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Obesity Genetics

A systematic review of genetic syndromes with obesity

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Summary

Syndromic monogenic obesity typically follows Mendelian patterns of inheritance and involves the co-presentation of other characteristics, such as mental retardation, dysmorphic features and organ-specific abnormalities. Previous reviews on obesity have reported 20 to 30 syndromes but no systematic review has yet been conducted on syndromic obesity. We searched seven databases using terms such as 'obesity', 'syndrome' and 'gene' to conduct a systematic review of literature on syndromic obesity. Our literature search identified 13,719 references. After abstract and full-text review, 119 relevant papers were eligible, and 42 papers were identified through additional searches. Our analysis of these 161 papers found that 79 obesity syndromes have been reported in literature. Of the 79 syndromes, 19 have been fully genetically elucidated, 11 have been partially elucidated, 27 have been mapped to a chromosomal region and for the remaining 22, neither the gene(s) nor the chromosomal location(s) have yet been identified. Interestingly, 54.4% of the syndromes have not been assigned a name, whereas 13.9% have more than one name. We report on organizational inconsistencies (e.g. naming discrepancies and syndrome classification) and provide suggestions for improvements. Overall, this review illustrates the need for increased clinical and genetic research on syndromes with obesity.

Keywords: syndromic obesity, disease heterogeneity, genetic elucidation, quality of evidence.

Abbreviations: aCGH, array comparative genomic hybridization; AS, Angelman syndrome; BBS, Bardet–Biedl syndrome; BMI, body mass index; CARE, Case report; CdLS, Cornelia de Lange syndrome; CNV, copy number variation; FISH, fluorescence in situ hybridization; GIANT, Genetic Investigation of ANthropometric Traits; GWAS, genome-wide association study; MEHMO, mental retardation, epileptic seizures, hypogonadism and -genitalism, microcephaly and obesity; MLPA, multiplex ligation-dependent probe amplification; MOMO, macrocephaly, obesity, mental disability and ocular abnormalities; ROHHADNET, rapid-onset obesity with hypothalamic dysfunction, hypoventilation, autonomic dysregulation and neural crest tumour; MS-MLPA, methylation-specific multiplex ligation-dependent probe amplification; ROHHAD, rapid-onset obesity with hypothalamic dysregulation, hypoventilation and autonomic dysregulation; PWLS, Prader–Willi like syndrome; PWS, Prader–Willi syndrome; SNP, single nucleotide polymorphism; SNV, single nucleotide variation; T2D, type 2 diabetes; WAGR, Wilm's tumour, aniridia, genitourinary abnormalities, and mental retardation; WAGRO, Wilm's tumour, aniridia, genitourinary abnormalities, mental retardation, and obesity; WC, waist circumference; WES, whole-exome sequencing; WGS, whole-genome sequencing; XLMR, X-linked mental retardation.

Introduction

Obesity is a chronic illness that is defined as the accumulation of body fat to the extent that it has negative effects on health (1). The prevalence of obesity has risen steadily over the past three decades in both men and women (2). Between 1980 and 2008, the worldwide prevalence of obesity (body mass index [BMI] ≥30 kg m^{-2}) has nearly doubled, with 10% of men and 14% of women being obese in 2008. Thirteen percent of the adult population was found to be obese in 2014, and 42 million children under the age of 5 were overweight or obese in 2013 (3). This increase in prevalence is a major public health concern because of the negative impacts of overweight and obesity on physical well-being. Some of the complications include an increased risk of psychological distress, osteoarthritis, gallbladder disease, type 2 diabetes (T2D), fatty liver, hypertension, coronary heart disease and certain forms of cancer (4). Moreover, compared with individuals with a BMI between 20 and 25 kg m^{-2}, individuals with a BMI of 30 kg m^{-2} or more have a 50% to 100% increase in mortality (5).

