Chapter 2

LEPTIN RECEPTORS

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Abstract: Leptin receptors belong to the class I cytokine receptor family. Although six isoforms of receptor have been identified, only two are thus far known to be linked with intracellular signaling, and only the longest isoform (ObRb) has full signaling capability. Structure/function analyses of the receptor suggest that it exists constitutively as a dimer in the plasma membrane; each receptor of the dimer pair reversibly binds a single leptin molecule. Upon binding, signaling cascades are initiated beginning with activation of receptor-associated janus kinase 2 (JAK2) and phosphorylation of two key tyrosine residues on the intracellular portion of the receptor. Of particular importance for the growing list of leptin actions is that binding of leptin to its longest receptor isoform activates numerous intracellular signals following JAK2 activation, which have been associated with a wide variety of biological actions in different tissues. Expression of the two longest forms of leptin receptor (ObRa and ObRb) appears to be nearly ubiquitous in mammalian tissues, although ObRb is abundantly expressed only in hypothalamus. Total loss of function mutations in ObRb appear to be rare in the human population, but polymorphisms in the regions of the gene that code for extracellular domains of the receptor are not uncommon, and are associated with weight gain and adiposity. An important area of future research will be the identification of the physiological functions of shorter isoforms of the leptin receptor, and continuing characterization of the types and frequencies of receptor polymorphisms in the human population.

Key words: Leptin receptor; domains; signaling mechanisms; localization; receptor structure and function; mouse; human; mammals
1. INTRODUCTION

The *ob*/*ob* and *db/db* mice display a similar phenotype, which includes obesity, hyperphagia, and infertility. Parabiosis experiments in the 1970s suggested that the *ob* gene encodes a soluble factor that circulates in blood, whereas the *db* gene encodes its receptor\(^1\). Shortly after *ob* was sequenced, and its product was named leptin\(^2\), the leptin receptor gene was identified using an expression library, and then mapped to the *db* locus\(^3\). The *db* gene is located on chromosome 4 in mice and 1p in humans\(^4\). It was the identification of a receptor and the functional link between receptor activation and cell function that defined leptin as a hormone. This review will focus on the structure and function of the mammalian receptor, using the murine and human receptors as well-characterized models. However, it should be noted that partial or complete sequences of leptin receptors have been obtained for many different mammalian species, including *S. scrofa*\(^5\), *B. taurus*\(^6\), *R. norvegicus*\(^7\), *M. lucifugus*\(^8\), and in other vertebrates, and in all cases the structural domains of the receptor are highly conserved (Table 1).

<table>
<thead>
<tr>
<th>SPECIES</th>
<th>ObRb % nucleotide homology to human</th>
</tr>
</thead>
<tbody>
<tr>
<td><em>Macaca mulatto</em> (macaque)</td>
<td>97%</td>
</tr>
<tr>
<td><em>Bos taurus</em> (cow)</td>
<td>88%</td>
</tr>
<tr>
<td><em>Canis familiaris</em> (dog)</td>
<td>88%</td>
</tr>
<tr>
<td><em>Sus scrofa</em> (pig)</td>
<td>88%</td>
</tr>
<tr>
<td><em>Ovis aries</em> (sheep)</td>
<td>88%</td>
</tr>
<tr>
<td><em>Myotis lucifugus</em> (little brown bat)</td>
<td>87%</td>
</tr>
<tr>
<td><em>Rattus norvegicus</em> (rat)</td>
<td>83%</td>
</tr>
<tr>
<td><em>Mus musculus</em> (mouse)</td>
<td>81%</td>
</tr>
<tr>
<td><em>Gallus gallus</em> (chicken)</td>
<td>62%</td>
</tr>
</tbody>
</table>

Table 1: Relative similarity of leptin receptor isoform B cDNA sequences of representative species to the human sequence. Mammalian sequences were compared using BLAST. The *G. gallus* comparison is from reference 144.

