REVIEW

Clinically relevant known and candidate genes for obesity and their overlap with human infertility and reproduction

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Abstract

Purpose Obesity is a growing public health concern now reaching epidemic status worldwide for children and adults due to multiple problems impacting on energy intake and expenditure with influences on human reproduction and infertility. A positive family history and genetic factors are known to play a role in obesity by influencing eating behavior, weight and level of physical activity and also contributing to human reproduction and infertility. Recent advances in genetic technology have led to discoveries of new susceptibility genes for obesity and causation of infertility. The goal of our study was to provide an update of clinically relevant candidate and known genes for obesity and infertility using high resolution chromosome ideograms with gene symbols and tabular form.
Methods We used computer-based internet websites including PubMed to search for combinations of key words such as obesity, body mass index, infertility, reproduction, azoospermia, endometriosis, diminished ovarian reserve, estrogen along with genetics, gene mutations or variants to identify evidence for development of a master list of recognized obesity genes in humans and those involved with infertility and reproduction. Gene symbols for known and candidate genes for obesity were plotted on high resolution chromosome ideograms at the 850 band level. Both infertility and obesity genes were listed separately in alphabetical order in tabular form and those highlighted when involved with both conditions.
Results By searching the medical literature and computer generated websites for key words, we found documented evidence for 370 genes playing a role in obesity and 153 genes for human reproduction or infertility. The obesity genes primarily affected common pathways in lipid metabolism, deposition or transport, eating behavior and food selection, physical activity or energy expenditure. Twenty-one of the obesity genes were also associated with human infertility and reproduction. Gene symbols were plotted on high resolution ideograms and their name, precise chromosome band location and description were summarized in tabular form.
Conclusions Meaningful correlations in the obesity phenotype and associated human infertility and reproduction are represented with the location of genes on chromosome ideograms along with description of the gene and position in tabular form. These high resolution chromosome ideograms and tables will be useful in genetic awareness and counseling, diagnosis and treatment to improve clinical outcomes.

Introduction

Obesity is a major public health concern and reaching epidemic status worldwide for both children and adults. Without intervention, estimates of 2 billion overweight and 1 billion obese individuals will be present by the year 2030 [1]. The worldwide prevalence of childhood overweight and obesity from 1990 to 2010 had increased from 4.2 to 6.7 % and is expected to reach over 9 % by 2020 [2]. Obesity now affects 35.7 % of the US population (aged 20 years and over [reproductive years]) and 61 % are overweight [3–5]. Correspondingly, 10–15 % of the US population experiences infertility with women in their mid-thirties having greater than 25 %

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chance of being infertile [6]. Both obesity and infertility are relatively prevalent conditions and clearly influenced by genetic and environmental factors. Increased weight gain during infancy does predispose to obesity later in life with an increased rate of developing type 2 diabetes, nonalcoholic fatty liver disease, cancer, sleep apnea, hypertension and infertility. The consequences of increased weight and obesity can shorten life expectancy as well as affecting reproduction with dysfunction in ovulation, spontaneous abortions, and overall infertility [3–7]. Adverse pregnancy outcomes including pre-eclampsia, fetal growth failure with premature delivery and gestational diabetes [8]. The prevalence of maternal obesity in the US population is increased with more women having obesity-related reproductive problems [3]. Gradual and sustained maternal weight loss is needed to improve menstrual cycles and ovulation and thus reproductive rates and outcomes [9]. Weight loss is considered the first line of treatment in those women with reproductive failure and obesity-related infertility [3, 9]. Bariatric surgical procedures and drug therapy options may also be considered in obese females to improve the likelihood of conception and delivery [10]. One of the most common causes of subfertility in women with obesity is polycystic ovarian syndrome which is associated with the androgen receptor (AR) gene [11]. Hence, obesity and infertility may have genes in common and their identification may provide insight into treatment options requiring further studies. One major goal of our study was to identify such genes and their relationship in both conditions.

Unhealthy calorically-dense diets, decreased physical activity and other common environmental causes of childhood obesity in western society illustrate an interaction with a complex obesogenic environment. A positive family history for obesity is a well-established risk predictor. For example, a child has a 2.5 to 4-fold higher risk of developing obesity if one parent is obese and a 10-fold risk if both parents are obese compared to both parents having a normal weight [12]. Strong heritability estimates for obesity and body mass index (BMI) indicate the role of genetics supported by twin and family studies. In twin studies, heritability estimates for BMI are between 20 and 86 % with an average of about 50 % in children and adults [13–16]. The definition of heritability is a measure of the fraction of the phenotypic variability that can be attributed to genetic variation or the relative contributions of genetic and non-genetic differences to the total phenotypic variation in a population. The highest heritability estimates are found in childhood obesity indicating the importance of genetic factors early in life. Important genetic influences have been found for body fat percentage, waist circumference, eating behavior, level of physical activity or energy expenditure [17–19].

Genetic forms of obesity can be grouped into Mendelian or single gene forms of obesity including recessive forms, partial gene deficiencies, genomic structural variations or copy number variants and polygenic forms [20–22]. Monogenic forms or single gene conditions causing obesity have been reported for at least eight genes including leptin (LEP), leptin receptor (LEPR), proopiomelanocortin (POMC), prohormone convertase 1 (PCSK1), melanocortin 4 receptor (MC4R), single-minded homolog 1 (SIM1), brain-derived neurotrophic factor (BDNF) and the neurotrophic tyrosine kinase receptor type 2 gene (NTRK2) [20, 21]. The hypothalamic leptin-melanocortin system is critical for regulating energy balance with disturbances leading to severe obesity disorders [20–25]. The latest update of the 2005 Human Obesity Gene Map reported in 2006 summarized 127 candidate genes for obesity and obesity-related traits [24].

Several obesity-related syndromic genetic disorders are identified in humans, both common and rare, but monogenic causes of morbid obesity are uncommon in the general population. Obesity and eating behavior (hyperphagia) are key features of several rare genetic syndromes including Prader-Willi, Alström, Bardet-Biedl, Albright hereditary osteodystrophy, Cohen and fragile X syndromes with recognized genes playing a role (e.g., SNRPN for Prader-Willi syndrome, GNAS1 for Albright hereditary osteodystrophy, FMR1 for fragile X syndrome) [25, 26]. Understanding the regulatory and molecular basis of these disorders should provide a better picture of mechanisms controlling food intake and energy balance in humans in the general population including epigenetics affecting gene expression without altering the DNA sequence. Environmental exposure or nutrition during critical periods of development can affect the epigenetic marks at the genome level with failures in imprinting or regulation of gene activity if they are genetic predispositions leading to extreme forms of obesity [26, 27]. In addition, coding and non-coding RNA expression patterns, specifically microRNAs and snoRNAs that play important regulatory roles in a variety of biological processes may impact appetite regulation, gene-environment interaction, adipocyte differentiation and biochemical pathways [20, 21, 25].

