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(54) Titre : PROTEINES MORPHOGENIQUES OSSEUSES (BMP), RECEPTEURS DESDITES PROTEINES ET PROTEINES DE LIAISON DE CES PROTEINES, ET LEUR UTILISATION POUR LE DIAGNOSTIC ET LE TRAITEMENT DU GLAUCOME

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BONE MORPHOGENIC PROTEINS (BMP), BMP RECEPTORS AND BMP BINDING PROTEINS AND THEIR USE IN THE DIAGNOSIS AND TREATMENT OF GLAUCOMA

1. Field of the Invention

The present invention discloses methods and reagents for diagnosing and treating glaucoma and related disorders.

2. Description of the Related Art

"Glaucomas" are a group of debilitating eye diseases that are the leading cause of irreversible blindness in the United States and other developed nations. Primary Open Angle Glaucoma ("POAG"), the most common form of glaucoma, is characterized by the degeneration of the trabecular meshwork, leading to obstruction of the normal ability of aqueous humor to leave the eye without closure of the space (e.g., the "angle") between the iris and cornea (Vaughan, D. *et al.*, (1992)). A characteristic of such obstruction in this disease is an increased intraocular pressure ("IOP"), resulting in progressive visual loss and blindness if not treated appropriately and in a timely fashion. The disease is estimated to affect between 0.4% and 3.3% of all adults over 40 years old (Leske, M. C. *et al.* (1986); Bengtsson, B. (1989); Strong, N. P. (1992)). Moreover, the prevalence of the disease rises with age to over 6% of those 75 years or older (Strong, N. P., (1992)).

Because increased IOP is a readily measurable characteristic of glaucoma, the diagnosis of the disease is largely screened for by measuring intraocular pressure (tonometry) (Strong, N. P. (1992); Greve, M. *et al.* (1993)). Unfortunately, because glaucomatous and normal pressure ranges overlap, such methods are of limited value

unless multiple readings are obtained (Hitchings, R. A., (1993); Tuck, M. W. *et al.* (1993); Vaughan, D. *et al.*, (1992); Vernon, S. A., (1993)). For this reason, additional methods, such as direct examination of the optic disk and determination of the extent of a patient's visual field loss are often conducted to improve the accuracy of diagnosis (Greve, M. *et al.*, (1993)).

Glaucoma affects three separate tissues in the eye. The elevated IOP associated with POAG is due to morphological and biochemical changes in the trabecular meshwork (TM), a tissue located at the angle between the cornea and iris. Most of the nutritive aqueous humor exits the anterior segment of the eye through the TM. The progressive loss of TM cells and the build-up of extracellular debris in the TM of glaucomatous eyes leads to increased resistance to aqueous outflow (Lutjen-Drecoll and Rohen 1996; Rohen 1983; Rohen *et al.* 1993; Grierson and Calthorpe 1988), thereby raising IOP. Elevated IOP, as well as other factors such as ischemia, cause degenerative changes in the optic nerve head (ONH) leading to progressive "cupping" of the ONH (Varma and Minckler 1996; Hernandez and Gong 1996; Hernandez *et al.* 1990; Hernandez and Pena 1997; Morrison *et al.* 1990) and loss of retinal ganglion cells (Quigley *et al.* 2000; Quigley 1999; Quigley *et al.* 1995; Kerrigan *et al.* 1997) and axons. The detailed molecular mechanisms responsible for glaucomatous damage to the TM, ONH, and the retinal ganglion cells are unknown.

Current glaucoma therapy is directed to lowering IOP, a major risk factor for the development and progression of glaucoma. These therapies lower IOP, but they do not directly address the pathogenic mechanisms, and the disease continues to progress. At least half of patients with glaucoma are undiagnosed, and by the time patients are diagnosed with glaucoma, they have already lost approximately 40% of their retinal

ganglion cells. Therefore, methods for earlier detection and diagnosis of glaucoma are needed.

In view of the importance of glaucoma, and the at least partial inadequacies of prior methods of diagnosis, it would be desirable to have an improved, more accurate method for diagnosing glaucoma in its early stages. In addition, it would be desirable to have new therapeutic agents that address glaucomatous pathogenic mechanisms.

SUMMARY OF THE INVENTION

The present invention overcomes these and other drawbacks of the prior art by providing methods and kits for the early diagnosis of glaucoma, for treating glaucoma, and for the identification of compounds useful in the treatment of glaucoma.

In certain specific embodiments, the invention provides a method for diagnosing glaucoma in a sample obtained from a cell or bodily fluid by detecting altered expression of a bone morphogenic protein family member gene. The method generally includes the steps of:

a) obtaining a tissue or fluid sample from a patient suspected of having glaucoma;

b) extracting DNA from said sample;

c) obtaining a plurality of PCR primers, wherein said primers each comprise a sequence consisting of from 18 to 1547 contiguous nucleotides from SEQ ID NO:1, SEQ ID NO:3, SEQ ID NO:5, SEQ ID NO:7, SEQ ID NO: 37, SEQ ID NO:39, SEQ ID NO:41, SEQ ID NO:43, SEQ ID NO:45, SEQ ID NO:47, or SEQ ID NO:53;

d) amplifying regions of the extracted DNA using said primers to obtain a PCR product;

e) resolving the PCR product; and

f) identifying differences between the sequence of the PCR product and the normal gene sequence;

where a difference between the amplified sequence and the normal gene sequence is diagnostic of glaucoma.

In general, the methods of the invention may include obtaining a sample from an individual and extracting DNA from said sample. Select PCR primers for specific members of the BMP gene family are then used to amplify relevant regions of the extracted gene to obtain a PCR product. The PCR product is resolved by a technique that effectively identifies DNA sequence differences between the normal and mutated form of the specific BMP family gene being evaluated (the extracted DNA). Identified differences between the sequences are indicative of glaucoma.

The tissue or fluid sample for use in the methods of the invention may be blood or buccal cells.

Typically, the primer sequences will have a length of between about 10, 15 or 18 nucleotides to about 20, or to about 30 nucleotides. Longer sequences, e.g., 40, 50, 80, 90, 95, 100, even up to full length, are even more preferred for certain embodiments. Lengths of oligonucleotides of at least about 18 to 20 nucleotides are well accepted by those of skill in the art as sufficient to allow sufficiently specific hybridization so as to be useful as a molecular probe, as described by Lathe (1985), which reference is specifically incorporated herein by reference for this purpose. Preferably, the nucleotide sequence will consist of from 20 to 100 contiguous nucleotides of SEQ ID NO:1, SEQ ID NO:3, SEQ ID NO:5, SEQ ID NO:7, SEQ ID NO:37, SEQ ID NO:39, SEQ ID NO:41, SEQ ID NO:43, SEQ ID NO:45, SEQ ID NO:47, or SEQ ID NO:53. It is also contemplated that the primer

sequences may consist of sequences of at least 10, 15 or 18 contiguous nucleotides from the sequences of BMP receptor genes and from BMP-associated proteins, the sequences of which are known.

Nucleic acid molecules having stretches of 10, 18, 20, 30, 50, 60, 65 or even up to and including 100 nucleotides or so, complementary to any one of SEQ ID NO: 1, SEQ ID NO:3, SEQ ID NO:5, SEQ ID NO:7, SEQ ID NO:37, SEQ ID NO:39, SEQ ID NO:41, SEQ ID NO:43, SEQ ID NO:45, SEQ ID NO:47, or SEQ ID NO:53, have utility as hybridization probes. Primers or probes having a nucleotide length of about 18 nucleotides are recognized by those of skill in the art to provide highly specific hybridization to a target sequence. The total size of the fragment, as well as the size of the complementary stretches, will ultimately depend on the intended use of application of the particular nucleic acid segment. Smaller fragments will generally find use in hybridization embodiments, wherein the length of the complementary region may be varied, such as between about 10, 18, 20 or 30 and about 50, 60, 70, 80, 80 or 100 nucleotides, or even full length according to the complementary sequences one wishes to detect.

In specifically preferred embodiments, the primers will consist of contiguous sequences from SEQ ID NO: 1, SEQ ID NO:3, SEQ ID NO:5, SEQ ID NO:7, SEQ ID NO:37, SEQ ID NO:39, SEQ ID NO:41, SEQ ID NO:43, SEQ ID NO:45, SEQ ID NO:47, or SEQ ID NO:53. In other preferred embodiments, the primers will consist of contiguous sequences from BMP receptor genes (disclosed in ten Dijke *et al.* 1993; Astrom *et al.* 1999; Nohno *et al.* 1995, all incorporated herein by reference) or from BMP-associated genes, such as chordin (NCBI NM_029130), gremlin (Murphy *et al.* 1999; McMahon *et al.* 2000), follistatin (NCBI NM_003892) or bambi (NCBI NM_005791).

Most preferably, the primers will consist of contiguous sequence from SEQ ID NO:3. In certain aspects, at least some of the primers may further include a detectable label.

In other embodiments, the invention provides a method for treating glaucoma by administering to a patient in need thereof a composition comprising a sequence consisting of at least one compound selected from the group consisting of a BMP2 agonist, a BMP4 agonist, a BMP5 agonist, a BMP7 agonist, a Smad 1/5 agonist, a chordin antagonist, a gremlin antagonist and a follistatin antagonist.

In additional aspects, the present invention provides a method for identifying a therapeutic agent for the treatment of glaucoma. Therapeutic agents may be identified, for example, by:

a) obtaining a first composition comprising a population of recombinant cells expressing BMP-2A, BMP4, BMP-5, or BMP7;

b) obtaining a candidate substance;

c) incubating said composition and said candidate substance;

testing said composition for its ability to turn on BMP-induced Smad signaling pathways and/or BMP-regulated gene expression; and identifying a candidate substance that inhibits, or stimulates, these downstream effects of BMP.

Another aspect of the invention are diagnostic kits containing sequences of the present invention and suitable reagents such as a detectable label linked to a protein, peptide or the antibody itself. Alternatively, the detectable label may be linked to a second sequence which selectively hybridizes to a sequence of the invention.

Related embodiments include therapeutic kits which include pharmaceutically-acceptable formulations of either the nucleic acid sequences or peptide or protein

sequences disclosed herein. Such kits are useful in the detection of altered expression of the BMP genes and proteins in clinical samples for the diagnosis of glaucoma.

BRIEF DESCRIPTION OF THE DRAWINGS

The drawings form part of the present specification and are included to further demonstrate certain aspects of the present invention. The invention may be better understood by reference to one or more of these drawings in combination with the detailed description of specific embodiments presented herein.

FIG. 1. Nucleotide and amino acid sequence of BMP2A.

FIG.2. Nucleotide and amino acid sequence of BMP4.

FIG. 3. Nucleotide and amino acid sequence of BMP5.

FIG. 4. Nucleotide and amino acid sequence of BMP7.

FIG. 5. Bone morphogenic protein signaling pathway. Bone Morphogenic Protein (BMP) dimers bind to a membrane complex composed of BMP receptors 1 and 2, which are serin/threonine kinases. The regulatory Smads (Smad1/Smad5) become phosphorylated and associate with a co-Smad (Smad 4). This resulting Smad complex enters the nucleus where it associates with transcription factors (TF) and regulates gene expression. BMP associated proteins act as BMP antagonists by binding BMPs and preventing BMP interaction with BMP receptors.

FIG. 6. BMP expression in human TM cells and tissues. Ethidium bromide-stained agarose gel of BMP PCR products from cDNA samples generated from RT-PCR analysis of BMP expression in human TM cells (lanes 1-5) and tissues (lanes 6-7). L = base pair markers. C = PCR negative control lane. β-actin was used as a positive RT-PCR internal control.

FIG. 7. BMP receptor expression in human TM cells and tissues. Ethidium bromide-stained agarose gel of PCR products from cDNA samples generated from RT-PCR analysis of BMP receptor expression in human TM cells (lanes 1-5) and tissues (lanes 6-7). L = base pair markers. C = PCR negative control lane. β-actin was used as a positive RT-PCR internal control.

FIG. 8. BMP expression in human ONH astrocytes, ONH tissues, and human brain astrocytes. Ethidium bromide-stained agarose gel of PCR products from cDNA samples generated from RT-PCR analysis of BMP expression in human ONH astrocyte (lanes 1-5), ONH tissue (lane 6), and human brain astrocytes (lane 7). L = base pair markers. C = PCR negative control lane. β-actin was used as a positive RT-PCR internal control.

FIG. 9. BMP expression in human lamina cribrosa cell lines. Ethidium bromide-stained agarose gel of PCR products from cDNA samples generated from RT-PCR analysis of human lamina cribrosa cells (lanes 1-9). L = base pair markers. C = PCR negative control lane. β-actin was used as a positive RT-PCR internal control.

FIG. 10. BMP receptor expression in human ONH astrocytes, ONH tissues, and human brain astrocytes. Ethidium bromide-stained agarose gel of PCR products from cDNA samples generated from RT-PCR analysis of BMP receptor expression in human optic nerve head astrocytes (ONA) (lanes 1-5), ONH tissue (lane 6), and human brain astrocytes (lane 7). L = base pair markers. C = PCR negative control lane. β-actin was used as a positive RT-PCR control.

FIG. 11. BMP receptor expression in human lamina cribrosa cell lines. Ethidium bromide-stained agarose gel of PCR products from cDNA samples generated from RT-PCR analysis of human lamina cribrosa cells (lanes 1-9). L = base pair markers. C = PCR negative control lane. β-actin was used as a positive RT-PCR control.

FIG. 12. Western immunoblot of BMP and BMP receptor expression in cultured human TM cells, optic nerve head astrocytes (ONA), and lamina cribrosa cells. Chemiluminescent detection of BMP proteins and BMP receptors in human trabecular meshwork cells (lanes 1-2), ONH astrocytes (lanes 3-4), and lamina cribrosa cells (lanes 5-6). Protein size indicated in kDa.

FIG. 13. BMP associated protein mRNA expression in human TM cells. Ethidium bromide-stained agarose gel of PCR products from cDNA samples generated from RT-PCR analysis of human TM cells (lanes 1-5). L = base pair markers. C = PCR negative control lane. β-actin was used as a positive RT-PCR internal control.

FIG. 14. BMP associated protein mRNA expression in human lamina cribrosa cells and ONH astrocytes. Ethidium bromide-stained agarose gel of PCR products from cDNA samples generated from RT-PCR analysis of lamina cribrosa (LC) cells (lanes 1-7) and ONH astrocytes (ONA) (lanes 8-11). L = base pair markers. C = PCR negative control lane. β-actin was used as a positive RT-PCR internal control.

FIG. 15. Illustrates increased expression of the BMP antagonist gremlin (CKTSF1B1) in glaucomatous TM cells. Gene expression was assessed using Affymetrix gene arrays (Affymetrix gene chip U133A).

DETAILED DESCRIPTION PREFERRED EMBODIMENTS

The trabecular meshwork has been proposed to play an important role in the normal flow of the aqueous humor, and has been presumed to be the major site of outflow resistance in glaucomatous eyes. Human trabecular meshwork (HTM) cells are specialized cells which line the outflow channels by which aqueous humor exits the eye.

Altered synthetic function of the cells may be involved in the pathogenesis of POAG, steroid glaucoma, and other types of glaucoma.

Despite years of intensive research, the precise molecular mechanisms responsible for glaucomatous damage to the eye are not known. Recent research has suggested that growth factors may be important in maintaining normal homeostasis in the ocular tissues associated with glaucoma, and alterations in growth factor/growth factor receptors may play a role in glaucoma pathogenesis. Growth factors area very large family of polypeptides that control cell growth and differentiation. These molecules have a variety of cell-specific effects on gene expression, extracellular matrix composition and deposition, cytoskeletal organization, and regulation of cellular functions. The TM expresses a wide variety of growth factors, growth factor receptors (Tripathi *et al.* 1993a; Tripathi *et al.* 1993b; Tripathi *et al.* 1994a; Tripathi *et al.* 1994b; Wordinger *et al.* 1998; Wordinger *et al.* 1999) as well as neurotrophin/neurotrophic factors and their receptors (Liu *et al.* 2001; Wordinger *et al.* 2000). ONH astrocytes and lamina cribrosa cells, two cell types of the optic nerve head, express growth factors, neurotrophins and their receptors (Lambert *et al.* 2001; Pena *et al.* 1999). The aqueous humor also contains a variety of growth factors including FGF2, EGF, TGFβ, HGF (Tripathi *et al.* 1996; Tripathi *et al.* 1991; Tripathi *et al.* 1992; Hu and Ritch 2001) as well as neurotrophins (Chundru *et al.* 2000). Elevated levels of aqueous humor TGFβ-2 and HGF have been reported in POAG patients (Tripathi *et al.* 1994c; Inatani *et al.* 2001; Picht *et al.* 2001). Growth factors may be involved in glaucoma by altering the normal development and/or function of the TM and ONH.

The present invention stems in part from the recognition that bone morphogenic proteins (BMPs) not only induce bone and cartilage formation but are multifunctional

cytokines having a wide range of effects on numerous cell types (Hogan 1996; Reddi 1997) and are expressed by both human trabecular meshwork (HTM) and optic nerve head (ONH) cells (Wordinger *et al.* 2002). BMPs are members of the TGFβ superfamily, and there are approximately 15-20 BMPs genes in man, 3 BMP receptors, and a number of BMP associated proteins that function as BMP antagonists (Yamashita *et al.* 1996). BMPs signal via a receptor complex consisting of BMPR-I and BMPR-II. It has been reported that superfamily members TGFβ and TGFβR (Agarwal *et al.* 1997; Lambert *et al.* 1997) and GDNF and GDNFR (Wordinger *et al.* 1999; Liu *et al.* 1999) are expressed by both HTM and ONH cells.

BMPs and BMP receptors are expressed in ocular tissues (Obata *et al.* 1999; You *et al.* 1999), but previous reports have focused on ocular development. The function of BMPs is important in ocular development since targeted disruption of genes encoding BMPs in mice leads to severe developmental defects in the retina and the lens (Jena *et al.* 1997; Luo *et al.* 1995; Dudley *et al.* 1995). BMP-2, BMP-4 and BMP-7 are involved in the development of the lens and retina (Jena *et al.* 1997; Furuta and Hogan 1998; Reddi 2000; Trousse *et al.* 2001). BMP-6 and BMP-7 also appear to play a role in protecting neurons from hypoglycemic or ischemic damage (Nonner *et al.* 2001; Liu *et al.* 2001), and BMP2 has been shown to enhance ganglion cell neurotrophin expression (Zhang *et al.* 1998). Heterozygous knock-out mice haploinsufficient for Bmp4 have ocular phenotypes including anterior segment dysgenesis, elevated IOP, and optic nerve abnormalities (Chang *et al.* 2001). There has been very limited information published concerning the role of BMPs in the human postnatal eye.

Mohan and colleagues (1998) reported that BMP-2 and BMP-4 and BMP receptors were expressed in cells of the adult cornea and suggested that BMP function might include

corneal keratocyte proliferation and apoptosis. You and colleagues (1999) verified this study and also reported the expression of BMP-3, BMP-5, and BMP-7 in ex vivo and cultured corneal epithelium and stromal cells. They reported that the level of BMP transcription was higher in the stroma while the level for receptors was higher in cultured corneal epithelial cells.

Using RT-PCR, the present inventors discovered mRNAs for BMPs, BMP receptors BMPR-IA, BMPR-IB and BMPR-II, as well as BMP binding proteins gremlin, chordin, follistatin, and bambi, in HTM, lamina cribosa (LC) and ONH astrocyte cell lines and tissues (Wordinger *et al.* 2002). The present inventors further discovered that HTM and ONH cells express proteins BMP-2, BMP-4, BMP-5 and BMP-7.

Glaucoma will be diagnosed by characterization of genetic changes in genes of members of the BMP signaling family. As used herein, the phrases "bone morphogenic protein family member gene" and "BMP signaling family" refer to all BMPs, BMP receptors and associated proteins. The term "genetic changes" is well known by those skilled in the art. There are numerous examples of diseases associated with genetic changes in specific genes (for examples see Cummings 1997; Strachan, *et al.* 1996; Jorde, *et al.* 1999). Genetic changes in a specific gene (e.g. BMP) can be determined using a variety of techniques well known by those skilled in the art, such as: SSCP, DGGE, ASO, RFLP, heteroduplex analysis, CCM, PTT, and RNase cleavage (see Birren, *et al.* 1998).

Glaucoma may be caused by altered expression of one or more BMP family genes in the eye, which leads to elevated IOP and/or glaucomatous optic neuropathy. "Altered BMP gene expression" means expression of this gene product that is different from normal. The term may also refer to alterations in the sequence of the gene or protein. The normal BMP gene has been well characterized (see above), and the expression of BMP has

been reported in a variety of tissues including the TM and ONH. Genetic changes in the coding region of BMP family genes may alter the function of these proteins. Genetic changes outside the coding region may also lead to glaucoma.

It is well known by those skilled in the art that "changes outside" of the coding region of a specific gene are important in the regulation of gene expression. For example, the region upstream (5') of the coding region of most genes is known as the promoter region which "promotes" and regulates the expression of that gene. The promoter region contains numerous nucleotide sequences recognized by various transcription factors and DNA binding proteins that are responsible for activation or repression of gene expression. Regions downstream (3') of the gene can determine poly-adenylation of the gene product, thereby regulating RNA processing and translation of the gene product.

The altered expression of BMP genes or mutations in the sequence of the genes that is indicative of glaucoma may be detected using techniques well known to those of skill in the art. For example, it is contemplated that a nucleic acid fragment of almost any length may be employed, with the total length preferably being limited by the ease of preparation and use in the intended protocol. The nucleic acid sequences disclosed herein may also have utility as probes or primers in nucleic acid hybridization embodiments. As such, it is contemplated that nucleic acid segments that comprise a sequence region that consists of at least a 14 nucleotide long contiguous sequence that has the same sequence as, or is complementary to, a 14 nucleotide long contiguous sequence of BMP-2A (SEQ ID NO:1), BMP-4 (SEQ ID NO:3), BMP-5 (SEQ ID NO:5), BMP-7 (SEQ ID NO:7), BMP-RIA (SEQ ID NO:37), BMP-RIB (SEQ ID NO:39), BMP-RII (SEQ ID NO:41), chordin (SEQ ID NO:43), gremlin (SEQ ID NO:45), follistatin (SEQ ID NO:47), or bambi (SEQ ID NO:53) will find particular utility. Longer contiguous identical or

complementary sequences, e.g., those of about 20, 30, 40, 50, 100, 200, 500, 1000 nucleotides (including all intermediate lengths), and even up to full length sequences of about 1547 nucleotides (for BMP-2A), 1946 nucleotides (for BMP-4), 2153 nucleotides (for BMP-5) and 1878 nucleotides (for BMP-7), 2932 nucleotides (for BMP-RIA), 2032 nucleotides (for BMP-RIB), 3611 nucleotides (for BMP-RII), 3561 nucleotides (for chordin), 4049 nucleotides (for gremlin), 1386 nucleotides (for follistatin), and 1523 nucleotides (for bambi) will also be of use in certain embodiments.

It will be readily understood that "intermediate lengths", in this context, means any length between the quoted ranges, such as 14, 15, 16, 17, 18, 19, 20, etc.; 21, 22, 23, etc.; 30, 31, 32, etc.; 50, 51, 52, 53, etc.; 100, 101, 102, 103, etc.; 150, 151, 152, 153, etc.; including all integers through the 200-500; 500-1,000; 1,000-2,000 ranges, up to and including sequences of 2,001, 2002, 2050, 2051, and the like.

The ability of such nucleic acid probes and primers to specifically hybridize to BMP coding sequences and primers to specifically amplify BMP sequences will enable them to be of use in detecting the presence of complementary sequences in a given sample. However, other uses are envisioned, including the use of the sequence information for the preparation of mutant species primers, or primers for use in preparing other genetic constructions.

Nucleic acid molecules having sequence regions consisting of contiguous nucleotide stretches of 10, 20, 30, 50, or even of 100-200 nucleotides or so, identical or complementary to BMP-2A (SEQ ID NO:1), BMP4 (SEQ ID NO:3), BMP-5 (SEQ ID NO:5), BMP7 (SEQ ID NO:7) , BMP-RIA (SEQ ID NO:37), BMP-RIB (SEQ ID NO:39), BMP-RII (SEQ ID NO:41), chordin (SEQ ID NO:43), gremlin (SEQ ID NO:45), follistatin (SEQ ID NO:47), or bambi (SEQ ID NO:53) are particularly contemplated as

hybridization probes for use in, e.g., SNP evaluation and solid phase hybridization assays, in addition to Southern and northern blotting. This would allow BMP structural or regulatory genes to be analyzed, both in tissues and cells. The total size of fragment, as well as the size of the complementary stretch(es), will ultimately depend on the intended use of application of the particular nucleic acid segment. Smaller fragments will generally find use in hybridization embodiments, wherein the length of the contiguous complementary region may be varied, such as between about 10 and about 100 nucleotides, but larger contiguous complementary stretches of up to about 1547 nucleotides (for BMP-2A), 1946 nucleotides (for BMP-4), 2153 nucleotides (for BMP-5) and 1878 nucleotides (for BMP-7), 2932 nucleotides (for BMP-RIA), 2032 nucleotides (for BMP-RIB), 3611 nucleotides (for BMP-RII), 3561 nucleotides (for chordin), 4049 nucleotides (for gremlin), 1386 nucleotides (for follistatin), and 1523 nucleotides (for bambi) may be used, according to the length complementary sequences one wishes to detect.

The use of a hybridization probe of about 10-14 nucleotides in length allows the formation of a duplex molecule that is both stable and selective. Molecules having contiguous complementary sequences over stretches greater than 10 bases in length are generally preferred, though, in order to increase stability and selectivity of the hybrid, and thereby improve the quality and degree of specific hybrid molecules obtained, one will generally prefer to design nucleic acid molecules having gene-complementary stretches of 15 to 20 contiguous nucleotides, or even longer where desired.

