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Genomic structure of the human M6P/IGF2 receptor

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The human mannose 6-phosphate/insulin-like growth factor 2 receptor (M6P/IGF2R) gene located at 6q26 (Rao et al. 1994) encodes for a multifunctional receptor that possesses distinct binding sites for phosphomannosyl glycoproteins and IGF2 (MacDonald et al. 1988; Morgan et al. 1987), retinoic acid (Kang et al. 1997), and urokinase-type plasminogen activator receptor (uPAR; Nykjaer et al. 1998). The receptor is involved in fetal development, tumor suppression, maternal regulation of intrauterine growth, and has recently been associated with the development of human cognitive ability (Chorney et al. 1998; De Souza et al. 1997; Kornfeld 1992; Wang et al. 1994). To facilitate further genetic analyses of the human M6P/IGF2R, we have determined its complete genomic organization, defined the intron-exon boundary sequences, and designed intronic oligonucleotides for PCR amplification of the 48 exons included in the 136-kb genomic sequence.

The M6P/IGF2R is a chimeric receptor possessing binding sites for four distinct classes of ligands (Kang et al. 1997; Nykjaer et al. 1998; MacDonald et al. 1988; Morgan et al. 1987). The M6P binding site enables the M6P/IGF2R to target to the lysosomes both newly synthesized lysosomal enzymes from the Golgi and phosphorylated proteolytic enzymes endocytosed from the extracellular environment (Kornfeld 1992). Furthermore, the latent complex of transforming growth factor beta (TGFβ), a potent growth inhibitor, binds to the M6P/IGF2R through these M6P binding sites, thereby facilitating its activation by plasmin (Dennis and Rifkin 1991). The effectiveness of TGFβ activation may be further enhanced by the direct binding of uPAR to the M6P/IGF2R (Nykjaer et al. 1998). The mammalian M6P/IGF2R also contains an independent IGF2 binding site that is absent in chickens (Zhou and Sly 1995). IGF2 binding to the M6P/IGF2R leads to lysosomal degradation rather than intracellular signaling, a process mediated by both the IGF1 and the insulin receptors (Kornfeld 1992). Therefore, loss of M6P/IGF2R function would be predicted to increase the extracellular concentration of IGF2, decrease the level of active TGFβ, and increase the secretion of proteolytic enzymes. These biological effects suggest the M6P/IGF2R functions normally as a tumor suppressor.

A number of reports now strongly support this postulate for a wide variety of human tumors. Briefly, the M6P/IGF2R is mutated in 60% of dysplastic liver lesions and HCCs in patients with or without hepatitis virus (HV) infection (De Souza et al. 1995a, 1995b; Yamada et al. 1997). Its inactivation also plays a prominent role in the early stage of breast cancer development (Hankins et al. 1996), and increased expression of the wild-type receptor in breast cancer cell lines leads to apoptosis (Oates et al. 1998). Furthermore, the M6P/IGF2R gene contains a poly-G region that is a common mutational target in colon, gastric, and endometrial tumors with mismatch repair deficiences and microsatellite instability (Souza et al. 1996). Thus, M6P/IGF2R inactivation is a frequent oncogenic event that occurs early in carcinogenesis.

A full parental complement of autosomal genes is inherited by all offspring, but not all are biallelically expressed. The phenomenon of monoallelic expression of the same parental allele is called genomic imprinting (Surani 1998). The *M6p/Igf2r* gene is imprinted in mice (Barlow et al. 1991) and is expressed only from the maternal allele in all tissues except potentially the brain (Hu et al. 1998). In contrast, imprinting of the M6P/IGF2R gene is a polymorphic trait in humans, with most people having biallelic expression in all tissues (Xu et al. 1993). Although imprinting of the M6P/IGF2R may have provided an evolutionary advantage to the mother during the emergence of mammalian intrauterine growth (Haig and Graham 1991), monoallelic expression of this gene would also be predicted to increase cancer susceptibility. In support of this postulate, Xu et al. and associates (1997) have recently demonstrated M6P/IGF2R imprinting in 50% of Wilm's tumors.