The advent of advanced genetic technology and genome-scanning technologies has led to the discovery that genetic differences among people can derive from copy number variants (CNVs) or structural rearrangements [20, 21, 28]. Rare deletions are also reported in the chromosome 16p11.2 region in about 0.5 % of individuals with severe obesity [29]. The SH2B adapter protein 1 (SH2B1) gene is localized in this chromosome region and linked to obesity [29, 30]. Common CNVs can also be found in linkage disequilibrium with single nucleotide polymorphisms (SNPs) and obesity including a 45-

Fig. 1 High-resolution human chromosome ideograms (850 band level) with the obesity gene symbol positioned at the chromosome band or sub-band location. The centromere area, *highlighted in black*, separates the upper 'p' and lower 'q' arms for each chromosome. The gene *symbol in alphabetical order*, expanded name and precise chromosome band location are listed in Table 1

b
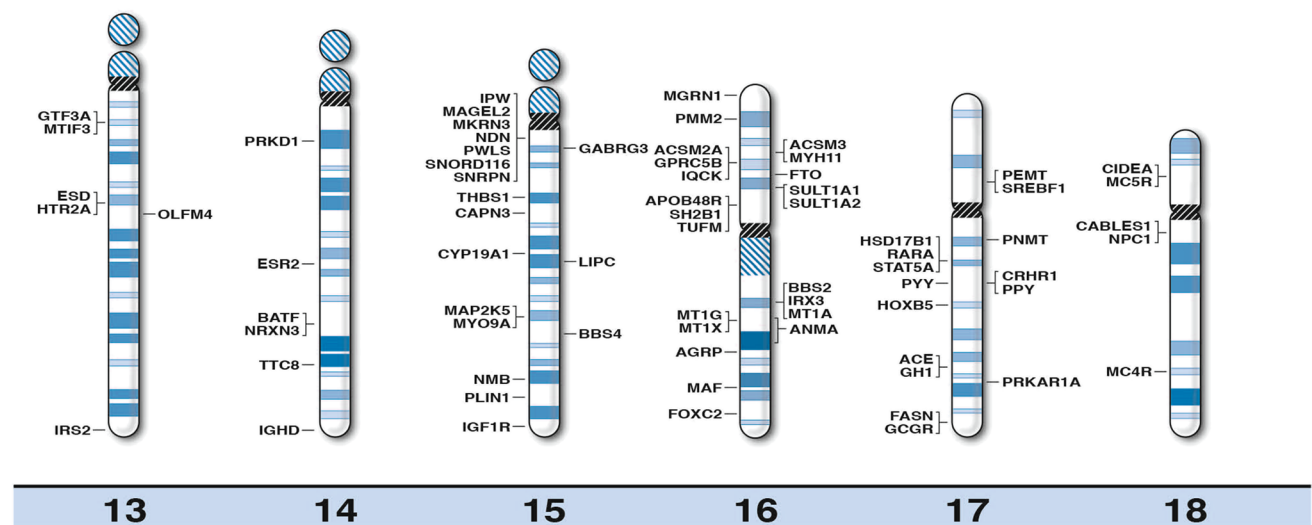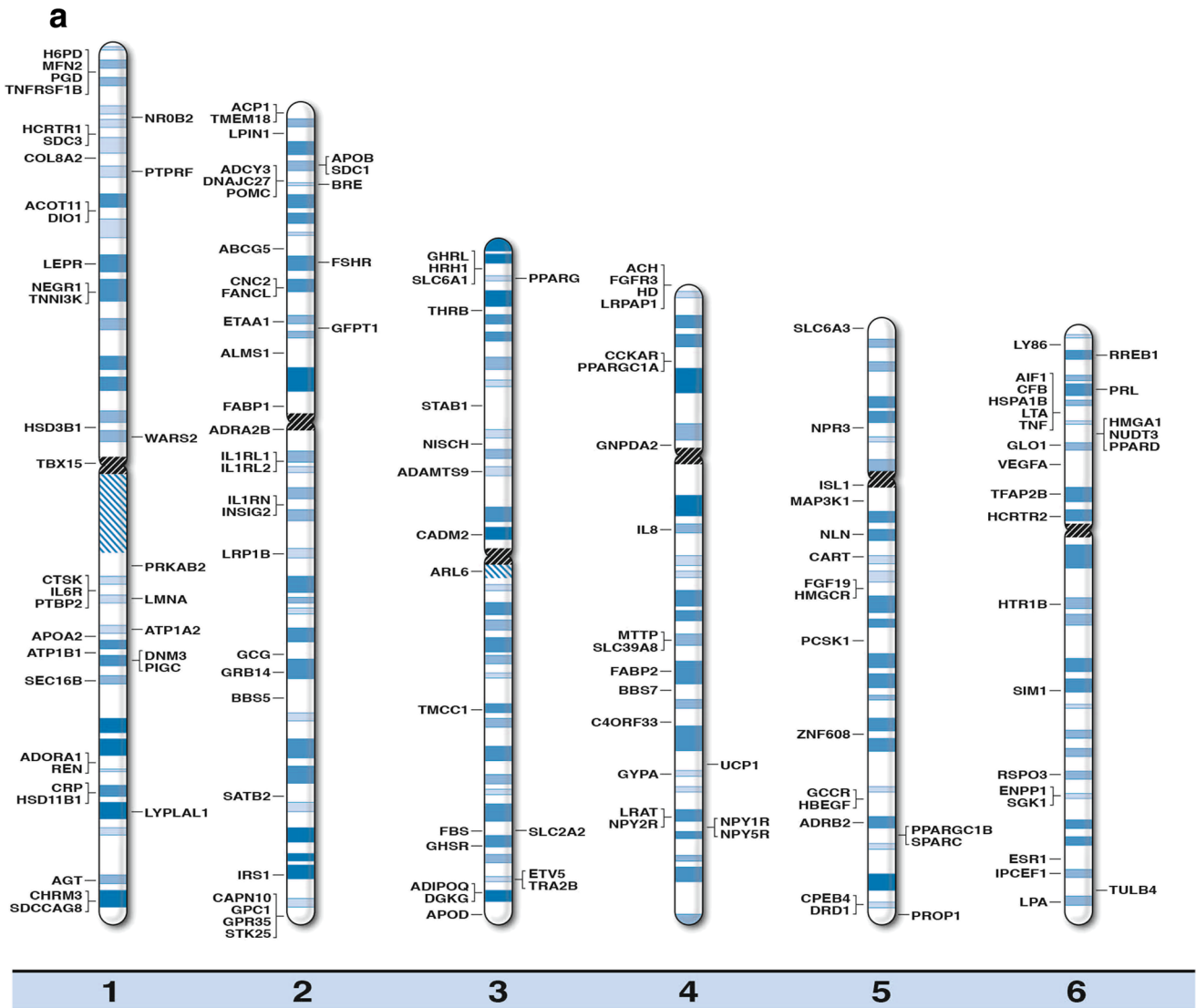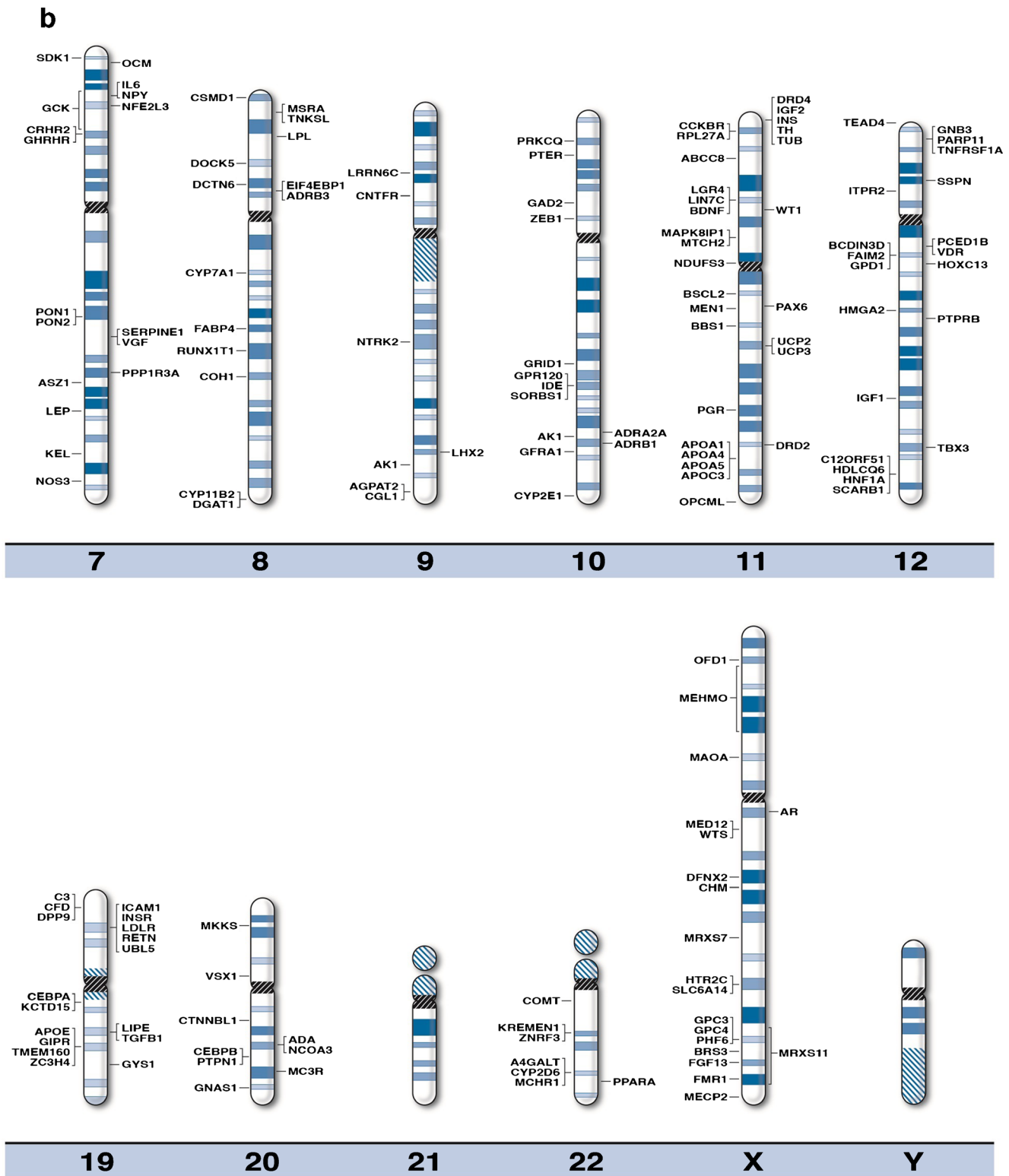
Fig. 1 continued.