Hybridization probes may be selected from any portion of any of the sequences disclosed herein. All that is required is to review the sequence set forth in SEQ ID NO:1, SEQ ID NO:3, SEQ ID NO:5, SEQ ID NO:7, SEQ ID NO:37, SEQ ID NO:39, SEQ ID

NO:41, SEQ ID NO:43, SEQ ID NO:45, SEQ ID NO:47 or SEQ ID NO:53 and to select any continuous portion of the sequence, from about 10 nucleotides in length up to and including the full length sequence, that one wishes to utilize as a probe or primer. The choice of probe and primer sequences may be governed by various factors, such as, by way of example only, one may wish to employ primers from towards the termini of the total sequence, or from the ends of the functional domain-encoding sequences, in order to amplify further DNA.

The process of selecting, and preparing a nucleic acid segment that includes a contiguous sequence from within BMP-2A (SEQ ID NO:1), BMP4 (SEQ ID NO:3), BMP-5 (SEQ ID NO:5), BMP7 (SEQ ID NO:7) , BMP-RIA (SEQ ID NO:37), BMP-RIB (SEQ ID NO:39), BMP-RII (SEQ ID NO:41), chordin (SEQ ID NO:43), gremlin (SEQ ID NO:45), follistatin (SEQ ID NO:47), or bambi (SEQ ID NO:53) may alternatively be described as preparing a nucleic acid fragment. Of course, fragments may also be obtained by other techniques such as, e.g., by mechanical shearing or by restriction enzyme digestion. Small nucleic acid segments or fragments may be readily prepared by, for example, directly synthesizing the fragment by chemical means, as is commonly practiced using an automated oligonucleotide synthesizer. Also, fragments may be obtained by application of nucleic acid reproduction technology, such as the PCR™ technology of U.S. Pat. No. 4,683,202 and U.S. Pat. No. 4,682,195 (each incorporated herein by reference), by introducing selected sequences into recombinant vectors for recombinant production, and by other recombinant DNA techniques generally known to those of skill in the art of molecular biology.

Accordingly, the nucleotide sequences of the invention may be used for their ability to selectively form duplex molecules with complementary stretches of BMP genes

or cDNAs. Depending on the application envisioned, one will desire to employ varying degrees of selectivity of hybridization to achieve varying degrees of selectivity of probe towards target sequence. For applications requiring high selectivity, one will typically desire to employ relatively stringent conditions to form the hybrids, e.g., one will select relatively low salt and/or high temperature conditions, such as provided by 0.02M-0.15M NaCl at temperatures of 50° C to 70° C. Such selective conditions tolerate little, if any, mismatch between the probe and the template or target strand, and would be particularly suitable for examining BMP genes.

Of course, for some applications, for example, where one desires to prepare or identify mutants employing a mutant primer strand hybridized to an underlying template or where one seeks to isolate BMP encoding sequences from related species, functional equivalents, or the like, less stringent hybridization conditions will typically be needed in order to allow formation of the heteroduplex. In these circumstances, one may desire to employ conditions such a 0.15M-1.0M salt, at temperatures ranging from 20° C to 55° C. Cross-hybridizing species can thereby be readily identified as positively hybridizing signals with respect to control hycbridizations. In any case, it is generally appreciated that conditions can be rendered more stringent by decreasing NaCl concentrations or by the addition of increasing amounts of formamide, which serves to destabilize the hybrid duplex in the same manner as increased temperature. Thus, hybridization conditions can be readily manipulated, and thus will generally be a method of choice depending on the desired results.

In certain embodiments, it will be advantageous to employ nucleic acid sequences of the present invention in combination with an appropriate means, such as a label, for determining hybridization. A wide variety of appropriate indicator means are known in

the art, including fluorescent, radioactive, enzymatic or other ligands, such as avidin/biotin, which are capable of giving a detectable signal. In preferred embodiments, one will likely desire to employ a fluorescent label or an enzyme tag, such as urease, alkaline phosphatase or peroxidase, instead of radioactive or other environmental undesirable reagents. In the case of enzyme tags, colorimetric indicator substrates are known that can be employed to provide a means visible to the human eye or spectrophotometrically, to identify specific hybridization with complementary nucleic acid-containing samples.

In general, it is envisioned that the hybridization probes described herein will be useful both as reagents in solution hybridization as well as in embodiments employing a solid phase. In embodiments involving a solid phase, the test DNA (or RNA) is adsorbed or otherwise affixed to a selected matrix or surface. This fixed, single-stranded nucleic acid is then subjected to specific hybridization with selected probes under desired conditions. The selected conditions will depend on the particular circumstances based on the particular criteria required (depending, for example, on the G+C contents, type of target nucleic acid, source of nucleic acid, size of hybridization probe, etc.). Following washing of the hybridized surface so as to remove nonspecifically bound probe molecules, specific hybridization is detected, or even quantified, by means of the label.

It will also be understood that this invention is not limited to the particular nucleic acid and amino acid sequences of BMP-2A (SEQ ID NO:1), BMP4 (SEQ ID NO:3), BMP-5 (SEQ ID NO:5), BMP7 (SEQ ID NO:7) , BMP-RIA (SEQ ID NO:37), BMP-RIB (SEQ ID NO:39), BMP-RII (SEQ ID NO:41), chordin (SEQ ID NO:43), gremlin (SEQ ID NO:45), follistatin (SEQ ID NO:47), or bambi (SEQ ID NO:53). Recombinant vectors and isolated DNA segments may therefore variously include the BMP coding regions

themselves, upstream or downstream regions of the genes, coding regions bearing selected alterations or modifications in the basic coding region, or they may encode larger polypeptides that nevertheless include BMP coding regions or may encode biologically functional equivalent proteins or polypeptides that have variant amino acid sequences.

The DNA segments of the present invention encompass biologically functional equivalent BMP proteins and polypeptides. Such sequences may arise as a consequence of codon redundancy and functional equivalency that are known to occur naturally within nucleic acid sequences and the proteins thus encoded. Alternatively, functionally equivalent proteins or polypeptides may be created via the application of recombinant DNA technology, in which changes in the protein structure may be engineered, based on considerations of the properties of the amino acids being exchanged. Changes designed by man may be introduced through the application of site-directed mutagenesis techniques, e.g., to introduce improvements to the antigenicity of the protein or to test BMP mutants in order to examine binding activity at the molecular level.

The therapeutic agent for the treatment of glaucoma can be: a peptide or protein, a peptide mimetic, an oligonucleotide or derivatized oligonucleotide, or small drug-like molecule, all which affect one or more aspects of the ocular BMP pathways. Preferred therapeutic agents are those that are: (1) BMP2, BMP4, BMP5, or BMP7 agonists; (2) chordin, gremlin, follistatin, or bambi antagonists; and/or (3) Smad1, Smad5 and/or Smad4 agonists.

The agent may be delivered directly to the eye (for example: topical ocular drops or ointments; slow release devices in the cul-de-sac or implanted adjacent to the sclera or within the eye; periocular, conjunctival, sub-Tenons, intracameral or intravitreal injections) or parenterally (for example: orally; intravenous, subcutaneous or intramuscular

injections; dermal delivery; etc.) using techniques well known by those skilled in the art.

The following are examples of possible formulations embodied by this invention.

(a) Topical ocular formulation	wt. %
Agent that increases ocular BMP-4 expression	0.01 – 2
HPMC	0.5
Sodium chloride	0.8
BAC	0.01%
EDTA	0.01
NaOH/HCl	qs pH 7.4
Purified water	qs 100 mL

(b) Topical ocular formulation	wt. %
Gremlin antagonist	0.01 – 2
HPMC	0.5
Sodium chloride	0.8
BAC	0.01
EDTA	0.01
NaOH/HCl	qs pH 7.4
Purified water	qs 100 mL

(c) Topical ocular formulation	wt. %
Smad 1/5 agonist	0.01 – 2
HPMC	0.5
Sodium chloride	0.8
BAC	0.01
EDTA	0.01
NaOH/HCl	qs pH 7.2
Purified water	qs 100 mL

It is further contemplated that the compounds of the invention could be formulated in intraocular insert devices.

A. Assay for therapeutic agents

This invention is also useful for the discovery of new anti-glaucoma therapeutic agents that are involved in the BMP signaling pathway (see FIG. 5). Selective BMP ligands bind to BMP type I and type II serine/threonine kinase receptors (BMP-RI and

BMP-RII) and transduce signal via Smad proteins. The BMP signal is propagated by Smads through protein-protein and protein-DNA interactions (Attisano and Tuen Lee-Hoeflich 2001). Regulatory Smad 1 and Smad 5 are activated (via phosphorylation) by ligand bound BMP receptors (von Bubnoff and Cho 2001). These regulatory Smads then interact with Smad 4 to form a heteromeric complex that translocates to the nucleus. This complex is able to activate or repress the transcription of selective genes that recognize this transcriptional complex, depending on which nuclear co-factors are present.

The BMP/Smad signaling pathway is negatively regulated by several mechanisms. Certain BMP-binding proteins (such as gremlin, BAMBI, or follistatin) bind BMPs and inhibit their interaction with BMP receptors. In addition, there are inhibitory Smad proteins (e.g. Smad 6 and Smad 7), which bind and inactivate BMP receptors. (Kowabata *et al.* 1998; Itoh *et al.* 2000; Miyazono 2000). The present inventors have discovered that human TM cells, ONH astrocytes and lamina cribrosa cells express message and protein for the BMP receptor complex. Thus, these cells could respond to endogenous BMP ligands.

Various methods may be used to discover new anti-glaucoma therapeutic agents, and these techniques are well known to those skilled in the art. For example, peptide or peptide mimetic agents that act as agonists or inhibitors of BMPs can be discovered through molecular modeling of BMP/BMP receptor structures (Nickel *et al.* 2001). BMP signal transduction involves select sets of Smad proteins (Kawabata *et al.* 1998; Itoh *et al.* 2000; Attiseno *et al.* 2000). Select BMP agonists and Smad agonists can be discovered using cell based assays. The test cell should express the appropriate BMP receptor(s) and possess the appropriate BMP signaling pathway. Because one of the major effects of BMP signaling is the alteration of gene expression, BMP agonists and Smad agonists can be

discovered by screening for BMP-induced genes. The induction of BMP regulated genes also may be assayed by quantitating levels of mRNA using quantitative RT-PCR (Wang *et al.* 2001), DNA microarrays, or reporter gene constructs. There are natural inhibitors of BMP signaling, the BMP binding proteins (also known as BMP-associated proteins), such as chordin, gremlin, and follistatin. Antagonists of the protein inhibitors can be discovered using ligand binding assays. For example, test agents can be added to recombinant purified gremlin, and those agents that bind to gremlin are identified using a variety of techniques known to those skilled in the art. To determine whether these agents are gremlin antagonists, a cell based assay similar to that described above is used.

It is contemplated that any known *in vitro* and *in vivo* screening models may be used in conjunction with the present invention to identify new glaucoma therapies directed to the BMP family of genes. Such models are well known to those skilled in the art and their practice has become routine. Small peptides or peptide mimetics can be designed based on structure/function knowledge of the BMP, BMPR, and/or BMP binding protein gene products. Ligand binding assays can be used to detect small molecules that bind to BMPs, BMPRs, or BMP binding proteins. Cell based assays can look at the effects of various agents on BMP signaling pathways. Knock-in cell lines containing BMP family gene promoters coupled to a reporter gene can be generated to look for agents that alter BMP family member gene expression. These assays can be used to identify both agonist and antagonist molecules. *Ex vivo* assays, such as perfusion cultured anterior segments from human eyes (Clark *et al.* 1995a; Pang *et al.* 2000), can be used to examine the effects of agents on IOP and on BMP signaling in TM tissue. Rodent models of glaucoma can be generated using well-known techniques to create stable BMP family member transgenic, knockout, or knock-in strains of mice and rats. These rodent models can be used to screen

for agents that alter the glaucoma-like phenotype(s) (*e.g.* tonometry to evaluate effects on IOP, histology to evaluate effects on glaucomatous optic neurology).

B. Kits

The present invention provides methods, compositions and kits for the early detection of glaucoma. The kits can contain a nucleic acid segment encoding a BMP polypeptide or protein. The kit can further contain reagents for detecting an interaction between a sample and a nucleic acid or peptide of the present invention. The provided reagent can be radio-, fluorescently- or enzymatically-labeled. The kit can contain a known radiolabeled agent capable of binding or interacting with a nucleic acid or peptide or protein of the present invention.

The reagent of the kit can be provided as a liquid solution, attached to a solid support or as a dried powder. Preferably, when the reagent is provided in a liquid solution, the liquid solution is an aqueous solution. Preferably, when the reagent provided is attached to a solid support, the solid support can be chromatography media, a test plate having a plurality of wells, or a microscope slide. When the reagent provided is a dry powder, the powder can be reconstituted by the addition of a suitable solvent, that may be provided.

In still further embodiments, the present invention concerns diagnostic methods and associated kits for the diagnosis of glaucoma. It is proposed that the BMP associated peptides and nucleic acids of the invention may be employed to detect polymorphisms or mutations in the BMP nucleic acids from patient samples. In general, these methods will include first obtaining a sample suspected of containing such a polymorphism or mutation, contacting the sample with a peptide or nucleic acid of the present invention, as the case

may be, under conditions effective to allow the formation of a complex, and then detecting the presence of the complex.

In general, the detection of complex formation is quite well known in the art and may be achieved through the application of numerous approaches. For example, the present invention contemplates the application of ELISA, RIA, indirect fluorescence techniques and the like. Generally, complex formation will be detected through the use of a label, such as a radiolabel or an enzyme tag (such as alkaline phosphatase, horseradish peroxidase, or the like). Of course, one may find additional advantages through the use of a secondary binding ligand.

The following examples are representative of the techniques employed by the inventors in carrying out aspects of the present invention. It should be appreciated that while these techniques are exemplary of preferred embodiments for the practice of the invention, those of skill in the art, in light of the present disclosure, will recognize that numerous modifications can be made without departing from the spirit and intended scope of the invention.

Example 1

Cell culture: Human TM cells and ONH cells were generated from donor eyes as described (Steely *et al.* 1992; Steely *et al.* 2000; Wilson *et al.* 1993; Clark *et al.* 1994; Clark *et al.* 1995b; Clark *et al.* 1995c; Clark *et al.* 1996; Clark *et al.* 2001a; Clark *et al.* 2001b; Dickerson *et al.* 1998; Wordinger *et al.* 1998; Wordinger *et al.* 1999; Wordinger *et al.* 2000; Wordinger *et al.* 2002; Lambert *et al.* 2001; Agarwal *et al.* 1999; Liu *et al.* 2001). TM cells were grown from TM explants of donors ranging in age from 6 days to 90 years. Human optic nerve head astrocytes and lamina cribrosa (LC) cells were generated from carefully dissected optic nerve heads (donors aged 2 days to 90 years) and

characterized according to previous reports (Lambert *et al.* 2001; Clark *et al.* 1995a). The cells wers grown to confluency in the following media: Ham's F10 media (JRH Biosciences, Lenexa, KS) containing 10% fetal bovine serum (HyClone, Logan, UT) and antibiotics (Gibco BRL-Life Technologies, Grand Island, NY) for TM cells; Dulbecco's modified Eagle's media (DMEM, HyClone) containing 10% FBS for LC cells; and astrocyte growth medium (AGM, Clonetics, San Diego, CA) containing 5% FBS for ONH astrocytes.

RT-PCR: Human TM and ONH tissues also were dissected from donor eyes (Wordinger *et al.* 1998; Wang *et al.* 2001). Total RNA was extracted from the TM and ONH cells and tissues using TRIzol extraction (Gibco BRL-Life Technologies), and cDNA prepared by reverse transcription using standard procedures (Wordinger *et al.* 1998; Wordinger *et al.* 1999; Wordinger *et al.* 2000; Wordinger *et al.* 2002). PCR primers were designed using the Oligos 4.0 software program (see primer pairs in Table 1). All primer pairs were designed so that amplification of potentially contaminated genomic DNA sequences would produce mRNA PCR products that would be substantially larger than expected, because intron sequences that were excised during RNA processing would be included in genomic DNA. The β-actin PCR primers, AGGCCAACCGCGAGAAGATGACC (upstream) and GAAGTCCAGGGCGACGTAGCAC (downstream) with an annealing temperature of 55 °C yielded a PCR product of 350 bp.

PCR reactions were run as described (Wordinger *et al.* 1998; Wordinger *et al.* 1999; Wordinger *et al.* 2000; Lambert *et al.* 2001; Wordinger *et al.* 2002) using Taq Start Antibody Hot Start with the following cycle conditions: 2 minutes at 94°C, 2 minutes at 92°C, and 40 cycles of 30 seconds at the optimal annealing temperature, extension for 90

seconds at 72°C and denaturation for 45 seconds at 92°C. The amplified PCR products were examined by horizontal electrophoresis in 1.5% agarose gels. To ensure specificity of the RT-PCR products, Southern blot analysis was performed with probes designed using Oligo 4.0 that hybridized to a region within the amplified PCR product. PCR products were sequenced to verify the specificity of the PCR reactions. Table 2 lists the members of the BMP family that are expressed in the human TM and ONH.

Table 1. PCR Primer Pairs, Annealing Temperature and Amplimer Size of BMPs

Name	Assession Number	Upstream PCR Primer	Downstream PCR Primer	Ampl. Size (bp)
BMP-2A	NM_001200	ACTGCGGTCTCCTAAA GGTCGA (SEQ ID NO:9)	GCTGACCTGAGTGCCT GCGAT (SEQ ID NO:10)	657
BMP-4	NM_001202	GAATGCTGATGGTCGT TTTTATTATG (SEQ ID NO:11)	AGACTGAAGCCGGTA AAGAT (SEQ ID NO:12)	348
BMP-5	NM_021073	AAGAGGACAAGAAGG ACTAAAAATAT (SEQ ID NO:13)	GTAGAGATCCAGCATA AAGAGAGGT (SEQ ID NO:14)	303
BMP-7	NM_001719	AGCCCGGGTAGCGCGT AGAG (SEQ ID NO:15)	GCGCCGGTGGATGAA GCTCGA (SEQ ID NO:16)	202
BMPR-1A	NM_004329	TAAAGGTGACAGTACA CAGGAACA (SEQ ID NO:17)	TCTATGATGGCAAAGC AATGTCC (SEQ ID NO:18)	298
BMPR-1B	NM_001203	TACAAGCCTGCCATAA GTGAAGAAGC (SEQ ID NO:19)	ATCATCGTGAAACAAT ATCCGTCTG (SEQ ID NO:20)	211
BMPR-II	NM_001204	TCCTCTCATCAGCCAT TTGTCCTTTC (SEQ ID NO:21)	AGTTACTACACATTCT TCATAG (SEQ ID NO:22)	457
Chordin (CHRD)	AF209930	CTCTGCTCACTCTGCA CCTG (SEQ ID NO:23)	CCGGTCACCATCAAAA TAGC (SEQ ID NO:24)	198
Gremlin (CKTSF1 B1)	NM_013372	ATCAACCGCTTCTGTT ACGG (SEQ ID NO:25)	ATGCAACGACACTGCT TCAC (SEQ ID NO:26)	197
Follistatin (FST)	NM_006350	TGCCACCTGAGAAAGG CTAC (SEQ ID NO:27)	ACAGACAGGCTCATCC GACT (SEQ ID NO:28)	201
Noggin (NOG)	NM_005450	CACTACGACCCAGGCT TCAT (SEQ ID NO:29)	CTCCGCAGCTTCTTGC TTAG (SEQ ID NO:30)	212
CER-1	NM_005454	ATAGTGAGCCCTTCCC ACCT (SEQ ID NO:33)	AATGAACAGACCCGC ATTTC (SEQ ID NO:34)	294
NMA (BAMBI)	NM_005791	GATCGCCACTCCAGCT ACATC (SEQ ID NO:35)	GGGCACGGCAATGAC C (SEQ ID NO:36)	471

Table 2. BMP Family Members Expressed in Human TM and ONH

BMP Family Member	Trabecular Meshwork	Optic Nerve Head
BMP-2	+	+
BMP-4	+	+
BMP-5	+	+
BMP-7	+	+
BMPR-IA	+	+
BMPR-IB	+	+
BMPR-II	+	+
Chordin	+	+
Gremlin	+	+
Follistatin	+	+
Bambi	+	+
Noggin	-	-
CER-1	-	-

Western immunoblotting: Protein was extracted from cultured cells using lysis buffer, and proteins were separated by denaturing polyacrylamide gel electrophoresis prior to electrophoretic transfer to nitrocellulose membranes (Lambert *et al.* 2001). The membranes were blocked with 5% milk (for BMPs) or 3% gelatin (for BMPRs) and incubated with the following primary antibodies: BMP2, BMP4, BMP5, BMP7 (all from Santa Cruz, Santa Cruz, CA), or BMP-RIA, BMP-RIB, BMP-RII (from Jackson Immuno Research, West Grove, PA). The membranes were washed, incubated with secondary antibodies (goat anti-mouse IgG-horseradish peroxidase for BMPs, Santa Cruz; donkey anti-goat-horseradish peroxidase for BMP receptors, Jackson Immuno Research), and developed using the WesternBreeze chemiluminescence immunodetection system (Invitrogen, Carlsbad, CA).

Expression of BMPs, BMPRs mRNA in human TM cells and tissues: Amplification products of expected for BMP-2, BMP-4, BMP-5 and BMP-7 primer pairs in human TM cells and tissues are shown in FIG. 6. Southern blots using specific probes verified that

these were the expected PCR products. All human TM cell lines and tissues expressed message for BMP-2, BMP-4, and BMP-7. However, message for BMP-5 was low to undetectable in human TM tissue samples (FIG. 6, lanes 6 and 7). Control reactions without cDNA did not result in amplification products indicating that reagents and primers were free of DNA or RNA contamination (FIG. 6, lane C).

FIG. 7 shows the amplification products of expected size for BMP-RIA, BMP-RIB, and BMP-RII primer pairs in human TM cells and tissues. All human TM cells and tissues expressed message for the BMP receptor complexes. Southern blots using specific probes verified that these were the expected PCR products. An alternate amplification product (350 bp) was detected in the BMP-RII PCR reaction. The alternate amplification product was present in all human TM cells and tissues. This alternate band is currently being identified to determine if it is an alternate spliced form of the receptor. Control reactions without cDNA did not result in amplification products (FIG. 7, lane C) indicating that reagents and primers were free of DNA or RNA contamination.

Expression of BMP and BMP receptor mRNA in human ONH cells and tissues: Amplification products of expected size for BMP-2, BMP-4, BMP-5 and BMP-7 primer pairs in human ONH astrocytes and ONH tissues are shown in FIG. 8. All ONH astrocytes and ONH tissue expressed message for the respective BMP. Human brain astrocytes were used as a positive control cell line. Southern blots using specific probes verified that these were the expected PCR products. With the exception of BMP-2, all other BMP were expressed by human brain astrocytes (FIG. 8, lane 7). Control reactions without cDNA did not result in amplification products (FIG. 8, lane C) indicating that reagents and primers were free of DNA or RNA contamination.

FIG. 9 shows the amplification products of expected sizes for BMP-2, BMP-4, BMP-5 and BMP-7 primer pairs in cultured human LC cells. All LC cell lines expressed message for each BMP. Southern blots using specific probes verified that these were the expected PCR products. Control reactions without cDNA did not result in amplification products (FIG. 9, lane C) indicating that reagents and primers were free of DNA or RNA contamination.

Amplification products of expected size for BMP-RIA, BMP-RIB, and BMP-RII primer pairs in human ONH astrocytes and ONH tissues are shown in FIG. 10. All ONH astrocyte cell lines and tissues expressed message for BMP-RIA and BMP-RIB. Southern blots using specific probes verified that these were the expected PCR products. With the exception of ONH tissue (FIG. 10, lane 6), BMP-RII was expressed by all ONH astrocyte cell lines. Message for all BMP receptors (FIG. 10, lane 7) was expressed by a human brain astrocyte cell line that served as a positive control. There appears to be a discrepancy in the expression of BMP-RII in ONH tissue and ONH cell lines. The reduced expression in ONH tissue may reflect a low level of expression. Control reactions without cDNA did not result in amplification products (FIG. 5, lane C) indicating that reagents and primers were free of DNA or RNA contamination.

FIG. 11 shows the amplification products of expected size for BMP-RIA, BMP-RIB, and BMP-RII primer pairs in cultured human LC cells. All LC cell lines expressed message for each BMP receptor. Southern blots using specific probes verified that these were the expected PCR products. Control reactions without cDNA did not result in amplification products (FIG. 11, lane C) indicating that reagents and primers were free of DNA or RNA contamination.

Expression of BMP proteins and BMP receptor proteins in human TM and ONH cells and tissues: FIG. 12 represents chemiluminescent immunoblot detection of BMP-2, BMP-4, BMP-5, BMP-7, BMP-RIA, BMP-RIB, and BMP-RII proteins in human TM and ONH cells and tissues. All cell lines studied expressed the respective BMP proteins. The BMP proteins were detected in cell lines the following molecular weights: 54-56 kDa for BMP-2, 25-27 kDa for BMP-4, 55-57 kDa for BMP-5, and 77 kDa for BMP-7. Multiple bands were detected for BMP-2 and BMP-4, which most likely represent glycosylated, and partially glycosylated forms of these BMPs as seen in other studies. However, we did not do glycosylation studies as they were beyond the scope of this study. The BMP receptor proteins were detected in cell lines at molecular weights: 38 kDa for BMP-RIA, 64 kDa for BMP-RIB, and 57 kDa for BMP-RII. Multiple bands were detected for BMP-RIB and BMP-RII in the TM cells, which most likely represent glycosylated, and partially glycosylated forms as seen in other studies. The expression levels of proteins for the BMP receptors appeared to be lower in the TM cells compared to ONH cells. For example BMP-RII was not detected in TM cells and BMP-RIB was greatly reduced.

