LETTER

Genomic Structure of the Human OB Receptor and Identification of Two Novel Intronic Microsatellites

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Identification of the OB (leptin) receptor (OBR) as the gene that is defective in diabetes (*Lepr^{db}*) mice and fatty (*Lepr^{fa}*) rats provides an important candidate gene for the study of the genetics of human obesity. We defined the boundaries of the 18 coding exons for the long form of OBR, and sequenced the immediately adjacent intronic regions. These sequences can be used to generate reagents for genetic analysis (e.g., direct sequencing, single-stranded conformational polymorphism analysis, etc.) of the possible role of OBR in the regulation of adiposity in humans. In addition, we have identified two highly polymorphic intronic microsatellites that can be scored with the polymerase chain reaction.

[The sequence data described in this paper have been submitted to GenBank under accession nos. U62487–U62521.]

Obesity is a major and increasing public health problem. At least 25% of Americans (adults and children) are overweight (Anon. 1994; Kuczmarski et al. 1994). The heritability of body mass index (BMI), a surrogate measure of obesity, has been estimated to be 0.77–0.84 (Stunkard et al. 1986), and the concordance of BMI or skinfold thickness is as high as 74–84% in monozygotic twins, compared with 22–44% in dizygotic twins (Bodurtha et al. 1990). Although there is clearly a genetic basis for body fat content, the genes responsible for determining adiposity in humans are not known (Bouchard and Bray 1995).

Five autosomal obesity mutations in mice—obese (*ob*), diabetes (*db*), fat (*fat*), tubby (*tub*), and Yellow (agouti *A^y*)—provide novel candidates that may play roles in the genetics of human obesity (Leibel et al. 1995). The cloning of the receptor OBR for the obese gene product (OB or leptin) (OBR) (Tartaglia et al. 1995) and the demonstration that mutations of this receptor are responsible for the diabetes (*db*) phenotype in mice (Chen et al. 1996; Lee et al. 1996) and fatty (*fa*) phenotype in rats (Chua et al. 1996a,b; Iida et al. 1996; Phillips et al. 1996) allow for genetic test-

ing by means of polymorphic markers located within the gene and by direct sequence analysis of OBR.

OBR has at least five splice variants in mice (Lee et al. 1996). Only one of these splice variants contains an intracytoplasmic domain with box motifs for JAK-mediated signaling (Tartaglia et al. 1995; Ghilardi et al. 1996; Lee et al. 1996). This splice variant with signaling potential is commonly referred to as the long form of OBR.

OBR is located on chromosome 1p in humans (Chung et al. 1996). We have characterized the genomic structure of OBR and have defined the intronic sequence adjacent to each of the 18 coding exons in the long form of the gene to provide reagents for detecting genomic sequence variants by either direct sequence analysis or other methods of mutation detection such as single-stranded conformational polymorphism (SSCP). We have also identified two polymorphic, repetitive sequence markers within two introns of OBR that should be useful in either linkage or association studies.

RESULTS

The genomic structure of the OBR long splice variant is outlined in Figure 1. The genomic se-

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GENOMIC STRUCTURE OF THE HUMAN OB RECEPTOR

Figure 1 Genomic structure of the long form of OBR. The number of each coding exon and the first nucleotide of each of these exons (according to GenBank accession no. U43168) are indicated above the schematic diagram of OBR with the size of each exon indicated *below*. The sizes of the two introns between exons 7 and 8 and between 11 and 12 are indicated *above*. The exons corresponding to those mutated in the *fatty rat* and *diabetes mouse* are indicated below. The transmembrane domain is located in exon 16.

quence immediately adjacent to each of the 18 coding exons contained within the long splice variant is shown in Table 1 (GenBank accession nos. U62487–U62521). The exact size of each intron is undetermined, except for the introns between exons 7 and 8, and between exons 11 and 12, which are 153 and 80 base pairs, respectively.

Two introns were incidentally discovered to contain repetitive sequences. The intron between coding exons 1 and 2 contained a CA repeat of variable length (OBR-CA), and the intron between coding exons 14 and 15 contained a complex CTTT repeat (OBR-CTTT) (Fig. 2). Primers

flanking the repetitive sequences were designed and used to amplify the regions from 100 unrelated nonobese individuals randomly selected from the New York City population. The heterozygosity scores for OBR-CA and OBR-CTTT were 0.448 and 0.535, respectively.

DISCUSSION

Knowledge of the genomic organization of OBR and the intronic sequence adjacent to each of the coding exons for the long form of the gene will enable testing of the plausible hypothesis that allelic variation in OBR contributes to interindividual differences in body fat stores. Additionally, the two highly polymorphic repetitive sequence markers within OBR provide reagents for linkage and association studies that may be performed prior to mutation screening to determine whether variation at the OBR locus is likely to be responsible for variation in body fat in any specific population.

We have analyzed the genomic structure relevant to the OBR splice variant (long form) that is apparently responsible for leptin signal transduction (Ghilardi et al. 1996). However, there are other splice variants for which the terminal coding exon is replaced by a smaller coding exon. Although mutations in these other alternatively spliced terminal exons have not yet been associated with genetic forms of obesity in rodents, it may prove necessary to analyze these alternative terminal exons in the future. For example, a short splice variant may be responsible for transport of leptin across the blood brain barrier (Campfield et al. 1995; Schwartz et al. 1996). Similarly, there is evidence for variability in the 5' untranslated region (Cioffi et al. 1996).

Figure 2 Polymorphic microsatellite markers OBR-CA (A) and OBR-CTTT (B). Five different alleles (151, 155, 157, 159, 161 bp) of OBR-CA, and four different alleles of OBR-CTTT (119, 123, 127, 135 bp) are demonstrated. Two alleles of OBR-CTTT migrate at 123 bp but can be distinguished by heteroduplexes on nondenatured gels or by direct sequence analysis (data not shown).