kb deletion near the *NEGR1* gene and a 21-kb deletion up-stream of the *GPRC5B* gene, both known to contribute to obesity. Genetic variants close to the *MC4R* and *FTO* genes will increase the body weight of an individual carrying these variants by approximately one pound, while mutations of the *MC4R* gene are present in about 2 % of all obese individuals with male and female heterozygous carriers weighing 15 to 30 kg more, respectively, than their relatives without the

mutations [31]. More research is needed to examine for rare CNVs and novel insights into the genetic causation and architecture of obesity and infertility.

A summary of obesity genes recorded on the 2005 Human Obesity Gene Map was reported in 2006 and included 176 single-gene mutations in 11 different genes, 50 loci were related to known Mendelian syndromes, 244 murine adiposity related-genes, 408 animal model based quantitative trait loci (QTLs) and 253 QTLs from 61 genome-wide scans [24]. Current updated lists of clinically relevant known and candidate genes for obesity and infertility in humans are needed for genetic diagnosis and counseling purposes for patients with non-syndromic and syndromic obesity and those presenting with infertility for medical services.

Materials and methods

We used PubMed and other computer-based internet websites to search for combined key words such as obesity, body mass index, genetics, gene mutations or variants to identify documented evidence (clinical, functional or experimental) of the genes causing obesity in humans. Often the research publication would contain the key word obesity and gene in the title of the article. We focused our attention to an updated study on the 2005 Human Obesity Gene Map, the 2005 update which was published in 2006 [24], a primary source of clinically relevant known and candidate genes for obesity with description and cited evidence of support for causation and, in addition, more recent whole-genome wide association and DNA sequencing studies of families with obesity and functional gene expression profiles analyses. Other informative websites (e.g., Online Mendelian Inheritance in Man-www.OMIM.org) and Gene Cards (www.genecards.org) were then used to compile an updated list of genes from these major sources for a total of 370 genes. The genes recognized, to date, play a role in obesity susceptibility affecting common pathways in lipid metabolism, deposition or transport, eating behavior and food selection, physical activity and energy expenditure. We then included gene symbols, their expanded name and chromosome band location for the separate obesity genes and highlighted those genes associated with human infertility or reproduction. The position for each known or candidate gene for obesity susceptibility is then plotted on high resolution chromosome ideograms (850 band level). Similarly, the genes for human infertility and reproduction were found by searching the medical literature via PubMed with associated key words such as genetics, genes, infertility, reproduction, azoospermia, endometriosis, diminished ovarian reserve and estrogen and documented evidence of involvement in the causation of infertility in humans. The resulting gene list was cross-referenced with the identified obesity genes and the overlapped genes with infertility were highlighted.

Results

We generated high resolution chromosome ideograms (850 band level) and included gene symbols plotted on the ideogram at the precise chromosome region/band for each of the 370 genes found to play a role in obesity after searching the medical literature and internet websites (Fig. 1). Gene symbols, expanded name and chromosome location are listed in Table 1 in alphabetical order for each of the 370 obesity genes. Similarly, 153 genes were found to be associated with human infertility and reproduction (Table 2) when searching the medical literature and based on genome-wide association, linkage and gene mutation or variant studies and 21 of these genes had a recognized role in obesity [32–44].

Discussion

In this review, we summarize the evidence that obesity is a heritable disorder with an increasing number of involved genes, and briefly provide an update on the molecular basis and list 370 clinically relevant known or candidate genes for obesity in humans and their location on chromosome ideograms and 153 genes implicated in human infertility and reproduction. Some genes cause Mendelian forms of obesity while other loci are known to contribute to polygenic obesity and/or infertility. Rare and common structural variants are also associated with obesity or infertility, but most remain to be discovered.

The study of recessive single gene causes of extreme obesity have been useful in identifying and delineating the role of causative genes involving the leptin / melanocortin pathways but explain only a small percentage of the obesity seen in the general population. For example, only 14 individuals with complete leptin deficiency have been identified. Moreover, MC4R protein deficiency is the most common cause of monogenic obesity. Loss of function mutation in the MC4R gene occurs in 0.07 % of the general population with a prevalence of 0.5 to 1 % among obese adults and 1 to 6 % among children with obesity [23]. Haplo-insufficiency for *BDNF*, *TRKB (NTRK2)* and *SIM1* genes have also been associated with severe obesity related to hyperphagia but often accompanied by syndromic features [20, 21].