Expression of BMP associated protein mRNAs in cultured human TM cells and in human ONH cells: Amplification products of expected size for BMP associated protein primer pairs in human TM cell lines are shown in FIG. 13. Human TM cell lines expressed message for DRM (gremlin), chordin, follistatin, and NMA (BAMBI). Southern blots using specific probes verified that these were the expected PCR products. There was no apparent difference in message expression between cell lines. All human TM cells examined failed to express mRNA for the BMP associated proteins noggin and Cer-1. Control reactions without cDNA did not result in amplification products indicating that reagents and primers were free of DNA or RNA contamination.

Amplification products of expected size for BMP associated protein primer pairs in ONH astrocytes and LC cell lines are shown in FIG. 14. All ONH astrocytes and LC cell lines expressed message for DRM (gremlin), follistatin and NMA (BAMBI). Southern blots using specific probes verified that these were the expected PCR products. The majority of LC cells and ONH astrocytes expressed message for chordin. All human ONH astrocytes and LC cells examined failed to express mRNA for the BMP associated proteins noggin and Cer-1. Control reactions without cDNA did not result in amplification products indicating that reagents and primers were free of DNA and RNA contamination.

FIG. 15 shows increased expression of the BMP antagonist gremlin (CKTSF1B1) in glaucomatous TM cells. Gene expression was assessed using Affymetrix gene arrays (Affymetrix gene chip U133A).

All of the compositions and/or methods disclosed and claimed herein can be made and executed without undue experimentation in light of the present disclosure. While the compositions and methods of this invention have been described in terms of preferred embodiments, it will be apparent to those of skill in the art that variations may be applied to the compositions and/or methods and in the steps or in the sequence of steps of the method described herein without departing from the concept, spirit and scope of the invention. More specifically, it will be apparent that certain agents which are both chemically and structurally related may be substituted for the agents described herein to achieve similar results. All such substitutions and modifications apparent to those skilled in the art are deemed to be within the spirit, scope and concept of the invention as defined by the appended claims.

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tgaccaatga agaaaatcct gaagagtcgg agtactcagt aagggcatcc ttggcagaag 1020

agaccagagg ggcaagaaag ggatacccag cctctcccaa tgggtatcct cgtcgcatac 1080

agttatctcg gacgactcct ctgaccaccc agagtcctcc tctagccagc ctccatgata 1140

ccaactttct gaatgatgct gacatggtca tgagctttgt caacttagtt gaaagagaca 1200

aggatttttc tcaccagcga aggcattaca aagaatttcg atttgatctt acccaaattc 1260

ctcatggaga ggcagtgaca gcagctgaat tccggatata caaggaccgg agcaacaacc 1320

gatttgaaaa tgaaacaatt aagattagca tatatcaaat catcaaggaa tacacaaata 1380

gggatgcaga tctgttcttg ttagacacaa gaaaggccca agctttagat gtgggttggc 1440

ttgtctttga tatcactgtg accagcaatc attgggtgat taatccccag aataatttgg 1500

gcttacagct ctgtgcagaa acaggggatg gacgcagtat caacgtaaaa tctgctggtc 1560

ttgtgggaag acagggacct cagtcaaaac aaccattcat ggtggccttc ttcaaggcga 1620

gtgaggtact tcttcgatcc gtgagagcag ccaacaaacg aaaaaatcaa aaccgcaata 1680

aatccagctc tcatcaggac tcctccagaa tgtccagtgt tggagattat aacacaagtg 1740

agcaaaaaca agcctgtaag aagcacgaac tctatgtgag cttccgggat ctgggatggc 1800

aggactggat tatagcacca gaaggatacg ctgcatttta ttgtgatgga gaatgttctt 1860

ttccacttaa cgcccatatg aatgccacca accacgctat agttcagact ctggttcatc 1920

tgatgtttcc tgaccacgta ccaaagcctt gttgtgctcc aaccaaatta aatgccatct 1980

ctgttctgta ctttgatgac agctccaatg tcattttgaa aaaatataga aatatggtag 2040

tacgctcatg tggctgccac taatattaaa taatattgat aataacaaaa agatctgtat 2100

taaggtttat ggctgcaata aaaagcatac tttcagacaa acagaaaaaa aaa 2153

<210> 6
<211> 454
<212> PRT
<213> homo sapiens

<400> SEQ ID NO:6

Met His Leu Thr Val Phe Leu Leu Lys Gly Ile Val Gly Phe Leu Trp
1 5 10 15

Ser Cys Trp Val Leu Val Gly Tyr Ala Lys Gly Gly Leu Gly Asp Asn
20 25 30

His Val His Ser Ser Phe Ile Tyr Arg Arg Leu Arg Asn His Glu Arg
35 40 45

Arg Glu Ile Gln Arg Glu Ile Leu Ser Ile Leu Gly Leu Pro His Arg
50 55 60

Pro Arg Pro Phe Ser Pro Gly Lys Gln Ala Ser Ser Ala Pro Leu Phe
65 70 75 80

Met Leu Asp Leu Tyr Asn Ala Met Thr Asn Glu Glu Asn Pro Glu Glu
85 90 95

Ser Glu Tyr Ser Val Arg Ala Ser Leu Ala Glu Glu Thr Arg Gly Ala
100 105 110

Arg Lys Gly Tyr Pro Ala Ser Pro Asn Gly Tyr Pro Arg Arg Ile Gln
115 120 125

Leu Ser Arg Thr Thr Pro Leu Thr Thr Gln Ser Pro Pro Leu Ala Ser
130 135 140

Leu His Asp Thr Asn Phe Leu Asn Asp Ala Asp Met Val Met Ser Phe
145 150 155 160

Val Asn Leu Val Glu Arg Asp Lys Asp Phe Ser His Gln Arg Arg His
165 170 175

Tyr Lys Glu Phe Arg Phe Asp Leu Thr Gln Ile Pro His Gly Glu Ala
180 185 190

Val Thr Ala Ala Glu Phe Arg Ile Tyr Lys Asp Arg Ser Asn Asn Arg
195 200 205

Phe Glu Asn Glu Thr Ile Lys Ile Ser Ile Tyr Gln Ile Ile Lys Glu
210 215 220

Tyr Thr Asn Arg Asp Ala Asp Leu Phe Leu Leu Asp Thr Arg Lys Ala
225 230 235 240

Gln Ala Leu Asp Val Gly Trp Leu Val Phe Asp Ile Thr Val Thr Ser
245 250 255

Asn His Trp Val Ile Asn Pro Gln Asn Asn Leu Gly Leu Gln Leu Cys
260 265 270

Ala Glu Thr Gly Asp Gly Arg Ser Ile Asn Val Lys Ser Ala Gly Leu
275 280 285

Val Gly Arg Gln Gly Pro Gln Ser Lys Gln Pro Phe Met Val Ala Phe
290 295 300

Phe Lys Ala Ser Glu Val Leu Leu Arg Ser Val Arg Ala Ala Asn Lys
305 310 315 320

Arg Lys Asn Gln Asn Arg Asn Lys Ser Ser Ser His Gln Asp Ser Ser
325 330 335

Arg Met Ser Ser Val Gly Asp Tyr Asn Thr Ser Glu Gln Lys Gln Ala
340 345 350

Cys Lys Lys His Glu Leu Tyr Val Ser Phe Arg Asp Leu Gly Trp Gln
355 360 365

Asp Trp Ile Ile Ala Pro Glu Gly Tyr Ala Ala Phe Tyr Cys Asp Gly
370 375 380

Glu Cys Ser Phe Pro Leu Asn Ala His Met Asn Ala Thr Asn His Ala
385 390 395 400

Ile Val Gln Thr Leu Val His Leu Met Phe Pro Asp His Val Pro Lys
405 410 415

Pro Cys Cys Ala Pro Thr Lys Leu Asn Ala Ile Ser Val Leu Tyr Phe
420 425 430

Asp Asp Ser Ser Asn Val Ile Leu Lys Lys Tyr Arg Asn Met Val Val
435 440 445

Arg Ser Cys Gly Cys His
450

<210> 7
<211> 1878
<212> DNA
<213> homo sapiens

<400> SEQ ID NO:7
gggcgcagcg gggcccgtct gcagcaagtg accgacggcc gggacggccg cctgcccccc 60
ctgccacctg gggcggtgcg ggcccggagc ccggagcccg ggtagcgcgt agagccggcg 120
cgatgcacgt gcgctcactg cgagctgcgg cgccgcacag cttcgtggcg ctctgggcac 180
ccctgttcct gctgcgctcc gccctggccg acttcagcct ggacaacgag gtgcactcga 240
gcttcatcca ccggcgcctc cgcagccagg agcggcggga gatgcagcgc gagatcctct 300
ccattttggg cttgccccac cgcccgcgcc cgcacctcca gggcaagcac aactcggcac 360
ccatgttcat gctggacctg tacaacgcca tggcggtgga ggagggcggc gggcccggcg 420
gccagggctt ctcctacccc tacaaggccg tcttcagtac ccagggcccc cctctggcca 480
gcctgcaaga tagccatttc ctcaccgacg ccgacatggt catgagcttc gtcaacctcg 540
tggaacatga caaggaattc ttccacccac gctaccacca tcgagagttc cggtttgatc 600
tttccaagat cccagaaggg gaagctgtca cggcagccga attccggatc tacaaggact 660
acatccggga acgcttcgac aatgagacgt tccggatcag cgtttatcag gtgctccagg 720
agcacttggg cagggaatcg gatctcttcc tgctcgacag ccgtaccctc tgggcctcgg 780
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agttggcggg cctgattggg cggcacgggc cccagaacaa gcagcccttc atggtggctt 960
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gccagaaccg ctccaagacg cccaagaacc aggaagccct gcggatggcc aacgtggcag 1080
agaacagcag cagcgaccag aggcaggcct gtaagaagca cgagctgtat gtcagcttcc 1140
gagacctggg ctggcaggac tggatcatcg cgcctgaagg ctacgccgcc tactactgtg 1200
aggggagtg tgccttccct ctgaactcct acatgaacgc caccaaccac gccatcgtgc 1260
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acagaaacat ggtggtccgg gcctgtggct gccactagct cctccgagaa ttcagaccct 1440
ttggggccaa gtttttctgg atcctccatt gctcgccttg gccaggaacc agcagaccaa 1500
ctgccttttg tgagaccttc ccctccctat ccccaacttt aaaggtgtga gagtattagg 1560
aaacatgagc agcatatggc ttttgatcag tttttcagtg gcagcatcca atgaacaaga 1620
tcctacaagc tgtgcaggca aaacctagca ggaaaaaaaa acaacgcata aagaaaaatg 1680
gccgggccag gtcattggct gggaagtctc agccatgcac ggactcgttt ccagaggtaa 1740

ttatgagcgc ctaccagcca ggccacccag ccgtgggagg aaggggggcgt ggcaaggggt 1800

gggcacattg gtgtctgtgc gaaaggaaaa ttgacccgga agttcctgta ataaatgtca 1860

caataaaacg aatgaatg 1878

<210> 8
<211> 431
<212> PRT
<213> homo sapiens

<400> SEQ ID NO:8

Met His Val Arg Ser Leu Arg Ala Ala Ala Pro His Ser Phe Val Ala
1 5 10 15

Leu Trp Ala Pro Leu Phe Leu Leu Arg Ser Ala Leu Ala Asp Phe Ser
20 25 30

Leu Asp Asn Glu Val His Ser Ser Phe Ile His Arg Arg Leu Arg Ser
35 40 45

Gln Glu Arg Arg Glu Met Gln Arg Glu Ile Leu Ser Ile Leu Gly Leu
50 55 60

Pro His Arg Pro Arg Pro His Leu Gln Gly Lys His Asn Ser Ala Pro
65 70 75 80

Met Phe Met Leu Asp Leu Tyr Asn Ala Met Ala Val Glu Glu Gly Gly
85 90 95

Gly Pro Gly Gly Gln Gly Phe Ser Tyr Pro Tyr Lys Ala Val Phe Ser
100 105 110

Thr Gln Gly Pro Pro Leu Ala Ser Leu Gln Asp Ser His Phe Leu Thr
115 120 125

Asp Ala Asp Met Val Met Ser Phe Val Asn Leu Val Glu His Asp Lys
130 135 140

Glu Phe Phe His Pro Arg Tyr His His Arg Glu Phe Arg Phe Asp Leu
145 150 155 160

Ser Lys Ile Pro Glu Gly Glu Ala Val Thr Ala Ala Glu Phe Arg Ile
165 170 175

Tyr Lys Asp Tyr Ile Arg Glu Arg Phe Asp Asn Glu Thr Phe Arg Ile
180 185 190

Ser Val Tyr Gln Val Leu Gln Glu His Leu Gly Arg Glu Ser Asp Leu
195 200 205

Phe Leu Leu Asp Ser Arg Thr Leu Trp Ala Ser Glu Glu Gly Trp Leu
210 215 220

Val Phe Asp Ile Thr Ala Thr Ser Asn His Trp Val Val Asn Pro Arg
225 230 235 240

His Asn Leu Gly Leu Gln Leu Ser Val Glu Thr Leu Asp Gly Gln Ser
245 250 255

Ile Asn Pro Lys Leu Ala Gly Leu Ile Gly Arg His Gly Pro Gln Asn
260 265 270

Lys Gln Pro Phe Met Val Ala Phe Phe Lys Ala Thr Glu Val His Phe
275 280 285

Arg Ser Ile Arg Ser Thr Gly Ser Lys Gln Arg Ser Gln Asn Arg Ser
290 295 300

Lys Thr Pro Lys Asn Gln Glu Ala Leu Arg Met Ala Asn Val Ala Glu
305 310 315 320

Asn Ser Ser Ser Asp Gln Arg Gln Ala Cys Lys Lys His Glu Leu Tyr
325 330 335

Val Ser Phe Arg Asp Leu Gly Trp Gln Asp Trp Ile Ile Ala Pro Glu
340 345 350

Gly Tyr Ala Ala Tyr Tyr Cys Glu Gly Glu Cys Ala Phe Pro Leu Asn
355 360 365

Ser Tyr Met Asn Ala Thr Asn His Ala Ile Val Gln Thr Leu Val His
370 375 380

Phe Ile Asn Pro Glu Thr Val Pro Lys Pro Cys Cys Ala Pro Thr Gln
385 390 395 400

Leu Asn Ala Ile Ser Val Leu Tyr Phe Asp Asp Ser Ser Asn Val Ile
405 410 415

Leu Lys Lys Tyr Arg Asn Met Val Val Arg Ala Cys Gly Cys His
420 425 430

<210> 9
<211> 22
<212> DNA
<213> homo sapiens

<400> SEQ ID NO:9
actgcggtct cctaaaggtc ga 22

<210> 10
<211> 21
<212> DNA
<213> homo sapiens

<400> SEQ ID NO:10
gctgacctga gtgcctgcga t 21

<210> 11
<211> 26
<212> DNA
<213> homo sapiens

<400> SEQ ID NO:11
gaatgctgat ggtcgttttt attatg 26

<210> 12
<211> 20
<212> DNA
<213> homo sapiens

<400> SEQ ID NO:12
agactgaagc cggtaaagat 20

<210> 13
<211> 26
<212> DNA
<213> homo sapiens

<400> SEQ ID NO:13
aagaggacaa gaaggactaa aaatat 26

<210> 14
<211> 25
<212> DNA
<213> homo sapiens

<400> SEQ ID NO:14
gtagagatcc agcataaaga gaggt 25

<210> 15
<211> 20
<212> DNA
<213> homo sapiens

<400> SEQ ID NO:15
agcccgggta gcgcgtagag 20

<210> 16
<211> 21
<212> DNA
<213> homo sapiens

<400> SEQ ID NO:16
gcgccggtgg atgaagctcg a 21

<210> 17
<211> 24
<212> DNA
<213> homo sapiens

<400> SEQ ID NO:17
taaaggtgac agtacacagg aaca 24

<210> 18
<211> 23
<212> DNA
<213> homo sapiens

<400> SEQ ID NO:18
tctatgatgg caaagcaatg tcc 23

<210> 19
<211> 26
<212> DNA
<213> homo sapiens

<400> SEQ ID NO:19
tacaagcctg ccataagtga agaagc 26

<210> 20
<211> 25
<212> DNA
<213> homo sapiens

<400> SEQ ID NO:20
atcatcgtga aacaatatcc gtctg 25

<210> 21
<211> 26
<212> DNA
<213> homo sapiens

<400> SEQ ID NO:21
tcctctcatc agccatttgt cctttc 26

<210> 22
<211> 22
<212> DNA
<213> homo sapiens

<400> SEQ ID NO:22
agttactaca cattcttcat ag 22

<210> 23
<211> 20
<212> DNA
<213> homo sapiens

<400> SEQ ID NO:23
ctctgctcac tctgcacctg 20

<210> 24
<211> 20
<212> DNA
<213> homo sapiens

<400> SEQ ID NO:24
ccggtcacca tcaaaatagc 20

<210> 25
<211> 20
<212> DNA
<213> homo sapiens

<400> SEQ ID NO:25
atcaaccgct tctgttacgg 20

<210> 26
<211> 20
<212> DNA
<213> homo sapiens

<400> SEQ ID NO:26
atgcaacgac actgcttcac 20

<210> 27
<211> 20
<212> DNA
<213> homo sapiens

<400> SEQ ID NO:27
tgccacctga gaaaggctac 20

<210> 28
<211> 20
<212> DNA
<213> homo sapiens

<400> SEQ ID NO:28
acagacaggc tcatccgact 20

<210> 29
<211> 20
<212> DNA
<213> homo sapiens

<400> SEQ ID NO:29
cactacgacc caggcttcat 20

<210> 30
<211> 20
<212> DNA
<213> homo sapiens

<400> SEQ ID NO:30
ctccgcagct tcttgcttag 20

<210> 31
<211> 20
<212> DNA
<213> homo sapiens

<400> SEQ ID NO:31
atccttcttc atctggctgc 20

<210> 32
<211> 20
<212> DNA
<213> homo sapiens

<400> SEQ ID NO:32
aattggtgtc ctgaggatcg 20

<210> 33
<211> 20
<212> DNA
<213> homo sapiens

<400> SEQ ID NO:33
atagtgagcc cttcccacct 20

<210> 34
<211> 20
<212> DNA

<213> homo sapiens

<400> SEQ ID NO:34
aatgaacaga cccgcatttc 20

<210> 35
<211> 21
<212> DNA
<213> homo sapiens

<400> SEQ ID NO:35
gatcgccact ccagctacat c 21

<210> 36
<211> 16
<212> DNA
<213> homo sapiens

<400> SEQ ID NO:36
gggcacggca atgacc 16

<210> 37
<211> 2932
<212> DNA
<213> homo sapiens

<400> SEQ ID NO:37
gctccgcgcc gagggctgga ggatgcgttc cctggggtcc ggacttatga aaatatgcat 60

cagtttaata ctgtcttgga attcatgaga tggaagcata ggtcaaagct gtttggagaa 120

aatcagaagt acagttttat ctagccacat cttggaggag tcgtaagaaa gcagtgggag 180

ttgaagtcat tgtcaagtgc ttgcgatctt ttacaagaaa atctcactga atgatagtca 240

tttaaattgg tgaagtagca agaccaatta ttaaaggtga cagtacacag gaaacattac 300

aattgaacaa tgactcagct atacatttac atcagattat tgggagccta tttgttcatc 360

atttctcgtg ttcaaggaca gaatctggat agtatgcttc atggcactgg gatgaaatca 420

gactccgacc agaaaaagtc agaaaatgga gtaaccttag caccagagga taccttgcct 480

tttttaaagt gctattgctc agggcactgt ccagatgatg ctattaataa cacatgcata 540

actaatggac attgctttgc catcatagaa gaagatgacc agggagaaac cacattagct 600

tcagggtgta tgaaatatga aggatctgat tttcagtgca aagattctcc aaaagcccag 660

ctacgccgga caatagaatg ttgtcggacc aatttatgta accagtattt gcaacccaca 720

ctgccccctg ttgtcatagg tccgtttttt gatggcagca ttcgatggct ggttttgctc 780

atttctatgg ctgtctgcat aattgctatg atcatcttct ccagctgctt ttgttacaaa 840

cattattgca agagcatctc aagcagacgt cgttacaatc gtgatttgga acaggatgaa 900

gcatttattc cagttggaga atcactaaaa gaccttattg accagtcaca aagttctggt 960

agtgggtctg gactaccttt attggttcag cgaactattg ccaaacagat tcagatggtc 1020

cggcaagttg gtaaaggccg atatggagaa gtatggatgg gcaaatggcg tggcgaaaaa 1080

gtggcggtga aagtattctt taccactgaa gaagccagct ggtttcgaga aacagaaatc 1140

taccaaactg tgctaatgcg ccatgaaaac atacttggtt tcatagcggc agacattaaa 1200

ggtacaggtt cctggactca gctctatttg attactgatt accatgaaaa tggatctctc 1260

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attgctgacc tgggccttgc tgttaaattc aacagtgaca caaatgaagt tgatgtgccc 1500

ttgaatacca gggtgggcac caaacgctac atggctcccg aagtgctgga cgaaagcctg 1560

aacaaaaacc acttccagcc ctacatcatg gctgacatct acagcttcgg cctaatcatt 1620

tgggagatgg ctcgtcgttg tatcacagga gggatcgtgg aagaatacca attgccatat 1680

tacaacatgg taccgagtga tccgtcatac gaagatatgc gtgaggttgt gtgtgtcaaa 1740

cgtttgcggc caattgtgtc taatcggtgg aacagtgatg aatgtctacg agcagttttg 1800

aagctaatgt cagaatgctg ggcccacaat ccagcctcca gactcacagc attgagaatt 1860

aagaagacgc ttgccaagat ggttgaatcc caagatgtaa aaatctgatg gttaaaccat 1920

cggaggagaa actctagact gcaagaactg tttttaccca tggcatgggt ggaattagag 1980

tggaataagg atgttaactt ggttctcaga ctctttcttc actacgtgtt cacaggctgc 2040

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tttttatgaa ctgcatcaag acttcaatcc tgattagtgt ctccagtcaa gctctgggta 2220

ctgaattgcc tgttcataaa acggtgcttt ctgtgaaagc cttaagaaga taaatgagcg 2280

cagcagagat ggagaaatag actttgcctt ttacctgaga cattcagttc gtttgtattc 2340

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gtttgtcctg tgtccttagt gatgtgtgtg tgtctccatg cacatgcacg ccgggattcc 2460

tctgctgcca tttgaattag aagaaaataa tttatatgca tgcacaggaa gatattggtg 2520

gccggtggtt ttgtgcttta aaaatgcaat atctgaccaa gattcgccaa tctcatacaa 2580

gccatttact ttgcaagtga gatagcttcc ccaccagctt tatttttaa catgaaagct 2640

gatgccaagg ccaaaagaag tttaaagcat ctgtaaattt ggactgtttt ccttcaacca 2700

ccatttttt tgtggttatt atttttgtca cggaaagcat cctctccaaa gttggagctt 2760

ctattgccat gaaccatgct tacaaagaaa gcacttctta ttgaagtgaa ttcctgcatt 2820

tgatagcaat gtaagtgcct ataaccatgt tctatattct ttattctcag taacttttaa 2880

aagggaagtt atttatattt tgtgtataat gtgctttatt tgcaaatcac cc 2932

<210> 38
<211> 532
<212> PRT
<213> homo sapiens

<400> SEQ ID NO:38

Met Thr Gln Leu Tyr Ile Tyr Ile Arg Leu Leu Gly Ala Tyr Leu Phe
1 5 10 15

Ile Ile Ser Arg Val Gln Gly Gln Asn Leu Asp Ser Met Leu His Gly
20 25 30

Thr Gly Met Lys Ser Asp Ser Asp Gln Lys Lys Ser Glu Asn Gly Val
35 40 45

Thr Leu Ala Pro Glu Asp Thr Leu Pro Phe Leu Lys Cys Tyr Cys Ser
50 55 60

Gly His Cys Pro Asp Asp Ala Ile Asn Asn Thr Cys Ile Thr Asn Gly
65 70 75 80

His Cys Phe Ala Ile Ile Glu Glu Asp Asp Gln Gly Glu Thr Thr Leu
85 90 95

Ala Ser Gly Cys Met Lys Tyr Glu Gly Ser Asp Phe Gln Cys Lys Asp
100 105 110

Ser Pro Lys Ala Gln Leu Arg Arg Thr Ile Glu Cys Cys Arg Thr Asn
115 120 125

Leu Cys Asn Gln Tyr Leu Gln Pro Thr Leu Pro Pro Val Val Ile Gly
130 135 140

Pro Phe Phe Asp Gly Ser Ile Arg Trp Leu Val Leu Leu Ile Ser Met
145 150 155 160

Ala Val Cys Ile Ile Ala Met Ile Ile Phe Ser Ser Cys Phe Cys Tyr
165 170 175

Lys His Tyr Cys Lys Ser Ile Ser Ser Arg Arg Arg Tyr Asn Arg Asp
180 185 190

Leu Glu Gln Asp Glu Ala Phe Ile Pro Val Gly Glu Ser Leu Lys Asp
195 200 205

Leu Ile Asp Gln Ser Gln Ser Ser Gly Ser Gly Ser Gly Leu Pro Leu
210 215 220

Leu Val Gln Arg Thr Ile Ala Lys Gln Ile Gln Met Val Arg Gln Val
225 230 235 240

Gly Lys Gly Arg Tyr Gly Glu Val Trp Met Gly Lys Trp Arg Gly Glu
245 250 255

Lys Val Ala Val Lys Val Phe Phe Thr Thr Glu Glu Ala Ser Trp Phe
260 265 270

Arg Glu Thr Glu Ile Tyr Gln Thr Val Leu Met Arg His Glu Asn Ile
275 280 285

Leu Gly Phe Ile Ala Ala Asp Ile Lys Gly Thr Gly Ser Trp Thr Gln
290 295 300

Leu Tyr Leu Ile Thr Asp Tyr His Glu Asn Gly Ser Leu Tyr Asp Phe
305 310 315 320

Leu Lys Cys Ala Thr Leu Asp Thr Arg Ala Leu Leu Lys Leu Ala Tyr
325 330 335

Ser Ala Ala Cys Gly Leu Cys His Leu His Thr Glu Ile Tyr Gly Thr
340 345 350

Gln Gly Lys Pro Ala Ile Ala His Arg Asp Leu Lys Ser Lys Asn Ile
355 360 365

Leu Ile Lys Lys Asn Gly Ser Cys Cys Ile Ala Asp Leu Gly Leu Ala
370 375 380

Val Lys Phe Asn Ser Asp Thr Asn Glu Val Asp Val Pro Leu Asn Thr
385 390 395 400

Arg Val Gly Thr Lys Arg Tyr Met Ala Pro Glu Val Leu Asp Glu Ser
405 410 415

Leu Asn Lys Asn His Phe Gln Pro Tyr Ile Met Ala Asp Ile Tyr Ser
420 425 430

Phe Gly Leu Ile Ile Trp Glu Met Ala Arg Arg Cys Ile Thr Gly Gly
435 440 445

Ile Val Glu Glu Tyr Gln Leu Pro Tyr Tyr Asn Met Val Pro Ser Asp
450 455 460

Pro Ser Tyr Glu Asp Met Arg Glu Val Val Cys Val Lys Arg Leu Arg
465 470 475 480

Pro Ile Val Ser Asn Arg Trp Asn Ser Asp Glu Cys Leu Arg Ala Val
485 490 495

Leu Lys Leu Met Ser Glu Cys Trp Ala His Asn Pro Ala Ser Arg Leu
500 505 510

Thr Ala Leu Arg Ile Lys Lys Thr Leu Ala Lys Met Val Glu Ser Gln
515 520 525

Asp Val Lys Ile
530

<210> 39
<211> 2032
<212> DNA
<213> homo sapiens

<400> SEQ ID NO:39
cgcggggcgc ggagtcggcg gggcctcgcg ggacgcgggc agtgcggaga ccgcggcgct 60

gaggacgcgg gagccgggag cgcacgcgcg gggtggagtt cagcctactc tttcttagat 120

gtgaaaggaa aggaagatca tttcatgcct tgttgataaa ggttcagact tctgctgatt 180

cataaccatt tggctctgag ctatgacaag agaggaaaca aaaagttaaa cttacaagcc 240

tgccataagt gagaagcaaa cttccttgat aacatgcttt tgcgaagtgc aggaaaatta 300

aatgtgggca ccaagaaaga ggatggtgag agtacagccc ccacccccg tccaaaggtc 360

ttgcgttgta aatgccacca ccattgtcca gaagactcag tcaacaatat ttgcagcaca 420

gacggatatt gtttcacgat gatagaagag gatgactctg ggttgcctgt ggtcacttct 480

ggttgcctag gactagaagg ctcagatttt cagtgtcggg acactcccat tcctcatcaa 540

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<211> 502
<212> PRT

<213> homo sapiens

<400> SEQ ID NO:40

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Asp Gly Glu Ser Thr Ala Pro Thr Pro Arg Pro Lys Val Leu Arg Cys
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Lys Cys His His His Cys Pro Glu Asp Ser Val Asn Asn Ile Cys Ser
        35                  40                  45