Table 1. Intronic Sequence Immediately Adjacent to Each of the 18 Coding Exons of the Long Form of OBR

Coding exon number	5' Intronic sequence	3' Intronic sequence
1	CATATTTATCAACATTGTGACGANITGNATTTAGTTAAATTCAGTCTTATCCCGT GATACCTGCTCGTGTGTTTATGGATAAAGGACATTCAGTTAAATTTTTCGANIT GTATTTTAAATGATGAAGATAGGATCGGTACAGGAATAAATCTNAGCCCTAAATTTA CGTGACATATTTCTCAGATATTCAGATATTCAGATGATCAATGTAATTTAGAGACTATC TATAATCCCTTTCATTTTATGTTCTTCACAGACAACTTATATATATGTTGTTTGT TTTGTGTGTTCTGATCCTAGATACACTCTTTCCA	GTAGTTATGCTCTTTGCTGTGTTAAATGCCCCCTTAAACAGGTGAGATTTGCTTTAGCA GATGCTGTTATTTATGCTTAAACAGAAATTTCTATTTCTAGTTAGGAATTTCTCATACAT GCTTATGATTTAAATGCAACCATAGTATAGGTGATCAGTGTGAAACAAACCCCTTCC CAACCTCTAAAGACAACTGATGGTATCTTCCGAATCTCTCTCTCACACACAC ACACACACAGACTCACACACAGACTCACACACATACACACACACACACATCATC TATAGCTGCAAAATAGCACTGGTCTGTACATGTTGTTCTGGATGTTTATTTNCTCATTTA ACGGTTTCCAAATTTATCATGA GTAAGCATTAGCTATTTTAAATGTTATGAAACATGTTTTTATTTCTTGATACCTGTA TGAATAGATGCTTTATGCTGCTATGTTTAAACATACATATTTTATTTATGATATAA AATTAGGATTCATTTATGTGAACAACTAAATAATTTCCAAATATCTTTGATCCCAT AAATATAATGAGGAAATTTTACTTTTAAGTACATCCTTG
2	AAAAATAAATATAAATGTGACGTTAAAGAGAAACATGAAGTGTGAGTCTTCAAAA AGAAAAGAGATGTCAAGAGTGCAGTAATTTCTACAAATGAATGCTCTTGAATG TAAACACATTGTAAGTGAAGGACAAAGTATTTCTATGACACTCACTGAGGACTTAG AAAGTTAAATATTTGAGCACTACATGTTTAAATCTCAGATACCTTCTATTCATG CTTAGTCAAAATGATTAATTTTCTATGTTCTTTTAAATATCCCTAAACAG GGGGTTTTTTTTTTTTTTTTTTTTTAAATTCAG	GTAGTACCAAAATAATTTGGCATTCTTAATACACAGTTTTTTTAAAGAGCTTTCAT ATACGGAAGTAGATTAAACCTCTTGGATCCCTACATTTCTATATATATGTTTATTTTT TAATATAGCATTCGCTGTAGGTTCTCTTTCTCTCTCTGCTAAATTCAGGTAGCAA GACATCAGGTTTAGGTCACGATGTCAGGTCCTCATGATACCAAATGTTTCAGTTCAG TTCAGTTCTAGCTCACACTCAGGTCCGA GTAAGTTATGCACTAAATGATGATAAGTGTAAACATCAGTCATATATAAGGTTAAA AATTCCTTACAAAATAATTTGCTAGCTTATCTCACTTTGCTTCCCACTGTAATGATGTAG ATGTAAGTCTGGGGTATTAAGAGTGGCTTCTAGAATGATTTAAACATGTTATGATATCT CTGCCATGTCACCTAAATTTCTGTTTGAACACTGTTTCTTCAATCCTGCTATGTA ATGGATGTATGATGATGATACATTTTTCACATCTCAGATAACTATTTTGAATAATAG TANCAATGTTCTGCTGAATTTATTCCTTA GTAAGTATATTTAGTAAGTAAAGGAAAGTTGAGAAATAAAGGCCCTCTTAAGTC CCATAGCAATTCCTCTGCACTAAATATATATATATATATCTTCTAAAGCAGATGAATAT AATTCACATTTTAT ATAGAAATCTAGTTACAGAACTTGAATTCATATATATATATATATATATATATATATAT ACTGATTTCTATTTTAAATTTGCTCAATCTATTTGAATGTTTCTGATGTGGCAAC AGAAATTTTCTGCTGGCTAACTAGTCAGGCTTCTGAATCTCTGCTAGCCGATCT GTGCATCTCTGTAATTCAGTTT GTAAGTATGATAGCCACTTCTACTGGAGGCAATATATATCTGAACTGCTTGT ATAGTATAGCATCTTCAATTTGAGGCTTAAATGAAGGAGCAACAGTATCACTT CCTGTTTAAACTTTGAAACGCGCAATTTGTGAATTAATTTCTGACAGGCTCTAGGC TTGTGTTTCTATGCGATATATGAGGATCACTTTTCTTATTAAGAAATATTA TATAACAGCTCCAATTAACAACTCAGAAAGCCATTTGATTTGATTAATTCCTTAATTTAC ATTTAAACCAAGCATATTTATTTGACAT