Dasouki et al. [30] summarized structural chromosome abnormalities in the literature and reported new cases associated with onset of obesity in childhood. Some reports were classical such as the 15q11-q13 deletion seen in Prader-Willi syndrome while other reports were more rare. Usually structural chromosome defects are associated with congenital

Table 1 Known and candidate genes for obesity with overlap with human infertility and reproduction and their chromosome locations

GENE SYMBOL	GENE NAME	LOCATION
A4GALT	Alpha-1,4-galactosyltransferase	22q13.2
ABCC8	ATP-binding cassette, subfamily C, member 8	11p15.1
ABCG5	ATP-binding cassette, subfamily G, member 5	2p21
ACE	Angiotensin I-converting enzyme	17q23.3
ACH	Achondroplasia	4p16.3
ACOT11	Acyl-CoA thioesterase 11	1p32.3
ACP1	Acid phosphatase 1, soluble	2p25.3
ACSM2A	Acyl-CoA synthetase medium chain family, member 2A	16p12.3
ACSM3	Acyl-CoA synthetase medium chain family, member 3	16p13.11
ADA	Adenosine deaminase	20q13.12
ADAMTS9	A disintegrin-like and metalloproteinase with thrombospondin type 1 motif	3p14.1
ADCY3	Adenylate cyclase 3	2p23.3
ADIPOQ	Adiponectin, C1q and collagen domain containing	3q27.3
ADORA1	Adenosine A1 receptor	1q32.1
ADRA2A	Alpha-2A-adrenergic receptor	10q25.2
ADRA2B	Alpha-2B-adrenergic receptor	2p13.1
ADRB1	Beta-1-adrenergic receptor	10q25.3
ADRB2	Beta-2-adrenergic receptor	5q32
ADRB3	Beta-3-adrenergic receptor	8p11.23
AGPAT2	1-acylglycerol-3-phosphate O-acyltransferase 2	9q34.3
AGRP	Agouti-related protein, mouse, homolog of	16q22.1
AGT	Angiotensinogen (serpin peptidase inhibitor, clade A, member 8)	1q42.2
AIF1	Allograft inflammatory factor 1	6p21.33
AK1	Adenylate kinase 1	9q34.11
ALMS1	Alstrom syndrome 1	2p13.1
ANMA	Anisomastia	16q13-q21
APOA1	Apolipoprotein A-I	11q23.3
APOA2	Apolipoprotein A-II	1q23.3
APOA4	Apolipoprotein A-IV	11q23.3
APOA5	Apolipoprotein A-V	11q23.3
APOB	Apolipoprotein B	2p24.1
APOB48R	Apolipoprotein B48 receptor	16p11.2
APOC3	Apolipoprotein C-III	11q23.3
APOD	Apolipoprotein D	3q29
APOE	Apolipoprotein E	19q13.32
AR	**Androgen receptor**	**Xq12**
ARL6	ADP-ribosylation factor-like 6	3q11.2
ASZ1	Ankyrin repeat, SAM (sterile alpha-motif), and basic leucine zipper domain-containing 1	7q31.2
ATP1A2	ATPase, Na+/K+ transporting, alpha-2 polypeptide	1q23.2
ATP1B1	ATPase, Na+/K+ transporting, beta-1 polypeptide	1q24.2
BATF	Basic leucine zipper transcription factor, ATF (activating transcription factor)-like	14q24.3
BBS1	Bardet-Biedl syndrome 1	11q13.2
BBS2	Bardet-Biedl syndrome 2	16q12.2
BBS4	Bardet-Biedl syndrome 4	15q24.1
BBS5	Bardet-Biedl syndrome 5	2q31.1
BBS7	Bardet-Biedl syndrome 7	4q27
BCDIN3D	BCDIN 3 (Bicoid-interacting 3), Drosophila, homolog of	12q13.12
BDNF	Brain-derived neurotrophic factor	11p14.1
BRE	Brain and reproductive organ-expressed protein	2p23.2
BRS3	Bombesin-like receptor 3	Xq26.3
BSCL2	Bernardinelli-Seip congenital lipodystrophy 2	11q12.3
C12orf51	High density lipoprotein cholesterol level quantitative trait locus 6	12q24.31
C3	Complement component 3	19p13.3
C4orf33	Chromosome 4 open reading frame 33	4q28.2
CABLES1	CDK5 (cyclin-dependent kinase 5) and ABL (Abelson murine leukemia viral oncogene homolog 1) enzyme substrate 1	18q11.2
CADM2	Immunoglobulin superfamily, member 4D	3p12.1
CAPN3	Calpain 3	15q15.1
CAPN10	Calpain 10	2q37.3
CART	Cocaine- and amphetamine-regulated transcript	5q13.2
CCKAR	Cholecystokinin A receptor	4p15.2
CCKBR	Cholecystokinin B receptor	11p15.4
CEBPA	CCAAT(cytosine-cytosine-adenosine-adenosine-thymidine)/Enhancer-binding protein, alpha	19q13.11
CEBPB	CCAAT (cytosine-cytosine-adenosine-adenosine-thymidine)/Enhancer-binding protein, beta	20q13.13
CFB	Complement factor B	6p21.33
CFD	Complement factor D	19p13.3
CGL1	Lipodystrophy, congenital generalized, type 1	9q34.3
CHM	Choroideremia (RAB escort protein 1)	Xq21.2
CHRM3	Cholinergic receptor, muscarinic 3	1q43
CIDEA	Cell death-inducing DFFA (DNA fragmentation factor, 45-kDa, alpha subunit)-like effector A	18p11.21
CNC2	Carney complex, type 2	2p16
CNTFR	Ciliary neurotrophic factor receptor	9p13.3
COH1	Cohen syndrome 1	8q22.2
COL8A2	Collagen, type VIII, alpha-2	1p34.3
COMT	Catechol-O-methyltransferase	22q11.21
CPEB4	Cytoplasmic polyadenylation element-binding protein 4	5q35.2
CRHR1	Corticotropin-releasing hormone receptor 1	17q21.31
CRHR2	Corticotropin-releasing hormone receptor 1	7p14.3
CRP	C-reactive protein, pentraxin-related	1q32.2
CSMD1	CUB (complement C1r/C1s, Uegf, Bmp1) and sushi multiple domains 1	8p23.2
CTNNBL1	Catenin, beta-like, 1	20q11.23
CTSK	Cathepsin K	1q21.3
CYP11B2	Cytochrome P450, subfamily XIB, polypeptide 2	8q24.3
CYP19A1	**Cytochrome P450, family 19, subfamily A, polypeptide 1**	**15q21.2**
CYP2D6	Cytochrome P450, subfamily IID, polypeptide 6	22q13.2
CYP2E1	Cytochrome p450, subfamily IIE	10q26.3
CYP7A1	Cytochrome P450, subfamily VIIA, polypeptide 1	8q12.1
DCTN6	Dynactin 6	8p12
DFNX2	Deafness, X-linked 2	Xq21.1
DGAT1	Diacylglycerol O-acyltransferase 1	8q24.3
DGKG	Diacylglycerol kinase, gamma, 90-kDa	3q27.3
DIO1	Deiodinase, iodothyronine, type I	1p32.3
DNAJC27	DNAJ/HSP40 homolog, subfamily C, member 27	2p23.3
DNM3	Dynamin 3	1q24.3
DOCK5	Dedicator of cytokinesis 5	8p21.2
DPP9	Dipeptidyl peptidase IX	19p13.3