2. DOMAIN STRUCTURE OF THE LEPTIN RECEPTOR

The leptin receptor is a member of the class I cytokine receptor family, also known as the gp130 receptor family, although unlike many other family members, the leptin receptor does not form oligomers with gp130\(^9\). Six different isoforms of the leptin receptor, ObRa-f, have been identified, also sometimes referred to as LepRa-f or LRa-f in the literature\(^10\) (Figure 1).
Leptin receptors

Figure 1: Domain structures of leptin receptor isoforms. Only those isoforms present in multiple mammalian species are shown. CK = cytokine receptor domain; F3 = fibronectin type 3 domain; Ig = immunoglobulin C2 domain; CRH = cytokine receptor homology domain. Y = tyrosines thought to be involved in signaling. Box 1 and 2 are cytokine boxes. The names of the unique terminal exon of each isoform are shown. Arrows symbolize receptor domains or residues that are involved in binding and activation of the signaling proteins indicated (see text for further description of signaling mechanisms).

All six receptor isoforms are products of the db gene and share the first 805 amino acids, comprising exons 1-14 in the mouse. The smallest isoform -ObRe- is not a receptor but rather is a soluble binding-protein, as it contains no transmembrane or cytoplasmic domains and is present in the circulation of some species. In rodents, to create ObRe, the splice site at the 3'-end of exon 14 is skipped, and a contiguous sequence, exon 14', which contains a stop codon and a polyadenylation signal, is transcribed. In humans, the sequence 5' of exon 14 does not have a polyadenylation signal, and this may be why no ObRe transcript has been found to exist in humans.
Instead, in humans the ObRe protein is generated by proteolytic cleavage\textsuperscript{12,13}.

The remaining larger isoforms share exons 1-15, exon 16, which contains the transmembrane domain, and exon 17, which contains the first 29 amino acids of the cytoplasmic domain\textsuperscript{11,14}. After this, amino acid 889 in the mouse, ObRa, c, and d have different terminal exons, encoding just 3, 5, and 11 amino acids respectively, whereas the terminal exon of ObRb, also called ObR long or ObRl, has an additional 273 amino acids. Although ObRa-c have been identified in multiple species, ObRd has thus far only been found in the mouse\textsuperscript{11}, and ObRf has only been found in the rat\textsuperscript{14}.

All six receptor isoforms possess the extracellular domains of the leptin receptor, which are the only portions of the receptor required for ligand binding\textsuperscript{2,15,16}. This part of the receptor is heavily N-glycosylated, with sugars accounting for 36\% of its total mass\textsuperscript{17}. There are nine disulfide bonds, which contribute to the three dimensional structure of the receptor\textsuperscript{17,18}. Near the N-terminus are adjacent conserved cytokine receptor and fibronectin type 3 (FN3) domains, together referred to as a CRH, or cytokine receptor homologous domain\textsuperscript{2}. This CRH is separated from a second CRH by a conserved immunoglobulin C2 domain. There are two additional FN3 domains in the extracellular portion of the receptor, distal to the second CRH. Only the CRH domain closest to the membrane is involved in ligand binding\textsuperscript{16,19}, possibly via hydrophobic interaction with the a and c helices of leptin\textsuperscript{20}. Two amino acids, F-500 and Y-441 are particularly important for leptin binding\textsuperscript{21}. The conserved WSXWS motif in the second, but not the first, CRH domain is glycosylated, suggesting that the first CRH domain may be buried within the tertiary structure of the receptor\textsuperscript{17}.

Each leptin receptor can bind one leptin molecule\textsuperscript{21-23}. However, intracellular signaling requires a dimerized receptor in which each receptor in the pair is bound to a leptin molecule. It is the extracellular portion of the leptin receptor that is sufficient for dimerization to occur\textsuperscript{22}. Unlike other cytokine receptors, unoccupied leptin receptors exist constitutively as dimers in the cell membrane\textsuperscript{22,24,25}. Disulfide bonds within the second CRH domains of each receptor are involved in assembling these pre-formed dimers\textsuperscript{20,21}. The binding of two leptin molecules, one to each receptor, does not enhance dimerization, which requires ligand binding in most other cytokine receptors\textsuperscript{23-25}. There is evidence, however, that leptin binding induces a conformational change in the dimers\textsuperscript{24}, and that this in turn may result in clustering of the homodimers\textsuperscript{19}. Once activated, the receptors induce intracellular signaling by the Janus kinase/signal transducer and activator of transcription (JAK/STAT) pathway. Two critical cysteine residues in the FN3 domains proximal to the membrane are required for clustering-induced signaling\textsuperscript{16,20}. In cells which co-express ObRa and b, heterodimerization does not occur in the absence of leptin\textsuperscript{22,24,25}, but may occur to a small degree in
the presence of leptin. Thus, coexpression of ObRa likely does not have any significant affect on signaling by pre-formed dimers of ObRb. The extracellular domain is followed by a single, short, hydrophobic domain which spans the membrane, and is contained by exon 16 in the mouse.