Thr Asp Gly Tyr Cys Phe Thr Met Ile Glu Glu Asp Asp Ser Gly Leu
    50                  55                  60

Pro Val Val Thr Ser Gly Cys Leu Gly Leu Glu Gly Ser Asp Phe Gln
65                  70                  75                  80

Cys Arg Asp Thr Pro Ile Pro His Gln Arg Arg Ser Ile Glu Cys Cys
                85                  90                  95

Thr Glu Arg Asn Glu Cys Asn Lys Asp Leu His Pro Thr Leu Pro Pro
            100                 105                 110

Leu Lys Asn Arg Asp Phe Val Asp Gly Pro Ile His His Arg Ala Leu
        115                 120                 125

Leu Ile Ser Val Thr Val Cys Ser Leu Leu Leu Val Leu Ile Ile Leu
    130                 135                 140

Phe Cys Tyr Phe Arg Tyr Lys Arg Gln Glu Thr Arg Pro Arg Tyr Ser
145                 150                 155                 160

Ile Gly Leu Glu Gln Asp Glu Thr Tyr Ile Pro Pro Gly Glu Ser Leu
                165                 170                 175

Arg Asp Leu Ile Glu Gln Ser Gln Ser Ser Gly Ser Gly Ser Gly Leu
            180                 185                 190

Pro Leu Leu Val Gln Arg Thr Ile Ala Lys Gln Ile Gln Met Val Lys
        195                 200                 205

Gln Ile Gly Lys Gly Arg Tyr Gly Glu Val Trp Met Gly Lys Trp Arg
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Gly Glu Lys Val Ala Val Lys Val Phe Phe Thr Thr Glu Glu Ala Ser
225                 230                 235                 240

Trp Phe Arg Glu Thr Glu Ile Tyr Gln Thr Val Leu Met Arg His Glu
                245                 250                 255

Asn Ile Leu Gly Phe Ile Ala Ala Asp Ile Lys Gly Thr Gly Ser Trp
            260                 265                 270
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Thr Gln Leu Tyr Leu Ile Thr Asp Tyr His Glu Asn Gly Ser Leu Tyr
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Asp Tyr Leu Lys Ser Thr Thr Leu Asp Ala Lys Ser Met Leu Lys Leu
290 295 300

Ala Tyr Ser Ser Val Ser Gly Leu Cys His Leu His Thr Glu Ile Phe
305 310 315 320

Ser Thr Gln Gly Lys Pro Ala Ile Ala His Arg Asp Leu Lys Ser Lys
325 330 335

Asn Ile Leu Val Lys Lys Asn Gly Thr Cys Cys Ile Ala Asp Leu Gly
340 345 350

Leu Ala Val Lys Phe Ile Ser Asp Thr Asn Glu Val Asp Ile Pro Pro
355 360 365

Asn Thr Arg Val Gly Thr Lys Arg Tyr Met Pro Pro Glu Val Leu Asp
370 375 380

Glu Ser Leu Asn Arg Asn His Phe Gln Ser Tyr Ile Met Ala Asp Met
385 390 395 400

Tyr Ser Phe Gly Leu Ile Leu Trp Glu Val Ala Arg Arg Cys Val Ser
405 410 415

Gly Gly Ile Val Glu Glu Tyr Gln Leu Pro Tyr His Asp Leu Val Pro
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Ser Asp Pro Ser Tyr Glu Asp Met Arg Glu Ile Val Cys Ile Lys Lys
435 440 445

Leu Arg Pro Ser Phe Pro Asn Arg Trp Ser Ser Asp Glu Cys Leu Arg
450 455 460

Gln Met Gly Lys Leu Met Thr Glu Cys Trp Ala His Asn Pro Ala Ser
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Arg Leu Thr Ala Leu Arg Val Lys Lys Thr Leu Ala Lys Met Ser Glu
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Ser Gln Asp Ile Lys Leu
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<212> PRT
<213> homo sapiens

<400> SEQ ID NO:42

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Leu Cys Ala Phe Lys Asp Pro Tyr Gln Gln Asp Leu Gly Ile Gly Glu
35 40 45

Ser Arg Ile Ser His Glu Asn Gly Thr Ile Leu Cys Ser Lys Gly Ser
50 55 60

Thr Cys Tyr Gly Leu Trp Glu Lys Ser Lys Gly Asp Ile Asn Leu Val
65 70 75 80

Lys Gln Gly Cys Trp Ser His Ile Gly Asp Pro Gln Glu Cys His Tyr
85 90 95

Glu Glu Cys Val Val Thr Thr Thr Pro Pro Ser Ile Gln Asn Gly Thr
100 105 110

Tyr Arg Phe Cys Cys Cys Ser Thr Asp Leu Cys Asn Val Asn Phe Thr
115 120 125

Glu Asn Phe Pro Pro Pro Asp Thr Thr Pro Leu Ser Pro Pro His Ser
130 135 140

Phe Asn Arg Asp Glu Thr Ile Ile Ile Ala Leu Ala Ser Val Ser Val
145 150 155 160

Leu Ala Val Leu Ile Val Ala Leu Cys Phe Gly Tyr Arg Met Leu Thr
165 170 175

Gly Asp Arg Lys Gln Gly Leu His Ser Met Asn Met Met Glu Ala Ala
180 185 190

Ala Ser Glu Pro Ser Leu Asp Leu Asp Asn Leu Lys Leu Leu Glu Leu
195 200 205

Ile Gly Arg Gly Arg Tyr Gly Ala Val Tyr Lys Gly Ser Leu Asp Glu
210 215 220

Arg Pro Val Ala Val Lys Val Phe Ser Phe Ala Asn Arg Gln Asn Phe
225 230 235 240

Ile Asn Glu Lys Asn Ile Tyr Arg Val Pro Leu Met Glu His Asp Asn
245 250 255

Ile Ala Arg Phe Ile Val Gly Asp Glu Arg Val Thr Ala Asp Gly Arg
260 265 270

Met Glu Tyr Leu Leu Val Met Glu Tyr Tyr Pro Asn Gly Ser Leu Cys
275 280 285

Lys Tyr Leu Ser Leu His Thr Ser Asp Trp Val Ser Ser Cys Arg Leu
290 295 300

Ala His Ser Val Thr Arg Gly Leu Ala Tyr Leu His Thr Glu Leu Pro
305 310 315 320

Arg Gly Asp His Tyr Lys Pro Ala Ile Ser His Arg Asp Leu Asn Ser
325 330 335

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Arg Asn Val Leu Val Lys Asn Asp Gly Thr Cys Val Ile Ser Asp Phe
            340                 345                 350

Gly Leu Ser Met Arg Leu Thr Gly Asn Arg Leu Val Arg Pro Gly Glu
        355                 360                 365

Glu Asp Asn Ala Ala Ile Ser Glu Val Gly Thr Ile Arg Tyr Met Ala
    370                 375                 380

Pro Glu Val Leu Glu Gly Ala Val Asn Leu Arg Asp Cys Glu Ser Ala
385                 390                 395                 400

Leu Lys Gln Val Asp Met Tyr Ala Leu Gly Leu Ile Tyr Trp Glu Ile
                405                 410                 415

Phe Met Arg Cys Thr Asp Leu Phe Pro Gly Glu Ser Val Pro Glu Tyr
            420                 425                 430

Gln Met Ala Phe Gln Thr Glu Val Gly Asn His Pro Thr Phe Glu Asp
        435                 440                 445

Met Gln Val Leu Val Ser Arg Glu Lys Gln Arg Pro Lys Phe Pro Glu
    450                 455                 460

Ala Trp Lys Glu Asn Ser Leu Ala Val Arg Ser Leu Lys Glu Thr Ile
465                 470                 475                 480

Glu Asp Cys Trp Asp Gln Asp Ala Glu Ala Arg Leu Thr Ala Gln Cys
                485                 490                 495

Ala Glu Glu Arg Met Ala Glu Leu Met Met Ile Trp Glu Arg Asn Lys
            500                 505                 510

Ser Val Ser Pro Thr Val Asn Pro Met Ser Thr Ala Met Gln Asn Glu
        515                 520                 525

Arg Asn Leu Ser His Asn Arg Arg Val Pro Lys Ile Gly Pro Tyr Pro
    530                 535                 540

Asp Tyr Ser Ser Ser Ser Tyr Ile Glu Asp Ser Ile His His Thr Asp
545                 550                 555                 560

Ser Ile Val Lys Asn Ile Ser Ser Glu His Ser Met Ser Ser Thr Pro
                565                 570                 575

Leu Thr Ile Gly Glu Lys Asn Arg Asn Ser Ile Asn Tyr Glu Arg Gln
            580                 585                 590

Gln Ala Gln Ala Arg Ile Pro Ser Pro Glu Thr Ser Val Thr Ser Leu
        595                 600                 605
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Ser Thr Asn Thr Thr Thr Thr Asn Thr Thr Gly Leu Thr Pro Ser Thr
    610                 615                 620

Gly Met Thr Thr Ile Ser Glu Met Pro Tyr Pro Asp Glu Thr Asn Leu
625                 630                 635                 640

His Thr Thr Asn Val Ala Gln Ser Ile Gly Pro Thr Pro Val Cys Leu
                645                 650                 655

Gln Leu Thr Glu Glu Asp Leu Glu Thr Asn Lys Leu Asp Pro Lys Glu
            660                 665                 670

Val Asp Lys Asn Leu Lys Glu Ser Ser Asp Glu Asn Leu Met Glu His
        675                 680                 685

Ser Leu Lys Gln Phe Ser Gly Pro Asp Pro Leu Ser Ser Thr Ser Ser
    690                 695                 700

Ser Leu Leu Tyr Pro Leu Ile Lys Leu Ala Val Glu Ala Thr Gly Gln
705                 710                 715                 720

Gln Asp Phe Thr Gln Thr Ala Asn Gly Gln Ala Cys Leu Ile Pro Asp
                725                 730                 735

Val Leu Pro Thr Gln Ile Tyr Pro Leu Pro Lys Gln Gln Asn Leu Pro
            740                 745                 750

Lys Arg Pro Thr Ser Leu Pro Leu Asn Thr Lys Asn Ser Thr Lys Glu
        755                 760                 765

Pro Arg Leu Lys Phe Gly Ser Lys His Lys Ser Asn Leu Lys Gln Val
    770                 775                 780

Glu Thr Gly Val Ala Lys Met Asn Thr Ile Asn Ala Ala Glu Pro His
785                 790                 795                 800

Val Val Thr Val Thr Met Asn Gly Val Ala Gly Arg Asn His Ser Val
                805                 810                 815

Asn Ser His Ala Ala Thr Thr Gln Tyr Ala Asn Gly Thr Val Leu Ser
            820                 825                 830

Gly Gln Thr Thr Asn Ile Val Thr His Arg Ala Gln Glu Met Leu Gln
        835                 840                 845

Asn Gln Phe Ile Gly Glu Asp Thr Arg Leu Asn Ile Asn Ser Ser Pro
    850                 855                 860

Asp Glu His Glu Pro Leu Leu Arg Arg Glu Gln Gln Ala Gly His Asp
865                 870                 875                 880

Glu Gly Val Leu Asp Arg Leu Val Asp Arg Arg Glu Arg Pro Leu Glu
                885                 890                 895
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Gly Gly Arg Thr Asn Ser Asn Asn Asn Asn Ser Asn Pro Cys Ser Glu
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Gln Asp Val Leu Ala Gln Gly Val Pro Ser Thr Ala Ala Asp Pro Gly
915 920 925

Pro Ser Lys Pro Arg Arg Ala Gln Arg Pro Asn Ser Leu Asp Leu Ser
930 935 940

Ala Thr Asn Val Leu Asp Gly Ser Ser Ile Gln Ile Gly Glu Ser Thr
945 950 955 960

Gln Asp Gly Lys Ser Gly Ser Gly Glu Lys Ile Lys Lys Arg Val Lys
965 970 975

Thr Pro Tyr Ser Leu Lys Arg Trp Arg Pro Ser Thr Trp Val Ile Ser
980 985 990

Thr Glu Ser Leu Asp Cys Glu Val Asn Asn Asn Gly Ser Asn Arg Ala
995 1000 1005

Val His Ser Lys Ser Ser Thr Ala Val Tyr Leu Ala Glu Gly Gly
1010 1015 1020

Thr Ala Thr Thr Met Val Ser Lys Asp Ile Gly Met Asn Cys Leu
1025 1030 1035

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<211> 3561
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ttcagtcaaa aaaaaaaaaa a 3561

<210> 44
<211> 94
<212> PRT
<213> homo sapiens

<400> SEQ ID NO:44

Met Pro Ser Leu Pro Ala Pro Pro Ala Pro Leu Leu Leu Leu Gly Leu
1 5 10 15

Leu Leu Leu Gly Ser Arg Pro Ala Arg Gly Ala Gly Pro Glu Pro Pro
20 25 30

Val Leu Pro Ile Arg Ser Glu Lys Glu Pro Leu Pro Val Arg Gly Ala
35 40 45

Ala Gly Cys Thr Phe Gly Gly Lys Val Tyr Ala Leu Asp Glu Thr Trp
50 55 60

His Pro Asp Leu Gly Glu Pro Phe Gly Val Met Arg Cys Val Leu Cys
65 70 75 80

Ala Cys Glu Ala Thr Gly Thr Leu Arg Pro Arg Glu Met Lys
85 90

<210> 45
<211> 4049
<212> DNA
<213> homo sapiens

<400> SEQ ID NO:45
gcggccgcac tcagcgccac gcgtcgaaag cgcaggcccc gaggacccgc cgcactgaca 60

gtatgagccg cacagcctac acggtgggag ccctgcttct cctcttgggg accctgctgc 120

cggctgctga agggaaaaag aaagggtccc aaggtgccat ccccccgcca gacaaggccc 180

agcacaatga ctcagagcag actcagtcgc cccagcagcc tggctccagg aaccgggggc 240

ggggccaagg gcggggcact gccatgcccg gggaggaggt gctggagtcc agccaagagg 300

ccctgcatgt gacggagcgc aaatacctga agcgagactg gtgcaaaacc cagccgctta 360

agcagaccat ccacgaggaa ggctgcaaca gtcgcaccat catcaaccgc ttctgttacg 420

gccagtgcaa ctctttctac atccccaggc acatccggaa ggaggaaggt tcctttcagt 480

cctgctcctt ctgcaagccc aagaaattca ctaccatgat ggtcacactc aactgccctg 540

aactacagcc acctaccaag aagaagagag tcacacgtgt gaagcagtgt cgttgcatat 600

ccatcgattt ggattaagcc aaatccaggt gcacccagca tgtcctagga atgcagcccc 660

aggaagtccc agacctaaaa caaccagatt cttacttggc ttaaacctag aggccagaag 720

aacccccagc tgcctcctgg caggagcctg cttgtgcgta gttcgtgtgc atgagtgtgg 780

atgggtgcct gtgggtgttt ttagacacca gagaaaacac agtctctgct agagagcact 840

ccctattttg taaacatatc tgctttaatg gggatgtacc agaaacccac ctcaccccgg 900

ctcacatcta aaggggcggg gccgtggtct ggttctgact ttgtgttttt gtgccctcct 960

ggggaccaga atctcctttc ggaatgaatg ttcatggaag aggctcctct gagggcaaga 1020

gacctgtttt agtgctgcat tcgacatgga aaagtccttt taacctgtgc ttgcatcctc 1080

ctttcctcct cctcctcaca atccatctct tcttaagttg atagtgacta tgtcagtcta 1140

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ttttgtgaag accctccaga ctctgggaga ggctggtgtg ggcaaggaca agcaggatag 1260

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gacattgcag aagcttgaaa ggccaatacc agaacacagg ctgatgcttc tgagaaagtc 1380

ttttcctagt atttaacaga acccaagtga acagaggaga aatgagattg ccagaaagtg 1440

attaactttg gccgttgcaa tctgctcaaa cctaacacca aactgaaaac ataaatactg 1500

accactccta tgttcggacc caagcaagtt agctaaacca aaccaactcc tctgctttgt 1560

ccctcaggtg gaaaagagag gtagtttaga actctctgca taggggtggg aattaatcaa 1620

aaacckcaga ggctgaaatt cctaatacct ttcctttatc gtggttatag tcagctcatt 1680

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ragagaagac gacgagagta aggaaataaa gggrattgcc tctggctaga gagtaagtta 1920

ggtgttaata cctggtagaa atgtaaggga tatgacctcc ctttctttat gtgctcactg 1980

aggatctgag gggaccctgt taggagagca tagcatcatg atgtattagc tgttcatctg 2040

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agggtgggtg aactttattg tactttggat ttggttaacc tgttttcttc aagcctgagg 2220

ttttatatac aaactccctg aatactcttt ttgccttgta tcttctcagc ctcctagcca 2280

agtcctatgt aatatggaaa acaaacactg cagacttgag attcagttgc cgatcaaggc 2340

tctggcattc agagaaccct tgcaactcga gaagctgttt ttatttcgtt tttgttttga 2400

tccagtgctc tcccatctaa caactaaaca ggagccattt caaggcggga gatattttaa 2460

acacccaaaa tgttgggtct gattttcaaa cttttaaact cactactgat gattctcacg 2520

ctaggcgaat ttgtccaaac acatagtgtg tgtgttttgt atacactgta tgaccccacc 2580

ccaaatcttt gtattgtcca cattctccaa caataaagca cagagtggat ttaattaagc 2640

acacaaatgc taaggcagaa ttttgagggt gggagagaag aaaagggaaa gaagctgaaa 2700

atgtaaaacc acaccaggga ggaaaaatga cattcagaac cagcaaacac tgaatttctc 2760

ttgttgtttt aactctgcca caagaatgca atttcgttaa tggagatgac ttaagttggc 2820

agcagtaatc ttcttttagg agcttgtacc acagtcttgc acataagtgc agatttggct 2880

caagtaaaga gaatttcctc aacactaact tcactgggat aatcagcagc gtaactaccc 2940

taaaagcata tcactagcca aagagggaaa tatctgttct tcttactgtg cctatattaa 3000

gactagtaca aatgtggtgt gtcttccaac tttcattgaa aatgccatat ctataccata 3060

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ttatggcaag atatttgtgg tcttgatcat acctattaaa ataatgccaa acaccaaata 3180

tgaattttat gatgtacact ttgtgcttgg cattaaaaga aaaaaacaca catcctggaa 3240

gtctgtaagt tgtttttgt tactgtaggt cttcaaagtt aagagtgtaa gtgaaaaatc 3300

tggaggagag gataatttcc actgtgtgga atgtgaatag ttaaatgaaa agttatggtt 3360

atttaatgta attattactt caaatccttt ggtcactgtg atttcaagca tgttttcttt 3420

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gagtcagtgc ctgaatcttt atttttaaa ttgaatgttc cttaaaggtt aacatttcta 3600

aagcaatatt aagaaagact ttaaatgtta ttttggaaga cttacgatgc atgtatacaa 3660

acgaatagca gataatgatg actagttcac acataaagtc cttttaagga gaaaatctaa 3720

aatgaaaagt ggataaacag aacatttata agtgatcagt taatgcctaa gagtgaaagt 3780

agttctattg acattcctca agatatttaa tatcaactgc attatgtatt atgtctgctt 3840

aaatcattta aaaacggcaa agaattatat agactatgag gtaccttgct gtgtaggagg 3900

atgaaagggg agttgatagt ctcataaaac taatttggct tcaagtttca tgaatctgta 3960

actagaattt aattttcacc ccaataatgt tctatatagc ctttgctaaa gagcaactaa 4020

taaattaaac ctattctttc aaaaaaaaa 4049

<210> 46
<211> 184
<212> PRT
<213> homo sapiens

<400> SEQ ID NO:46

Met Ser Arg Thr Ala Tyr Thr Val Gly Ala Leu Leu Leu Leu Leu Gly
1 5 10 15

Thr Leu Leu Pro Ala Ala Glu Gly Lys Lys Lys Gly Ser Gln Gly Ala
20 25 30

Ile Pro Pro Pro Asp Lys Ala Gln His Asn Asp Ser Glu Gln Thr Gln
35 40 45

Ser Pro Gln Gln Pro Gly Ser Arg Asn Arg Gly Arg Gly Gln Gly Arg
50 55 60

Gly Thr Ala Met Pro Gly Glu Glu Val Leu Glu Ser Ser Gln Glu Ala
65 70 75 80

Leu His Val Thr Glu Arg Lys Tyr Leu Lys Arg Asp Trp Cys Lys Thr
85 90 95

Gln Pro Leu Lys Gln Thr Ile His Glu Glu Gly Cys Asn Ser Arg Thr
100 105 110

Ile Ile Asn Arg Phe Cys Tyr Gly Gln Cys Asn Ser Phe Tyr Ile Pro
115 120 125

Arg His Ile Arg Lys Glu Glu Gly Ser Phe Gln Ser Cys Ser Phe Cys
130 135 140

Lys Pro Lys Lys Phe Thr Thr Met Met Val Thr Leu Asn Cys Pro Glu
145 150 155 160

Leu Gln Pro Pro Thr Lys Lys Lys Arg Val Thr Arg Val Lys Gln Cys
165 170 175

Arg Cys Ile Ser Ile Asp Leu Asp
180

<210> 47
<211> 1386
<212> DNA
<213> homo sapiens

<400> SEQ ID NO:47
gctcctcgcc ccgcgcctgc ccccaggatg gtccgcgcga ggcaccagcc gggtgggctt 60