Gene	Description	Location
DRD1	Dopamine receptor D1	5q35.2
DRD2	Dopamine receptor D2	11q23.2
DRD4	Dopamine receptor D4	11p15.5
EIF4EBP1	Eukaryotic translation initiation factor 4E-binding protein 1	8p11.23
ENPP1	Ectonucleotide pyrophosphatase/phosphodiesterase 1	6q23.2
ESD	Esterase D	13q14.2
ESR1	Estrogen receptor 1	6q25.1
ESR2	Estrogen receptor 2	14q23.2
ETAA1	Ewing tumor-associated antigen 1	2p14
ETV5	ETS (E26 transformation-specific) variant gene 5	3q27.2
FABP1	Fatty acid-binding protein 1	2p11.2
FABP2	Fatty acid-binding protein 2	4q26
FABP4	Fatty acid-binding protein 4	8q21.13
FAIM2	FAS apoptotic inhibitory molecule 2	12q13.12
FANCL	Fanconi anemia, complementation group L	2p16.1
FASN	Fatty acid synthase	17q25.3
FBS	Fanconi-Bickel syndrome	3q26.2
FGF13	Fibroblast growth factor 13	Xq27.1
FGF19	Fibroblast growth factor 19	5q13.3
FGFR3	Fibroblast growth factor receptor 3	4p16.3
FMR1	Fragile X mental retardation 1	Xq27.3
FOXC2	Forkhead box C2	16q24.1
FSHR	Follicle-stimulating hormone receptor	2p16.3
FTO	Fat mass- and obesity-associated gene	16q12.2
GABRG3	GABA (gamma-aminobutyric acid receptor) A receptor, gamma-3	15q12
GAD2	Glutamate decarboxylase 2	10p11.23
GCCR	Glucocorticoid receptor	5q31.3
GCG	Glucagon	2q24.2
GCGR	Glucagon receptor	17q25.3
GCK	Glucokinase	7p15.3-p15.1
GFPT1	Glutamine: fructose-6-phosphate amidotransferase 1	2p13.3
GFRA1	GDNF (glial cell line-derived neurotrophic factor) family receptor alpha-1	10q26.11
GH1	Growth hormone 1	17q23.3
GHRHR	Growth hormone-releasing hormone receptor	7p14.3
GHRL	Ghrelin	3p25.3
GHSR	Growth hormone secretagogue receptor	3q26.31
GIPR	Gastric inhibitory polypeptide receptor	19q13.32
GLO1	Glyoxalase I	6p21.2
GNAS1	Guanine nucleotide-binding protein, alpha-stimulating activity polypeptide 1, included	20q13.32
GNB3	Guanine nucleotide-binding protein, beta-3	12p13.31
GNPDA2	Glucosamine-6-phosphate deaminase 2	4p12
GPC1	Glypican 1	2q37.3
GPC3	Glypican 3	Xq26.2
GPC4	Glypican 4	Xq26.2
GPD1	Glycerol-3-phosphate dehydrogenase 1	12q13.12
GPR35	G protein-coupled receptor 35	2q37.3
GPR120	G protein-coupled receptor 120	10q23.33
GPRC5B	G protein-coupled receptor, family C, group 5, member B	16p12.3
GRB14	Growth factor receptor-bound protein 14	2q24.3
GRID1	Glutamate receptor, ionotropic, delta 1	10q23.2
GTF3A	General transcription factor IIIA	13q12.2
GYPA	Glycophorin A	4q31.21
GYS1	Glycogen synthase 1	19q13.33
H6PD	Hexose-6-phosphate dehydrogenase	1p36.22
HBEGF	Heparin-binding EGF (epidermal growth factor)-like growth factor	5q31.3
HCRTR1	Hypocretin receptor 1	1p35.2
HCRTR2	Hypocretin receptor 2	6p12.1
HD	Huntington disease	4p16.3
HDLCQ6	High density lipoprotein cholesterol level quantitative trait locus 6	12q24.31
HMGA1	High mobility group AT-hook 1	6p21.31
HMGA2	High mobility group AT-hook 2	12q14.3
HMGCR	3-hydroxy-3-methylglutaryl-CoA reductase	5q13.3
HNF1A	HNF1 (hepatocyte nuclear factor 1) homeobox A	12q24.31
HOXB5	Homeobox B5	17q21.32
HOXC13	Homeobox C13	12q13.13
HSD11B1	11-beta-hydroxysteriod dehydrogenase, type 1	1q32.2
HSD17B1	17-beta-hydroxysteroid dehydrogenase I	17q21.2
HRH1	Histamine receptor H1	3p25.3
HSD3B1	3-beta-hydroxysteroid dehydrogenase I	1p13.1
HSPA1B	Heat-shock 70-kDa protein 1B	6p21.33
HTR1B	5-hydroxytryptamine receptor 1B	6q14.1
HTR2A	5-hydroxytryptamine receptor 2A	13q14.2
HTR2C	5-hydroxytryptamine receptor 2C	Xq23
ICAM1	Intercellular Adhesion molecule 1	19p13.2
IDE	Insulin-degrading enzyme	10q23.33
IGF1	Insulin-like growth factor I	12q23.2
IGF1R	Insulin-like growth factor I receptor	15q26.3
IGF2	Insulin-like growth factor II	11p15.5
IGHD	Immunoglobulin heavy constant delta	14q32.33
IL1RL1	Interleukin 1 receptor-like 1	2q12.1
IL1RL2	Interleukin 1 receptor-like 2	2q12.1
IL1RN	Interleukin 1 receptor antagonist	2q14.2
IL6	Interleukin 6	7p15.3
IL6R	Interleukin 6 receptor	1q21.3
IL8	Interleukin 8	4q13.3
INS	Insulin	11p15.5
INSIG2	Insulin-induced gene 2	2q14.2
INSR	Insulin receptor	19p13.2
IPCEF1	Interaction protein for cytohesin exchange factors 1	6q25.2
IPW	Imprinted in Prader-Willi syndrome	15q11.2
IQCK	IQ motif containing K	16p12.3
IRS1	Insulin receptor substrate 1	2q36.3
IRS2	Insulin receptor substrate 2	13q34
IRX3	Iroquois homeobox protein 3	16q12.2
ISL1	ISL LIM (Lin11, Isl-1, and Mec-3) homeobox 1	5q11.1
ITPR2	Inositol 1,4,5-triphosphate receptor, type 2	12p11.23
KCTD15	Potassium channel tetramerization domain-containing protein 15	19q13.11
KEL	Kell blood group metalloendopeptidase	7q34
KREMEN1	Kringle domain-containing transmembrane protein 1	22q12.1
LDLR	Low density lipoprotein receptor	19p13.2
LEP	Leptin	7q32.1
LEPR	Leptin receptor	1p31.3