Plomin and his colleagues have also identified the M6P/IGF2R as a putative ''IQ gene'' (Chorney et al. 1998). By comparing Caucasian children with an IQ of 160 or higher with those with an average IQ, they showed that the M6P/IGF2R is linked to human cognitive ability. If a polymorphism in the M6P/IGF2R coding sequence or its regulatory region is subsequently shown to functionally affect IQ, it would be the first identified gene known to contribute to intelligence. Thus, the M6P/IGF2R plays a fundamental role in biological processes ranging from embryogenesis to carcinogenesis. How the M6P/IGF2R could possess such diverse biological functions is an intriguing enigma that remains to be solved.

To facilitate future studies on the human M6P/IGF2R, we have characterized its complete genomic structure. The human cDNA sequence was divided into 48 exons based upon the mouse genomic structure (Szebenyi and Rotwein 1994), and PCR primers were designed to traverse these putative introns. All the introns except 1, 2, and 4 were amplified from human genomic DNA with either long-template PCR (Boehringer Mannheim Corp., Indianapolis, Ind.) or traditional PCR (Qiagen, Inc, Santa Clarita, Calif.). PCR products were sequenced on an ABI automated sequencer (Perkin-Elmer Corp., Foster City, Calif.). The sizes of introns 1 and 2 and their 5′ and 3′ boundary sequences were previously defined (Riesewijk et al. 1996; Smrzka et al. 1995); this information is available on GenBank (Accession Nos. X83699, X83700, and X83701). To sequence intron 4, human BAC clones (174E20 and 650K6) were first obtained by probing filters from Research Genetics, Inc. (Huntsville, Ala.) with an RT-PCR product spanning exons 1 to 6. A 13-kb stretch of DNA containing intron 4 was then PCR amplified from this BAC clone and the exon-intron boundaries sequenced. With the exception of intron 15, all exon-intron splice sites (93/94) conformed to the AG/GT rule (Mount 1982). Interestingly, the single intron splice site exception is also present in the mouse *M6p/Igf2r* homolog (Szebenyi and Rotwein 1994).

Intron sizes were determined by sequencing the entire intron or estimated by electrophoresis. Twenty introns were sequenced entirely (that is, introns 8, 9, 13–17, 21, 23, 24, 27, 28, 32–34, 37, 38, 42, 43, and 46), and at least 100 bp of flanking intronic sequence were determined for the remaining introns. The entire human M6P/IGF2R gene was then reconstructed with the use of the previously

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Table 1. Human M6P/IGF2R intron-exon boundaries.