3	AAACATAAATATAAATGTGACGTTAAAGAGAAACATGAAGTGTGAGTCTTCAAAA AGAAAAGAGATGTCAAGAGTGCAGTAATTTCTACAAATGAATGCTCTTGAATG TAAACACATTGTAAGTGAAGGACAAAGTATTTCTATGACACTCACTGAGGACTTAG AAAGTTAAATATTTGAGCACTACATGTTTAAATCTCAGATACCTTCTATTCATG CTTAGTCAAAATGATTAATTTTCTATGTTCTTTTAAATATCCCTAAACAG GGGGTTTTTTTTTTTTTTTTTTTTTAAATTCAG	GTAGTACCAAAATAATTTGGCATTCTTAATACACAGTTTTTTTAAAGAGCTTTCAT ATACGGAAGTAGATTAAACCTCTTGGATCCCTACATTTCTATATATATGTTTATTTTT TAATATAGCATTCGCTGTAGGTTCTCTTTCTCTCTCTGCTAAATTCAGGTAGCAA GACATCAGGTTTAGGTCACGATGTCAGGTCCTCATGATACCAAATGTTTCAGTTCAG TTCAGTTCTAGCTCACACTCAGGTCCGA GTAAGTTATGCACTAAATGATGATAAGTGTAAACATCAGTCATATATAAGGTTAAA AATTCCTTACAAAATAATTTGCTAGCTTATCTCACTTTGCTTCCCACTGTAATGATGTAG ATGTAAGTCTGGGGTATTAAGAGTGGCTTCTAGAATGATTTAAACATGTTATGATATCT CTGCCATGTCACCTAAATTTCTGTTTGAACACTGTTTCTTCAATCCTGCTATGTA ATGGATGTATGATGATGATACATTTTTCACATCTCAGATAACTATTTTGAATAATAG TANCAATGTTCTGCTGAATTTATTCCTTA GTAAGTATATTTAGTAAGTAAAGGAAAGTTGAGAAATAAAGGCCCTCTTAAGTC CCATAGCAATTCCTCTGCACTAAATATATATATATATATCTTCTAAAGCAGATGAATAT AATTCACATTTTAT ATAGAAATCTAGTTACAGAACTTGAATTCATATATATATATATATATATATATATATAT ACTGATTTCTATTTTAAATTTGCTCAATCTATTTGAATGTTTCTGATGTGGCAAC AGAAATTTTCTGCTGGCTAACTAGTCAGGCTTCTGAATCTCTGCTAGCCGATCT GTGCATCTCTGTAATTCAGTTT GTAAGTATGATAGCCACTTCTACTGGAGGCAATATATATCTGAACTGCTTGT ATAGTATAGCATCTTCAATTTGAGGCTTAAATGAAGGAGCAACAGTATCACTT CCTGTTTAAACTTTGAAACGCGCAATTTGTGAATTAATTTCTGACAGGCTCTAGGC TTGTGTTTCTATGCGATATATGAGGATCACTTTTCTTATTAAGAAATATTA TATAACAGCTCCAATTAACAACTCAGAAAGCCATTTGATTTGATTAATTCCTTAATTTAC ATTTAAACCAAGCATATTTATTTGACAT
4	GGGGGGTTTTTTTTTTCAGATACCCCTTAAAGCTGGGTGCTCCCAATAGTTTACTTCAA TTACTATTTAGTATCCTGCTTAAAGGCTTAATCCAGTATTTTTCATATCTGTTTAAAT ATTTAGCTCTAATTTTCAATATAG	GTAGTACCAAAATAATTTGGCATTCTTAATACACAGTTTTTTTAAAGAGCTTTCAT ATACGGAAGTAGATTAAACCTCTTGGATCCCTACATTTCTATATATATGTTTATTTTT TAATATAGCATTCGCTGTAGGTTCTCTTTCTCTCTCTGCTAAATTCAGGTAGCAA GACATCAGGTTTAGGTCACGATGTCAGGTCCTCATGATACCAAATGTTTCAGTTCAG TTCAGTTCTAGCTCACACTCAGGTCCGA GTAAGTTATGCACTAAATGATGATAAGTGTAAACATCAGTCATATATAAGGTTAAA AATTCCTTACAAAATAATTTGCTAGCTTATCTCACTTTGCTTCCCACTGTAATGATGTAG ATGTAAGTCTGGGGTATTAAGAGTGGCTTCTAGAATGATTTAAACATGTTATGATATCT CTGCCATGTCACCTAAATTTCTGTTTGAACACTGTTTCTTCAATCCTGCTATGTA ATGGATGTATGATGATGATACATTTTTCACATCTCAGATAACTATTTTGAATAATAG TANCAATGTTCTGCTGAATTTATTCCTTA GTAAGTATATTTAGTAAGTAAAGGAAAGTTGAGAAATAAAGGCCCTCTTAAGTC CCATAGCAATTCCTCTGCACTAAATATATATATATATATCTTCTAAAGCAGATGAATAT AATTCACATTTTAT ATAGAAATCTAGTTACAGAACTTGAATTCATATATATATATATATATATATATATATAT ACTGATTTCTATTTTAAATTTGCTCAATCTATTTGAATGTTTCTGATGTGGCAAC AGAAATTTTCTGCTGGCTAACTAGTCAGGCTTCTGAATCTCTGCTAGCCGATCT GTGCATCTCTGTAATTCAGTTT GTAAGTATGATAGCCACTTCTACTGGAGGCAATATATATCTGAACTGCTTGT ATAGTATAGCATCTTCAATTTGAGGCTTAAATGAAGGAGCAACAGTATCACTT CCTGTTTAAACTTTGAAACGCGCAATTTGTGAATTAATTTCTGACAGGCTCTAGGC TTGTGTTTCTATGCGATATATGAGGATCACTTTTCTTATTAAGAAATATTA TATAACAGCTCCAATTAACAACTCAGAAAGCCATTTGATTTGATTAATTCCTTAATTTAC ATTTAAACCAAGCATATTTATTTGACAT