Symbol	Name	Location
LGR4	Leucine-rich repeat-containing G protein-coupled receptor 4	11p14.1
LHX2	LIM (Lin11, Isl-1, and Mec-3) homeobox gene 2	9q33.3
LIN7C	LIN7, C. elegans, homolog of, C	11p14.1
LIPC	Lipase, hepatic	15q21.3
LIPE	Lipase, hormone-sensitive	19q13.2
LMNA	Lamin A/C	1q22
LPA	Lipoprotein, Lp(A)	6q26
LPIN1	Lipin 1	2p25.1
LPL	Lipoprotein lipase	8p21.3
LRAT	Lecithin retinol acyltransferase	4q32.1
LRP1B	Low density lipoprotein receptor-related protein 1B	2q21.2
LRPAP1	Low density lipoprotein receptor-related protein-associated protein 1	4p16.3
LRRN6C	Leucine-rich repeat protein, neuronal, 6C	9p21.2
LTA	Lymphotoxin-alpha	6p21.33
LY86	Lymphocyte antigen 86	6p25.1
LYPLAL1	Lysophospholipase-like 1	1q41
MAF	V-Maf avian musculoaponeurotic fibrosarcoma oncogene homolog	16q23.2
MAGEL2	MAGE (melanoma-associated antigen)-like 2	15q11.2
MAOA	Monoamine oxidase A	Xp11.3
MAP2K5	Mitogen-activated protein kinase kinase 5	15q23
MAP3K1	Mitogen-activated protein kinase kinase 1	5q11.2
MAPK8IP1	Mitogen-activated protein kinase 8-interacting protein 1	11p11.2
MC3R	Melanocortin 3 receptor	20q13.2
MC4R	Melanocortin 4 receptor	18q21.32
MC5R	Melanocortin 5 receptor	18p11.21
MCHR1	Melanin-concentrating hormone receptor 1	22q13.2
MECP2	Methyl-CpG-binding protein 2	Xq28
MED12	Mediator complex subunit 12	Xq13.1
MEHMO	Mental retardation, epileptic seizures, hypogonadism and hypogenitalism, microcephaly, and obesity	Xp22.13-p21.1
MEN1	Multiple endocrine neoplasia 1	11q13.1
MFN2	Mitofusin 2	1p36.22
MGRN1	Mahogunin, ring finger 1	16p13.3
MKKS	McKusick-Kaufman syndrome	20p12.2
MKRN3	Makorin 3	15q11.2
MRXS7	Mental retardation, X-linked, syndromic 7	Xq22.1

Symbol	Name	Location
MRXS11	Mental retardation, X-linked, syndromic 11	Xq26-q27
MSRA	Peptide methionine sulfoxide reductase	8p23.1
MT1A	Metallothionein 1A	16q12.2
MT1G	Metallothionein 1G	16q13
MT1X	Metallothionein 1X	16q13
MTCH2	Mitochondrial carrier homolog 2	11p11.2
MTIF3	Mitochondrial translational initiation factor 3	13q12.2
MTTP	Transfer RNA, mitochondrial, proline	4q24
MYH11	Myosin, heavy chain 11, smooth muscle	16p13.11
MYO9A	Myosin IXA	15q23
NCOA3	Nuclear receptor coactivator 3	20q13.12
NDN	Necdin	15q11.2
NDUFS3	NADH-ubiquinone oxidoreductase Fe-S protein 3	11p11.11
NEGR1	Neuronal growth regulator 1	1p31.1
NFE2L3	Nuclear factor erythroid 2-like 3	7p15.2
NISCH	Nischarin	3p21.1
NLN	Neurolysin	5q12.3
NMB	Neuromedin B	15q25.3
NOS3	Nitric oxide synthase 3	7q36.1
NPC1	NPC1 (Niemann-Pick disease, type C1) gene	18q11.2
NPR3	Natriuretic peptide receptor C	5p13.3
NPY	Neuropeptide Y	7p15.3
NPY1R	Neuropeptide Y receptor Y1	4q32.2
NPY2R	Neuropeptide Y receptor Y2	4q31.1
NPY5R	Neuropeptide Y receptor Y5	4q32.2
NR0B2	Nuclear receptor subfamily 0, group B, member 2	1p36.11
NRXN3	Neurexin III	14q24.3
NTRK2	Neurotrophic tyrosine kinase, receptor, type 2	9q21.33
NUDT3	Nucleoside diphosphate-linked moiety X motif 3	6p21.31
OCM	Oncomodulin	7p22.1
OFD1	Oral-facial-digital syndrome 1	Xp22.2
OLFM4	Olfactomedin 4	13q14.3
OPCML	Opioid-binding protein/cell adhesion molecule-like	11q25
PARP11	Poly (ADP-ribose) polymerase family, member 11	12p13.3
PAX6	Paired box gene 6	11p13

Symbol	Name	Location
PCED1B	PC (pyruvate carboxylase) -esterase domain containing 1B	12q13.11
PCSK1	Proprotein convertase, subtilisin/kexin-type, 1	5q15
PEMT	Phosphatidylethanolamine N-methyltransferase	17p11.2
PGD	6-phosphogluconate dehydrogenase, erythrocyte	1p36.22
PGR	Progesterone receptor	11q22.1
PHF6	PHD (plant homeodomain) finger protein 6	Xq26.2
PIGC	Phosphatidylinositol glycan, class C	1q24.3
PLIN1	Perilipin 1	15q26.1
PMM2	Phosphomannomutase 2	16p13.2
PNMT	Phenylethanolamine N-methyltransferase	17q12
POMC	Proopiomelanocortin	2p23.3
PON1	Paraoxonase 1	7q21.3
PON2	Paraoxonase 2	7q21.3
PPARA	Peroxisome proliferator-activated receptor-alpha	22q13.31
PPARD	Peroxisome proliferator-activated receptor-delta	6p21.31
PPARG	Peroxisome proliferator-activated receptor-gamma	3p25.2
PPARGC1A	Peroxisome proliferator-activated receptor-gamma, coactivator 1, alpha	4p15.2
PPARGC1B	Peroxisome proliferator-activated receptor-gamma, coactivator 1, beta	5q33.1
PPP1R3A	Protein phosphatase 1, regulatory subunit 3A	7q31.1
PPY	Pancreatic polypeptide/pancreatic icosapeptide	17q21.31
PRKAB2	Protein kinase, AMP (adenosine monophosphate-activated protein)-activated, noncatalytic, beta-2	1q21.1
PRKAR1A	Protein kinase, cAMP-dependent, regulatory, type 1, alpha	17q24.2
PRKCQ	Protein kinase C, theta	10p14
PRKD1	Protein kinase D1	14q12
PRL	Prolactin	6p22.3
PROP1	PROP (prophet of pit1) paired-like homeodomain transcription factor	5q35.3