Exon	cDNA (nt)	Exon size (bp)	5′ splice donor	Intron size (kb)	3′ splice acceptor	Intron phase[a]
1	1	296	CAGgtgggtggcccgccc	22.0	tttcttcctttccagTTA	2
2	296	140	TGGgtaagtagaactacc	17.0	tttctctccaaatagGTG	1
3	437	125	CTGgtgagtccacacagg	1.5	atttttttttaatagGGA	0
4	562	99	GAGgtaacatgggaactt	13.0	cttcctcccttccagGTG	0
5	661	133	TAGgtatgaatctttgtg	2.0	atacatgattttcagACA	1
6	794	130	CAGgtcagtcaaggcctc	2.2	atgtggctctcccagGCT	2
7	924	106	GAGgtaagtgactcgtct	2.7	cattgttcctgatagGGC	0
8	1030	163	GAGgtaagcaggtgcttt	0.227	tttccctgtttttagGTT	1
9	1193	166	CCGgtacgtcaacaacct	1.315	ttcacaaaaatctagATA	2
10	1359	104	CAGgtaagtgtgcgctgg	5.5	tcttgaattgtgcagGTA	1
11	1463	165	CAGgtactgccctccttg	2.5	tttgttttgttacagAAC	1
12	1628	141	TGGgtgagttgtgcctgg	1.2	ccctttctctttccagATA	1
13	1769	144	CAGgtaaaaattttaaaa	1.095	tttccccattgacagGTG	1
14	1913	138	CAGgtctgtgtccaagca	0.614	tttaatctttctaagGGT	1
15	2051	148	AAGgcaagtagcttctca	0.511	cgtgtgttaattcagTGA	2
16	2199	178	CAGgtaggaatgtttgtc	0.456	ctgccgtgggattagGAA	0
17	2377	116	CAGgtgaggcagagtcag	0.468	gctttgaaattttagTCT	2
18	2493	169	CAGgtgaatctgttttca	2.0	ctggttttcttgcagGGC	0
19	2662	180	CTGgtaaggcactgctgc	5.0	gatttgcccattcagAAC	0
20	2842	102	CAGgtacgtgtgctttca	1.5	ttttgtttcctgtagGCT	0
21	2944	102	ATGgtaagagcgatatga	0.78	ccgtctgacctgcagTTT	0
22	3046	193	AAGgtgagctcagagcca	1.6	cttcttgctttacagGTA	1
23	3239	171	CCGgtaaggccgtgcggc	0.781	tttgttgtgtttcagACC	1
24	3410	144	AGGgtgagttctccttgg	0.105	attctgttcttccagGCA	1
25	3554	176	TCGgtgtgtgttcagacc	0.8	tgatttatattacagGGC	0
26	3730	88	AAGgtaggactgggcctg	1.5	tccatgttcttgaagGGG	1
27	3818	216	CAGgtaccattgtttgtc	0.771	tctccttctttacagGTC	1
28	4034	131	CGGgtgagcatgtaccga	0.271	tcttaacttttttagCCA	0
29	4165	98	CAAgtaagtccatggatg	3.0	ttttcttcttttcagAGA	2
30	4265	137	CTGgtgagagagggcctc	1.5	tgtctggtgctgcagAGC	1
31	4400	191	GTGgtaagggactgttcc	1.5	tgtgctttgttgtagAAC	0
32	4591	127	CAGgtgagaggtggtgcc	0.732	tcttccaccctacagGAC	1
33	4718	120	TGGgtgagtgctgtggtc	0.327	tcccttgtggtgcagGGG	1
34	4838	257	GCGgtgagttttcagatg	0.286	tttcctacttaacagACC	0
35	5095	219	ATAgtaagtatgacaaat	2.0	tcgctctttgtttagGAT	0
36	5344	150	ATGgtaagtgtgggcctg	2.3	tcttcctggcaacagGGA	0
37	5464	162	AAGgtaatgcgttcaccc	1.233	atggtttttgtccagGTG	0
38	5626	208	CAGgtaaatatttgaaat	0.341	tcttcttctttccagAAA	1
39	5834	147	ACTgtgagtaggacggct	3.6	ccntacactccccagCAA	1
40	5981	235	CTCgtgagtgccttccca	1.0	tgtgtcgttttctagGTA	2
41	6216	137	TAGgtaaggcctgtgggt	3.0	atttgtgtgtttcagGTG	1
42	6353	115	GAGgtcaggagactgggg	0.957	cttccctcctcctagGTT	2
43	6468	147	TAAgtaagtaaaacgttt	0.662	tttctgtctcttcagGCT	2
44	6615	188	AAGgtaatccgtggcttc	6.5	cttcccgtatgacagACG	1
45	6803	187	GGGgtgagtatgaaatcc	5.5	gtgacgtccttgcagGGT	2
46	6990	153	GAGgtaagcgggtggcag	1.081	ccttttttttatagGGA	2
47	7143	70	AAGgtaattttctgtggc	1.8	gttgatccctggcagGTG	0
48	7213	1878				

[a] Intron-exon splice junctions are categorized as phase 0, uninterrupted codon; phase 1, codon interrupted after the first nucleotide; and phase2, codon interrupted after the second nucleotide.