The two major potentially modifiable environmental causes underlying the increase in obesity rates are an excessive consumption of energy-dense food and a reduction in energy expenditure (6). In addition to physical activity and diet, factors such as socioeconomic status, parental overweight, birth weight, assortative mating, stress, pollution and microbial infections have been shown to play a role in the obesity epidemic (1,7–9).

Twin studies have estimated the heritability of obesity to be between 40% and 75% (10). Genetic forms of obesity display a continuum of clinical features but have been historically subdivided into three different subtypes: Mendelian (monogenic) syndromic obesity, Mendelian non-syndromic obesity and polygenic obesity (11). Mendelian forms of obesity result from chromosomal abnormalities and from rare pathogenic variants in genes that encode pivotal proteins in the regulation of energy balance (12). They follow a Mendelian pattern of inheritance and are autosomal or X-linked. A syndrome has been defined as a collection of signs and symptoms known to frequently appear together. Syndromic forms of Mendelian obesity, also known as pleiotropic syndromes, are relatively rare in the general population. Syndromic obesity is defined as the presence of obesity along with additional characteristic features such as intellectual disability, dysmorphic features and congenital abnormalities affecting specific organ systems. Prader–Willi and Bardet–Biedl syndromes are among the most well-known obesity syndromes (12). The non-syndromic forms of Mendelian obesity recognized to date are mainly characterized by genetic defects in the leptin/melanocortin pathway leading to hyperphagic obesity (13). Examples include mutations in genes that encode leptin, the leptin receptor, prohormone convertase 1, pro-opiomelanocortin or melanocortin 4 receptor (13). In contrast to monogenic obesity, polygenic obesity is not caused by a single gene with a major effect on the development of obesity. Polygenic forms of obesity are thought to be determined by the aggregate effect of multiple common genetic variants, each with modest effects (14). For instance, common variants in the intron 1 of fat mass and obesity-associated gene (*FTO*) are the more important contributors to polygenic obesity, accounting for 1% of the variance of BMI in the general population (15,16).

The past three decades have seen numerous technological improvements in the field of human disease gene identification. The development of genome-wide association studies (GWAS) and next-generation sequencing has increased dramatically the speed at which new genetic associations are discovered (17). Despite the recent technological progress, the genetic causes of most obesity syndromes have not been fully elucidated, mostly because of their extremely low prevalence (12). A comprehensive description of obesity syndromes and the status of their genetic elucidation have not yet been published, and it is a crucial step to increase awareness of obesity syndromes, identify causal genes and understand the molecular underpinnings of weight regulation in humans. It is also an essential part of enhanced genetic counselling, diagnostic tools and innovative treatments for obesity syndromes. This knowledge gap prompted us to do a systematic review of the literature on genetic syndromes with obesity. We also identify and discuss the methodological problems faced by this field and propose suggestions for improvements.

Methods

Literature search

In collaboration with an information specialist (LEB), we developed search strategies and conducted a systematic search of MEDLINE, EMBASE, CINAHL, Pubmed, Orphanet, Web of Science (for conference proceedings only) and the Cochrane Library databases to identify studies describing syndromic obesity in humans. We used search terms such as 'obesity', 'syndrome', 'developmental disability', 'intellectual disability', 'pedigree', 'genes' and 'mutation' in conjunction with Boolean operators to identify articles describing syndromic forms of obesity (See Table S1 for the full search strategy). We restricted ourselves to human syndromes – animal and cellular studies were excluded from the search. The initial search was conducted from inception of each database through 20 June 2014 and updated on 20 August 2016.

Article review

Titles and abstracts of all retrieved articles were screened by one reviewer (Y. K.) to identify articles for full-text review.

Any abstracts describing human observational or experimental studies with potentially new or unique information regarding an obesity syndrome and its genetic determinant(s), if elucidated, were retrieved for full-text review. A sample of ~10% of abstracts were screened in duplicate by R. J. d.S. and Y. K. in a training exercise. A BMI of 30 kg m^{-2} or more or a BMI *Z*-score higher the 95th percentile for age, sex and ancestry matched controls was used to define obesity. Studies published in languages in which the reviewers are proficient (English and French) were included. After full-text review, papers that contained original scientific research pertaining to obesity syndromes and/or their genetic elucidation were included, and all review articles were excluded. The eligibility of all full-text articles was assessed by the primary author (Y. K.) and a subject matter expert (D. M.).