Gene	Description	Locus
PTBP2	Polypyrimidine tract-binding protein 2	1p21.3
PTER	Phosphotriesterase-related protein	10p13
PTPN1	Protein-tyrosine phosphatase, nonreceptor-type, 1	20q13.13
PTPRB	Protein-tyrosine phosphatase, receptor- type, beta	12q15
PTPRF	Protein-tyrosine phosphatase, receptor- type, F	1p34.2
PWLS	Prader-Willi-like syndrome	15q11.2
PYY	Peptide YY	17q21.31
RARA	Retinoic acid receptor, alpha	17q21.2
REN	Renin	1q32.1
RETN	Resistin	19p13.2
RPL27A	Ribosomal protein L27A	11p15.4
RREB1	RAS-responsive element binding protein 1	6p24.3
RSPO3	R-spondin family, member 3	6q22.33
RUNX1T1	Runt-related transcription factor 1, translocated to, 1	8q21.3
SATB2	Special AT-rich sequence-binding protein 2	2q33.1
SCARB1	Scavenger receptor class B, member 1	12q24.31
SDC1	Syndecan 1	2p24.1
SDC3	Syndecan 3	1p35.2
SDCCAG8	Serologically defined colon cancer antigen 8	1q43
SDK1	Sidekick, Drosophila, homolog of, 1	7p22.2
SEC16B	SEC16, S. cerevisiae, homolog of, B	1q25.2
SERPINE1	Serpin peptidase inhibitor, clade E (nexin, plasminogen activator inhibitor type 1), member 1	7q22.1
SGK1	Serum/glucocorticoid-regulated kinase 1	6q23.2
SH2B1	SH2B (Src-homology-2-B) adaptor protein 1	16p11.2
SIM1	Single-minded, Drosophila, homolog of, 1	6q16.3
SLC2A2	Solute carrier family 2 (facilitated glucose transporter), member 2	3q26.2
SLC39A8	Solute carrier family 39 (zinc transporter), member 8	4q24
SLC6A1	Solute carrier family 6 (neurotransmitter transporter, GABA), member 1	Xq23
SLC6A14	Solute carrier family 6 (neurotransmitter transporter), member 14	-
SLC6A3	Solute carrier family 6 (neurotransmitter transporter, dopamine), member 3	5p15.33
SNORD116	small nucleolar RNA, C/D box, 116-1	15q11.2
SNRPN	Small nuclear ribonucleoprotein polypeptide N	15q11.2
SORBS1	Sorbin and SH3 domain containing 1	10q23.33
SPARC	Secreted protein, acidic, cysteine-rich	5q33.1
SREBF1	Sterol regulatory element-binding transcription factor 1	17p11.2
SSPN	Sarcospan	12p12.1
STAB1	Stabilin 1	3p21.31
STAT5A	Signal transducer and activator of transcription 5A	17q21.2
STK25	Serine/threonine protein kinase 25	2q37.3
SULT1A1	Sulfotransferase family, cytosolic, 1A, phenol-preferring, member 1	16p12.1
SULT1A2	Sulfotransferase family, cytosolic, 1A, phenol-preferring, member 2	16p12.1
TBX15	T-box 15	1p11.1
TBX3	T-box 3	12q24.21
TEAD4	TEA (transcriptional enhancer activator) domain family member 4	12p13.33
TFAP2B	Transcription factor AP2 (adaptor-related protein complex 2)-beta	6p12.3
TGFB1	Transforming growth factor, beta-1	19q13.2
TH	Tyrosine hydroxylase	11p15.5
THBS1	Thrombospondin I	15q14
THRB	Thyroid hormone receptor, beta	3p24.2
TMCC1	Transmembrane and coiled-coil domain family 1	3q22.1
TMEM160	Transmembrane protein 160	19q13.32
TMEM18	Transmembrane protein 18	2p25.3
TNF	Tumor necrosis factor	6p21.33
TNFRSF1A	Tumor necrosis factor receptor superfamily, member 1A	12p13.31
TNFRSF1B	Tumor necrosis factor receptor superfamily, member 1B	1p36.22
TNKS	TRF1 (telomeric repeat-binding factor 1)-interacting, ankyrin-related ADP-ribose polymerase	8p23.1
TNNI3K	TNNI3 (troponin I, cardiac) - interacting kinase	1p31.1
TRA2B	Transformer 2, Drosophila, homolog of, beta	3q27.2
TTC8	Tetratricopeptide repeat domain-containing protein 8	14q31.3
TUB	Tubby, mouse, homolog of	11p15.5
TUFM	Tu translation elongation factor, mitochondrial	16p11.2
TULB4	Tubby like protein 4	6q25.3
UBL5	Ubiquitin-like 5	19p13.2
UCP1	Uncoupling protein 1	4q31.1
UCP2	Uncoupling protein 2	11q13.4
UCP3	Uncoupling protein 3	11q13.4
VDR	Vitamin D receptor	12q13.11
VEGFA	Vascular endothelial growth factor A	6p21.1
VGF	VGF, nerve growth factor-inducible	7q22.1
VSX1	Visual system homeobox gene 1, zebrafish, homolog of	20p11.21
WARS2	Tryptophanyl-tRNA	1p12
WT1	Wilms tumor 1	11p13
WT5	Wilson-Turner X-linked mental retardation syndrome	Xq13.1
ZC3H4	Zinc finger CCCH-type containing 4	19q13.32
ZEB1	Zinc finger E box-binding homeobox 1	10p11.22
ZNF608	Zinc finger protein 608	5q23.2
ZNRF3	Zinc finger and ring finger protein 3	22q12.1

Bracketed genes represent those found to be involved with human infertility and reproduction. See Table 2 for list of infertility genes.

Table 2 Known and candidate genes for human infertility and reproduction

AHC	EREG	MAS1L	TRA2B
AIRE	**ESR1**	MCHR2	TRIM66
AMH	**ETAA1**	MKL2	TRMT11
ANKRD7	**ETV5**	NFAT5	TSKU
AR	**FMR1**	**NFE2L3**	TSPY2
AREG	FN1	NPHP3	TUBA4A
ARHGAP42	FOXL2	NR4A2	TUSC1
ARNTL	**FSHR**	NR5A1	TXNDC3
AS1	**FTO**	NROB1	UBD
AURKC	FUSSEL18	PAGE1	USP8
AZF	GAB2	PCSK2	USP9Y
BCL2	GALT	**PCSK1**	VCAN
BEGAIN	GDF9	PDHA2	VEZT
BPY2	GNAO1	PHF15	VGLL3
BSX	GNRH1	PICK1	WNT4
C6orf173	GNRHR	PLCL1	**WT1**
CA10	GREB1	POF1	YRBM
CATSPER1	GREM1	PRDM13	ZNF483
CCDC85A	GYP17	PRKACG	
CDC42	HAS2	**PROP1**	
CDKN2BAS	HESX1	PSAT1	
CDY1	HIST1H1T	PTGS2	
CDYL	HNRNPA3P1	PXMP3	
CDY2A	HOXA13	RBM6	
CFTR	HSD17B3	RBMY1A1	
CGA	HSPC157	RND3	
CHD2	ID4	RNF144B	
CREB1	**IGF1**	RPS6KA2	
CRTC1	**IGF2**	RXRG	
CYP11A1	**IGF1R**	SDC4	
CYP19A1	IGF2R	**SEC16B**	
CYP1B1	LHCGR	SERPINA5	
CYP2B7P	INHBA	SOHLH1	
DAZ	JHDM2A	SOX9	
DAZ1	KAL1	SPATA16	
DAZL	KLHDC8B	SPGFY1	
DDX3Y	**LEP**	SPGFY2	
DIAPH2	**LEPR**	SPRY4	
DMPK	LHB	SRD5A2	
DNAH8	LHCGR	SRY	
DPF3	LIN28B	TCEB3B	
DPY19L2	LRRC32	TMEM108	
DSCAML1	MAGEC2	**TMEM18**	
EGFR	**MAGEL2**	TMEM38B	
ELOVL2		TNFAIP6	
EPSTI1			