5	ACTTCAGATAAGTTTAGGATGCTGGGTTTAAAGTAAAGTGGGATCTTACAAAG GGAAATCACATTTAGCAAAATAATCTCATTTACTGATTCATAGCTTTTACCACCTAAG GGGAGGTTAATGAATATACATGATGCTATGATAGGTTACAGGACAGACCCAGTA TTCAAGCTTGTTCGGTTCTATAATGATGCTTGGATAGTCACTTTTAAAGTACTT GAAAGGCAAGATATGATGAAATTTATCTGACTTTATTTTATTCAGCTATATTTGTC ATGAAATTTACTTGACTTAAAGATTCAGCTATATTTGATGATGAAATTTACTGACT TAAAGTATCTCTTTTTTCTTAAAG TTGCTACCCCTGCACAGCATTTTAAACAGGTTGTTATAGGTTGAGTGTGAGTGGC TTAAAGCTTCCACAGATTTAGTGCATTTCTTAAATCTAAAGGTCATATATCA TCATGATTTCAATTAACAGATTTGTTATATATATATATATATTTCTGACCCATGG GCTATTTAAATTTTATGACTAATGTGCAACTTTTTTGGTTATGATGTTTGT TTAATTCGCTGTGCGCAGATAACTACTGTGAAGATATTAATTTCTGAAATTTGATG AGATTAGCTTATCTCACTTTAGTAACGGTTCACATCACTTGTATGTTCTGATGTT TTAATAATAATTTAAACAG	GTAGTACCAAAATAATTTGGCATTCTTAATACACAGTTTTTTTAAAGAGCTTTCAT ATACGGAAGTAGATTAAACCTCTTGGATCCCTACATTTCTATATATATGTTTATTTTT TAATATAGCATTCGCTGTAGGTTCTCTTTCTCTCTCTGCTAAATTCAGGTAGCAA GACATCAGGTTTAGGTCACGATGTCAGGTCCTCATGATACCAAATGTTTCAGTTCAG TTCAGTTCTAGCTCACACTCAGGTCCGA GTAAGTTATGCACTAAATGATGATAAGTGTAAACATCAGTCATATATAAGGTTAAA AATTCCTTACAAAATAATTTGCTAGCTTATCTCACTTTGCTTCCCACTGTAATGATGTAG ATGTAAGTCTGGGGTATTAAGAGTGGCTTCTAGAATGATTTAAACATGTTATGATATCT CTGCCATGTCACCTAAATTTCTGTTTGAACACTGTTTCTTCAATCCTGCTATGTA ATGGATGTATGATGATGATACATTTTTCACATCTCAGATAACTATTTTGAATAATAG TANCAATGTTCTGCTGAATTTATTCCTTA GTAAGTATATTTAGTAAGTAAAGGAAAGTTGAGAAATAAAGGCCCTCTTAAGTC CCATAGCAATTCCTCTGCACTAAATATATATATATATATCTTCTAAAGCAGATGAATAT AATTCACATTTTAT ATAGAAATCTAGTTACAGAACTTGAATTCATATATATATATATATATATATATATATAT ACTGATTTCTATTTTAAATTTGCTCAATCTATTTGAATGTTTCTGATGTGGCAAC AGAAATTTTCTGCTGGCTAACTAGTCAGGCTTCTGAATCTCTGCTAGCCGATCT GTGCATCTCTGTAATTCAGTTT GTAAGTATGATAGCCACTTCTACTGGAGGCAATATATATCTGAACTGCTTGT ATAGTATAGCATCTTCAATTTGAGGCTTAAATGAAGGAGCAACAGTATCACTT CCTGTTTAAACTTTGAAACGCGCAATTTGTGAATTAATTTCTGACAGGCTCTAGGC TTGTGTTTCTATGCGATATATGAGGATCACTTTTCTTATTAAGAAATATTA TATAACAGCTCCAATTAACAACTCAGAAAGCCATTTGATTTGATTAATTCCTTAATTTAC ATTTAAACCAAGCATATTTATTTGACAT
6	TTAATAATAATTTAAACAG	GTAGTACCAAAATAATTTGGCATTCTTAATACACAGTTTTTTTAAAGAGCTTTCAT ATACGGAAGTAGATTAAACCTCTTGGATCCCTACATTTCTATATATATGTTTATTTTT TAATATAGCATTCGCTGTAGGTTCTCTTTCTCTCTCTGCTAAATTCAGGTAGCAA GACATCAGGTTTAGGTCACGATGTCAGGTCCTCATGATACCAAATGTTTCAGTTCAG TTCAGTTCTAGCTCACACTCAGGTCCGA GTAAGTTATGCACTAAATGATGATAAGTGTAAACATCAGTCATATATAAGGTTAAA AATTCCTTACAAAATAATTTGCTAGCTTATCTCACTTTGCTTCCCACTGTAATGATGTAG ATGTAAGTCTGGGGTATTAAGAGTGGCTTCTAGAATGATTTAAACATGTTATGATATCT CTGCCATGTCACCTAAATTTCTGTTTGAACACTGTTTCTTCAATCCTGCTATGTA ATGGATGTATGATGATGATACATTTTTCACATCTCAGATAACTATTTTGAATAATAG TANCAATGTTCTGCTGAATTTATTCCTTA GTAAGTATATTTAGTAAGTAAAGGAAAGTTGAGAAATAAAGGCCCTCTTAAGTC CCATAGCAATTCCTCTGCACTAAATATATATATATATATCTTCTAAAGCAGATGAATAT AATTCACATTTTAT ATAGAAATCTAGTTACAGAACTTGAATTCATATATATATATATATATATATATATATAT ACTGATTTCTATTTTAAATTTGCTCAATCTATTTGAATGTTTCTGATGTGGCAAC AGAAATTTTCTGCTGGCTAACTAGTCAGGCTTCTGAATCTCTGCTAGCCGATCT GTGCATCTCTGTAATTCAGTTT GTAAGTATGATAGCCACTTCTACTGGAGGCAATATATATCTGAACTGCTTGT ATAGTATAGCATCTTCAATTTGAGGCTTAAATGAAGGAGCAACAGTATCACTT CCTGTTTAAACTTTGAAACGCGCAATTTGTGAATTAATTTCTGACAGGCTCTAGGC TTGTGTTTCTATGCGATATATGAGGATCACTTTTCTTATTAAGAAATATTA TATAACAGCTCCAATTAACAACTCAGAAAGCCATTTGATTTGATTAATTCCTTAATTTAC ATTTAAACCAAGCATATTTATTTGACAT

