGAAAGTGCTCAAGGCCCAAGGAGCCATCCCCTTTGTTAAGACCAACATCCCACTG

FAAH       650  TCCATGTTCAGCTATGACTGCAGTAACCCCC-TCTTTGGCCAGACCGTGAACCCATGGAA
FAAH-OUT  1537  ACGCTGCTCAGCTTTGAATGCGGCAACTCCCATCTATGGCCAGATGTTGAGCCCACTGAA

FAAH       709  GTCCTCCAAAAGCCCAG--GGGGCTCCTCAGGGGGTGAAGGGGCCCTCATCGGGTCTGGA
FAAH-OUT  1597  CT--TAAAGAAGACATGTGGGGGCTCCTCAGGGGGTGA-GGGGCTCTGCTGGCAGAAAGG

FAAH       767  GGCTCCCCCCTGGGCTTAGGCACTGATATCGGAGGCAGCATCCGCTTCCCCTCCTCCTTC
FAAH-OUT  1654  GGGTCCATCCTAGGCATGGGTACTGACACAGGTGACAGCATCTGCATACCAGCCAGCTTC

FAAH       827  TGCGGCATCTGCGGCCTCAAGCCCACAGGGAACCGCCTCAGCAAGAGTGGCCTGAAGGGC
FAAH-OUT  1714  TGTGGTGTTTATGGCCTCTGGACCACAGGTTCCCGCCTCAGCTACACTGGAATT---GCC

FAAH       887  TGTG---TCTATGG-ACAGGAGGCAGTGCGTCTCTCCGTGG---GCCCCATGGCCCGGGA
FAAH-OUT  1771  TCTGCCATCAAGGGGAAAAAAATCGGTGAC---CACGGTGGCTGGCCCCATGGCCCAGGA

FAAH       940  CGTGGAGAGCCTGGCACTGTGCCTGCGAGCCCTGCTGTGCGAGGACATGTTCCGCTTGGA
FAAH-OUT  1828  CGTGGAGAGCCTGGCGCTGTGCCTGCAAGCCCTGCTGAGTGAAGACATGTACCGACTGGA

FAAH       1000 CCCCACTGTGCCTCCCTTGCCCTTCAGAGAAGAGGT
FAAH-OUT   1888 CCCCACTGTGCTCCAGATGCCCTTTAGGGAGGAGGT
```

68% identity

```
FAAH       1568 CTGTACAACTGCCTGGACTTCCCTGCAGGGGTGGTGCCTGTCACCACGGTGACTGCTGAG
FAAH-OUT   2216 CTGTACAACCTCCTGGACTTTCCCGCGGGCGTGGTGCCTGTCACTATCGTGACACTACAG

FAAH       1628 GACGAGGCCCAGATGGAACATTACAGGGGCTACTTTGGGGATA--TCTGGGACAAGATGC
FAAH-OUT   2276 GACGAGGAGGAACTGGCCTTCTACAAGGGGTGCTACGGAGATAGTTCTGACAAAAATTTC

FAAH       1686 TGCAGAAGGGCATGAAGAAGA-GTGTGGGGCTGCCGGTGGCCGTGCAGTGTGTGGCTCTG
FAAH-OUT   2336 T-CAGA--GGCGGTAAGAGGATCCGTCGGACTTCTGGTGACTGTGCAGTGCATTGCTTTG

FAAH       1745 CCCTGGCAAGAAGAGTTGTGTCTGCGGTTCATGCGGGAGGTGGA
FAAH-OUT   2393 CCATGGGAAGAGGAGCTGTGTCTCCGGTTCATGAAGGAGGTGGA
```

71% identity

Figure 7

B

MLSPVCFLPLLDTSCFGFLAIWSHSLTPKKLWEQHTAVEEYEQEFIAKWR
SLDLDVLLVPVLGSAFYIGSSSLASESQSYVTLYNLLDFPAGVVPVTIVT
LQDEEELAFYKGCYGDSSDKNFSEAVRGSVGLLVTVQCIALPWEEELCLR
FMKEVDTLVKNQRGPK

C

69% homology