Prevalence and type of mutation search

The prevalence estimates were retrieved through an independent supplemental search for each syndrome on *Pubmed* using search terms such as the syndrome name and ('epidemiology'[Subheading] or 'epidemiology'[All Fields] or 'prevalence'[All Fields] or 'prevalence'[MeSH Terms]) in order to identify updated prevalence rates. Descriptions of the type of mutation or chromosomal abnormality were obtained using a separate Pubmed search (see Table S2 for search terms).

Additional references identified

As we limited our search to human studies, recognizing that the genetic elucidation of some syndromes was first confirmed in animal models, we found those studies through the reference list of relevant full texts (Table S3). An expert (D. M.) in the field reviewed all the full-text articles to identify relevant publications not identified by our search.

Statistics

Inter-rater agreement was calculated using *Kappa* (κ) to measure the validity of our inclusion and exclusion criteria. The following equation was used to calculate κ:

$$\kappa = \frac{p_0 - p_e}{1 - p_e}$$

where p_0 is the relative observed agreement among raters and p_e is the hypothetical probability of chance agreement.

Results

Literature flow

The initial search of the seven databases (performed on 20 June 2014) resulted in 13,719 references after the elimination of duplicates. To ensure that the inclusion and exclusion criteria were applied appropriately, a sample of ~10% of abstracts (n = 1,372) were screened in duplicate by R. J. d.S. and Y. K. in a training exercise. The inter-rater reliability was excellent (κ = 0.84). Twelve abstracts, representing 0.9% of the total screened in this training set, were discordant. Both reviewers discussed these articles with the senior author (D. M.), and additional training was provided. One screener (Y. K.) proceeded with the remaining abstracts. After filtering the abstracts, 332 were considered eligible for full-text review, 264 full texts were retrieved and the 68 articles for which no full text could be found were assessed for a second time based on abstract only. The full-text review eliminated 213 references, and 119 final papers were included in this systematic review (Fig. 1). This search was updated on 20 August 2016, and seven new papers were added. Mutation/chromosomal abnormality search led to the addition of 17 new references (Table S2). Fifteen additional papers based on animal studies were added (Table S3), and three key papers not found in the literature search were identified by a subject matter expert (D. M.; Table S4), resulting in 161 total references used to collect data for the systematic review.

Number of identified syndromes

Our search identified 79 syndromes with obesity, out of which only 19 (24.1%) have been fully genetically elucidated and 11 (13.9%) have been partially elucidated (Tables 1 and 2). A fully elucidated syndrome is one in which all the disease-causing genes have been identified, whereas partial elucidation refers to the identification of some sub-fraction of the disease-causing genes. Of the remaining 49 non-elucidated syndromes, 27 syndromes have been mapped to a chromosomal region. Thus, for 34.2% of the syndromes, only the chromosomal location is known, and for the remaining 22 (27.8%) syndromes, neither the gene(s) nor the chromosomal location(s) have yet been identified.

Naming discrepancies for syndromes

Out of the 79 syndromes, 43 (54.4%) have not been assigned a name. As an illustration, an inverted paternal duplication of 6q24.3 to 6q27 was found in a patient with unique clinical features (18). It was associated with moderate to severe intellectual delay, short stature, small hands and feet, eye abnormalities, small mouth and obesity