3. SIGNALING PATHWAYS INITIATED BY INTRACELLULAR DOMAINS OF THE ACTIVATED LEPTIN RECEPTOR

Activation of leptin receptors directly or indirectly activates multiple signaling pathways that involve kinase-induced phosphorylation of proteins, including JAK2/STAT3, erbB2, ERK, IRS1 and rho/rac. Signaling requires the presence of intact intracellular domains of the receptor. The leptin receptor is an external tyrosine kinase receptor; upon ligand binding each receptor can bind and activate the tyrosine kinase JAK2, which then cross-phosphorylates tyrosine residues in the other receptor in the dimer (Fig. 1). There is an absolute requirement of the intracellular cytokine box 1 motif of the receptor for activation of JAK2. This sequence is present in all the transmembrane isoforms. Most studies, however, have focused on signaling mediated by ObRb, the only isoform which has conserved intracellular tyrosine residues and which is capable of activating the transcription factor STAT3. In addition, only ObRb has a cytokine box 2, which does not seem to be required for JAK2 activation, and a sequence of 15 amino acids downstream of box 1 that are required for optimal JAK2 activation.

The numbering of the crucial tyrosine residues that can be phosphorylated by JAK2 follows the mouse sequence. Phosphorylation of Y1138 is required for binding of the SH2 domains of STATs and of SOCS3, a suppressor of cytokine signaling that reduces ObRb signaling partly by inhibiting JAK2 phosphorylation. SOCS3 also is activated by binding to Y985 and to a lesser extent to Y1077. Binding of STAT3 or SOCS3 to the phosphorylated leptin receptor enables their phosphorylation, and thus activation, by JAK2. Although STAT1, STAT5, and STAT6 can be phosphorylated upon leptin treatment in vitro, only STAT3 activation has been observed in vivo, although this has only been determined in hypothalamus and blood mononuclear cells. In addition to tyrosine phosphorylation of STAT3 mediated by binding of STAT3 to phospho-Y1138, STAT3 must be activated (phosphorylated) by the serine kinase ERK for nuclear translocation and full induction of gene expression. One of the genes activated by leptin-induced STAT3 signaling, is SOCS3, which
therefore represents a negative feedback action on the leptin receptor\textsuperscript{37}.

Phosphorylation of Y985 of ObRb by JAK2 leads to the phosphorylation of SH2 domain-containing proteins SHC and the tyrosine phosphatase SHP2\textsuperscript{34-36}. The extent to which SHP2 inhibits JAK/STAT signaling is unclear. In most studies, SHP2 activation does not inhibit phosphorylation of STAT3\textsuperscript{35,45-47}, but mutation of Y985 does enhance STAT3 phosphorylation, suggesting an inhibitory role of SHP2\textsuperscript{34}. SHP2 can dephosphorylate a tyrosine residue at position 974 of the receptor, but the role if any of this tyrosine in intracellular signaling has not been defined\textsuperscript{48}. The phosphorylated SHC binds and activates Grb2, which in turn leads to activation of the MEK/ERK pathway\textsuperscript{49}. Grb2 is also activated by SHP2\textsuperscript{36} and may also be able to interact directly with JAK2\textsuperscript{45}.

Unlike Y985 and Y1138, the third intracellular tyrosine residue on ObRb, Y1077, appears to reside in a hydrophobic region of the receptor that would not be accessible to ligand binding and kinase activity, and therefore this residue appears to be less important for leptin signaling. Indeed, in one study when Y985 and Y1138 were mutated by site-directed mutagenesis, Y1077 did not become phosphorylated, showing that it is incapable of being independently activated\textsuperscript{35}. Further, this tyrosine was not required for STAT3 or ERK activation in vivo in the hypothalamus\textsuperscript{45}. However, Y1077 was shown to activate STAT5 in pancreatic cells in vitro\textsuperscript{36}, suggesting that it may have a role in mediating at least some of the actions of leptin.