GENOMIC STRUCTURE OF THE HUMAN OB RECEPTOR

Table 1. (Continued)

Coding exon number	5' Intronic sequence	3' Intronic sequence
7	<p>AACAGACATAGCGGCAATCATTTTACTTCTCAGGATTTGGCTTCATAGTGATTGGC TTTAAGAACTTGCTAGTTTCTAGTTTCTCAGATCTCCAAAGCAGGCTGTTGGAAATATGTC ATTGTTGAATTAAGCTATATTTTGTAGTCACTTCTCTGCTAGTTCAGTCAAGTGC ACAATTACTGCTAAACATATTTATGATGAATAGCCCTCTGTTTAGAAGATAGT AAGACATTCATGGAAGCTCAACTCACTTGAATGAGAGCACTGGGACACTAGATA ACTGTACACAACAGTAAATTTTCCAGATATCCAGTTTAAATACACTCACTTATT TTGGCAGTGAAGTCTGGAAGTGTGTAATTTTTCGATGCTGCTACAAATTAAT TACGAATGTTTCTCTCATCTGATATCTTCTCTCCCTCAATACAG</p>	<p>GTAGAAACACAGAGGTTTGTCATTTTGTCCACAACTTGAATTTTCATTATGGACCTC CTTATATTACAGTCTGTTAAAGATGTAAAGAAATTTTTCATTGAATTTTGGAGT TTTGCTTATATAATTTTAAATGTTTCAATAG'ATGCAATCAATATCTCATG TGAACCTCATGGCTACTTAACATAAATGACTTGCAGATGTCACCACTGACATCCAGTCA CTTGGAAAGCACTTTGCAATGAGGTATCATAGGTAGTATTTTGTGTTTTGTT TTTCTGGGCAAGTACATGAATTTTCTTACAAATATTACAACTAGTCTTACAG ATTATTGCTCTCTGAAGAGGAAAGTATAATAATGAATC</p>
8	<p>GTAGAAACACAGAGGTTTGTTATTTTGTCCAACTTGAATTTTCAATATGGACCC TCTTATATTAGAGTCTCTGTTAAAGATGTAAAGAAATTTTTCATTGAATTTT TTGGAGTTTTCCTTATATAATTTTAAATGTTTCAATAG</p>	<p>GTACGTATTATTGCTGTTTTGTTTTCTGGGCAAGTACAGATAAAATTTCTTTA GAAATATTACAACTAGTCTTACAGATTTTCTCTCTGAAAGAGGAAAGTATAATATA ATGAATCAGGAAATTTTGAGGATATATAAATGCTGATCTTGAAATATTACACC TGAGATTAAAAATTTGTAATTTGTTTTTACTTCAAAATTAATTTCTGAAATCAATCAAT TCTGAAAAATTTGT</p>
9	<p>AGCCGAGCATTAGATTCTAGAGGAGCAACCCCTATTGTGAACGGGCAATCGGCTCC TCATGAAATCTAATCCCTCTCATCTGAAGTGGAGAGTTTATCCCGTTACCTGA ACCATCTCCCAATCCCAATAGTGAATAATTTGCTTCCATGAACCGTCCCTGGTG CCAAAGGTTGGGACTGCTGTTTAAACAACAATCAGAACTCTCAGATATCTTCT GTTGCTTTTATTAATGATATAATGACTATTGTTGATCTTTTAAAG</p>	<p>GTATGTCAGGCTGCTGTTGCTCTTCTTGTGTAGCAGATTTGTATGAGATTTGATCGAG ATTAACTTATATTTGCCATTTCTGATCAGATAGATTTTGAAGAAATTTGTTCTCT GTTACAGTGGTATTGAAATAATCAGCCCTAGCAAGTTTAACTTTGAATTCATTTCAA ATTATTAGCAAACTTTTGTAGCAATAGAAATATTTCTGCG</p>
10	<p>TTTTGATTTTTAGTAGAGCGGGTTTCCCGTGTAGCCAGGATCGGCACTGTAT CTTTGCTTGCAGAGCCAATGGTTCAATTTCTAATCAGGTACTACTACTAGCTTTAG AGTACATGAATATGATTGACTTTTTTCAGTCAAGTCTATATTTGCGAAAGAGA TAAATCCNTCTTTTAAATATACATAAAGTAATAGGAAACAAATCAGATAATGAGT GAGAAAGTTATGAAGAGATATGCTGATGAATACAGATGTATGAATAATAACACA ATGTTTTAGGCATTATTAATTTAAATACCATCACTTAATACTATTGTAAAAAT TCTAG</p>	<p>GTACCTTTACTTAGAACTTCAGCTTCCCTCATTAATGCTATTTTATAATATGAAGAG TTAAATGCAATAGATTTTATTTTGGCATAAAGTACATCTCTCTGATTTGTAGCTTA TTTTTCAATTAATGATTTATAGTCTAAGTCTAATTTTTTAAAGAAAGTTTCTGAAATCC ATCATCTCCCTGAAGTGTGTTTATAGCAACCTGTTGTCATATATGTTCTTGGAAAAAGA TAAATGGCTAAATCAGTTAGGAAACCTGTATCATCTCTCTTGTGTAGTCAAGG TATACATATTACATATTCAAGTTTGGGAAAGTCTCTCATTAAGAAATTTGTGACCTTAT TTCACTCATGTTCCCAAACTAATTTT</p>
11	<p>CAGCGATTTGTACAGTAGTCTATCTAACCAATACGTTTAAATCTTTTAAATCT TAAACATCTTTGTGGTACAGGATAGTGGACAGGATAGTAGGAGGGTAAAGAG TGTTTGGGAAACAAGTTGCAAGTAAACCGATTCAAAATCTGTATCATCAGCAAGG GAGTGACAGATAAATGAATAATCTTGAAGTGAAGGATTTACATCAAGCCCTAA TTGTGATATTTCTGAAGGCAAGACACAGAAATCAGTTCTCTTAAATTTGGAAATAGT GAATGGTTTAAATAAATGTACTTCAAGGCTTTAGATACATATGTTGTTGAT GATCAATCTAATGCTTTGACTTATTTACAG</p>	<p>GTCTGACAGATTTTGAATGTTTGAAGTGCATAAGTGTGCTTCAAAATATGGCT GAAAGTATTCTTCAAAACATATACAACTTTGCTATTTTGC</p>
12	<p>AGGCTGCAGAGATTTGTAATGTTTGAAGTGCATAAGTGTGCTTCAATA TGGCTGAAAGTATTTCTTCAAAACATATACAACTTTGCTATTTTGCAG</p>	<p>GTATCCCAATTTTAAATTAATCTTAAATGTTATTTTATCTTAAATTTACTTCA TGGTCCATAATCTGTTTAAATCTTGGGAAAGCTCAACAACTCTGTTTTCATTGCTAT TTATGAGATGTTTAAAGAGAGCTAAGATGATAGTGGCTGAGCACTGGCATAGTGTTA GGAAGCTTTCTCTCTTCTAGCTTCAATATATATAGTACGTGAG</p>
13	<p>ACCCATNTCCCAAGCTTTACGCTTGTAAATAGTACCTGCCNTGATGCGCCCTGCT CCTAATAAGAAATGTAAGATGAGAGTATGTGAGCTCAGTTAGTATAAAAGCAGTGC AGCCCTTAACTAATCAATTTCTATATTACTACAG</p>	<p>GTAGAAAGATACAGAGTGTATCCATTCCTCTTTTAAATTTTAACTTTTGGAACTCT CCTATTTAAATTTCTTCAAGCAGCTGCAATTTCTGCACTCTGAAAGTCTCTTTTCA CCTTTCACTTCTTGTCTGGAATAAATAACAAAGTACATTGTACAAATCATACATAACA GTCTTCAAGCTTCAATTTGGGAAACATTTGTTAAATGGTGTATTAATAGATGAGATGTT TTAGTCAATCTAATCTTAACTTTTGGACCAATGGAGATCTTTAGGTCAATATCTCT CTCCCTATGTACATATACATATATTTTATTTATATACATACACATATAAATATGTA AAATAAGTATATATCATATTAATATATATTAACTATGTAAATAGTAAATAGCATGA CATGTTATATGATGATGAGGTTAAATTTGCTGAG</p>