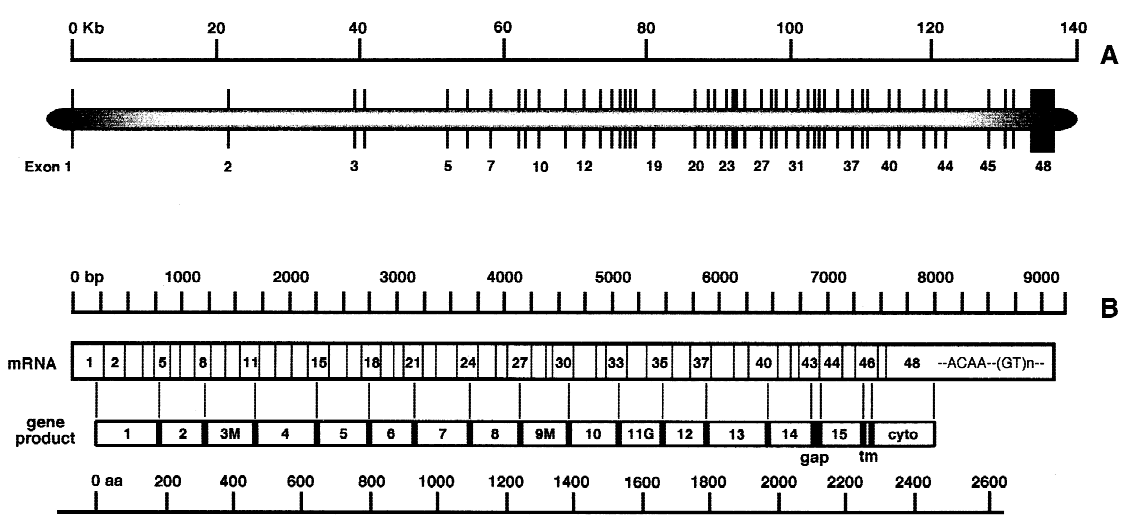

Fig. 1. Genomic organization of the human M6P/IGF2R. **A)** The 48 exons of the human M6P/IGF2R are distributed over approximately 136 kb. **B)** The mRNA is subdivided into exons, and the ACAA tetranucleotide insertion (Hol et al. 1992) and the $(GT)_n$ dinucleotide (Goto et al. 1992) polymorphic sites in the 3′-UTR (exon 48) are shown. The mRNA is also aligned with the protein sequence, which is divided into 15 structural repeats, each of approximately 150 amino acids; a 27-amino acid gap between repeats 14 and 15 (gap); a single 23-amino acid transmembrane domain (tm); and a 164-amino acid cytoplasmic tail (cyto) (Morgan et al. 1987). Repeats 3 and 9 (M) contain the M6P-binding domains, and repeat 11 (G) forms the IGF2-binding domain (Dahms et al. 1993; Schmidt et al. 1995).

Table 2. Intronic oligonucleotides for PCR amplification of the 48 human M6P/IGF2R exons.