```
FAAH      438  SRSAGKLWELQHEIEVYRKTVIAQWRALDLDVVLTPMLAPALDLNAPGRATGAVSYTMLY
               S +  KLWE    +E Y +  IA+WR+LDLDV+L P+L  A  + +   A+ + SY  LY
FAAH-OUT  25   SLTPKKLWEQHTAVEEYEQEFIAKWRSLDLDVLLVPVLGSAFYIGSSSLASESQSYVTLY

FAAH      498  NCLDFPAGVVPVTTVTAEDEAQMEHYRGYFGDIWDKMLQKGMKKSVGLPVAVQCVALPWQ
               N LDFPAGVVPVT VT +DE ++  Y+G +GD  DK   + ++ SVGL V VQC+ALPW+
FAAH-OUT  85   NLLDFPAGVVPVTIVTLQDEEELAFYKGCYGDSSDKNFSEAVRGSVGLLVTVQCIALPWE

FAAH      558  EELCLRFMREVERLMTPEK
               EELCLRFM+EV+ L+  ++
FAAH-OUT  145  EELCLRFMKEVDTLVKNQR
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Figure 7 (cont)

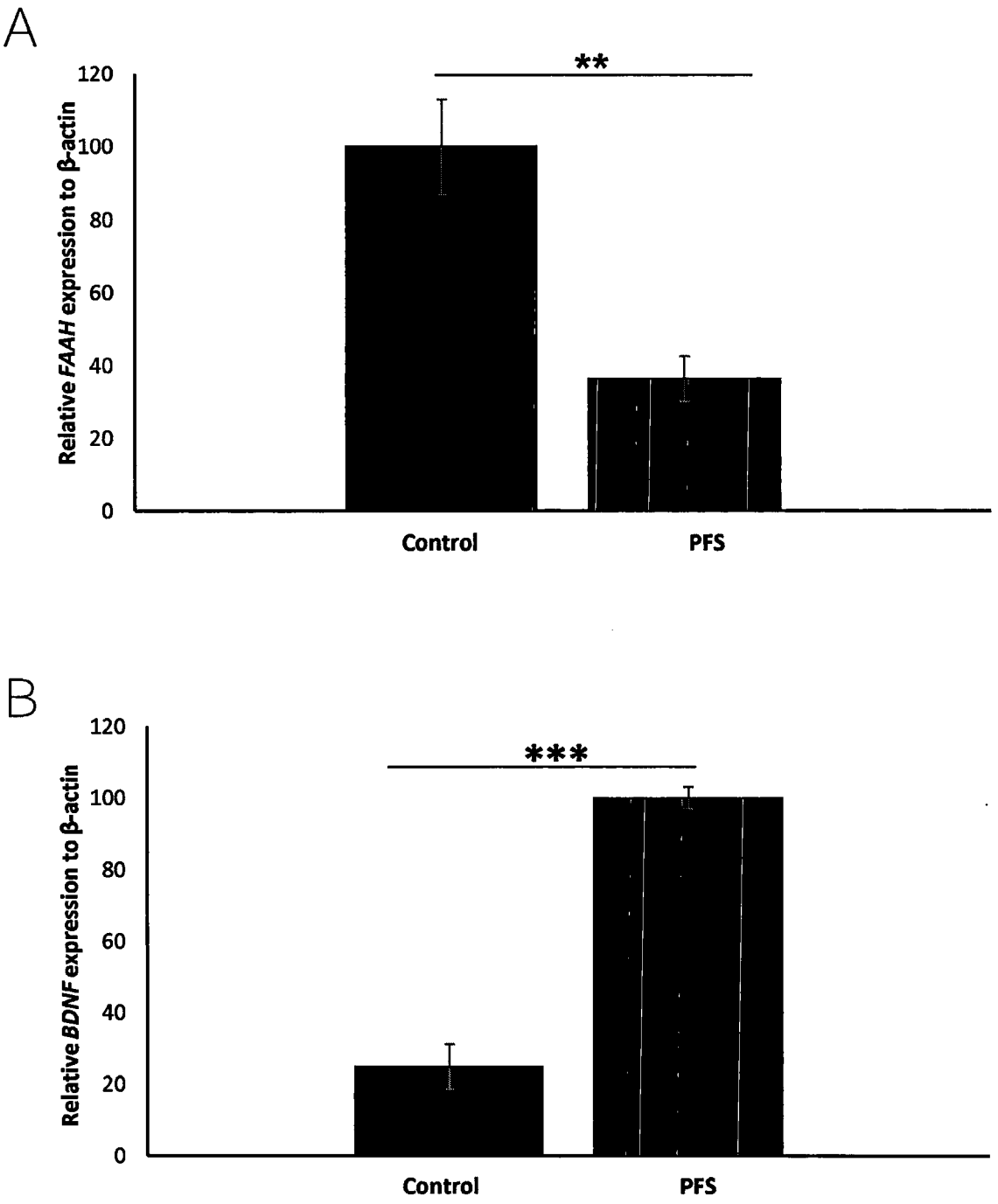
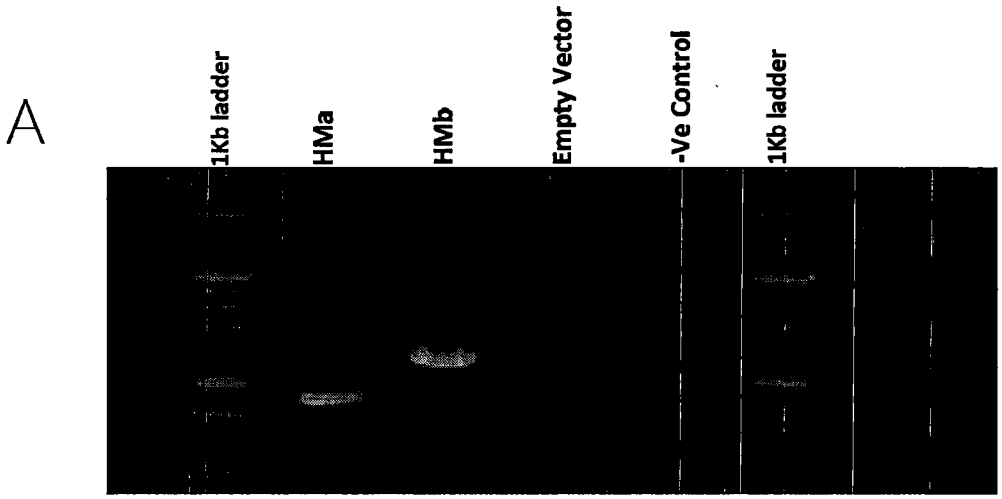

A
**
120
100
80
60
40
20
0
Relative FAAH expression to β-actin
Control
PFS
B
***
120
100
80
60
40
20
0
Relative BDNF expression to β-actin
Control
PFS

Figure 8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HMa
HMb
Empty Vector
-Ve Control
1Kb ladder