Table 1. (Continued)

Coding exon number	5' Intronic sequence	3' Intronic sequence
14	GAATATTCAAAAATGCTTTTAAAGGTTTAGGGAGTATCATGTTCTCTCAAGT CATCTATCCCATATCTCNGTTTAAATGACTCTCATGATGCAAGTAATTGTCATG TACATATTATGGTGAAATGCTGCTCTCTCTCTATCCCTTTAGTAGGTTA TAAGTCTCCACAGATTTAGTAGATTTTAAATTTTAAATTTAAAAATTAATTC CTCTTTCCCTCAG	GTAACTTACTATACCTTTAGTGAAGTTCCTCATGGATTAAATGACACTACAGATTATTA ATCTATTAAATATAGCCAGTTAATGAAATCTTCAAAATATAGAGATACCTACCTCTAA TACATAATCCTATAACCTTTATCAAAACATTAAATCTCTCTCTCTCTCTCTCTCTCT CTCTCTCTCTCTCTCGGCACGGTCTGNGTGT
15	AGATTTCACAAGACTTAGTCTCCAGCTACCTTGAATGGTGAATGGGAACTAAGTA AGCTATCTATTAAAAAAGAGATATGCCACTTTGGGGTAAGGAGAGGTAGT AGACATATTGCTCGAAAAGGAATGAAGGAAAGAAAGCTCATACACCTCGCAC TTGAACAAATGGCTACTGCACTGGAACATGCCCTTTGAAATTTGCAATCTCTGCTCT GGCTAAGATTTTAGAAAATATGGAACATTTGTCTAGCTAGATAAATAGAAAT GCTTAAGTTGTTTGAACCTCCCTGATATTAATTAATCCACAATAATAGTAATTC TATGTTGGAAATATATAGATAGTACCTTAATCTTTTAAATGATATGTTCCACT CAITACTAATTTGTATAAATGAGCCCTTTACGTATTTTCTCCTCAG	GTAAAAATTAAATTTAGTTTCTTTTACACCAATGTGTGCGCTAAATTTGTTTGCAGTA ATATGCGCATCTGATTATCTTTCTGATAGAATCATGGAAGAGTCCAAAGTCTCTGTGA GATTTTCATGGTGAGTCCAAAGGAATATTTTCTCTCTAAATTAACACTGGAGCT ATAGAATAGACTGCTGGCCCTCTATATTTCTGATTCATCTTACTGCTACTTGGATACC AACATTTGATTTTG
16	CAAAAGCATTCGAGCAAGGACAGTGTGGAAGGCGCTTAAGAGTGGGGATGCT TGCTGTTCAAGAACACGCAAGGAATCAGTGTGTGGAGTGAACAAGATAGAGATT GCCAGGTGTGAAGGTTGGTCTCCAGGAGTAGATCTGAGACAGTCTATACAAACA GTTTGACACTTTGGCCCATTAATGTAAATGATTATTAATGATGATCACAACAT ATTTTATCTCTATTTTATTTTATATTTTGAAGGTAAAGAGATTGTGATGA TTCAGAAAATGCTACTAATATTTTGATACAGAAAGAAATTAATTTTCTCAAGT TCTGAGTTGTAAATGTATTTCTTTTCTCAG	GTATTGACTTGAGGTTAAGAACTTTTACGGCAGAAAGTCTTACGCGTATTTCAAAACCCTGA TTTAAACCTTCTAAATTAGGAATTTAAGCTCTTCTAAGTCTTTATATAGTGTGTA TACAATTAAAGATATCAAAAAGGAAAGGCTGTGTGTCAGGAAATGGCATTTCCATTTTGTCT AGGACTGTAAAGTTAAAGAACTGAGGAAAGAAACACGAAACACAGCTTAACAGTTAAAGAC AGGTTTCTTTAGATAAAACCTGAGGGGCTTCTGGCCAATTTTTCANGAGCCCTTTCTCT CTTACAGACTAAGGANTATGTAT
17	GAGAACTCAGTGTGGTTATTTTACACATGCTGAGAAACCATCTCTCTC AGCAGAAAGAGAGAGAGAGATTTTAGAATCTGAATTTATCTGTAGTTAAGTGAG TTGATGGGGCCACATCAAAATGGAATTTTCTGTGACCACCTTTGTACCATTTTAA TATTTCAATTTCTTGAGAGAAATCTCAGTGTGATGACATGCTGTTGGCACACAG CTTTCAATAGTATTGGCTATTCTATTATACAGTGTATTTTCAAGTCTGGCTCTACAT AAAATTTGTAGAAATCTTATGGGCTAGCATGTGAATGATCATGACCCCTACGGA GGCATAGTTGATCTGTGGCAATATTTCTAGCTTGTCTGTTTCACTAAGTCTCAGAT TTTCCAATAGGATGTTTTCTCTAATTTGATGGCCCTGTATATCTCTTTGTAG AGTTTATGGATGTAATTTGCTACAAAATATTAGCAAGGAAATCTTTCAGAACATAG CATTTCCAATGACAGTAACCAATCTTCTGAGAGCTAAGCACTTGACACACTAAT TTATTTCTAGCCACTTATCCATGAGCAGCATTTTATAGATGATGAAATGAAAGGCA GAGAGGTAGTACTGTTCTGATGGTTGAGAAATGGGAAGCACTCAAGTCAAGTCTG TCTTGTCCACATTTCAATGCTATCATCTTAAAGGGCTCTCTCTTATGCTTTTTCAT ATATGATTTTAGTCAAAACTAGTAATTTGTTGTTGACTTATGTTCTTTATATTA ACTTAACACACTTCCATTTCTCCAGTATGACTATTAGAAAGCAAAATTTTAAACATA ATTGAGCCTTAAATGTCTTTCTTTTATG	GTGCTTTTCAATTTTTTAAACCAGAAATATATANGATTGCAATCTAGACGCCCATCA CTTAGCATTAAGCATTTTAAAGATTTAAAGGTATATTTTATTTCAATCTCTTAAATATA TCTGTTATTTATCTTCAAGATAGCAGGATGCGGGATTTTCAATCAGGAAAGAAACA ATTTACGCGCATGTTTATCTGATGAGATTTCAATATACATATGTTGCTTCTGTGTCNC AGTACATAATAAATAATATAGAAATTAAGGGTCAATCTGATGAGCAACAGATATTTG GATACACTTTTTTGGTATAAACTGTATTTAGGCAAAAGGCTGGAATCAATATTTTTT
18		