Exon	F1 (5′ to 3′)	R1 (5′ to 3′)	Nested Primer (5′ to 3′)[a]
1	gctgtcacgtgacgcggttc	accgcgagcggagcctgcgtc	gccgccgctgccgctgtcgcF2
2	ctagtttgtggcagttttaagcaaatg	attgccaatccagtaatttcagg	gataaatcagtgacattgacaagttgF2
3	ggttatgtatgtttatagcctg	ttaaagaaatacatcaagtgcctgtg	aatacatcaagtgcctgtgtggacR2
4	tttattttagtagcctttactgcattctca	gataaagttccccagagtatacttc	ccagagtatacttcataagcatgR2
5	ctgattgaccaagatgtatactg	gaaaggcaaagatattgaagccatag	cctcaccaccaccccctcagR2
6	ctaagggtacgtgtgattatcactc	gaaagtcaggtccttgctggag	aaacgccaacagcatcggaggR2
7	ggcaacatatgaatttggatgtac	caacccaggctactgtgcgc	gtgcgccacattagtgatcaggR2
8	gtggaaaatctgcattaagctgcatg	ccttcttcctaagcagcgcc	caggaggcagaaagcacctgcR2
9	gactaagtaagactgtaatcttctaatacc	cgcacagaggttgttgacgtac	aatacctattcatataaaacaagcctcF2
10	cccaaacacatttgtctgtgtattc	acaagcacatgcccatgaatgc	gcaaagaggaggggctgaacR2
11	gctgttcctcaattttggtcacg	gaaaatgttccatgagcatgtggac	gactaagacccgcatggcaaggR2
12	gtgactcagagaaatcagcattgc	ctaactcattccaaactggatgcc	gaaaagcatcacctagatcttccR2
13	gtcacttctttgtctgcgtgatgatc	atatgaagaatgcaggacctctgg	caggacctctggcagaagccR2
14	gtcccttccaagtctacttctagc	gtggttccaagtcacattaaagcag	cacattaaagcagaggtcctgcR2
15	gttgggaacctcctgggaag	cttagcatataatgcctaagaatgaaac	ctaagaatgaaacagaactgagaagcR2
16	gtgactcctcacgtcgctcacg	cacaggcatgagtatcctcagg	gtatcctcagggagcgcgatgR2
17	ctcattgggaacattgctctcg	cagcaacacttgcaacctcagc	caacctcagcatctgtaccagR2
18	gtaagctttacttccccaactacatag	ctcccactaagtcatggaattagg	taggagggcaaaggagacaagcR2
19	ccaccaataacgaatcgactg	cacataaggcaacgctcagtc	aatgcagcagtgaaggtcaccR2
20	agtattcttttggttctatcaagttcc	gtccagcaggcagctcagc	ctcagcacgagggccaggtgR2
21	gtgctgtatgtatgttatgttcctgtg	gtgacttcaataatgcactctcc	ctgtttcaaagcaaactggaaatgcR2
22	tcttgtctgtggtgagatacgagg	ctacactcaggaaggtgcatggc	atggccagccacagagccacR2
23	ctgcactgtgcttgtgggctgc	gactcttgaccggcctctcagttc	gaccggcctctcagttcttaggR2
24	gcagttcttgagtgctcacaagg	caaatgctctaataaatgaacagacgc	cagacgccaatcaagagaccaagR2
25	gagcatttgactcaaggtcatcgc	gaaatgggaaatggagtcacccg	gggacaacatctcattgctggtcR2
26	gattacaggtgtgagccaccgtg	catcgttcagaacgtctgctactctatac	aaaatgacttgtagggacaggcR2
27	cgtgtgtggttgcagttgcc	ctcaagggaaaattcatcttcagc	gttgcagttgcccttcacttcF2
28	gtgtcacatgtcttaggctaag	aatatgatcccagcagcctgag	gtttgacagcctagggacF2
29	caaagtataaactaaagttttgcattctcac	gcaaaatcataccaagttagtctgtcc	gttttgcattctcacttttatatatgtgF2
30	acgaccaagcctaactaactgc	ctctcaccagtgctggcctgtg	cctgtgatacactcactgcaaacR2
31	tgatgaagttctgttctagcctg	gcagaaggtgcaggaacagtccc	gggagtcactaaaggcaactcF2
32	ccacttgtaagttgaaatcatgatagac	caccgtctctcacctgcgctg	gctggggttaacgactggcacR2
33	gcctcccaagtctcagctcc	gcaaagagactgaggacaacc	ccctggagtcactgtgtccF2
34	gaaattgatggtcctgacttgcg	gcactggagatgcacttctcc	catcagaaaattggccatcgagtcF2
35	ggatgacctagtggtgattagg	cgcaaaggttatcactaaaagtcttgc	gtcttgcaaaaattatctccacccttgR2
36	ccttgggaatggttaatttcctg	cgcactttctggttgtctagcc	gccttggctcactaacccgcagR2
37	tgtcactgctatctatcccctatgcc	cagcacctggcacctggtacacc	gtacacctgcaccagcaacgR2
38	actttgagacctgggtgc	cagcttctttctgctgctatgtc	gctgccactctgctgacggcF2
39	ctgaggtgattgtgcctggcg	ctcagtgtgaatcgagccttgac	cgaggcacagctgccacactgF2
40	gcatagacacagtgacagtctgatc	gcagtctgaagttcacatgc	gttcacatgctgagggtgtggcR2
41	cagggcagagacgtcacttgc	cacctcccggttcagatgctg	gttcagatgctgctccttgaaccR2
42	gaattgacaggtgtgagccactg	ctccagtatgctcactgcacag	gcacagtcccgctctgagccR2
43	gttttgcagtcttcccttatgtctg	gcattgctggtttaattttgaacac	catttcacagctcagaaggaaaacgR2
44	ctgagggtttatgtcatgaatgcc	ccttccttggaggaagttaaatgtg	gaagttaaatgtggaactttgtgggR2
45	ggagctaagctcagtctgctcgtg	cacttattcttaagggaagatgtgg	gatgtggggtacaagtgctaagcR2
46	caggttgtggctgtggcagc	tagctatggaggcatgcatcc	catccacccgccccacctcR2
47	ccatgccctctctacactggag	cctgatgagaacgacatggacagcg	ggcaggccttcaagagactcgR2
48	ggctcacgtggtctctgctgttg	gcctgacctcctcaccctc	gcatcatcgagtggaagtcR2

[a] Nested primers F2 and R2 should be paired with R1 and F1, respectively, during second-round PCR.