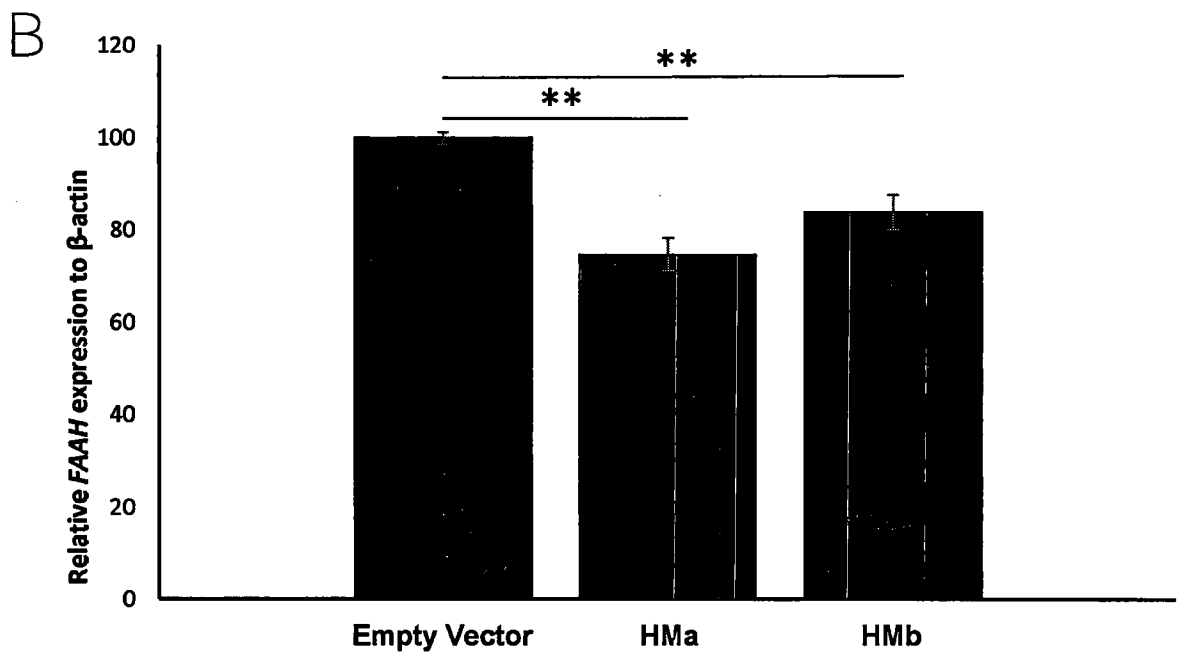
B
120
100
80
60
40
20
0
Relative FAAH expression to β-actin
**
**
Empty Vector
HMa
HMb

Figure 9

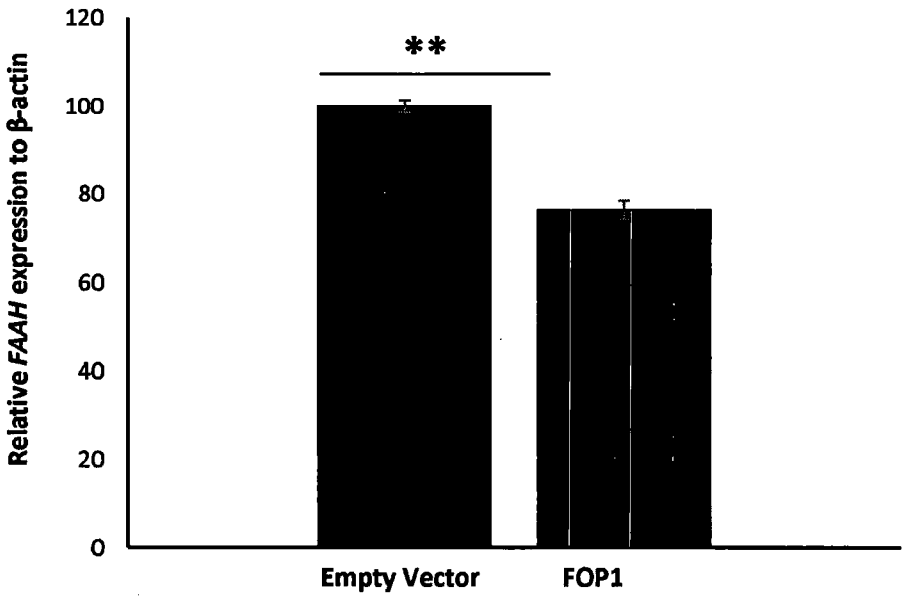
120
100
80
60
40
20
0
**
Relative FAAH expression to β-actin
Empty Vector
FOP1

Figure 10