tgcctcctgc tgctgctgct ctgccagttc atggaggacc gcagtgccca ggctgggaac 120

tgctggctcc gtcaagcgaa gaacggccgc tgccaggtcc tgtacaagac cgaactgagc 180

aaggaggagt gctgcagcac cggccggctg agcacctcgt ggaccgagga ggacgtgaat 240

gacaacacac tcttcaagtg gatgattttc aacgggggcg cccccaactg catcccctgt 300

aaagaaacgt gtgagaacgt ggactgtgga cctgggaaaa aatgccgaat gaacaagaag 360

aacaaacccc gctgcgtctg cgccccggat tgttccaaca tcacctggaa gggtccagtc 420

tgcgggctgg atgggaaaac ctaccgcaat gaatgtgcac tcctaaaggc aagatgtaaa 480

gagcagccag aactggaagt ccagtaccaa ggcagatgta aaaagacttg tcgggatgtt 540

ttctgtccag gcagctccac atgtgtggtg gaccagacca ataatgccta ctgtgtgacc 600

tgtaatcgga tttgcccaga gcctgcttcc tctgagcaat atctctgtgg gaatgatgga 660

gtcacctact ccagtgcctg ccacctgaga aaggctacct gcctgctggg cagatctatt 720

ggattagcct atgagggaaa gtgtatcaaa gcaaagtcct gtgaagatat ccagtgcact 780

ggtgggaaaa aatgtttatg ggatttcaag gttgggagag gccggtgttc cctctgtgat 840

gagctgtgcc ctgacagtaa gtcggatgag cctgtctgtg ccagtgacaa tgccacttat 900

gccagcgagt gtgccatgaa ggaagctgcc tgctcctcag gtgtgctact ggaagtaaag 960

cactccggat cttgcaactg aatctgcccg taaaacctga gccattgatt cttcagaact 1020

ttctgcagtt tttgacttca tagattatgc tttaaaaaat ttttttaac ttattgcata 1080

acagcagatg ccaaaaacaa aaaaagcatc tcactgcaag tcacataaaa atgcaacgct 1140

gtaatatggc tgtatcagag ggctttgaaa acatacactg agctgcttct gcgctgttgt 1200

tgtccgtatt taaacaacag ctcccctgta ttccccccatc tagccatttc ggaagacacc 1260

gaggaagagg aggaagatga agaccaggac tacagctttc ctatatcttc tattctagag 1320

tggtaaactc tctataagtg ttcagtgttc acatagcctt tgtgcaaaaa aaaaaaaaaa 1380

aaaaaa 1386

<210> 48
<211> 317
<212> PRT
<213> homo sapiens

<400> SEQ ID NO:48

Met Val Arg Ala Arg His Gln Pro Gly Gly Leu Cys Leu Leu Leu Leu
1 5 10 15

Leu Leu Cys Gln Phe Met Glu Asp Arg Ser Ala Gln Ala Gly Asn Cys
20 25 30

Trp Leu Arg Gln Ala Lys Asn Gly Arg Cys Gln Val Leu Tyr Lys Thr
35 40 45

Glu Leu Ser Lys Glu Glu Cys Cys Ser Thr Gly Arg Leu Ser Thr Ser
50 55 60

Trp Thr Glu Glu Asp Val Asn Asp Asn Thr Leu Phe Lys Trp Met Ile
65 70 75 80

Phe Asn Gly Gly Ala Pro Asn Cys Ile Pro Cys Lys Glu Thr Cys Glu
85 90 95

Asn Val Asp Cys Gly Pro Gly Lys Lys Cys Arg Met Asn Lys Lys Asn
100 105 110

Lys Pro Arg Cys Val Cys Ala Pro Asp Cys Ser Asn Ile Thr Trp Lys
115 120 125

Gly Pro Val Cys Gly Leu Asp Gly Lys Thr Tyr Arg Asn Glu Cys Ala
130 135 140

Leu Leu Lys Ala Arg Cys Lys Glu Gln Pro Glu Leu Glu Val Gln Tyr
145 150 155 160

Gln Gly Arg Cys Lys Lys Thr Cys Arg Asp Val Phe Cys Pro Gly Ser
165 170 175

Ser Thr Cys Val Val Asp Gln Thr Asn Asn Ala Tyr Cys Val Thr Cys
180 185 190

Asn Arg Ile Cys Pro Glu Pro Ala Ser Ser Glu Gln Tyr Leu Cys Gly
195 200 205

Asn Asp Gly Val Thr Tyr Ser Ser Ala Cys His Leu Arg Lys Ala Thr
210 215 220

Cys Leu Leu Gly Arg Ser Ile Gly Leu Ala Tyr Glu Gly Lys Cys Ile
225 230 235 240

Lys Ala Lys Ser Cys Glu Asp Ile Gln Cys Thr Gly Gly Lys Lys Cys
245 250 255

Leu Trp Asp Phe Lys Val Gly Arg Gly Arg Cys Ser Leu Cys Asp Glu
260 265 270

Leu Cys Pro Asp Ser Lys Ser Asp Glu Pro Val Cys Ala Ser Asp Asn
275 280 285

Ala Thr Tyr Ala Ser Glu Cys Ala Met Lys Glu Ala Ala Cys Ser Ser
290 295 300

Gly Val Leu Leu Glu Val Lys His Ser Gly Ser Cys Asn
305 310 315

<210> 49
<211> 699
<212> DNA
<213> homo sapiens

<400> SEQ ID NO:49
atggagcgct gccccagcct aggggtcacc ctctacgccc tggtggtggt cctggggctg 60

cgggcgacac cggccggcgg ccagcactat ctccacatcc gcccggcacc cagcgacaac 120

ctgcccctgg tggacctcat cgaacaccca gaccctatct ttgaccccaa ggaaaaggat 180

ctgaacgaga cgctgctgcg ctcgctgctc gggggccact acgacccagg cttcatggcc 240

acctcgcccc ccgaggaccg gcccggcggg ggcgggggtg cagctggggg cgcggaggac 300

ctggcggagc tggaccagct gctgcggcag cggccgtcgg gggccatgcc gagcgagatc 360

aaagggctag agttctccga gggcttggcc cagggcaaga agcagcgcct aagcaagaag 420

ctgcggagga agttacagat gtggctgtgg tcgcagacat tctgccccgt gctgtacgcg 480

tggaacgacc tgggcagccg cttttggccg cgctacgtga aggtgggcag ctgcttcagt 540

aagcgctcgt gctccgtgcc cgagggcatg gtgtgcaagc cgtccaagtc cgtgcacctc 600

acggtgctgc ggtggcgctg tcagcggcgc gggggccagc gctgcggctg gattcccatc 660

cagtacccca tcatttccga gtgcaagtgc tcgtgctag 699

<210> 50
<211> 232
<212> PRT
<213> homo sapiens

<400> SEQ ID NO:50

Met Glu Arg Cys Pro Ser Leu Gly Val Thr Leu Tyr Ala Leu Val Val
1 5 10 15

Val Leu Gly Leu Arg Ala Thr Pro Ala Gly Gly Gln His Tyr Leu His
20 25 30

Ile Arg Pro Ala Pro Ser Asp Asn Leu Pro Leu Val Asp Leu Ile Glu
35 40 45

His Pro Asp Pro Ile Phe Asp Pro Lys Glu Lys Asp Leu Asn Glu Thr
50 55 60

Leu Leu Arg Ser Leu Leu Gly Gly His Tyr Asp Pro Gly Phe Met Ala
65 70 75 80

Thr Ser Pro Pro Glu Asp Arg Pro Gly Gly Gly Gly Gly Ala Ala Gly
85 90 95

Gly Ala Glu Asp Leu Ala Glu Leu Asp Gln Leu Leu Arg Gln Arg Pro
100 105 110

Ser Gly Ala Met Pro Ser Glu Ile Lys Gly Leu Glu Phe Ser Glu Gly
115 120 125

Leu Ala Gln Gly Lys Lys Gln Arg Leu Ser Lys Lys Leu Arg Arg Lys
130 135 140

Leu Gln Met Trp Leu Trp Ser Gln Thr Phe Cys Pro Val Leu Tyr Ala
145 150 155 160

Trp Asn Asp Leu Gly Ser Arg Phe Trp Pro Arg Tyr Val Lys Val Gly
165 170 175

Ser Cys Phe Ser Lys Arg Ser Cys Ser Val Pro Glu Gly Met Val Cys
180 185 190

Lys Pro Ser Lys Ser Val His Leu Thr Val Leu Arg Trp Arg Cys Gln
195 200 205

Arg Arg Gly Gly Gln Arg Cys Gly Trp Ile Pro Ile Gln Tyr Pro Ile
210 215 220

Ile Ser Glu Cys Lys Cys Ser Cys
225 230

<210> 51
<211> 804
<212> DNA
<213> homo sapiens

<400> SEQ ID NO:51
atgcatctcc tcttatttca gctgctggta ctcctgcctc taggaaagac cacacggcac 60

caggatggcc gccagaatca gagttctctt tcccccgtac tcctgccaag gaatcaaaga 120

gagcttccca caggcaacca tgaggaagct gaggagaagc cagatctgtt tgtcgcagtg 180

ccacaccttg tagccaccag ccctgcaggg gaaggccaga ggcagagaga gaagatgctg 240

tccagatttg gcaggttctg gaagaagcct gagagagaaa tgcatccatc cagggactca 300

gatagtgagc ccttcccacc tgggacccag tccctcatcc agccgataga tggaatgaaa 360

atggagaaat ctcctcttcg ggaagaagcc aagaaattct ggcaccactt catgttcaga 420

aaaactccgg cttctcaggg ggtcatcttg cccatcaaaa gccatgaagt acattgggag 480

acctgcagga cagtgccctt cagccagact ataacccacg aaggctgtga aaaagtagtt 540

gttcagaaca acctttgctt tgggaaatgc gggtctgttc attttcctgg agccgcgcag 600

cactcccata cctcctgctc tcactgtttg cctgccaagt tcaccacgat gcacttgcca 660

ctgaactgca ctgaactttc ctccgtgatc aaggtggtga tgctggtgga ggagtgccag 720

tgcaaggtga agacggagca tgaagatgga cacatcctac atgctggctc ccaggattcc 780

tttatcccag gagtttcagc ttga 804

<210> 52
<211> 267
<212> PRT
<213> homo sapiens

<400> SEQ ID NO:52

Met His Leu Leu Leu Phe Gln Leu Leu Val Leu Leu Pro Leu Gly Lys
1 5 10 15

Thr Thr Arg His Gln Asp Gly Arg Gln Asn Gln Ser Ser Leu Ser Pro
20 25 30

Val Leu Leu Pro Arg Asn Gln Arg Glu Leu Pro Thr Gly Asn His Glu
35 40 45

Glu Ala Glu Glu Lys Pro Asp Leu Phe Val Ala Val Pro His Leu Val
50 55 60

Ala Thr Ser Pro Ala Gly Glu Gly Gln Arg Gln Arg Glu Lys Met Leu
65 70 75 80

Ser Arg Phe Gly Arg Phe Trp Lys Lys Pro Glu Arg Glu Met His Pro
85 90 95

Ser Arg Asp Ser Asp Ser Glu Pro Phe Pro Pro Gly Thr Gln Ser Leu
100 105 110

Ile Gln Pro Ile Asp Gly Met Lys Met Glu Lys Ser Pro Leu Arg Glu
115 120 125

Glu Ala Lys Lys Phe Trp His His Phe Met Phe Arg Lys Thr Pro Ala
130 135 140

Ser Gln Gly Val Ile Leu Pro Ile Lys Ser His Glu Val His Trp Glu
145 150 155 160

Thr Cys Arg Thr Val Pro Phe Ser Gln Thr Ile Thr His Glu Gly Cys
165 170 175

Glu Lys Val Val Val Gln Asn Asn Leu Cys Phe Gly Lys Cys Gly Ser
180 185 190

Val His Phe Pro Gly Ala Ala Gln His Ser His Thr Ser Cys Ser His
195 200 205

Cys Leu Pro Ala Lys Phe Thr Thr Met His Leu Pro Leu Asn Cys Thr
210 215 220

Glu Leu Ser Ser Val Ile Lys Val Val Met Leu Val Glu Glu Cys Gln
225 230 235 240

Cys Lys Val Lys Thr Glu His Glu Asp Gly His Ile Leu His Ala Gly
245 250 255

Ser Gln Asp Ser Phe Ile Pro Gly Val Ser Ala
260 265

<210> 53
<211> 1523
<212> DNA
<213> homo sapiens

<400> SEQ ID NO:53
ctggcgcggg cgggagctgc ggcggatacc cttgcgtgct gtggagaccc tactctcttc 60

gctgagaacg gccgctagcg gggactgaag gccgggagcc cactcccgac ccggggctag 120

cgtgcgtccc tagagtcgag cggggcaagg gagccagtgg ccgccgacgg gggaccggga 180

aacttttctg ggctcctggg cgcgccctgt agccgcgctc catgctccgg cagcggcccg 240

aaacccagcc ccgccgctga cggcgcccgc cgctccgggc agggcccatg ccctgcgcgc 300

tccgggggtc gtaggctgcc gccgagccgg ggctccggaa gccggcgggg gcgccgcggc 360

cgtgcggggc gtcaatggat cgccactcca gctacatctt catctggctg cagctggagc 420

tctgcgccat ggccgtgctg ctcaccaaag gtgaaattcg atgctactgt gatgctgccc 480

actgtgtagc cactggttat atgtgtaaat ctgagctcag cgcctgcttc tctagacttc 540

ttgatcctca gaactcaaat tccccactca cccatggctg cctggactct cttgcaagca 600

cgacagacat ctgccaagcc aaacaggccc gaaaccactc tggcaccacc atacccacat 660

tggaatgctg tcatgaagac atgtgcaatt acagagggct gcacgatgtt ctctctcctc 720

ccaggggtga ggcctcagga caaggaaaca ggtatcagca tgatggtagc agaaacctta 780

tcaccaaggt gcaggagctg acttcttcca aagagttgtg gttccgggca gcggtcattg 840

ccgtgcccat tgctggaggg ctgattttag tgttgcttat tatgttggcc ctgaggatgc 900

ttcgaagtga aaataagagg ctgcaggatc agcggcaaca gatgctctcc cgtttgcact 960

acagctttca cggacaccat tccaaaaagg ggcaggttgc aaagttagac ttggaatgca 1020

tggtgccggt cagtgggcac gagaactgct gtctgacctg tgataaaatg agacaagcag 1080

acctcagcaa cgataagatc ctctcgcttg ttcactgggg catgtacagt gggcacggga 1140

agctggaatt cgtatgacgg agtcttatct gaactacact tactgaacag cttgaaggcc 1200

ttttgagttc tgctggacag gagcacttta tctgaagaca aactcattta atcatctttg 1260

agagacaaaa tgacctctgc aaacagaatc ttggatattt cttctgaagg attatttgca 1320

cagacttaaa tacagttaaa tgtgttattt gcttttaaaa ttataaaaag caaagagaag 1380

actttgtaca cactgtcacc agggttattt gcatccaagg gagctggaat tgagtaccta 1440

aataaacaaa aatgtgccct atgtaagctt ctacatcttg atttattgta aagatttaaa 1500

agaaatatat atattttgtc tga 1523

<210> 54
<211> 260
<212> PRT
<213> homo sapiens

<400> SEQ ID NO:54

Met Asp Arg His Ser Ser Tyr Ile Phe Ile Trp Leu Gln Leu Glu Leu
1 5 10 15

Cys Ala Met Ala Val Leu Leu Thr Lys Gly Glu Ile Arg Cys Tyr Cys
20 25 30

Asp Ala Ala His Cys Val Ala Thr Gly Tyr Met Cys Lys Ser Glu Leu
35 40 45

Ser Ala Cys Phe Ser Arg Leu Leu Asp Pro Gln Asn Ser Asn Ser Pro
50 55 60

Leu Thr His Gly Cys Leu Asp Ser Leu Ala Ser Thr Thr Asp Ile Cys
65 70 75 80

Gln Ala Lys Gln Ala Arg Asn His Ser Gly Thr Thr Ile Pro Thr Leu
85 90 95

Glu Cys Cys His Glu Asp Met Cys Asn Tyr Arg Gly Leu His Asp Val
100 105 110

Leu Ser Pro Pro Arg Gly Glu Ala Ser Gly Gln Gly Asn Arg Tyr Gln
115 120 125

His Asp Gly Ser Arg Asn Leu Ile Thr Lys Val Gln Glu Leu Thr Ser
130 135 140

Ser Lys Glu Leu Trp Phe Arg Ala Ala Val Ile Ala Val Pro Ile Ala
145 150 155 160

Gly Gly Leu Ile Leu Val Leu Leu Ile Met Leu Ala Leu Arg Met Leu
165 170 175

Arg Ser Glu Asn Lys Arg Leu Gln Asp Gln Arg Gln Gln Met Leu Ser
180 185 190

Arg Leu His Tyr Ser Phe His Gly His His Ser Lys Lys Gly Gln Val
195 200 205

Ala Lys Leu Asp Leu Glu Cys Met Val Pro Val Ser Gly His Glu Asn
210 215 220

Cys Cys Leu Thr Cys Asp Lys Met Arg Gln Ala Asp Leu Ser Asn Asp
225 230 235 240

Lys Ile Leu Ser Leu Val His Trp Gly Met Tyr Ser Gly His Gly Lys
245 250 255

Leu Glu Phe Val
260

We Claim:

1. A method for diagnosing glaucoma in a sample obtained from a cell or bodily fluid by detecting altered expression of a bone morphogenic family member gene, said method comprising the steps of:

g) obtaining a tissue or fluid sample from a patient suspected of having glaucoma;

h) extracting DNA from said sample;

i) obtaining a plurality of PCR primers, wherein said primers each comprise a sequence consisting of from 18 to 1547 contiguous nucleotides from SEQ ID NO:1, SEQ ID NO:3, SEQ ID NO:5, SEQ ID NO:7, SEQ ID NO:37, SEQ ID NO:39, SEQ ID NO:41, SEQ ID NO:43, SEQ ID NO:45, SEQ ID NO:47, or SEQ ID NO:53;

j) amplifying regions of the extracted DNA using said primers to obtain a PCR product;

k) resolving the PCR product; and

l) identifying differences between the sequence of the amplified extracted DNA and the sequence of the primer;

where a difference between the amplified sequence and the primer is diagnostic of glaucoma.

2. The method of claim 1, wherein said tissue or fluid sample is blood or buccal cells.

3. The method of claim 1, wherein the primers comprise sequences consisting of from 20 to 100 contiguous nucleotides of SEQ ID NO:1, SEQ ID NO:3, SEQ ID NO:5, SEQ ID NO:7, SEQ ID NO:37, SEQ ID NO:39, SEQ ID NO:41, SEQ ID NO:43, SEQ ID NO:45, SEQ ID NO:47, or SEQ ID NO:53.

4. The method of claim 1, wherein the primers comprise sequences consisting of from 20 to 50 contiguous nucleotides of SEQ ID NO:3.

5. The method of claim 1, wherein the PCR product is resolved by SSCP, DGGE, ASO or RFLP.

6. A method for treating glaucoma comprising administering to a patient in need thereof a composition comprising a sequence consisting of at least one compound selected from the group consisting of a BMP2 agonist, a BMP4 agonist, a BMP5 agonist, a BMP7 agonist, a Smad 1/5 agonist, a chordin antagonist, a gremlin antagonist and a follistatin antagonist.

7. A method for identifying a therapeutic agent for the treatment of glaucoma, said method comprising:

d) obtaining a first composition comprising a population of recombinant cells expressing BMP-2A, BMP4, BMP-5, or BMP7;

e) obtaining a candidate substance;

f) incubating said composition and said candidate substance;

g) testing said composition for its ability to turn on BMP-induced Smad signaling pathways or BMP-regulated gene expression; and

h) identifying a candidate substance that inhibits, or stimulates, BMP-induced Smad signaling pathways or BMP-regulated gene expression.

FIG. 1a / 15

```
1     ggggacttct tgaacttgca gggagaataa cttGCGCACC CCACTTTGCG CCGGTGCCTT

61    TGCCCCAGCG GAGCCTGCTT CGCCATCTCC GAGCCCCACC GCCCCTCCAC TCCTCGGCCT

121   TGCCCGACAC TGAGACGCTG TTCCCAGCGT GAAAAGAGAG ACTGCGCGGC CGGCACCCGG

181   GAGAAGGAGG AGGCAAAGAA AAGGAACGGA CATTCGGTCC TTGCGCCAGG TCCTTTGACC

241   AGAGTTTTTC CATGTGGACG CTCTTTCAAT GGACGTGTCC CCGCGTGCTT CTTAGACGGA

                                    THR   MET   VAL   ALA   GLY   THR   ARG     7
301   CTGCGGTCTC    CTAAAGGTCG      ACC   ATG   GTG   GCC   GGG   ACC   CGC

      CYS   LEU   LEU   ALA   LEU   LEU   LEU   PRO   GLN   VAL   LEU     18
342   TGT   CTT   CTA   GCG   TTG   CTG   CTT   CCC   CAG   GTC   CTC

      LEU   GLY   GLY   ALA   ALA   GLY   LEU   VAL   PRO   GLU   LEU     29
375   CTG   GGC   GGC   GCG   GCT   GGC   CTC   GTT   CCG   GAG   CTG

      GLY   ARG   ARG   LYS   PHE   ALA   ALA   ALA   SER   SER   GLY     40
408   GGC   CGC   AGG   AAG   TTC   GCG   GCG   GCG   TCG   TCG   GGC

      ARG   PRO   SER   SER   GLN   PRO   SER   ASP   GLU   VAL   LEU     51
441   CGC   CCC   TCA   TCC   CAG   CCC   TCT   GAC   GAG   GTC   CTG

      SER   GLU   PHE   GLU   LEU   ARG   LEU   LEU   SER   MET   PHE     62
474   AGC   GAG   TTC   GAG   TTG   CGG   CTG   CTC   AGC   ATG   TTC

      GLY   LEU   LYS   GLN   ARG   PRO   THR   PRO   SER   ARG   ASP     73
507   GGC   CTG   AAA   CAG   AGA   CCC   ACC   CCC   AGC   AGG   GAC

      ALA   VAL   VAL   PRO   PRO   TYR   MET   LEU   ASP   LEU   TYR     84
540   GCC   GTG   GTG   CCC   CCC   TAC   ATG   CTA   GAC   CTG   TAT

      ARG   ARG   HIS   SER   GLY   GLN   PRO   GLY   SER   PRO   ALA     95
573   CGC   AGG   CAC   TCA   GGT   CAG   CCG   GGC   TCA   CCC   GCC

      PRO   ASP   HIS   ARG   LEU   GLU   ARG   ALA   ALA   SER   ARG    106
606   CCA   GAC   CAC   CGG   TTG   GAG   AGG   GCA   GCC   AGC   CGA

      LA    ASN   THR   VAL   ARG   SER   PHE   HIS   HIS   GLU   GLU    117
639   GCC   AAC   ACT   GTG   CGC   AGC   TTC   CAC   CAT   GAA   GAA
```

FIG. 1b / 15

	SER	LEU	GLU	GLU	LEU	PRO	GLU	THR	SER	GLY	LYS	128
672	TCT	TTG	GAA	GAA	CTA	CCA	GAA	ACG	AGT	GGG	AAA	
	THR	THR	ARG	ARG	PHE	PHE	PHE	ASN	LEU	SER	SER	139
705	ACA	ACC	CGG	AGA	TTC	TTC	TTT	AAT	TTA	AGT	TCT	
	ILE	PRO	THR	GLU	GLU	PHE	ILE	THR	SER	ALA	GLU	150
738	ATC	CCC	ACG	GAG	GAG	TTT	ATC	ACC	TCA	GCA	GAG	
	LEU	GLN	VAL	PHE	ARG	GLU	GLN	MET	GLN	ASP	ALA	161
771	CTT	CAG	GTT	TTC	CGA	GAA	CAG	ATG	CAA	GAT	GCT	
	LEU	GLY	ASN	ASN	SER	SER	PHE	HIS	HIS	ARG	ILE	172
804	TTA	GGA	AAC	AAT	AGC	AGT	TTC	CAT	CAC	CGA	ATT	
	ASN	ILE	TYR	GLU	ILE	ILE	LYS	PRO	ALA	THR	ALA	183
837	AAT	ATT	TAT	GAA	ATC	ATA	AAA	CCT	GCA	ACA	GCC	
	ASN	SER	LYS	PHE	PRO	VAL	THR	ARG	LEU	LEU	ASP	194
870	AAC	TCG	AAA	TTC	CCC	GTG	ACC	AGA	CTT	TTG	GAC	
	THR	ARG	LEU	VAL	ASN	GLN	ASN	ALA	SER	ARG	TRP	205
903	ACC	AGG	TTG	GTG	AAT	CAG	AAT	GCA	AGC	AGG	TGG	
	GLU	SER	PHE	ASP	VAL	THR	PRO	ALA	VAL	MET	ARG	216
936	GAA	AGT	TTT	GAT	GTC	ACC	CCC	GCT	GTG	ATG	CGG	
	TRP	THR	ALA	GLN	GLY	HIS	ALA	ASN	HIS	GLY	PHE	227
969	TGG	ACT	GCA	CAG	GGA	CAC	GCC	AAC	CAT	GGA	TTC	
	VAL	VAL	GLU	VAL	ALA	HIS	LEU	GLU	GLU	LYS	GLN	238
1002	GTG	GTG	GAA	GTG	GCC	CAC	TTG	GAG	GAG	AAA	CAA	
	GLY	VAL	SER	LYS	ARG	HIS	VAL	ARG	ILE	SER	ARG	249
1035	GGT	GTC	TCC	AAG	AGA	CAT	GTT	AGG	ATA	AGC	AGG	
	SER	LEU	HIS	GLN	ASP	GLU	HIS	SER	TRP	SER	GLN	260
1068	TCT	TTG	CAC	CAA	GAT	GAA	CAC	AGC	TGG	TCA	CAG	
	ILE	ARG	PRO	LEU	LEU	VAL	THR	PHE	GLY	HIS	ASP	271
1101	ATA	AGG	CCA	TTG	CTA	GTA	ACT	TTT	GGC	CAT	GAT	
	GLY	LYS	GLY	HIS	PRO	LEU	HIS	LYS	ARG	GLU	LYS	282
1134	GGA	AAA	GGG	CAT	CCT	CTC	CAC	AAA	AGA	GAA	AAA	

FIG. 1c / 15

	ARG	GLN	ALA	LYS	HIS	LYS	GLN	ARG	LYS	ARG	LEU	293
1167	CGT	CAA	GCC	AAA	CAC	AAA	CAG	CGG	AAA	CGC	CTT	
	LYS	SER	SER	CYS	LYS	ARG	HIS	PRO	LEU	TYR	VAL	304
1200	AAG	TCC	AGC	TGT	AAG	AGA	CAC	CCT	TTG	TAC	GTG	
	ASP	PHE	SER	ASP	VAL	GLY	TRP	ASN	ASP	TRP	ILE	315
1233	GAC	TTC	AGT	GAC	GTG	GGG	TGG	AAT	GAC	TGG	ATT	
	VAL	ALA	PRO	PRO	GLY	TYR	HIS	ALA	PHE	TYR	CYS	326
1266	GTG	GCT	CCC	CCG	GGG	TAT	CAC	GCC	TTT	TAC	TGC	
	HIS	GLY	GLU	CYS	PRO	PHE	PRO	LEU	ALA	ASP	HIS	337
1299	CAC	GGA	GAA	TGC	CCT	TTT	CCT	CTG	GCT	GAT	CAT	
	LEU	ASN	SER	THR	ASN	HIS	ALA	ILE	VAL	GLN	THR	348
1332	CTG	AAC	TCC	ACT	AAT	CAT	GCC	ATT	GTT	CAG	ACG	
	LEU	VAL	ASN	SER	VAL	ASN	SER	LYS	ILE	PRO	LYS	359
1365	TTG	GTC	AAC	TCT	GTT	AAC	TCT	AAG	ATT	CCT	AAG	
	ALA	CYS	CYS	VAL	PRO	THR	GLU	LEU	SER	ALA	ILE	370
1398	GCA	TGC	TGT	GTC	CCG	ACA	GAA	CTC	AGT	GCT	ATC	
	SER	MET	LEU	TYR	LEU	ASP	GLU	ASN	GLU	LYS	VAL	381
1431	TCG	ATG	CTG	TAC	CTT	GAC	GAG	AAT	GAA	AAG	GTT	
	VAL	LEU	LYS	ASN	TYR	GLN	ASP	MET	VAL	VAL	GLU	392
1464	GTA	TTA	AAG	AAC	TAT	CAG	GAC	ATG	GTT	GTG	GAG	
	GLY	CYS	GLY	CYS	ARG							397
1497	GGT	TGT	GGG	TGT	CGC							