characterized genomic sequence for exons 1 to 3 (Riesewijk et al. 1996; Smrzka et al. 1995) and the sequence from our overlapping PCR-generated products. The complete set of intron-exon boundary sequences for the M6P/IGF2R and all of the intron and exon sizes are presented in Table 1. The codon position that is interrupted by the intron is indicated by the intron phase. The intron-exon splice junctions for the human M6P/IGF2R are identical in position to those in the mouse (Szebenyi and Rotwein 1994). The total size of the human M6P/IGF2R gene is estimated to be 136 kb (Table 1, Fig. 1). This is approximately 43 kb larger than that for the mouse gene, and introns 2 and 4 account for much of this increased size. The M6P and IGF2 receptor binding domains are also assigned to the appropriate exons (Fig. 1). The intron-exon boundary sequences were deposited with GenBank (Accession Nos. AFO69333-378), and will also be available on the M6P/IGF2R Information Core (http://www.radonc.duke.ed/~jirtle/homepage.html).

We have also designed intronic oligonucleotides for PCR amplification of the 48 human exons, including nested primers to allow for second-round DNA amplification (Table 2). DNA amplification from formalin-fixed, paraffin-embedded tissues requires primers that minimize the size of the amplified regions while including the splice sites flanking the exons. All 48 primer sets have been successfully employed to PCR amplify DNA isolated from either frozen tissue or formalin-fixed, paraffin-embedded samples. These nested primer sets yield a single PCR product approximately the size of the exon (Table 1) plus 80 bp. The PCR conditions used for all primer sets were 94°C × 20 s, 55°C × 30 s, and 72°C × 20 s for the 25-cycle first round and 30-cycle second round DNA amplifications.

In conclusion, we have determined the genomic structure and the intron-exon boundaries of the human M6P/IGF2R. These sequence data have been used to design PCR primers that allow for the systematic analysis of the 48 exons that encode for the human M6P/IGF2R gene. This should greatly facilitate linkage, phylogenetic, functional, and mutational analyses of the M6P/IGF2R, thereby enhancing further our understanding of this receptor's function in evolution, cancer biology, and human intelligence.

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References

Barlow DP, Stöger R, Herrmann BG, Saito K, Schweifer N (1991) The mouse insulin-like growth factor type-2 receptor is imprinted and closely linked to the Tme locus. Nature 349, 84–87

Chorney MJ, Chorney K, Seese N, Owen MJ, Daniels J, et al. (1998) A quantitative trait locus associated with cognitive ability in children. Psych Sci 9, 159–166

Dahms NM, Rose PA, Molkentin JD, Zhang Y, Brzycki MA (1993) The bovine mannose 6-phosphate/insulin-like growth factor II receptor, the role of arginine residues in mannose 6-phosphate binding. J Biol Chem 268, 5457–5463

Dennis PA, Rifkin DB (1991) Cellular activation of latent transforming growth factor beta requires binding to the cation-independent mannose 6-phosphate/insulin-like growth factor type II receptor. Proc Natl Acad Sci USA 88, 580–584

De Souza AT, Hankins GR, Washington MK, Fine RL, Orton TC, et al. (1995a) Frequent loss of heterozygosity on 6q at the mannose 6-phosphate/insulin-like growth factor II receptor locus in human hepatocellular tumors. Oncogene 10, 1725–1729

De Souza AT, Hankins GR, Washington MK, Orton TC, Jirtle RL (1995b) M6P/IGF2R gene is mutated in human hepatocellular carcinomas with loss of heterozygosity. Nat Genet 11, 447–449

De Souza AT, Yamada T, Mills JJ, Jirtle RL (1997) Imprinted genes in liver carcinogenesis. FASEB J 11, 60–67

Goto J, Figlewicz DA, Marineau C, Khodr N, Rouleau GA (1992) Dinucleotide repeat polymorphism at the IGF2R locus. Nucleic Acids Res 20, 923

Haig D, Graham C (1991) Genomic imprinting and the strange case of the insulin-like growth factor II receptor. Cell 64, 1045–1046

Hankins GR, De Souza AT, Bentley RC, Patel MR, Marks JR, et al. (1996) M6P/IGF2 receptor: a candidate breast tumor suppressor gene. Oncogene 12, 2003–2009

Hol FA, Geurds MP, Hamel BC, Mariman EC (1992) Improving the polymorphism content of the 3′ UTR of the human IGF2R gene. Hum Mol Genet 1, 347