All sequences are from 5' to 3'. Underlined sequences may be used as primers for SSCP analysis of each exon although exons 2 and 18 are too large to be analyzed in a single PCR product.

All sequences are from 5' to 3'. Underlined sequences may be used as primers for SSCP analysis of each exon although exons 2 and 18 are too large to be analyzed in a single PCR product.

Table 2. Sequences of Nested Primer Sets Used to Define the Boundaries of Each of the 18 Coding Exons and the Adjacent Intronic Sequence

Location of intronic sequence	Outer primer	Nested primer
5' of exon 1	5'-GTAACAAAACACACAGAATTTTGG	5'-AACCACACAGAATTTTGGACAAATC
3' of exon 1	5'-GCTATTGGACTGACTTTTCTTAT	5'-GATGTGCCTTAGAGGATTATG
5' of exon 2	5'-ATAAGTTAGAAAAGTGAGTACCACTTG	5'-AAAAGGAAGTAGTCATAGGTTGAAT
3' of exon 2	5'-AATTCGAATGGACATTATGA	5'-CTGTTGAACCTAAGTTTAATTCAAG
5' of exon 3	5'-CCACATAACAGATGAATAATTTTAAG	5'-TTAGCCAGCACTGTATGTTT
3' of exon 3	5'-GAACATACAGTGCTGGCTAA	5'-CTTAAATTTATTCATCTGTTATGTGG
5' of exon 4	5'-ACATAAGGAGAGTGTCGT	5'-ATTCACAACATTCATGAACAC
3' of exon 4	5'-GTGTTTCATGAATGTTGTGAAT	5'-ACGACACTCTCCTTATGT
5' of exon 5	5'-AGACCCAGGAAGTATACTGTCTACTA	5'-AAGAAATCTTTAAATTACCATCATCT
3' of exon 5	5'-AGATGATGGTAATTTAAAGATTCTT	5'-CACCATTGGTACCATTTCAC
5' of exon 6	5'-CCCTCACCTGAACCTCATAC	5'-AGACCCAGGAAGTATACTGTCTACTA
3' of exon 6	5'-CAGAGAATTCTACAACAGTTATCAGAG	5'-TACATCCCTGCTAGTAGACAGTATAC
5' of exon 7	5'-AGTACACTGCATCATAGGTAACT	5'-AGAATTTTAGGTGGAAAGTATATGAC
3' of exon 7	5'-ATCTATAAGAAGGAAAACAAGATTGT	5'-CAAAGAGATTGTTTGGTGGATG
5' of exon 8	5'-CTGGTTGACCATCTGCAAGTC	5'-TTTAGTTAAGTACCCATCAGTTTC
3' of exon 8	5'-AGTTTACCTATGATGCAGTGACTGCTGCAAT	5'-GAATTATATGTGATTGATGTCAATATC
5' of exon 9	5'-TAGGAAGATTGGCTGGAAAA	5'-AACCATCACTCTGCAAATA
3' of exon 9	5'-TCCATCTATTTCATCCCATATC	5'-CAGAGTGATGGTTTTTATGAAT
5' of exon 10	5'-TTTTCCCAAGATATTTTCAATAAT	5'-AATGTTTATAGTAATTTCTGCTTTCAC
3' of exon 10	5'-CAGAGTGATGGTTTTTATGAAT	5'-GCAGAAATTACTATAAACATTGGATTA
5' of exon 11	5'-ATATCCATGACAACCTGTGTA	5'-ATTACTCCAATATCCCACT
3' of exon 11	5'-ACTGGGATATTGGAGTAAT	5'-TACACAGTTGTCATGGATAT
5' of exon 12	5'-AAAGTAAAGTGACATTTTCTCCT	5'-CATAGTATCTCCATTAATTATTCTCC
3' of exon 12	5'-GGAGAATAATTAATGGAGATACTATG	5'-AGGAGAAAAATGTCACCTTACTTT
5' of exon 13	5'-TTAAATTAATAATTTGCAACAGAAG	5'-AGAACCCTAACAGTATGTGCT
3' of exon 13	5'-AGCACATACTGTTACGGTCT	5'-CAAATTTTAATTTAACCTTTTCATG
5' of exon 14	5'-ACTTCTTAACAGATGAAGAGATTCT	5'-ATTTTATTTTACCATTCTTCATTAAG
3' of exon 14	5'-TTCCTGGATACTATCACCCAG	5'-CTAATGTATTTTATTATTGAGTGGAAA
5' of exon 15	5'-TGAACTATTAATTATCTTTGGTTTTT	5'-CACTCCTTCCATAAATATTGGGT
3' of exon 15	5'-ATCATTTTATCCCCATTGAGAAG	5'-GAAAACCAAAGATAATTAAGTTTCA
5' of exon 16	5'-ATAAGATGGAAGAGGAAATAATTAC	5'-ATTACATATAAACCTGCATCACTCT
3' of exon 16	5'-AGAGTGATGCAGGTTTATATGTAAT	5'-GTAATTATTTCTCTTCCATCTTAT
5' of exon 17	5'-AAAATTAAGTCCTTGTC	5'-TGCCCAGGAACAATTCTTGGGGTT
3' of exon 17	5'-AACCCCAAGAATTGTTCTGGGCA	5'-GCACAAGGACTTAATTTT
5' of exon 18	5'-CTTTATTTTCCATGATGTATCAACACTG	5'-TGAAATTGTTTCAGGCTGGAAAAGAAG

METHODS

Generation of Genomic Fragments Defining Splice Sites