Although ObRb is sometimes referred to as the “signaling isoform,” there is evidence of signaling by other isoforms, particularly ObRa (also called the “short isoform” before the discovery of isoforms c-f). For example, in cells transfected with ObRa and not any other ObR isoform, leptin treatment induces activation of JAK2, erbB2, IRS1 and ERK/MAPK\textsuperscript{29,30,50}, although ERK activation is not as great as that induced by ObRb\textsuperscript{30}. JAK2 can activate ERK without phosphorylation of receptor Y985, suggesting a mechanism different from the ERK activation pathway in ObRb\textsuperscript{56}. Leptin treatment increased expression of c-fos, c-jun and jun-B via ObRa in transfected CHO cells\textsuperscript{51}, but failed to induce c-fos expression in COS cells transiently transfected with ObRa\textsuperscript{30}. The ability of ObRa to induce immediate-early gene expression in vivo is unknown.

4. TISSUE DISTRIBUTION OF LEPTIN RECEPTORS

Leptin receptors are nearly ubiquitously expressed (Table 2; references 52-82). ObRa is expressed in almost every tissue that has been examined\textsuperscript{83,84}. ObRb expression, by contrast, is abundant only in the hypothalamus, but is expressed at lower levels elsewhere.
Table 2. Localization of leptin receptor isoforms in mammals. The specific short isoform (a, c, etc.) is given where known. References are not necessarily inclusive.

<table>
<thead>
<tr>
<th>Tissue</th>
<th>ObR long</th>
<th>ObR short</th>
<th>ObR soluble</th>
<th>References</th>
</tr>
</thead>
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<tr>
<td>Adipose</td>
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<td>a, c</td>
<td></td>
<td>52, 53</td>
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<tr>
<td>Adrenal gland</td>
<td></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Medulla</td>
<td>No</td>
<td>Yes</td>
<td></td>
<td>54, 55</td>
</tr>
<tr>
<td>Cortex</td>
<td>Yes</td>
<td>Yes</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Bone</td>
<td>Yes</td>
<td>a, c</td>
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<td>56</td>
</tr>
<tr>
<td>Brain</td>
<td>Yes</td>
<td>a, c</td>
<td>Yes</td>
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<td>Endothelial</td>
<td>Yes</td>
<td></td>
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<td>Fetal</td>
<td>Yes</td>
<td>Yes</td>
<td></td>
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<tr>
<td>Heart</td>
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<td>Kidney</td>
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<tr>
<td>Liver</td>
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<td>a,c</td>
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<tr>
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<tr>
<td>Peripheral nerves</td>
<td>Yes</td>
<td>a</td>
<td>Yes</td>
<td>75</td>
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<tr>
<td>Pituitary</td>
<td>Yes</td>
<td>Yes</td>
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<tr>
<td>Placenta</td>
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<td>8, 77</td>
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<td>Salivary gland</td>
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<td>Skin</td>
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<tr>
<td>Taste buds</td>
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<tr>
<td>Thyroid</td>
<td>Yes</td>
<td></td>
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Initial studies using RNase protection assays and RT-PCR on extracts of whole tissues, also identified the rest of the brain, adrenal, fat, heart, lymph nodes, lungs and spleen as tissues in which ObRb accounted for more than 5% of ObR expression. That these receptors may mediate physiological functions is suggested by the fact that expression of the receptor has in some cases been found to be regulated and to change under certain circumstances. For example, expression of multiple forms of the receptor increase in placenta during the course of pregnancy in several species, including rat, baboon, mouse and bat.
In addition to leptin receptor expression in normal tissues, functional leptin receptors may play a role in a variety of cancers including adipocyte\textsuperscript{87}, adrenal\textsuperscript{88}, breast\textsuperscript{89}, bladder\textsuperscript{90}, endometrial\textsuperscript{91}, liver\textsuperscript{92}, leukemia\textsuperscript{93}, ovarian\textsuperscript{94}, pituitary\textsuperscript{95} and prostate\textsuperscript{96} cancers. Evidence for this hypothesis stems from the observation that leptin receptors are expressed in the above cancers, and leptin induces proliferation in at least some human cancer cells \textit{in vitro}\textsuperscript{97}.