1512 TAG TACAGCAAAATTAAATACATAAATATATATATA

FIG. 2a / 15

```
1     GAAAGCGAGG GAGGGAAAGA GGAGGAAGGA AGATGCGAGA AGGCAGAGGA GGAGGGAGGG

61    AGGGAAGGAG CGCGGAGCCC GGCCCGGAAG CTAGGTGAGT GTGGCATCCG AGCTGAGGGA

121   CGCGAGCCTG AGACGCCGCT GCTGCTCCGG CTGAGTATCT AGCTTGTCTC CCCGATGGGA

181   TTCCCGTCCA AGCTATCTCG AGCCTGCAGC GCCACAGTCC CCGGCCCTCG CCCAGGTTCA

241   CTGCAACCGT TCAGAGGTCC CCAGGAGCTG CTGCTGGCGA GCCCGCTACT GCAGGGACCT

301   ATGGAGCCAT TCCGTAGTGC CATCCCGAGC AACGCACTGC TGCAGCTTCC CTGAGCCTTT

361   CCAGCAAGTT TGTTCAAGAT TGGCTGTCAA GAATCATGGA CTGTTATTAT ATGCCTTGTT

                          Met   Ile   Pro   Gly   Asn   Arg   Met   Leu    8
421   TTCTGTCAAG ACACC    ATG   ATT   CCT   GGT   AAC   CGA   ATG   CTG

      Met   Val   Val   Leu   Leu   Cys   Gln   Val   Leu   Leu   Gly    19
460   ATG   GTC   GTT   TTA   TTA   TGC   CAA   GTC   CTG   CTA   GGA

      Gly   Ala   Ser   His   Ala   Ser   Leu   Ile   Pro   Glu   Thr    30
493   GGC   GCG   AGC   CAT   GCT   AGT   TTG   ATA   CCT   GAG   ACG

      Gly   Lys   Lys   Lys   Val   Ala   Glu   Ile   Gln   Gly   His    41
526   GGG   AAG   AAA   AAA   GTC   GCC   GAG   ATT   CAG   GGC   CAC

      Ala   Gly   Gly   Arg   Arg   Ser   Gly   Gln   Ser   His   Glu    52
559   GCG   GGA   GGA   CGC   CGC   TCA   GGG   CAG   AGC   CAT   GAG

      Leu   Leu   Arg   Asp   Phe   Glu   Ala   Thr   Leu   Leu   Gln    63
592   CTC   CTG   CGG   GAC   TTC   GAG   GCG   ACA   CTT   CTG   CAG

      Met   Phe   Gly   Leu   Arg   Arg   Arg   Pro   Gln   Pro   Ser    74
625   ATG   TTT   GGG   CTG   CGC   CGC   CGC   CCG   CAG   CCT   AGC

      Lys   Ser   Ala   Val   Ile   Pro   Asp   Tyr   Met   Arg   Asp    85
658   AAG   AGT   GCC   GTC   ATT   CCG   GAC   TAC   ATG   CGG   GAT

      Leu   Tyr   Arg   Leu   Gln   Ser   Gly   Glu   Glu   Glu   Glu    96
691   CTT   TAC   CGG   CTT   CAG   TCT   GGG   GAG   GAG   GAG   GAA

      Glu   Gln   Ile   His   Ser   Thr   Gly   Leu   Glu   Tyr   Pro   107
724   GAG   CAG   ATC   CAC   AGC   ACT   GGT   CTT   GAG   TAT   CCT
```

FIG. 2b / 15

	Glu	Arg	Pro	Ala	Ser	Arg	Ala	Asn	Thr	Val	Arg	118
757	GAG	CGC	CCG	GCC	AGC	CGG	GCC	AAC	ACC	GTG	AGG	
	Ser	Phe	His	His	Glu	Glu	His	Leu	Glu	Asn	Ile	129
790	AGC	TTC	CAC	CAC	GAA	GAA	CAT	CTG	GAG	AAC	ATC	
	Pro	Gly	Thr	Ser	Glu	Asn	Ser	Ala	Phe	Arg	Phe	140
823	CCA	GGG	ACC	AGT	GAA	AAC	TCT	GCT	TTT	CGT	TTC	
	Leu	Phe	Asn	Leu	Ser	Ser	Ile	Pro	Glu	Asn	Glu	151
856	CTC	TTT	AAC	CTC	AGC	AGC	ATC	CCT	GAG	AAC	GAG	
	Ala	Ile	Ser	Ser	Ala	Glu	Leu	Arg	Leu	Phe	Arg	162
889	GCG	ATC	TCC	TCT	GCA	GAG	CTT	CGG	CTC	TTC	CGG	
	Glu	Gln	Val	Asp	Gln	Gly	Pro	Asp	Trp	Glu	Arg	173
922	GAG	CAG	GTG	GAC	CAG	GGC	CCT	GAT	TGG	GAA	AGG	
	Gly	Phe	His	Arg	Ile	Asn	Ile	Tyr	Glu	Val	Met	184
955	GGC	TTC	CAC	CGT	ATA	AAC	ATT	TAT	GAG	GTT	ATG	
	Lys	Pro	Pro	Ala	Glu	Val	Val	Pro	Gly	His	Leu	195
988	AAG	CCC	CCA	GCA	GAA	GTG	GTG	CCT	GGG	CAC	CTC	
	Ile	Thr	Arg	Leu	Leu	Asp	Thr	Arg	Leu	Val	His	206
1021	ATC	ACA	CGA	CTA	CTG	GAC	ACG	AGA	CTG	GTC	CAC	
	His	Asn	Val	Thr	Arg	Trp	Glu	Thr	Phe	Asp	Val	217
1054	CAC	AAT	GTG	ACA	CGG	TGG	GAA	ACT	TTT	GAT	GTG	
	Ser	Pro	Ala	Val	Leu	Arg	Trp	Thr	Arg	Glu	Lys	228
1087	AGC	CCT	GCG	GTC	CTT	CGC	TGG	ACC	CGG	GAG	AAG	
	Gln	Pro	Asn	Tyr	Gly	Leu	Ala	Ile	Glu	Val	Thr	239
1120	CAG	CCA	AAC	TAT	GGG	CTA	GCC	ATT	GAG	GTG	ACT	
	His	Leu	His	Gln	Thr	Arg	Thr	His	Gln	Gly	Gln	250
1153	CAC	CTC	CAT	CAG	ACT	CGG	ACC	CAC	CAG	GGC	CAG	
	His	Val	Arg	Ile	Ser	Arg	Ser	Leu	Pro	Gln	Gly	261
1186	CAT	GTC	AGG	ATT	AGC	CGA	TCG	TTA	CCT	CAA	GGG	
	Ser	Gly	Asn	Trp	Ala	Gln	Leu	Arg	Pro	Leu	Leu	272
1219	AGT	GGG	AAT	TGG	GCC	CAG	CTC	CGG	CCC	CTC	CTG	

FIG. 2c / 15

	Val	Thr	Phe	Gly	His	Asp	Gly	Arg	Gly	His	Ala	283
1252	GTC	ACC	TTT	GGC	CAT	GAT	GGC	CGG	GGC	CAT	GCC	
	Leu	Thr	Arg	Arg	Arg	Arg	Ala	Lys	Arg	Ser	Pro	294
1285	TTG	ACC	CGA	CGC	CGG	AGG	GCC	AAG	CGT	AGC	CCT	
	Lys	His	His	Ser	Gln	Arg	Ala	Arg	Lys	Lys	Asn	305
1318	AAG	CAT	CAC	TCA	CAG	CGG	GCC	AGG	AAG	AAG	AAT	
	Lys	Asn	Cys	Arg	Arg	His	Ser	Leu	Tyr	Val	Asp	316
1351	AAG	AAC	TGC	CGG	CGC	CAC	TCG	CTC	TAT	GTG	GAC	
	Phe	Ser	Asp	Val	Gly	Trp	Asn	Asp	Trp	Ile	Val	327
1384	TTC	AGC	GAT	GTG	GGC	TGG	AAT	GAC	TGG	ATT	GTG	
	Ala	Pro	Pro	Gly	Tyr	Gln	Ala	Phe	Tyr	Cys	His	338
1417	GCC	CCA	CCA	GGC	TAC	CAG	GCC	TTC	TAC	TGC	CAT	
	Gly	Asp	Cys	Pro	Phe	Pro	Leu	Ala	Asp	His	Leu	349
1450	GGG	GAC	TGC	CCC	TTT	CCA	CTG	GCT	GAC	CAC	CTC	
	Asn	Ser	Thr	Asn	His	Ala	Ile	Val	Gln	Thr	Leu	360
1483	AAC	TCA	ACC	AAC	CAT	GCC	ATT	GTG	CAG	ACC	CTG	
	Val	Asn	Ser	Val	Asn	Ser	Ser	Ile	Pro	Lys	Ala	371
1516	GTC	AAT	TCT	GTC	AAT	TCC	AGT	ATC	CCC	AAA	GCC	
	Cys	Cys	Val	Pro	Thr	Glu	Leu	Ser	Ala	Ile	Ser	382
1549	TGT	TGT	GTG	CCC	ACT	GAA	CTG	AGT	GCC	ATC	TCC	
	Met	Leu	Tyr	Leu	Asp	Glu	Tyr	Asp	Lys	Val	Val	393
1582	ATG	CTG	TAC	CTG	GAT	GAG	TAT	GAT	AAG	GTG	GTA	
	Leu	Lys	Asn	Tyr	Gln	Glu	Met	Val	Val	Ala	Gly	404
1615	CTG	AAA	AAT	TAT	CAG	GAG	ATG	GTA	GTA	GAG	GGA	
	Cys	Gly	Cys	Arg								408
1648	TGT	GGG	TGC	CGC	TGA	GATCAGGCAGTCCTTGAGGATAGACAGATATAC						

1696 ACACCACACACACACACCACATACACCACACACACACGTTCCCATCCACTCACCCACACACTA

1759 CACAGACTGCTTCCTTATAGCTGGACTTTTATTTAAAAAAAAAAAAAAAAAAATGGAAAAAAT

FIG. 2d / 15

1822 CCCTAAACATTCACCTTGACCTTATTTATGACTTTACGTGCAAATGTTTTGACCATATTGATC

1885 ATATATTTTGACAAAATATATTTATAACTACGTATTAAAAGAAAAAAATAAAATGAGTCATT

FIG. 3a / 15

```
1     CTGGTATATT TGTGCCTGCT GGAGGTGGAA TTAACAGTAA GAAGGAGAAA GGGATTGAAT

61    GGACTTACAG GAAGGATTTC AAGTAAATTC AGGGAAACAC ATTTACTTGA ATAGTACAAC

121   CTAGAGTATT ATTTTACACT AAGACGACAC AAAAGATGTT AAAGTTATCA CCAAGCTGCC

181   GGACAGATAT ATATTCCAAC ACCAAGGTGC AGATCAGCAT AGATCTGTGA TTCAGAAATC

241   AGGATTTGTT TTGGAAAGAG CTCAAGGGTT GAGAAGAACT CAAAAGCAAG TGAAGATTAC

301   TTTGGGAACT ACAGTTTATC AGAAGATCAA CTTTTGCTAA TTCAAATACC AAAGGCCTGA

361   TTATCATAAA TTCATATAGG AATGCATAGG TCATCTGATC AAATAATATT AGCCGTCTTC

421   TGCTACATCA ATGCAGCAAA AACTCTTAAC AACTGTGGAT AATTGGAAAT CTGAGTTTCA

481   GCTTTCTTAG AAATAACTAC TCTTGACATA TTCCAAAATA TTTAAAATAG GACAGGAAAA

541   TCGGTGAGGA TGTTGTGCTC AGAAATGTCA CTGTCATGAA AAATAGGTAA ATTTGTTTTT

601   TCAGCTACTG GGAAACTGTA CCTCCTAGAA CCTTAGGTTT TTTTTTTTTT AAGAGGACAA

                                                  Met   His   Leu   Thr      4
661   GAAGGACTAA AAATATCAAC TTTTGCTTTT GGACAAAA ATG   CAT   CTG   ACT

      Val   Phe   Leu   Leu   Lys   Gly   Ile   Val   Gly   Phe   Leu      15
711   GTA   TTT   TTA   CTT   AAG   GGT   ATT   GTG   GGT   TTC   CTC

      Trp   Ser   Cys   Trp   Val   Leu   Val   Gly   Tyr   Ala   Lys      26
744   TGG   AGC   TGC   TGG   GTT   CTA   GTG   GGT   TAT   GCA   AAA

      Gly   Gly   Leu   Gly   Asp   Asn   His   Val   His   Ser   Ser      37
777   GGA   GGT   TTG   GGA   GAC   AAT   CAT   GTT   CAC   TCC   AGT

      Phe   Ile   Tyr   Arg   Arg   Leu   Arg   Asn   His   Glu   Arg      48
810   TTT   ATT   TAT   AGA   AGA   CTA   CGG   AAC   CAC   GAA   AGA

      Arg   Glu   Ile   Gln   Arg   Glu   Ile   Leu   Ser   Ile   Leu      59
843   CGG   GAA   ATA   CAA   AGG   GAA   ATT   CTC   TCT   ATC   TTG

      Gly   Leu   Pro   His   Arg   Pro   Arg   Pro   Phe   Ser   Pro      70
876   GGT   TTG   CCT   CAC   AGA   CCC   AGA   CCA   TTT   TCA   CCT

      Gly   Lys   Gln   Ala   Ser   Ser   Ala   Pro   Leu   Phe   Met      81
909   GGA   AAA   CAA   GCG   TCC   TCT   GCA   CCT   CTC   TTT   ATG

      Leu   Asp   Leu   Tyr   Asn   Ala   Met   Thr   Asn   Glu   Glu      92
942   CTG   GAT   CTC   TAC   AAT   GCC   ATG   ACC   AAT   GAA   GAA
```

FIG. 3b / 15

	Asn	Pro	Glu	Glu	Ser	Glu	Tyr	Ser	Val	Arg	Ala	103
975	AAT	CCT	GAA	GAG	TCG	GAG	TAC	TCA	GTA	AGG	GCA	
	Ser	Leu	Ala	Glu	Glu	Thr	Arg	Gly	Ala	Arg	Lys	114
1008	TCC	TTG	GCA	GAA	GAG	ACC	AGA	GGG	GCA	AGA	AAG	
	Gly	Tyr	Pro	Ala	Ser	Pro	Asn	Gly	Tyr	Pro	Arg	125
1041	GGA	TAC	CCA	GCC	TCT	CCC	AAT	GGG	TAT	CCT	CGT	
	Arg	Ile	Gln	Leu	Ser	Arg	Thr	Thr	Pro	Leu	Thr	136
1074	CGC	ATA	CAG	TTA	TCT	CGG	ACG	ACT	CCT	CTG	ACC	
	Thr	Gln	Ser	Pro	Pro	Leu	Ala	Ser	Leu	His	Asp	147
1107	ACC	CAG	AGT	CCT	CCT	CTA	GCC	AGC	CTC	CAT	GAT	
	Thr	Asn	Phe	Leu	Asn	Asp	Ala	Asp	Met	Val	Met	158
1140	ACC	AAC	TTT	CTG	AAT	GAT	GCT	GAC	ATG	GTC	ATG	
	Ser	Phe	Val	Asn	Leu	Val	Glu	Arg	Asp	Lys	Asp	169
1173	AGC	TTT	GTC	AAC	TTA	GTT	GAA	AGA	GAC	AAG	GAT	
	Phe	Ser	His	Gln	Arg	Arg	His	Tyr	Lys	Glu	Phe	180
1206	TTT	TCT	CAC	CAG	CGA	AGG	CAT	TAC	AAA	GAA	TTT	
	Arg	Phe	Asp	Leu	Thr	Gln	Lle	Pro	His	Gly	Glu	191
1239	CGA	TTT	GAT	CTT	ACC	CAA	ATT	CCT	CAT	GGA	GAG	
	Ala	Val	Thr	Ala	Ala	Glu	Phe	Arg	Ile	Tyr	Lys	202
1272	GCA	GTG	ACA	GCA	GCT	GAA	TTC	CGG	ATA	TAC	AAG	
	Asp	Arg	Ser	Asn	Asn	Arg	Phe	Glu	Asn	Glu	Thr	213
1305	GAC	CGG	AGC	AAC	AAC	CGA	TTT	GAA	AAT	GAA	ACA	
	Ile	Lys	Ile	Ser	Ile	Tyr	Gln	Ile	Ile	Lys	Glu	224
1338	ATT	AAG	ATT	AGC	ATA	TAT	CAA	ATC	ATC	AAG	GAA	
	Tyr	Thr	Asn	Arg	Asp	Ala	Asp	Leu	Phe	Leu	Leu	235
1371	TAC	ACA	AAT	AGG	GAT	GCA	GAT	CTG	TTC	TTG	TTA	
	Asp	Thr	Arg	Lys	Ala	Gln	Ala	Leu	Asp	Val	Gly	246
1404	GAC	ACA	AGA	AAG	GCC	CAA	GCT	TTA	GAT	GTG	GGT	
	Trp	Leu	Val	Phe	Asp	Ile	Thr	Val	Thr	Ser	Asn	257
1437	TGG	CTT	GTC	TTT	GAT	ATC	ACT	GTG	ACC	AGC	AAT	

FIG. 3c / 15

	His	Trp	Val	Ile	Asn	Pro	Gln	Asn	Asn	Leu	Gly	268
1470	CAT	TGG	GTG	ATT	AAT	CCC	CAG	AAT	AAT	TTG	GGC	
	Leu	Gln	Leu	Cys	Ala	Glu	Thr	Gly	Asp	Gly	Arg	279
1503	TTA	CAG	CTC	TGT	GCA	GAA	ACA	GGG	GAT	GGA	CGC	
	Ser	Ile	Asn	Val	Lys	Ser	Ala	Gly	Leu	Val	Gly	290
1536	AGT	ATC	AAC	GTA	AAA	TCT	GCT	GGT	CTT	GTG	GGA	
	Arg	Gln	Gly	Pro	Gln	Ser	Lys	Gln	Pro	Phe	Met	301
1569	AGA	CAG	GGA	CCT	CAG	TCA	AAA	CAA	CCA	TTC	ATG	
	Val	Ala	Phe	Phe	Lys	Ala	Ser	Glu	Val	Leu	Leu	312
1602	GTG	GCC	TTC	TTC	AAG	GCG	AGT	GAG	GTA	CTT	CTT	
	Arg	Ser	Val	Arg	Ala	Ala	Asn	Lys	Arg	Lys	Asn	323
1635	CGA	TCC	GTG	AGA	GCA	GCC	AAC	AAA	CGA	AAA	AAT	
	Gln	Asn	Arg	Asn	Lys	Ser	Ser	Ser	His	Gln	Asp	334
1668	CAA	AAC	CGC	AAT	AAA	TCC	AGC	TCT	CAT	CAG	GAC	
	Ser	Ser	Arg	Met	Ser	Ser	Val	Gly	Asp	Tyr	Asn	345
1701	TCC	TCC	AGA	ATG	TCC	AGT	GTT	GGA	GAT	TAT	AAC	
	Thr	Ser	Glu	Gln	Lys	Gln	Ala	Cys	Lys	Lys	His	356
1734	ACA	AGT	GAG	CAA	AAA	CAA	GCC	TGT	AAG	AAG	CAC	
	Glu	Leu	Tyr	Val	Ser	Phe	Arg	Asp	Leu	Gly	Trp	367
1767	GAA	CTC	TAT	GTG	AGC	TTC	CGG	GAT	CTG	GGA	TGG	
	Gln	Asp	Trp	Ile	Ile	Ala	Pro	Glu	Gly	Tyr	Ala	378
1800	CAG	GAC	TGG	ATT	ATA	GCA	CCA	GAA	GGA	TAC	GCT	
	Ala	Phe	Tyr	Cys	Asp	Gly	Glu	Cys	Ser	Phe	Pro	389
1833	GCA	TTT	TAT	TGT	GAT	GGA	GAA	TGT	TCT	TTT	CCA	
	Leu	Asn	Ala	His	Met	Asn	Ala	Thr	Asn	His	Ala	400
1866	CTT	AAC	GCC	CAT	ATG	AAT	GCC	ACC	AAC	CAC	GCT	
	Ile	Val	Gln	Thr	Leu	Val	His	Leu	Met	Phe	Pro	411
1899	ATA	GTT	CAG	ACT	CTG	GTT	CAT	CTG	ATG	TTT	CCT	
	Asp	His	Val	Pro	Lys	Pro	Cys	Cys	Ala	Pro	Thr	422
1932	GAC	CAC	GTA	CCA	AAG	CCT	TGT	TGT	GCT	CCA	ACC	

FIG. 3d / 15

```
      Lys   Leu   Asn   Ala   Ile   Ser   Val   Leu   Tyr   Phe   Asp   433
1965  AAA   TTA   AAT   GCC   ATC   TCT   GTT   CTG   TAC   TTT   GAT

      Asp   Ser   Ser   Asn   Val   Ile   Leu   Lys   Lys   Tyr   Arg   444
1998  GAC   AGC   TCC   AAT   GTC   ATT   TTG   AAA   AAA   TAT   AGA

      Asn   Met   Val   Val   Arg   Ser   Cys   Gly   Cys   His         454
2031  AAT   ATG   GTA   GTA   CGC   TCA   TGT   GGC   TGC   CAC   TAA

2064  TATTAAATAATATTGATAATAACAAAAAGATCTGTATTAAGGTTTATGGCTGCAATAAAAAGCA

2128  TACTTTCAGACAAACAGAAAAAAAAA
```

FIG. 4a / 15

```
1      GGGCGCAGCG GGGCCCGTCT GCAGCAAGTG ACCGACGGCC GGGACGGCCG CCTGCCCCCT

61     CTGCCACCTG GGGCGGTGCG GGCCCGGAGC CCGGAGCCCG GGTAGCGCGT AGAGCCGGCG

              Met   His   Val   Arg   Ser   Leu   Arg   Ala   Ala   Ala    10
121    CG     ATG   CAC   GTG   CGC   TCA   CTG   CGA   GCT   GCG   GCG

       Pro   His   Ser   Phe   Val   Ala   Leu   Trp   Ala   Pro   Leu    21
153    CCG   CAC   AGC   TTC   GTG   GCG   CTC   TGG   GCA   CCC   CTG

       Phe   Leu   Leu   Arg   Ser   Ala   Leu   Ala   Asp   Phe   Ser    32
186    TTC   CTG   CTG   CGC   TCC   GCC   CTG   GCC   GAC   TTC   AGC

       Leu   Asp   Asn   Glu   Val   His   Ser   Ser   Phe   Ile   His    43
219    CTG   GAC   AAC   GAG   GTG   CAC   TCG   AGC   TTC   ATC   CAC

       Arg   Arg   Leu   Arg   Ser   Gln   Glu   Arg   Arg   Glu   Met    54
252    CGG   CGC   CTC   CGC   AGC   CAG   GAG   CGG   CGG   GAG   ATG

       Gln   Arg   Glu   Ile   Leu   Ser   Ile   Leu   Gly   Leu   Pro    65
285    CAG   CGC   GAG   ATC   CTC   TCC   ATT   TTG   GGC   TTG   CCC

       His   Arg   Pro   Arg   Pro   His   Leu   Gln   Gly   Lys   His    76
318    CAC   CGC   CCG   CGC   CCG   CAC   CTC   CAG   GGC   AAG   CAC

       Asn   Ser   Ala   Pro   Met   Phe   Met   Leu   Asp   Leu   Tyr    87
351    AAC   TCG   GCA   CCC   ATG   TTC   ATG   CTG   GAC   CTG   TAC

       Asn   Ala   Met   Ala   Val   Glu   Glu   Gly   Gly   Gly   Pro    98
384    AAC   GCC   ATG   GCG   GTG   GAG   GAG   GGC   GGC   GGG   CCC

       Gly   Gly   Gln   Gly   Phe   Ser   Tyr   Pro   Tyr   Lys   Ala   109
417    GGC   GGC   CAG   GGC   TTC   TCC   TAC   CCC   TAC   AAG   GCC

       Val   Phe   Ser   Thr   Gln   Gly   Pro   Pro   Leu   Ala   Ser   120
450    GTC   TTC   AGT   ACC   CAG   GGC   CCC   CCT   CTG   GCC   AGC

       Leu   Gln   Asp   Ser   His   Phe   Leu   Thr   Asp   Ala   Asp   131
483    CTG   CAA   GAT   AGC   CAT   TTC   CTC   ACC   GAC   GCC   GAC

       Met   Val   Met   Ser   Phe   Val   Asn   Leu   Val   Glu   His   142
516    ATG   GTC   ATG   AGC   TTC   GTC   AAC   CTC   GTG   GAA   CAT

       Asp   Lys   Glu   Phe   Phe   His   Pro   Arg   Tyr   His   His   153
549    GAC   AAG   GAA   TTC   TTC   CAC   CCA   CGC   TAC   CAC   CAT
```