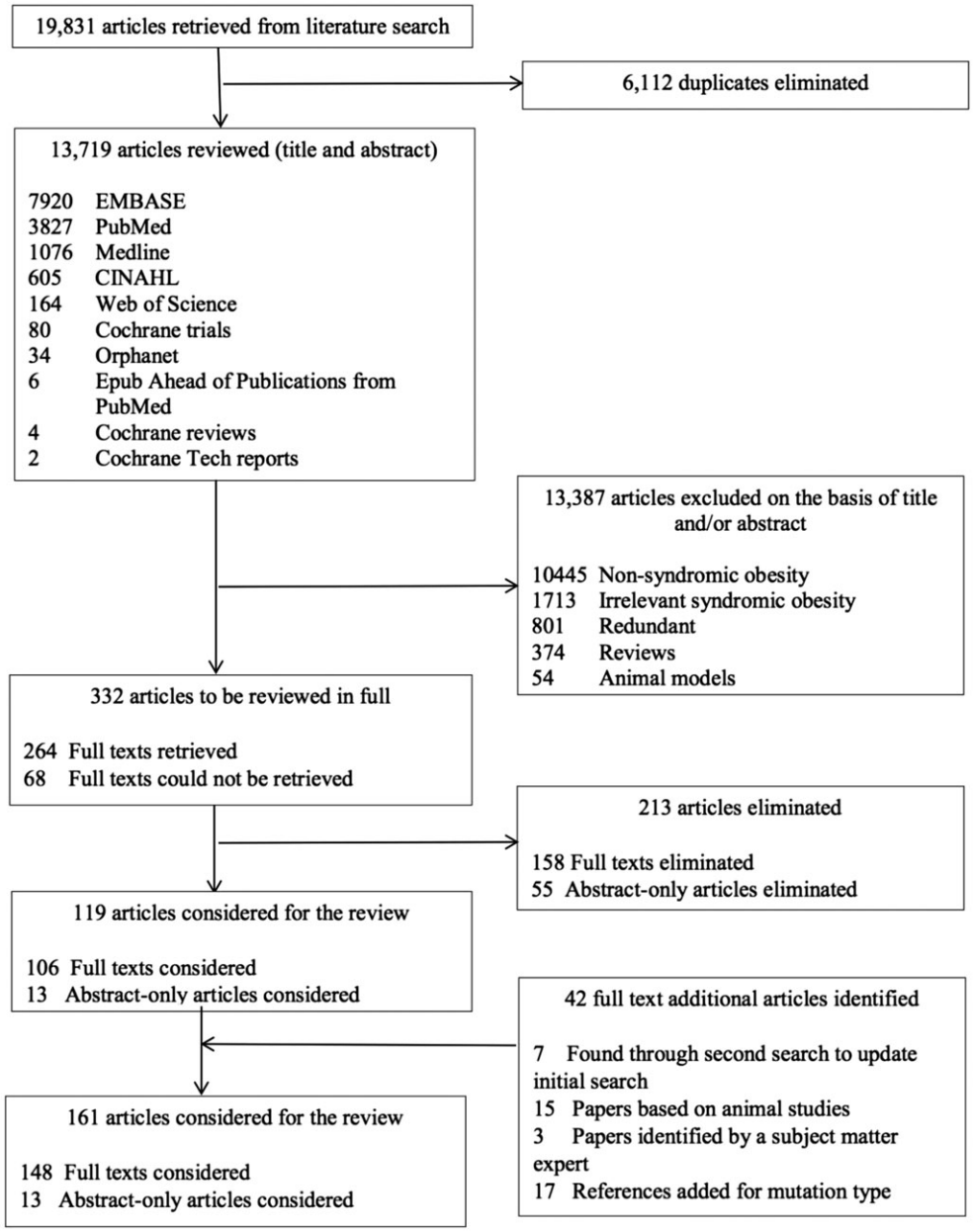

Figure 1 Hierarchy of elimination of records during literature search.

beginning in mid-childhood (18). Although it was concluded to be a case of syndromic obesity, the syndrome was not assigned a name, and would not meet current, more stringent criteria for syndromic definition (which require a minimum of three independent cases with similar genetic lesions to attribute causality) (19). Similarly, X-linked mental retardation (XLMR) is a group of multiple syndromes, some of which are associated with obesity. However, several XLMR syndromes have not been named, and are referred to as a varying form of XLMR (20,21). On the other hand, 11 syndromes have been described in scientific literature using more than one name (Tables S5 and S6). Examples include Carpenter syndrome, which is also called acrocephalopolysyndactyly type II and Kabuki syndrome, also known as Niikawa–Kuroki syndrome (22,23).

