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(54) Title: MODULATORS OF BODY WEIGHT, CORRESPONDING NUCLEIC ACIDS AND PROTEINS, AND DIAGNOSTIC AND THERAPEUTIC USES THEREOF

(57) Abstract

The present invention relates generally to the control of body weight of animals including mammals and humans, and more particularly to materials identified herein as modulators of weight, and to the diagnostic and therapeutic uses to which such modulators may be put. In its broadest aspect, the present invention relates to the elucidation and discovery of nucleotide sequences, and proteins putatively expressed by such nucleotides or degenerate variations thereof, that demonstrate the ability to participate in the control of mammalian body weight. The nucleotide sequences in object represent

the genes corresponding to the murine and human *OB* gene, that have been postulated to play a critical role in the regulation of body weight and adiposity. Preliminary data, presented herein, suggests that the polypeptide product of the gene in question functions as a hormone. The present invention further provides nucleic acid molecules for use as molecular probes, or as primers for polymerase chain reaction (PCR) amplification, i.e., synthetic or natural oligonucleotides. In further aspects, the present invention provides a cloning vector, which comprises the nucleic acids of the invention; and a bacterial, insect, or a mammalian expression vector, which comprises the nucleic acid molecules of the invention, operatively associated with an expression control sequence. Accordingly, the invention further relates to a bacterial or a mammalian cell transfected or transformed with an appropriate expression vector, and correspondingly, to the use of the above-mentioned constructs in the preparation of the modulators of the invention. Also provided are antibodies to the *OB* polypeptide. Moreover, a method for modulating body weight of a mammal is provided. In specific examples, genes encoding two isoforms of both the murine and human *OB* polypeptides are provided.



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INTERNATIONAL SEARCH REPORT

International Application No

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A. CLASSIFICATION OF SUBJECT MATTER

IPC 6 C12N15/12 C07K14/47 C12Q1/68 A61K38/17 A61K7/00
G01N33/68 C12N5/10 C12N1/18 C12N1/20

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC 6 C07K A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	EP,A,0 566 410 (SANKYO CO) 20 October 1993 see claims 1-28 ---	1,3,11, 13, 15-17, 24,25, 28,32, 36-46, 61,62,65
X	WO,A,94 00558 (JOSLIN DIABETES CENTER INC) 6 January 1994 see claims 1-37 --- -/--	1,3,11, 15-17, 24,32, 36-46, 51-60

☒ Further documents are listed in the continuation of box C.☒ Patent family members are listed in annex.

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C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	PENNINGTON CENT. NUTR. SER., 1992, 2, 22-36, WEIGLE, DAVID S. ET AL 'Identification of candidate genes for a factor regulating energy balance in humans' see the whole document ---	1,3, 15-17, 24,32, 36,40, 44,47
Y	WORKSHOP ON CHILD AND ADOLESCENT OBESITY: WHAT, HOW, AND WHO, AIRLIE, VIRGINIA, USA, NOVEMBER 20-22, 1991. CRIT REV FOOD SCI NUTR, 33 (4-5). 1993. 351-358., LEIBEL R L ET AL 'STRATEGIES FOR THE MOLECULAR GENETIC ANALYSIS OF OBESITY IN HUMANS' see the whole document ---	1,3, 15-17, 24,32, 36,40, 44,47
Y	MAMM GENOME, 1 (3). 1991. 130-144., FRIEDMAN J M ET AL 'MOLECULAR MAPPING OF OBESITY GENES' see the whole document ---	1,3, 15-17, 24,32, 36,40, 44,47
A	MAMMALIAN GENOME, 4 (9). 1993. 511-515., BAHARY N ET AL 'Microdissection of proximal mouse Chromosome 6: Identification of RFLPs tightly linked to the ob mutation' see the whole document ---	1,3, 15-17, 24,32, 36,40, 44,47
A	PROC NATL ACAD SCI U S A, 87 (21). 1990. 8642-8646., BAHARY N ET AL 'MOLECULAR MAPPING OF THE MOUSE DB MUTATION' cited in the application see the whole document ---	1,3, 15-17, 24,32, 36,40, 44,47
A	GENOMICS, 11 (4). 1991. 1054-1062., FRIEDMAN J M ET AL 'MOLECULAR MAPPING OF THE MOUSE OB MUTATION' see the whole document ---	1,3, 15-17, 24,32, 36,40, 44,47
A	TRENDS IN BIOTECHNOLOGY, 13 (2). 1995. 52-55., FROGUEL P ET AL 'Human diabetes and obesity: Tracking down the genes' see the whole document ---	1,3, 15-17, 24,32, 36,40, 44,47

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INTERNATIONAL SEARCH REPORT

International Application No

PC1/US 95/10479

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
P,X	NATURE (LONDON), 372 (6505). 1994. 425-432., ZHANG Y ET AL 'Positional cloning of the mouse obese gene and its human homologue' see the whole document ---	1,2,9, 15,24,32
T	BIOCHEMICAL AND BIOPHYSICAL RESEARCH COMMUNICATIONS, 214 (1). 1995. 131-136., RENTSCH J ET AL 'Recombinant ob-gene product reduces food intake in fasted mice' see the whole document -----	1,2,9, 15,24,32

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No

PCT/US 95/10479

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
EP-A-0566410	20-10-93	AU-B- 3695293	21-10-93
		CN-A- 1082112	16-02-94
		HU-A- 66598	28-12-94
		JP-A- 6277065	04-10-94
		NZ-A- 247419	26-10-94
		ZA-A- 9302660	26-10-93

WO-A-9400558	06-01-94	EP-A- 0646170	05-04-95