FIG. 4b / 15

	Arg	Glu	Phe	Arg	Phe	Asp	Leu	Ser	Lys	Ile	Pro	164
582	CGA	GAG	TTC	CGG	TTT	GAT	CTT	TCC	AAG	ATC	CCA	
	Glu	Gly	Glu	Ala	Val	Thr	Ala	Ala	Glu	Phe	Arg	175
615	GAA	GGG	GAA	GCT	GTC	ACG	GCA	GCC	GAA	TTC	CGG	
	Ile	Tyr	Lys	Asp	Tyr	Ile	Arg	Glu	Arg	Phe	Asp	186
648	ATC	TAC	AAG	GAC	TAC	ATC	CGG	GAA	CGC	TTC	GAC	
	Asn	Glu	Thr	Phe	Arg	Ile	Ser	Val	Tyr	Gln	Val	197
681	AAT	GAG	ACG	TTC	CGG	ATC	AGC	GTT	TAT	CAG	GTG	
	Leu	Gln	Glu	His	Leu	Gly	Arg	Glu	Ser	Asp	Leu	208
714	CTC	CAG	GAG	CAC	TTG	GGC	AGG	GAA	TCG	GAT	CTC	
	Phe	Leu	Leu	Asp	Ser	Arg	Thr	Leu	Trp	Ala	Ser	219
747	TTC	CTG	CTC	GAC	AGC	CGT	ACC	CTC	TGG	GCC	TCG	
	Glu	Glu	Gly	Trp	Leu	Val	Phe	Asp	Ile	Thr	Ala	230
780	GAG	GAG	GGC	TGG	CTG	GTG	TTT	GAC	ATC	ACA	GCC	
	Thr	Ser	Asn	His	Trp	Val	Val	Asn	Pro	Arg	His	241
813	ACC	AGC	AAC	CAC	TGG	GTG	GTC	AAT	CCG	CGG	CAC	
	Asn	Leu	Gly	Leu	Gln	Leu	Ser	Val	Glu	Thr	Leu	252
846	AAC	CTG	GGC	CTG	CAG	CTC	TCG	GTG	GAG	ACG	CTG	
	Asp	Gly	Gln	Ser	Ile	Asn	Pro	Lys	Leu	Ala	Gly	263
879	GAT	GGG	CAG	AGC	ATC	AAC	CCC	AAG	TTG	GCG	GGC	
	Leu	Ile	Gly	Arg	His	Gly	Pro	Gln	Asn	Lys	Gln	274
912	CTG	ATT	GGG	CGG	CAC	GGG	CCC	CAG	AAC	AAG	CAG	
	Pro	Phe	Met	Val	Ala	Phe	Phe	Lys	Ala	Thr	Glu	285
945	CCC	TTC	ATG	GTG	GCT	TTC	TTC	AAG	GCC	ACG	GAG	
	Val	His	Phe	Arg	Ser	Ile	Arg	Ser	Thr	Gly	Ser	296
978	GTC	CAC	TTC	CGC	AGC	ATC	CGG	TCC	ACG	GGG	AGC	
	Lys	Gln	Arg	Ser	Gln	Asn	Arg	Ser	Lys	Thr	Pro	307
1011	AAA	CAG	CGC	AGC	CAG	AAC	CGC	TCC	AAG	ACG	CCC	
	Lys	Asn	Gln	Glu	Ala	Leu	Arg	Met	Ala	Asn	Val	318
1044	AAG	AAC	CAG	GAA	GCC	CTG	CGG	ATG	GCC	AAC	GTG	

FIG. 4c / 15

	Ala	Glu	Asn	Ser	Ser	Ser	Asp	Gln	Arg	Gln	Ala	329
1077	GCA	GAG	AAC	AGC	AGC	AGC	GAC	CAG	AGG	CAG	GCC	
	Cys	Lys	Lys	His	Glu	Leu	Tyr	Val	Ser	Phe	Arg	351
1110	TGT	AAG	AAG	CAC	GAG	CTG	TAT	GTC	AGC	TTC	CGA	
	Asp	Leu	Gly	Trp	Gln	Asp	Trp	Ile	Ile	Ala	Pro	362
1143	GAC	CTG	GGC	TGG	CAG	GAC	TGG	ATC	ATC	GCG	CCT	
	Glu	Gly	Tyr	Ala	Ala	Tyr	Tyr	Cys	Glu	Gly	Glu	373
1176	GAA	GGC	TAC	GCC	GCC	TAC	TAC	TGT	GAG	GGG	GAG	
	Cys	Ala	Phe	Pro	Leu	Asn	Ser	Tyr	Met	Asn	Ala	384
1209	TGT	GCC	TTC	CCT	CTG	AAC	TCC	TAC	ATG	AAC	GCC	
	Thr	Asn	His	Ala	Ile	Val	Gln	Thr	Leu	Val	His	395
1242	ACC	AAC	CAC	GCC	ATC	GTG	CAG	ACG	CTG	GTC	CAC	
	Phe	Ile	Asn	Pro	Glu	Thr	Val	Pro	Lys	Pro	Cys	406
1275	TTC	ATC	AAC	CCG	GAA	ACG	GTG	CCC	AAG	CCC	TGC	
	Cys	Ala	Pro	Thr	Gln	Leu	Asn	Ala	Ile	Ser	Val	417
1308	TGT	GCG	CCC	ACG	CAG	CTC	AAT	GCC	ATC	TCC	GTC	
	Leu	Tyr	Phe	Asp	Asp	Ser	Ser	Asn	Val	Ile	Leu	428
1341	CTC	TAC	TTC	GAT	GAC	AGC	TCC	AAC	GTC	ATC	CTG	
	Lys	Lys	Tyr	Arg	Asn	Met	Val	Val	Arg	Ala	Cys	439
1374	AAG	AAA	TAC	AGA	AAC	ATG	GTG	GTC	CGG	GCC	TGT	
	Gly	Cys	His									442
1407	GGC	TGC	CAC	TAG								

1419 CTCCTCCGAGAATTCAGACCCTTTGGGGCCAAGTTTTTCTGGATCCTCCATTGCTCGCCTTGGC

1483 CAGGAACCAGCAGACCAACTGCCTTTTGTGAGACCTTCCCCTCCCTATCCCCAACTTTAAAGGT

1547 GTGAGAGTATTAGGAAACATGAGCAGCATATGGCTTTTGATCAGTTTTTCAGTGGCAGCATCCA

1611 ATGAACAAGATCCTACAAGCTGTGCAGGCAAAACCTAGCAGGAAAAAAAAACAACGCATAAAGA

1675 AAAATGGCCGGGCCAGGTCATTGGCTGGGAAGTCTCAGCCATGCACGGACTCGTTTCCAGAGGT

FIG. 4d / 15

1739 AATTATGAGCGCCTACCAGCCAGGCCACCCAGCCGTGGGAGGAAGGGGGCGTGGCAAGGGGTGG

1803 GCACATTGGTGTCTGTGCGAAAGGAAAATTGACCCGGAAGTTCCTGTAATAAATGTCACAATAA

1867 AACGAATGAATG

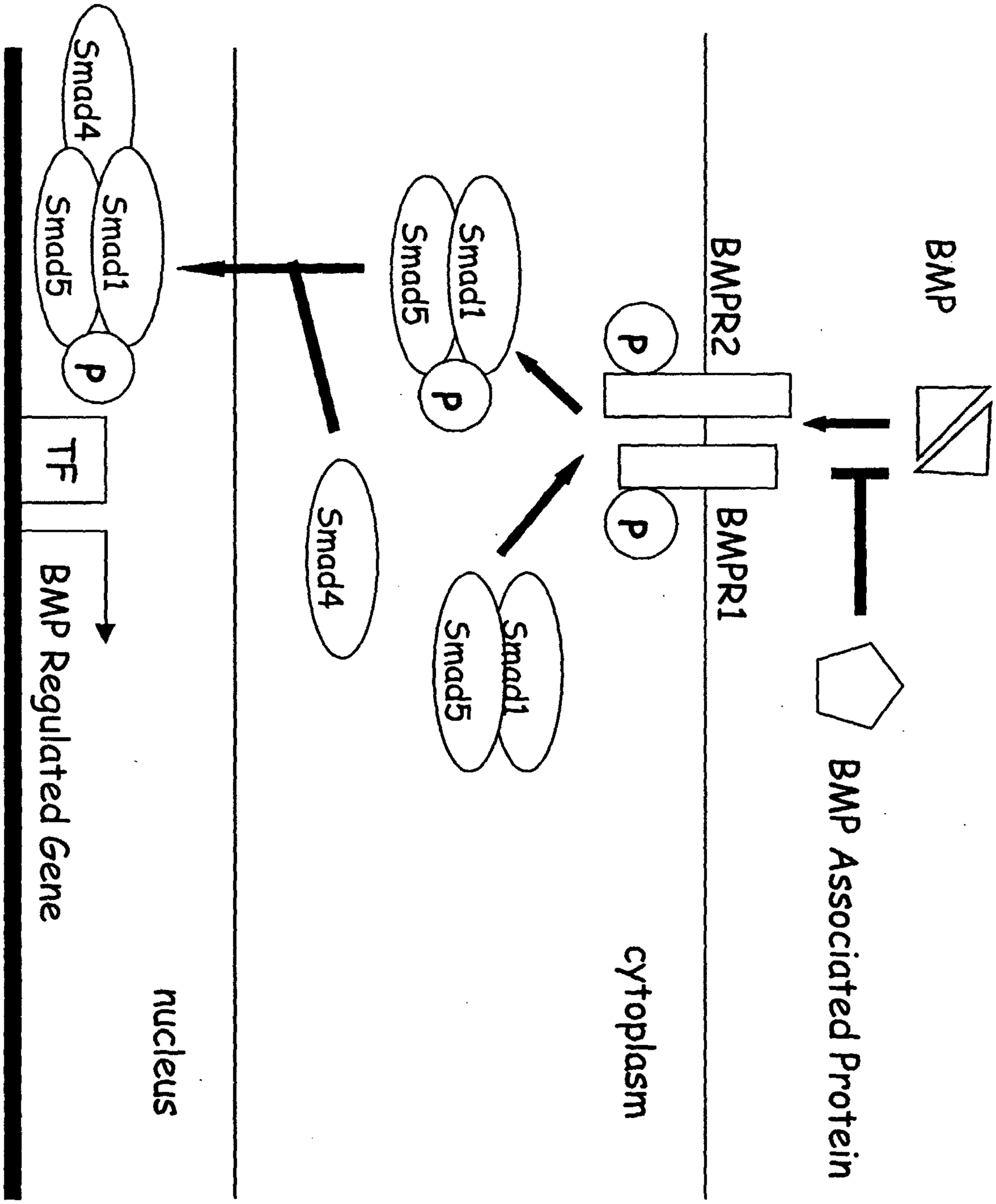

BMP
BMPR2
BMPR1
P
P
P
Smad1
Smad5
Smad4
TF
BMP Regulated Gene
BMP Associated Protein
cytoplasm
nucleus

FIG. 5

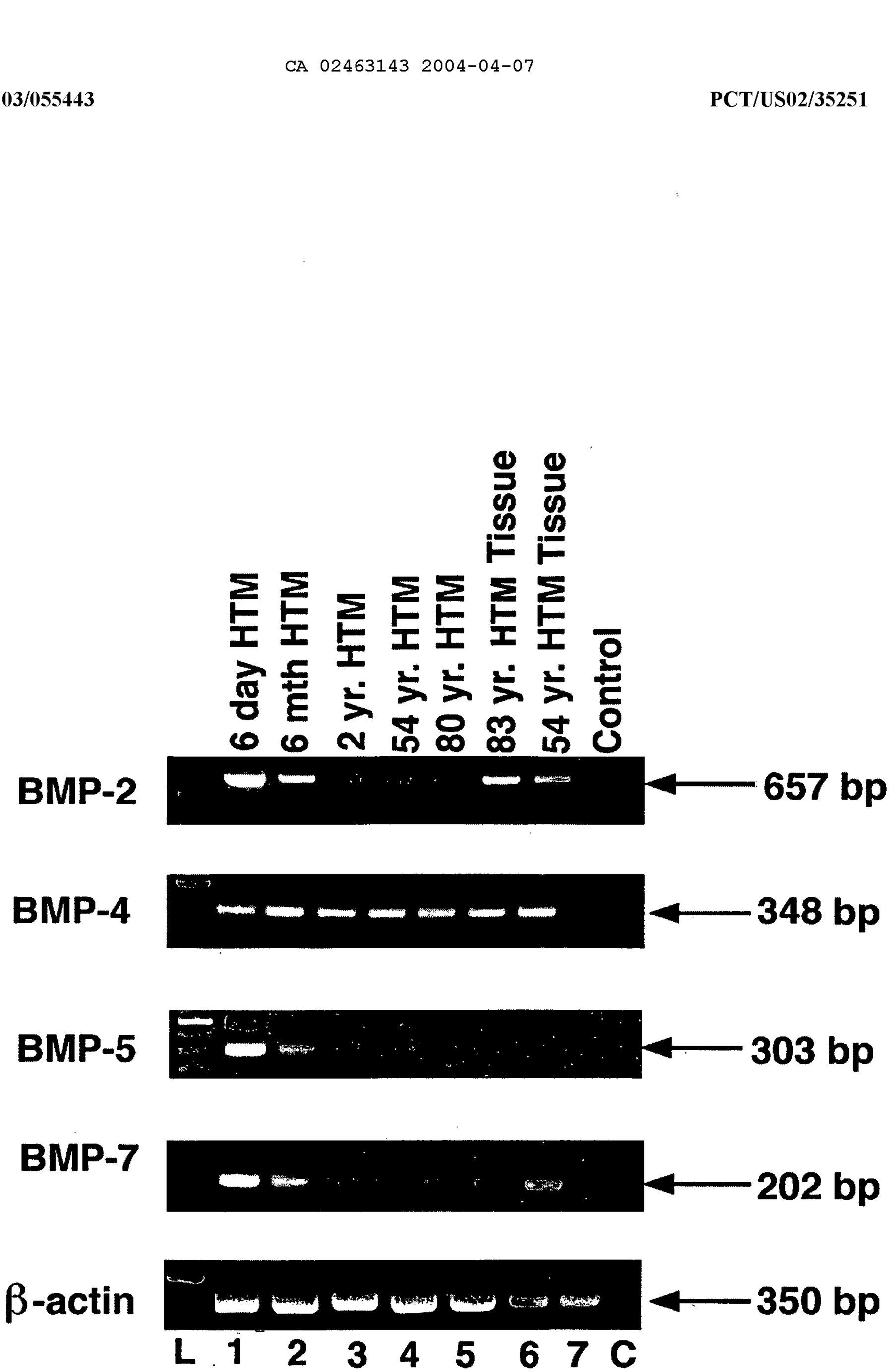

6 day HTM
6 mth HTM
2 yr. HTM
54 yr. HTM
80 yr. HTM
83 yr. HTM Tissue
54 yr. HTM Tissue
Control
BMP-2
657 bp
BMP-4
348 bp
BMP-5
303 bp
BMP-7
202 bp
β-actin
350 bp
L 1 2 3 4 5 6 7 C

FIG. 6

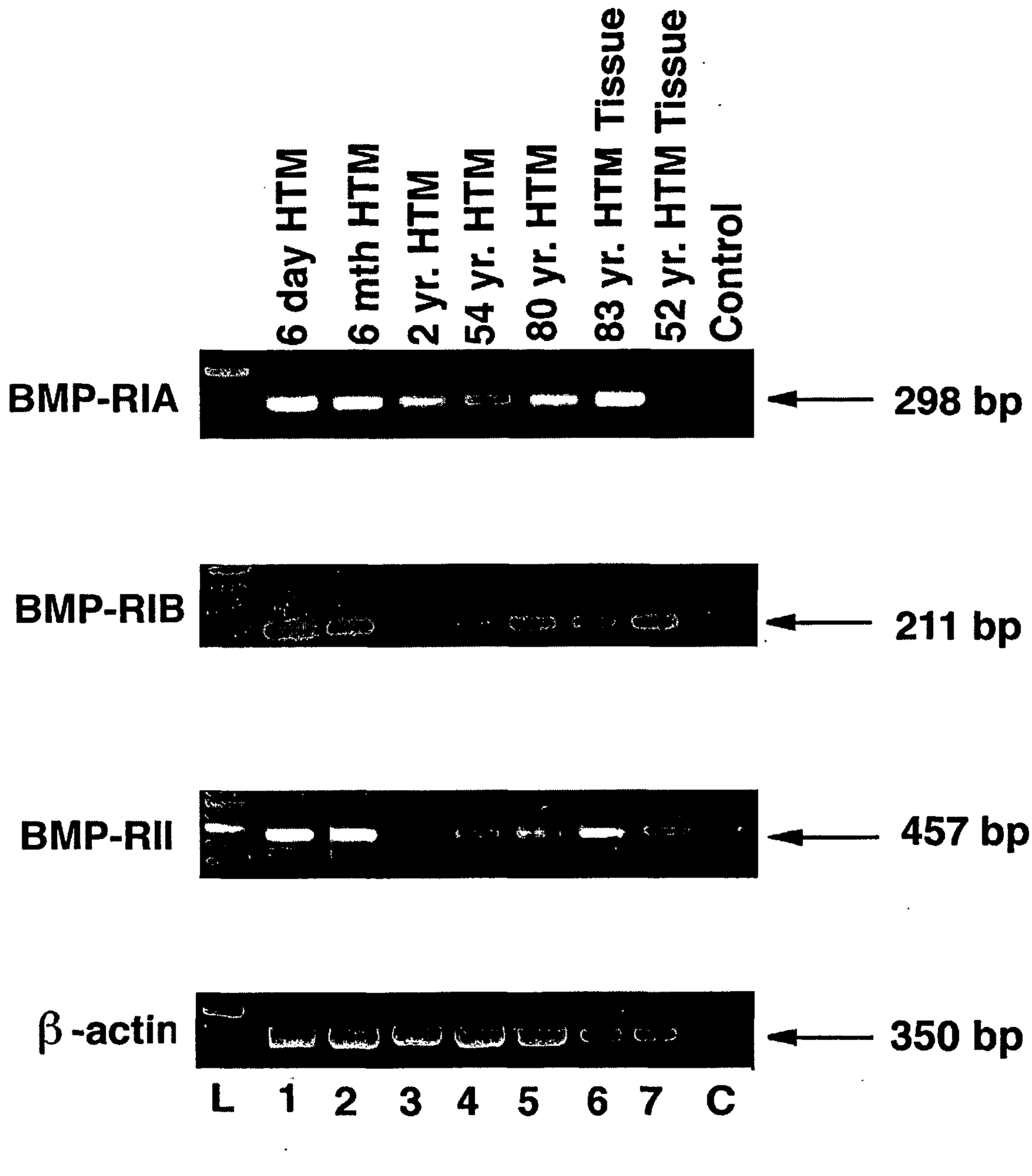

6 day HTM
6 mth HTM
2 yr. HTM
54 yr. HTM
80 yr. HTM
83 yr. HTM Tissue
52 yr. HTM Tissue
Control
BMP-RIA
298 bp
BMP-RIB
211 bp
BMP-RII
457 bp
β-actin
350 bp
L 1 2 3 4 5 6 7 C

FIG. 7

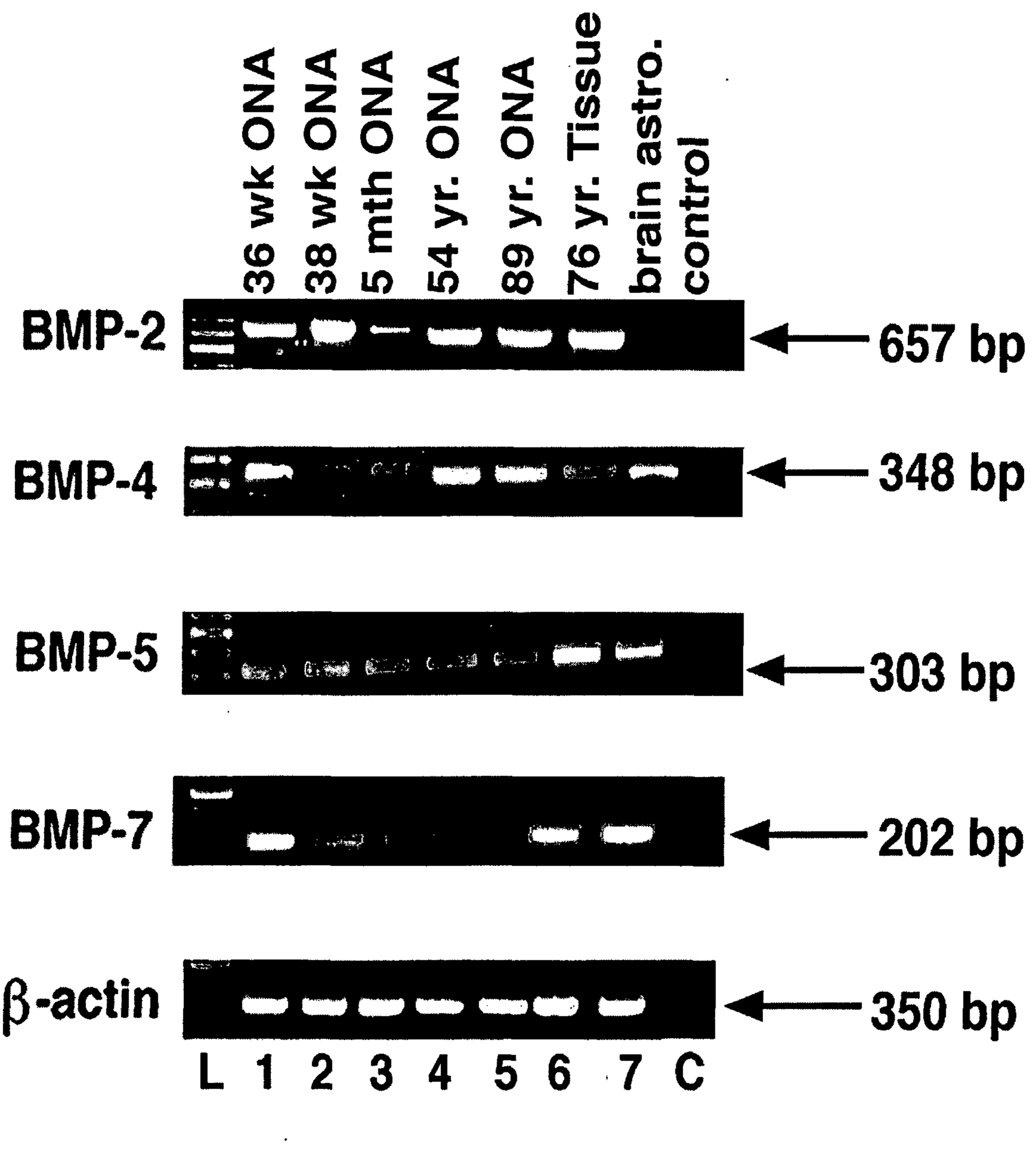

36 wk ONA
38 wk ONA
5 mth ONA
54 yr. ONA
89 yr. ONA
76 yr. Tissu
brain astro.
control
BMP-2
657 bp
BMP-4
348 bp
BMP-5
303 bp
BMP-7
202 bp
β-actin
350 bp
L 1 2 3 4 5 6 7 C

FIG. 8

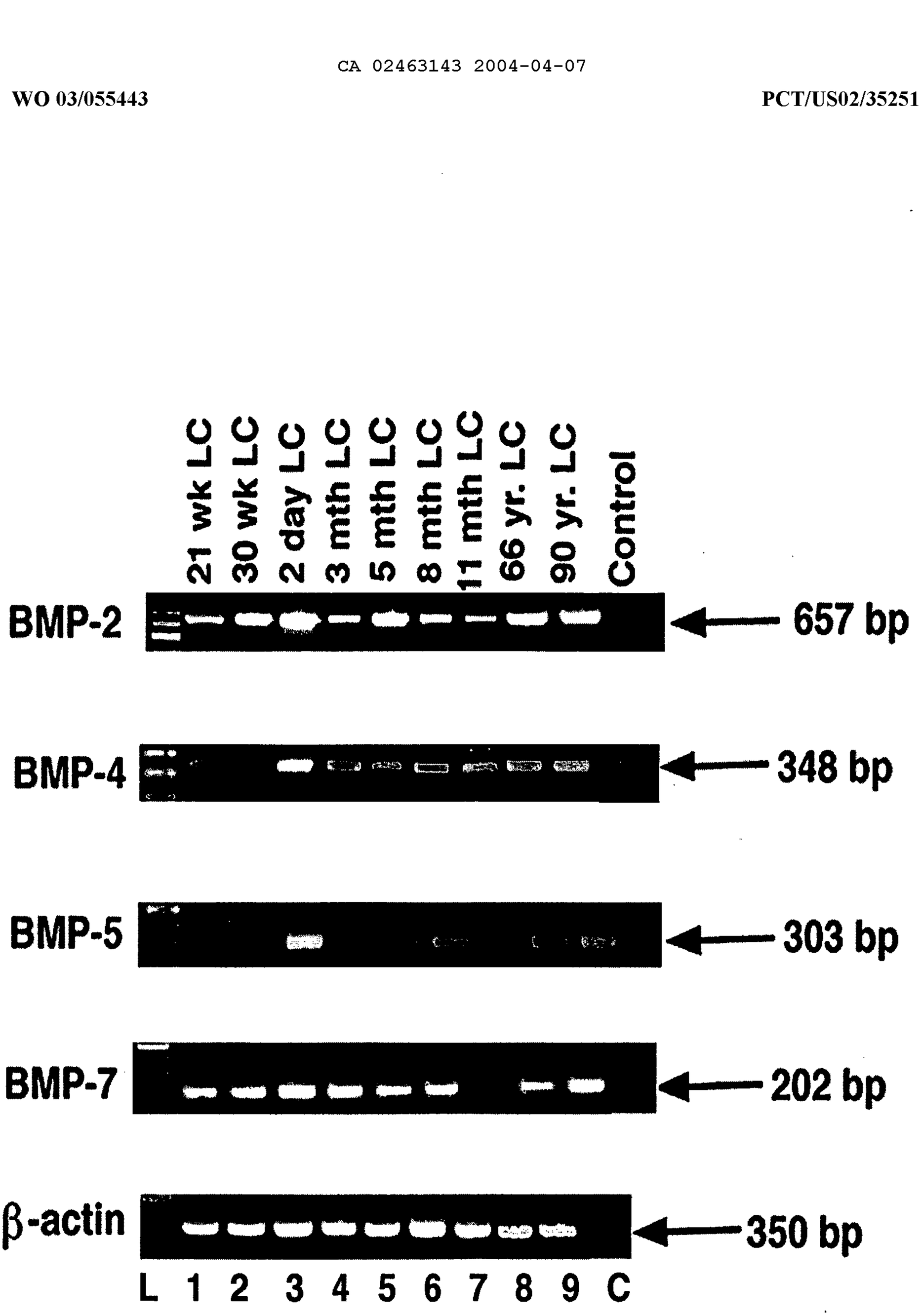

21 wk LC
30 wk LC
2 day LC
3 mth LC
5 mth LC
8 mth LC
11 mth LC
66 yr. LC
90 yr. LC
Control
BMP-2
657 bp
BMP-4
348 bp
BMP-5
303 bp
BMP-7
202 bp
β-actin
350 bp
L 1 2 3 4 5 6 7 8 9 C