Hu JF, Oruganti H, Vu TH, Hoffman AR (1998) Tissue-specific imprinting of the mouse insulin-like growth factor II receptor gene correlates with differential allele-specific DNA methylation. Mol Endocrinol 12, 220–232

Kang JX, Li Y, Leaf A (1997) Mannose-6-phosphate/insulin-like growth factor-II receptor is a receptor for retinoic acid. Proc Natl Acad Sci USA 94, 13671–13676

Kornfeld S (1992) Structure and function of the mannose 6-phosphate/insulinlike growth factor II receptors. Annu Rev Biochem 61, 307–330

MacDonald RG, Pfeffer SR, Coussens L, Tepper MA, Brocklebank CM, et al. (1988) A single receptor binds both insulin-like growth factor II and mannose 6-phosphate. Science 239, 1134–1137

Morgan DO, Edman JC, Standring DN, Fried VA, Smith MC, et al. (1987) Insulin-like growth factor II receptor as a multifunctional binding protein. Nature 329, 301–307

Mount SM (1982) A catalogue of splice junction sequences. Nucleic Acids Res 10, 459–472

Nykjaer A, Christensen EI, Vorum H, Hager H, Petersen CM, et al. (1998) Mannose 6-phosphate/insulin-like growth factor-II receptor targets the urokinase receptor to lysosomes via a novel binding interaction. J Cell Biol 141, 815–828

Oates AJ, Schumaker LM, Jenkins SB, Pearce AA, DaCosta SA, et al. (1998) The mannose 6-phosphate/insulin-like growth factor 2 receptor (M6P/IGF2R), a putative breast tumor suppressor gene. Breast Cancer Res Treat 47, 269–281

Rao PH, Murty VVVS, Gaidano G, Hauptschein R, Dalla-Favera R, et al. (1994) Subregional mapping of 8 single copy loci to chromosome 6 by fluorescence in situ hybridization. Cytogenet Cell Genet 66, 272–273

Riesewijk AM, Schepens MT, Welch TR, Van den Berg-Loonen EM, Mariman EM, et al. (1996) Maternal-specific methylation of the human *IGF2R* gene is not accompanied by allele-specific transcription. Genomics 31, 158–166

Schmidt B, Kiecke-Siemsen C, Waheed A, Braulke T, von Figura K (1995) Localization of the insulin-like growth factor II binding site to amino acids 1508-1566 in repeat 11 of the mannose 6-phosphate/insulin-like growth factor II receptor. J Biol Chem 270, 15975–14982

Smrzka OW, Fae I, Stöger R, Kruzbauer R, Fischer GF, et al. (1995) Conservation of a maternal-specific methylation signal at the human IGF2R locus. Hum Mol Genet 4, 1945–1952

Souza RF, Appel R, Yin J, Wang S, Smolinski KN, et al. (1996) The insulin-like growth factor II receptor gene is a target of microsatellite instability in human gastrointestinal tumours. Nat Genet 14, 255–257

Surani MA (1998) Imprinting and the initiation of gene silencing in the germ line. Cell 93, 309–312

Szebenyi G, Rotwein P (1994) The mouse insulin-like growth factor II/cation-independent mannose 6-phosphate (IGF-II/MPR) receptor gene: molecular cloning and genomic organization. Genomics 19, 120–129

Wang ZQ, Fung MR, Barlow DP, Wagner EF (1994) Regulation of embryonic growth and lysosomal targeting by the imprinted *Igf2/Mpr* gene. Nature 372, 464–467

Xu Y, Goodyer CG, Deal C, Polychronakos C (1993) Functional polymorphism in the parental imprinting of the human IGF2R gene. Biochem Biophys Res Commun 197, 747–754

Xu YQ, Grundy P, Polychronakos C (1997) Aberrant imprinting of the insulin-like growth factor II receptor gene in Wilms' tumor. Oncogene 14, 1041–1046

Yamada T, De Souza AT, Finkelstein S, Jirtle RL (1997) Loss of the gene encoding mannose 6-phosphate/insulin-like growth factor II receptor is an early event in liver carcinogenesis. Proc Natl Acad Sci USA 94, 10351–10355

Zhou M, Sly WS (1995) Cloning and expression of the cDNA of chicken cation-independent mannose-6-phosphate receptor. Proc Natl Acad Sci USA 92, 9762–9766