5. ISOFORM-SPECIFIC FUNCTIONS OF LEPTIN RECEPTORS

The widespread expression of leptin receptors in tissues throughout the mammalian body suggests that in addition to its well-characterized role in regulating appetite and metabolic rate via actions in the hypothalamus, leptin receptors may mediate numerous other physiological functions, and indeed this turns out to be the case. Many of these functions are covered elsewhere in this volume. In this review, we will focus on select functions that have been attributed to specific receptor isoforms. The physiological importance of ObRb is the best established. The \textit{db/db} mouse mutation is caused by a single substitution that creates a splice site that results in the production of almost no ObRb\textsuperscript{98}. Thus, it is essentially an ObRb knockout mouse. The gross phenotype of the \textit{db/db} mouse is indistinguishable from that of the leptin-deficient \textit{ob/ob} mouse; it is obese, hyperglycemic, hyperinsulinemic and infertile\textsuperscript{1}. Neuron-specific transgenic expression of ObRb in \textit{db/db} mice has demonstrated that many, but not all ObRb functions occur in neuronal tissue\textsuperscript{99}. Neuronal expression of ObRb corrected almost completely for adiposity, fertility, thermal regulation, and glucose regulation in \textit{db/db} mice. Of note, however, is that the regulation of leptin secretion is not normal in \textit{db/db} mice expressing neuronal ObRb, suggesting that ObRb expression on adipocytes may be important in regulating leptin secretion.

A mouse model called the LepR1138 mouse has been created with a single substitution at Y1138 of ObRb, which prevents phosphorylation of STAT3, and presumably inhibits SOCS3 phosphorylation, but is otherwise intact\textsuperscript{100}. This mouse is obese and hyperphagic, indicating the importance of the ObRb-mediated STAT3 pathway in mediating effects of leptin. More specifically, the appetite-regulating peptides proopiomelanocortin and agouti-related peptide are abnormally expressed, but neuropeptide Y is unaffected in the Y1138 mutants. STAT3 signaling appears to mediate most, but not all of weight-regulating actions of ObRb, as these mice weigh 10\% (males) - 20\% (females) less than \textit{db/db} mice. The Lepr1138 mice are hyperglycemic, but only about half as much as \textit{db/db} mice. Similarly, changes in thermoregulation, thyroid function and locomotor activity exist,
but are less severe in the Lepr1138 mice than in db/db mice. The Lepr1138 mice are actually longer than normal mice, in contrast to the short ob/ob and db/db mice. Thus, leptin activation of STAT3 actually inhibits linear growth, at least in this strain of mouse.

The STAT3 pathway is less important for the regulation of reproduction than for the regulation of energy balance. Female Lepr1138 mice have normal estrous cycles, unlike female db/db mice, although their cycles begin at a slightly later age than in normal mice. Ovulation and corpus luteum function appear normal, but overall fecundity may be reduced; only 3 of 7 Lepr1138 mice bore young in this study. Further research is needed to determine whether this is significantly less than in normal mice, and whether it is due to specific effects on the reproductive axis or to changes in activity due to impaired energy balance.

One or more of the short receptor isoforms is involved in transporting leptin across the blood brain barrier, but they are not the only, or possibly even the primary, transport mechanism. ObRa and ObRc are highly expressed in the choroid plexus and in brain capillary endothelium. ObRf has a similar distribution in the rat, but is less abundant than ObRa and c. The putative transport activity of ObRa is not a function of its location in neural tissue, per se. Both ObRa and c are capable of binding and internalizing leptin in transfected CHO cells, while ObRa-transfected kidney cells, but not untransfected controls, transport leptin from the apical to the basolateral side.

The data on the relative importance of leptin receptors in leptin transport in intact animals are less clear. In Koletsky rats, which have no functional leptin receptors, leptin concentrations in the cerebrospinal fluid are normal, whereas plasma leptin concentrations are sharply elevated. However, in young Koletsky rats, the plasma leptin concentration is well below the saturating concentration for the leptin transport system in normal rats. Intravenously injected leptin also crosses the blood brain barrier at a reduced rate in Koletsky rats. Thus, leptin transport may occur in the genetic absence of leptin receptors, but it is reduced. Similarly, the brains of Koletsky rats perfused with radiolabeled leptin show specific leptin transport into the brain at a rate identical to that of normal rats, but this transport was saturated at a lower concentration in the leptin receptor null rats. The New Zealand obese mouse model is characterized by peripheral, but not central, leptin resistance. Leptin transport into the brain is reduced in this mouse, but this is not associated with decreased expression of ObRa or ObRc, suggesting the existence of another transporter.