FIG. 9

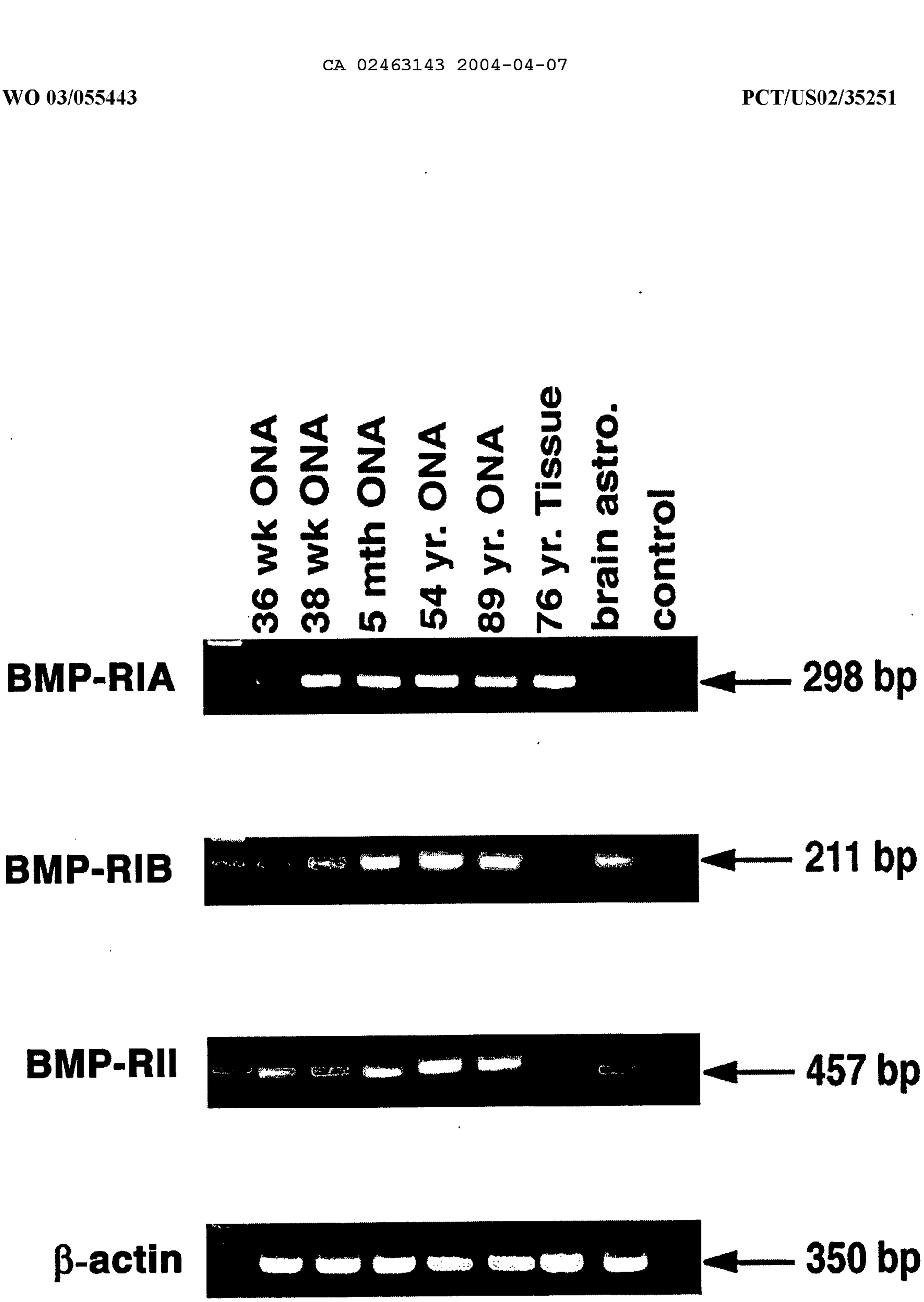

36 wk ONA
38 wk ONA
5 mth ONA
54 yr. ONA
89 yr. ONA
76 yr. Tissue
brain astro.
control
BMP-RIA
298 bp
BMP-RIB
211 bp
BMP-RII
457 bp
β-actin
350 bp
L 1 2 3 4 5 6 7 C

FIG. 10

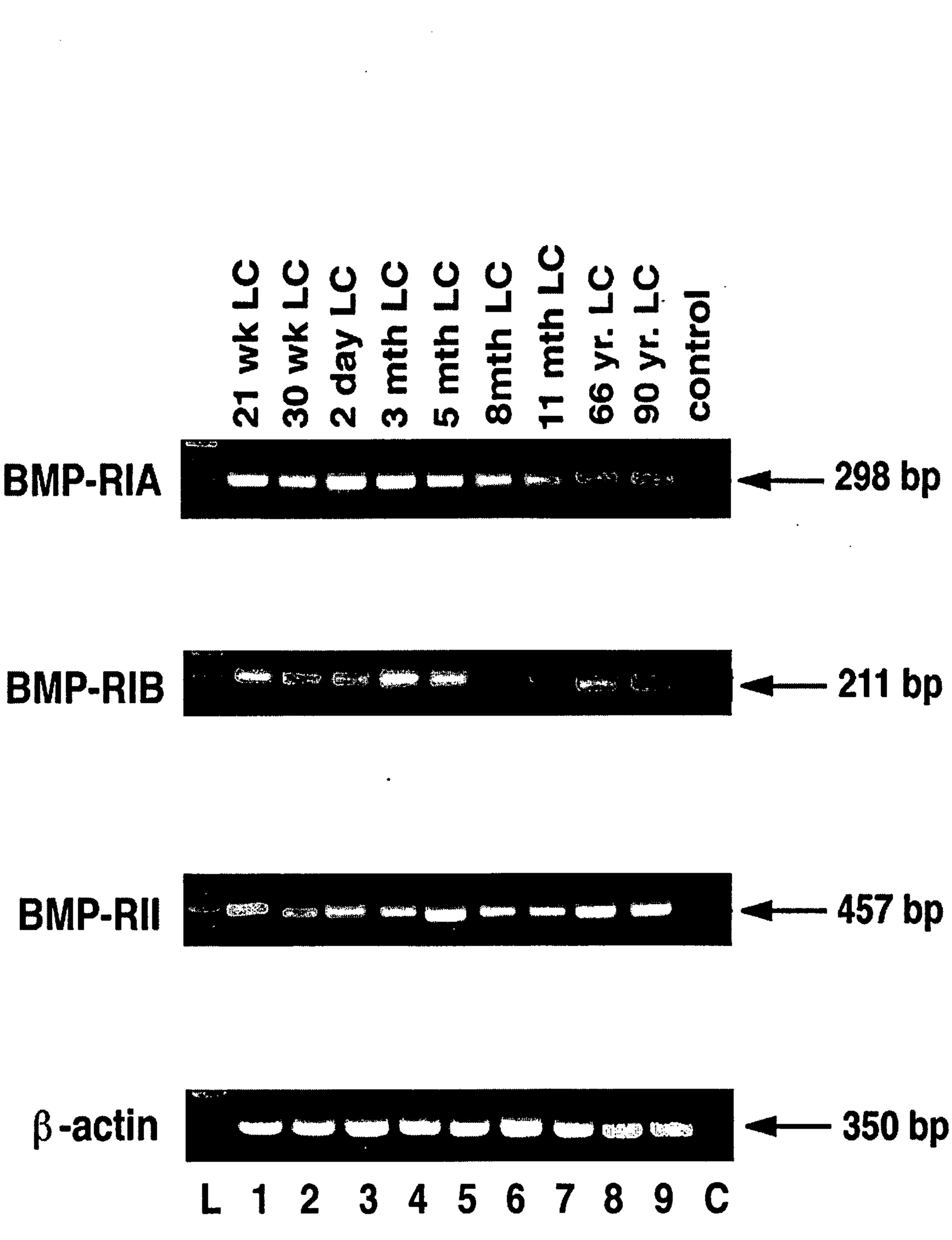

21 wk LC
30 wk LC
2 day LC
3 mth LC
5 mth LC
8mth LC
11 mth LC
66 yr. LC
90 yr. LC
control
BMP-RIA
298 bp
BMP-RIB
211 bp
BMP-RII
457 bp
β-actin
350 bp
L 1 2 3 4 5 6 7 8 9 C

FIG. 11

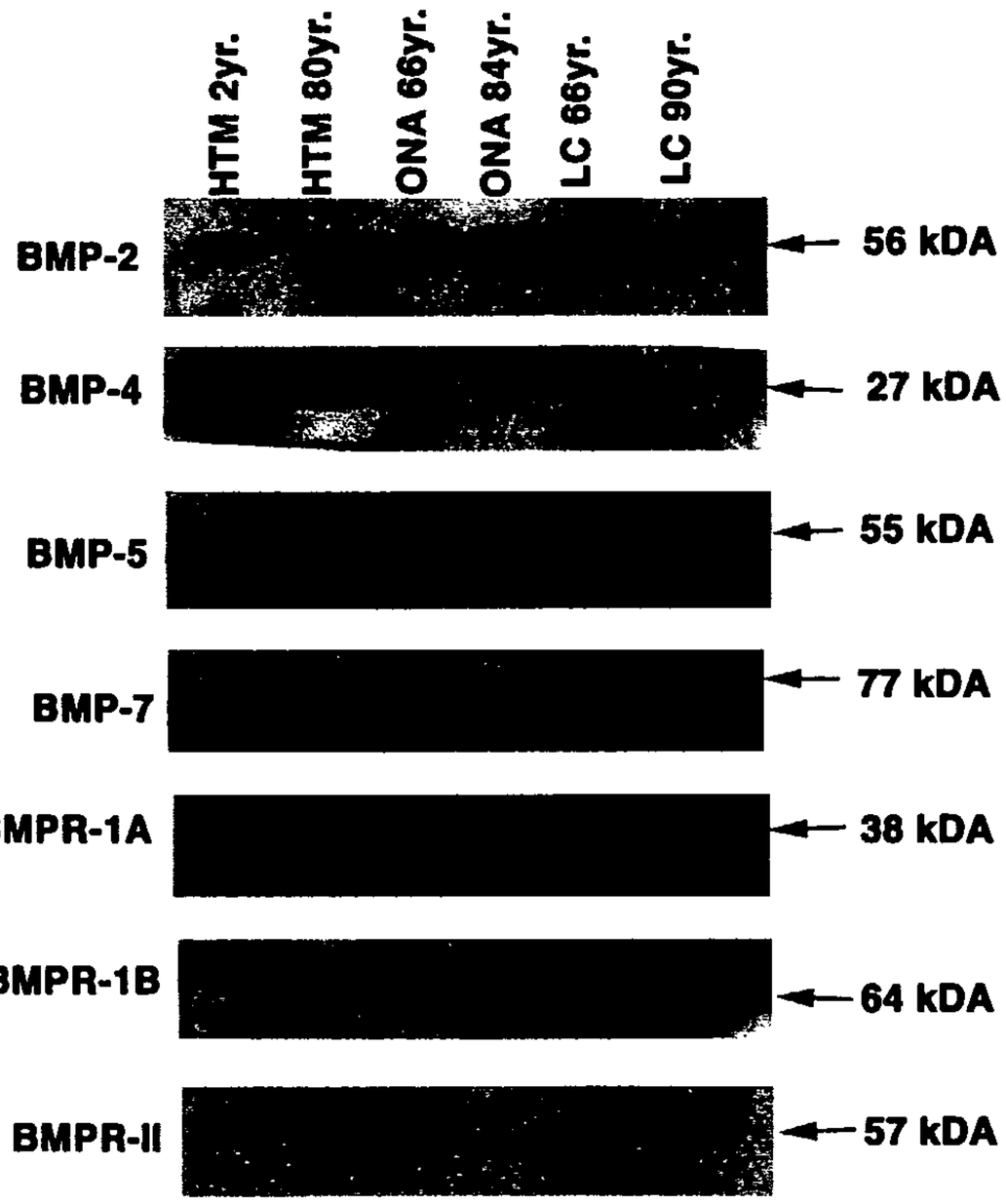

HTM 2yr.
HTM 80yr.
ONA 66yr.
ONA 84yr.
LC 66yr.
LC 90yr.
BMP-2
56 kDA
BMP-4
27 kDA
BMP-5
55 kDA
BMP-7
77 kDA
BMPR-1A
38 kDA
BMPR-1B
64 kDA
BMPR-II
57 kDA

FIG. 12

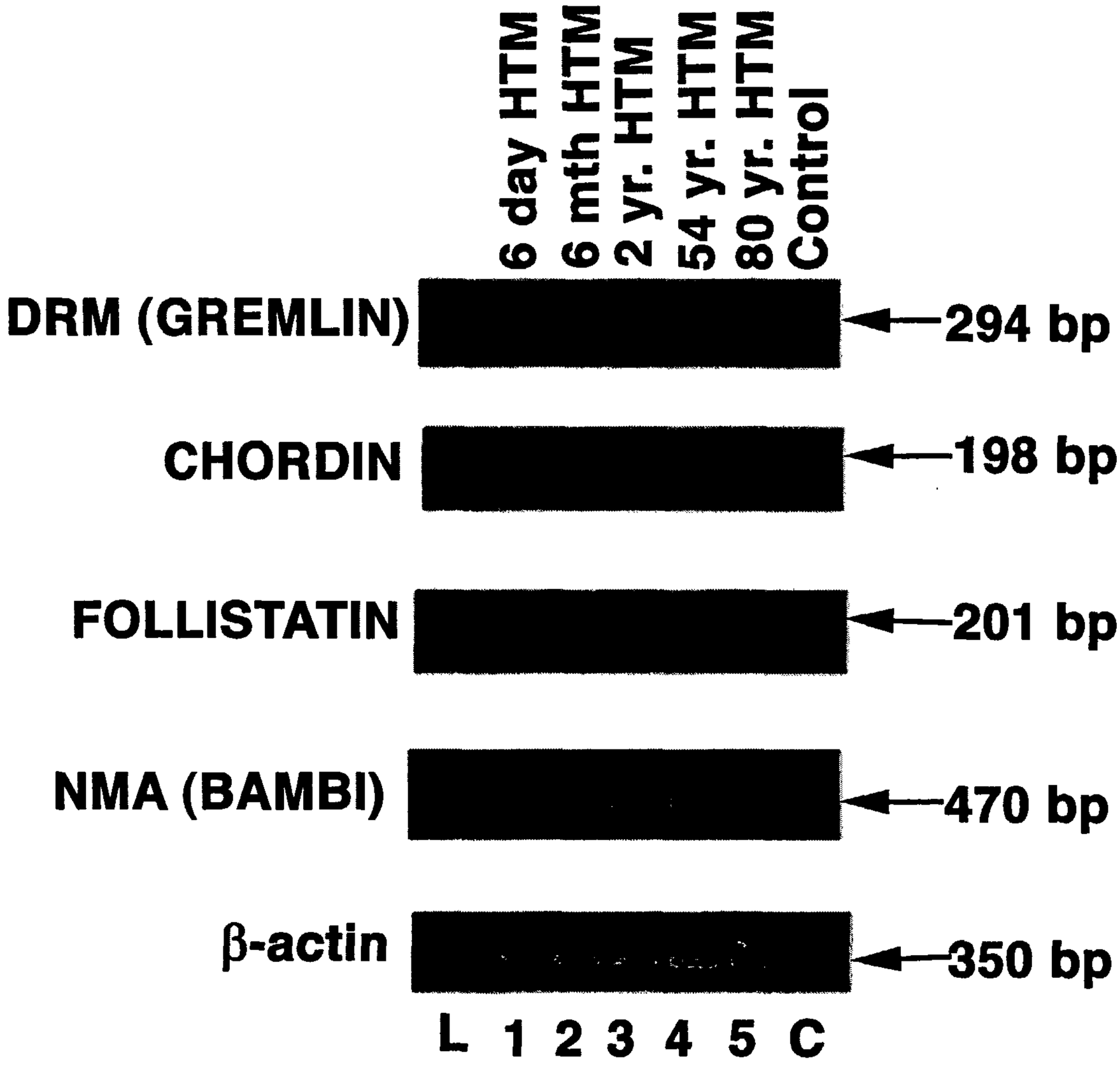

6 day
6 mth
2 yr. H
54 yr.
80 yr.
Contro
DRM (GREMLIN)
294 bp
CHORDIN
198 bp
FOLLISTATIN
201 bp
NMA (BAMBI)
470 bp
β-actin
350 bp
L 1 2 3 4 5 C

FIG. 13

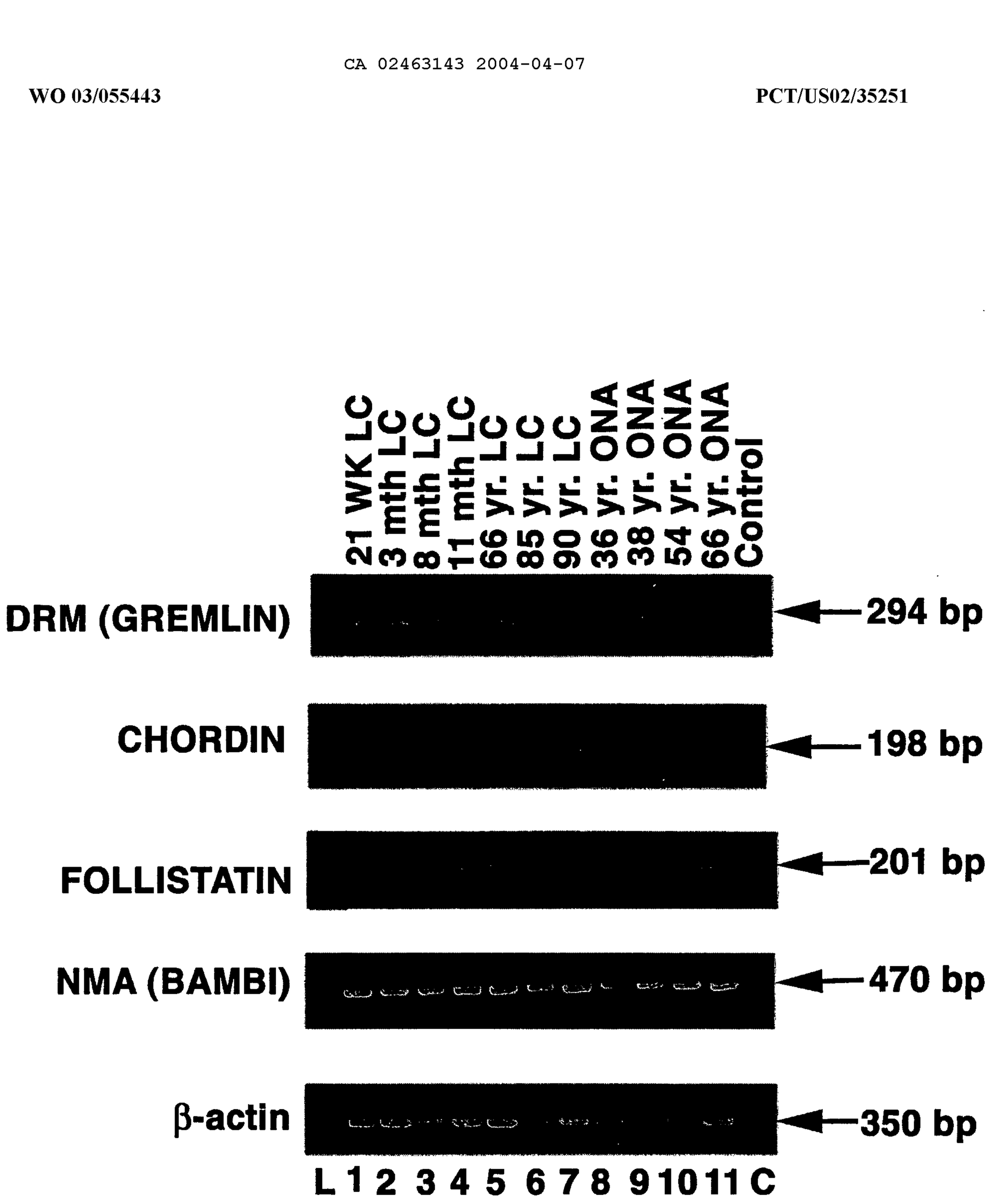

21 WK LC
3 mth LC
8 mth LC
11 mth LC
66 yr. LC
85 yr. LC
90 yr. LC
36 yr. ONA
38 yr. ONA
54 yr. ONA
66 yr. ONA
Control
DRM (GREMLIN)
294 bp
CHORDIN
198 bp
FOLLISTATIN
201 bp
NMA (BAMBI)
470 bp
β-actin
350 bp
L 1 2 3 4 5 6 7 8 9 10 11 C

FIG. 14

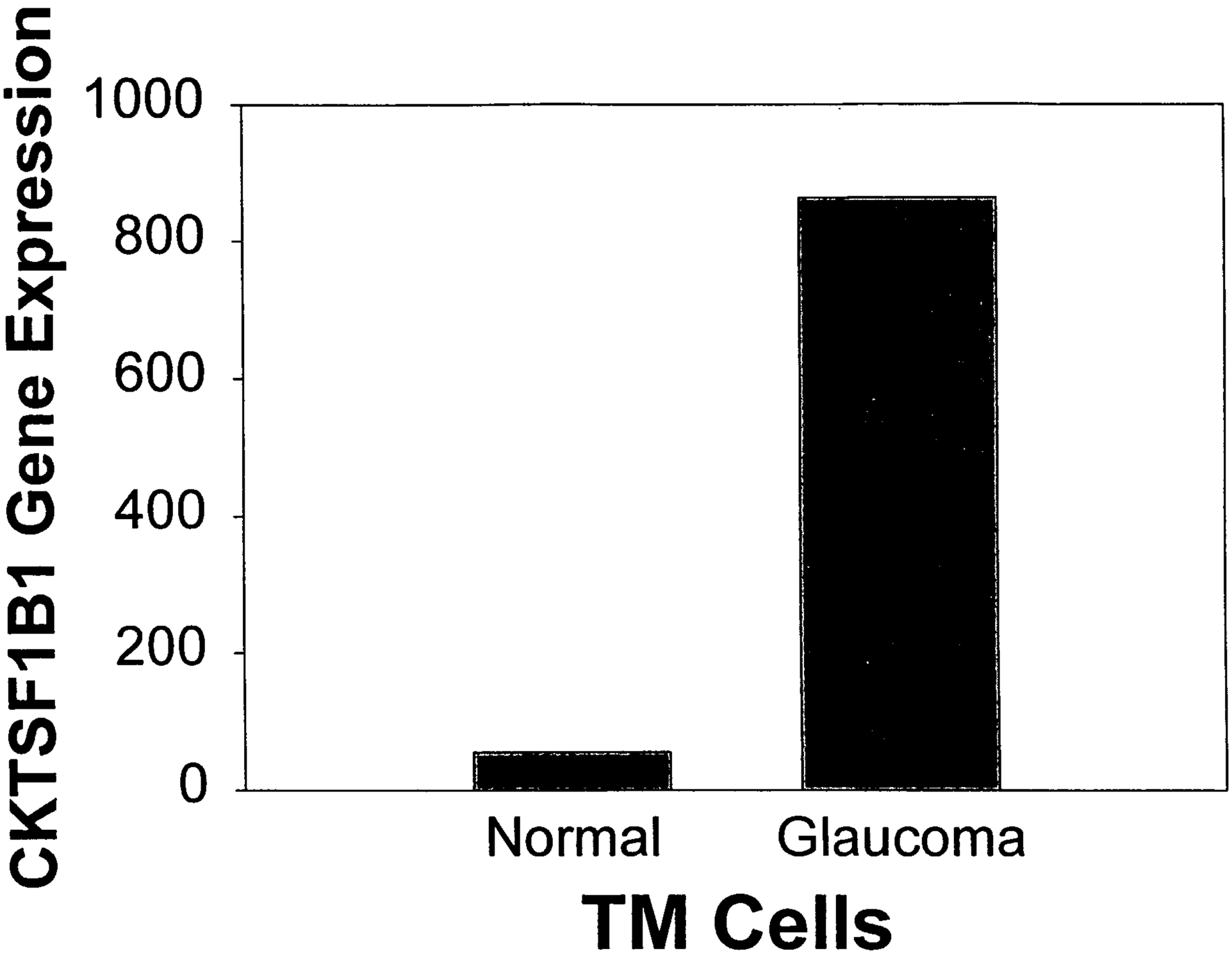

CKTSF1B1 Gene Expression
1000
800
600
400
200
0
Normal
Glaucoma
TM Cells

FIG. 15