Bracketed genes represent those found to be involved with obesity. See Table 1 for list of obesity genes

anomalies, growth retardation and developmental delay but occasionally can be associated with hyperphagia and obesity. Every chromosome except chromosome number 13 was found to be reported with structural anomalies (i.e., deletions, duplications) and related to obesity. These include chromosome 1 with a recognized 1p36 deletion obesity syndrome [45]; chromosome 6 with a 6q16.2 deletion involving *SIM1* gene [46]; chromosome 11 with 11p deletions involving the *BDNF* gene [47]; chromosome 15 with the 15q11-q13 deletion seen in Prader-Willi syndrome [25]; chromosome 16 with 16p11.2 deletions involving the *SH2B1* gene [25, 26] and 16q11.2 duplications involving the *FTO* gene [48]; chromosome 18 with 18q deletions involving the *MC4R* gene [49]; chromosome 20 with 20q deletions seen in Albright hereditary osteodystrophy involving the complex *GNAS1* gene locus [50]; chromosome 22 with the 22q11.2 deletion seen in DiGeorge syndrome [51]; and chromosome X with a Xq27 deletion involving the *FMR1* gene seen in fragile X syndrome [52]. These multiple chromosome abnormalities support the polygenic nature of obesity useful for the identification of candidate genes and their location for more precise genetic characterization and testing. Large cohorts of obese adults have been studied using genome-wide linkage scans and genotyping results with highly polymorphic microsatellite markers regularly spaced across the whole genome. Many of these cohorts would also be at risk for infertility as a clear association does exist between the two conditions (obesity and infertility). More than 80 genetic linkage studies of over 31,000 individuals have been reported to examine obesity-related traits and significant evidence for linkage were found [20]. For example, significant linkage in childhood obesity was found for chromosome 6q22.31-q23.2 [53] and severe obesity for chromosome 4p15-p14 [54].

Genome-wide association studies (GWAS) involving large numbers of individuals with obesity have been reported using thousands of genetic variants such as SNPs. Candidate genes that play a role in body weight regulation and obesity have been reported. Specifically, four GWAS meta-analyses involving several thousand individuals of European descent confirmed a strong association for the *FTO* locus and BMI with identification of 35 new SNPs found in 33 additional loci but many new loci are yet to be discovered [55–57]. For example, of 19 loci identified, five were associated with BMI / obesity (*FTO, MC4R, TFAP2B, NRXN3, MSRA*) [20, 58, 59]. Additional likely causative genes for extreme obesity include *TMEM18, NPC1, PTER, PRL* and *SDCCAG8* [20, 60, 61]. The biological role of several candidate genes for obesity (e.g., *FTO, MC4R, POMC, SH2B1, BDNF, NPC1, NRX3* and *NEGR1*) [20, 21] involve adipose tissue development and function or are known to act at the brain level indicating a role in regulation of eating behavior, hyperphagia and food intake. Obesity impacts fertility as well as reproduction and share overlap in genetic liability. Several reports indicate that

the *FTO* gene, one of the most important obesity-related genes, is also implicated in human infertility and reproduction. A recent review of GWAS data showed that the onset of menarche involves at least 35 genes including not only *FTO* but also *TRA2B, ETV5, TMEM18* and *SEC16B* which are also known to play a role in obesity [62]. Obesity in women impacts fertility status with an increased time to conception and a relative risk for anovulatory infertility estimated at 2.7 [63–65]. Spontaneous conceptions decrease with subsequent increases in BMI for women.

There are several mechanisms whereby obesity can cause subfertility including hormonal and peptide based disturbances, e.g., an increase in leptin levels produced by the adipose tissue and a decrease in adiponectin levels [66, 67]. Leptin inhibits ovarian steroidogenesis while lower adiponectin levels are associated with increased insulin levels thereby causing hyperandrogenemia. This process influences sex hormone binding and relationship with the androgen receptor. Obesity also acts on insulin production and insulin-like growth factor 1 (IGF1) which enhances lutenizing hormone (LH) mediated steroidogenesis in the ovary and thus increase ovarian androgens [68–70]. Increased levels of androgen can result in apoptosis of granulosa cells and conversion of androgens peripherally to estrogens in fat cells inhibiting gonadotrophen secretion further impacting hormone imbalance and fertility status in obese women [66, 71–73].

Polycystic ovary syndrome is a classical obesity-related disorder characterized by menstrual irregularities, hyperandrogenism and subfertility [74, 75]. Obesity is seen in 30–75 % of women with this disorder implicating several genes involved in hormonal and metabolic function. These obesity-related genes impacting hormone and related peptide production include *LEP, IGF1* and *IGF2* and receptors (*AR, ESR1, FSHR, LEPR, IGF1R*). Other reported obesity and infertility-related genes are involved with metabolism (*CYP19A1*) or testes function with spermatogonial cell production (*ETV5*), premature ovarian failure (*FMR1*), obesity formation or susceptibly (*FTO, PCSK1*), transcriptional activator (*NFE2L3*) , transcription factor for development of somatotrophs and gonadotrophs (*PROP1*), organization of endoplasmic reticulum and protein export (*SEC16B*) and recycling (*MAGEL2*), neuronal influence on body weight regulation (*TMEM18*), testes-specific RNA splicing factors (*TRA2B*) and transcription factors involved with genitourinary development (*WT1*) (genes reviewed in OMIM-www.ncbi.nlm.hih.gov/omim/). Clearly, obesity in women impacts reproduction and fertility status with genetics playing a role. An increased BMI reduces the conception rate leading to infertility by requiring higher doses of gonadotrophins that respond more poorly to ovarian stimulation. These women often have fewer oocytes to harvest but weight loss improves the likelihood of

reproductive outcomes. Weight loss should be sustained and gradual in order to improve the hormone imbalance leading to a successful pregnancy.

Current methods in genetic technology with improved computer software and advanced bioinformatics have increased genetic testing options and outcomes in the clinical setting. Several obesity-related genetic syndromes and causative genes are now recognized as well as non-syndromic targets. Identification of genetic defects in the causation of obesity are now made possible with high resolution microarray technology and next generation sequencing. The addition of DNA probes recognizing SNPs combined with copy number probes in microarrays not only identify segmental deletions and duplications in the genome at a 100 fold greater level than standard routine chromosome studies but can also identify regions of homozygosity. These regions can be used to identify genomic areas harboring recessive genes for obesity but also can be used to calculate the inbreeding coefficients to determine the consanguinity status of an individual as well as uniparental disomy of individual chromosomes. This added information has the potential to also identify genetic factors contributing to obesity and infertility.

A goal for next generation exome and/or RNA sequencing is to allow for discoveries of disease-causing genes and regulatory sequences required for normal function. The investigation of non-coding RNA and their coding gene targets may be fruitful. Identification of commonly disturbed mechanisms in the development of hyperphagia, energy expenditure, obesity and/or infertility may lead to targeted treatments aimed at metabolic processes and allow for management and eventually prevention of obesity in a significant number of individuals. Characterizing molecular signatures and disease-specific gene profiles and patterns of expression and their overlap with related conditions should lead to recognition of interconnected disturbed gene pathways in many diseases including a growing body of genetic evidence for obesity or infertility. Genetic dissection of obesity and its interface with infertility will help to characterize disease mechanisms and processes and provide new targets for drug design and therapy. Characterization of these relationships should lead to earlier diagnosis, potential treatment strategies and prevention in individuals with obesity and/or infertility.

Our summary of validated human genes associated with obesity susceptibility found in the medical literature plotted on high resolution chromosome ideograms along with tabular information for both obesity and infertility genes can be used to inform diagnosis and genetic testing options required for genetic counseling purposes of family members presenting for genetic services. The cross-reference of obesity genes against known fertility genes should enhance clinical application and relevance. The authors encourage the use of this current collection of clinically relevant known and candidate genes for obesity susceptibility and human infertility in their evaluation of patients and families in the clinical setting.

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