The human PromoterFinder DNA walking kit library (Clontech, Palo Alto, CA) was used to generate polymerase chain reaction (PCR) fragments containing the genomic DNA adjacent each exon by performing two long PCR reactions with one of the manufacturer's adaptor primers and one of a set of two nested primers derived from the OBR cDNA sequence. The pairs of nested primers that were used to determine the boundaries of each exon and the

adjacent intronic sequence are listed in Table 2. Long PCR reactions were performed in 50 μ l volumes consisting of 1 $\times$ TaKaRa Ex Taq buffer, 200 mM each dNTP, 100 ng DNA library, 0.2 μ M adaptor primer 1, 200 ng nested primer, and 2.5 units TaKaRa Ex Taq. Cycling conditions consisted of 35 cycles of 94°C for 30 sec, 55°C for 30 sec, and 72°C for 4 min.

PCR products from the second, nested PCR were electrophoresed through a 2% agarose gel and stained with ethidium bromide. PCR products were isolated by cutting bands from the agarose gels, centrifuging the DNA through a cotton plug, and removing contaminating primers using Qiagen (Chatsworth, CA) Qiaquick spin pu-

CHUNG ET AL.

rification columns according to the manufacturer's instructions.

PCR template (250 ng), 50 ng of primers, and fluorescent terminators were used in a 10 μ l cycle sequencing reaction electrophoresed on an ABI 377 automated sequencer (Applied Biosystems; Foster City, CA) according to manufacturer's protocols.

Exon junctions were identified as the point at which the genomic sequence diverged from the cDNA sequence reading in both the 5' and 3' direction and which contained an adjacent consensus splice site.

Isotopically Labeled Genotyping

End-labeling

Forward and reverse primer (100 pmole of each) were end-labeled in a 25 μ l reaction volume containing 10 mCuries [γ - 32 P]ATP, 1 $\times$ polynucleotide kinase buffer (New England Biolabs, Beverly, MA), and 20 units polynucleotide kinase for 30 min at 37°C.

PCR

PCR reactions for amplification of small fragments including complex repeat sequences utilizing end-labeled primers consisted of 20 μ l reaction volumes comprised of 100 ng genomic DNA, 1 $\times$ reaction buffer supplied by Boehringer Mannheim (Indianapolis, IN) in which the [MgCl₂] is 1.5 mM, 0.25 mM each dNTP, 30 pmole of each end-labeled PCR primer, and 1 unit Taq polymerase. Primer sequences for the two polymorphic microsatellites were as follows: OBR-CA forward: 5'-GACAACCTGATG-GTGTATCCTTC-3'; OBR-CA reverse: 5'-CATCCAGAACATGTACAGAC-3'; OBR-CTTT forward: 5'-AGAGGATACTACCATCCTAATAC-3'; and OBR-CTTT reverse: 5'-CAACACAACCAGACCGTGCCG-3'. All thermocycling was performed in a Perkin Elmer 9600 with 35 cycles of denaturation at 94°C for 30 sec, annealing at 55°C for 30 sec, and extension at 72°C for 30 sec.

Electrophoresis of Polymorphic Markers

Five microliters of the PCR reaction was electrophoresed on a 6% polyacrylamide gel at 60 W for 2.5 hr. Gels were dried and exposed to film.

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