In contrast, in an ObR-knockout mouse which lacks all leptin receptor isoforms, leptin transport in vivo was sharply reduced, and remaining leptin transport appeared to be non-specific. In support of the
idea that ObR contributes to the portion of blood-brain barrier transport that is regulated is the finding that a high fat diet induces ObRa expression. Other studies, however, have failed to find any change in expression of ObR short forms at the blood brain barrier in response to a brief fast or a high fat diet, despite changes in leptin transport.

The soluble leptin receptor, ObRe, acts as a binding protein for leptin in the plasma in humans and mice. It was initially proposed that the soluble receptor may contribute to elevated plasma leptin levels during pregnancy or obesity by inhibiting binding of leptin to its target cell receptors, as has been established for other hormone-binding proteins. In vitro, leptin bound to ObRe cannot activate ObRb, although the presence of this complex does not interfere with the ability of equal concentrations of free leptin to bind ObRb. However, the overall effect of ObRe in vivo, is to enhance leptin activity. Infusion of soluble receptor enhances the effectiveness of leptin treatment in leptin null ob/ob mice. This may simply be due to higher plasma leptin concentrations resulting from the predicted decreased leptin clearance from the circulation. Overexpression of the soluble receptor leads to elevated plasma leptin concentrations, without increasing adipose leptin expression. By contrast, decreased soluble leptin receptor concentrations are present in obesity, a leptin resistant state, and fasting and weight loss both increase plasma ObRe concentrations in mice and humans.

6. LEPTIN RECEPTORS AND HUMAN HEALTH

Leptin receptors have been found to play a role in several aspects of human health. Not surprisingly, they are most associated with energy homeostasis, but there are other conditions in which leptin receptor function appears to be important. The genetics of obesity and leptin will be reviewed in more depth in another chapter. However, it should be noted that leptin receptor alleles have been associated with obesity in humans. A mutation which results in loss of the transmembrane and intracellular domains of the receptor has been identified, and is associated with a phenotype that includes morbid obesity and infertility. Thus, leptin receptor mutation in humans results in a phenotype as severe as that seen in mouse models.

Polymorphisms in the leptin receptor gene which typically affect the extracellular portion of the receptor and which do not result in such severe loss of function are more common. The Q223R mutation has been particularly well studied. It has been associated with obesity, weight gain, increased body fat and increased abdominal fat, although no association with obesity was seen in other studies. In a group of Pima Indians, Q223R was associated with altered energy expenditure and
abdominal adipocyte size, but did not have a significant effect on total body fat\textsuperscript{134}. In a study of Japanese men, Q223R was associated with elevated low density lipoprotein levels and reduced effectiveness of the cholesterol-lowering drug Simvastatin\textsuperscript{135}.

In addition to the involvement of leptin receptors in obesity, elevated soluble leptin receptor concentrations are associated with sleep apnea, independent of BMI\textsuperscript{136}. Significantly lower soluble leptin concentrations are observed in women with endometriosis\textsuperscript{137}. As discussed above, leptin receptors are expressed in many tumor cell types. In addition, the leptin receptor polymorphism Q223R, in combination with a mutation in leptin itself, has been associated with an increased incidence of non-Hodgkins lymphoma\textsuperscript{138}. The Q223R variant is also associated with increased bone mineral density\textsuperscript{139}, whereas the A861G variant is correlated with the severity of spine ossification\textsuperscript{140}.

Finally, leptin receptors are also important in animal production. In pigs, leptin receptor gene polymorphisms have been identified that are associated with litter size, backfat thickness and feed efficiency\textsuperscript{141,142}. In dairy cattle, a leptin receptor polymorphism has been associated with leptin concentrations in late pregnancy\textsuperscript{143}. Leptin receptors have also been cloned in the chicken and turkey, but associations between specific polymorphisms and production traits have not yet been identified\textsuperscript{144,145}.

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**ABBREVIATIONS NOT DEFINED IN THE TEXT**

- BMI: body mass index
- CHO: Chinese hamster ovary (cells)
- ERK: extracellular signal regulated kinase
- GRB2: growth factor receptor-bound protein 2
- IRS1: insulin receptor substrate 1
- MEK: MAPK (mitogen-activated protein kinase)/ERK kinase
- SH2: src homology domain 2
- SHC: SH2 domain-containing protein
- SHP2: SH2 domain-containing phosphotyrosine phosphatase 2
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