Prevalence

Monogenic obesity syndromes have a low prevalence (Tables S5 and S6). Prevalence estimates were available for 12 obesity syndromes and ranged from 1 in 565 to <1 in 1,000,000 (24,25)

Table 1 Genetically elucidated •syndromes identified by our systematic search of literature

Name(s) of the syndrome/ gene and OMIM number	Prevalence	Clinical features	Is the obesity feature mandatory?	Wide clinical heterogeneity	Is it fully genetically elucidated?	Type of inheritance	Likely causal gene/ chromosomal area	Examples of genetic defects	References
5p13 microduplication syndrome	Unknown	Developmental delay, autistic behaviour, obesity, lymphedema, hypertension and macrocephaly	No	No	Yes	Autosomal dominant	*NIPBL*	Microduplications	Oexle *et al.* (117); Novara *et al.* (42)
Albright hereditary osteodystrophy/ pseudohypoparathyroidism type Ia	Unknown	Brachymetaphalangism, short stature, obesity and mental retardation	Yes	Yes	Yes	Autosomal dominant	*GNAS1/ GNAS*	Missense, frameshift, nonsense, splice-site, deletions, insertions	Rao *et al.* (118); Thiele *et al.* (119)
Alström syndrome (OMIM #203800)	<1 in 1 million Katagiri *et al.* (24)	Blindness, hearing impairment, childhood obesity, insulin resistance and type 2 diabetes mellitus	Yes	Yes	Yes	Autosomal recessive	*ALMS1*	Frameshift, nonsense, missense	Hearn *et al.* (49); Piñeiro-Gallego *et al.* (120)
Angelman syndrome (OMIM #105830)	1 in 10,000–40,000 Leyser *et al.* (121)	Developmental delay, speech impairment, epilepsy and gait ataxia	No	Yes	Yes	NA	Chromosome 15 abnormalities	*De novo* maternal deletions, paternal uniparental disomy	Chan *et al.* (122)
							UBE3A	Loss of function mutations: frameshift, premature termination of translation, deletions	Kishino *et al.* (123)
Bardet–Biedl syndrome/ Laurence-Moon-Bardet–Biedl syndrome (OMIM #209900)	1 in 13,500–175,000 White *et al.* (124)	Retinitis pigmentosa, obesity, kidney dysfunction, polydactyly, behavioural dysfunction and hypogonadism	No	Yes	No	Autosomal recessive	*BBS1*	Missense, nonsense, splice-site and frame-shift mutations	Mykytyn *et al.* (125)
							BBS2	Missense, nonsense, frameshift, splice-site, duplications	Nishimura *et al.* (126); Fattahi *et al.* (127)
							BBS3/ARL6	Stop mutations, null mutations, deletions	Chiang *et al.* (69); Fan *et al.* (128); Chen *et al.* (129); Pereiro *et al.* (130)
							BBS4	Deletions, splice-site, nonsense, missense	Mykytyn *et al.* (131); Fattahi *et al.* (127); Ece Solmaz *et al.* (132)
							BBS5	Missense, frameshift mutations, deletions, splice-site mutations	Li *et al.* (133); Hjortshøj *et al.* (134); Chen *et al.* (129)
							BBS6/MKKS	Missense, frameshift mutations	Katsanis *et al.* (135); Slavotinek *et al.* (136)

(*Continues*)

Table 1 (Continued)

Name(s) of the syndrome/ gene and OMIM number	Prevalence	Clinical features	Is the obesity feature mandatory?	Wide clinical heterogeneity	Is it fully genetically elucidated?	Type of inheritance	Likely causal gene/ chromosomal area	Examples of genetic defects	References
							BBS7	Frameshift, missense, deletion, nonsense	Badano *et al.* (137); Fattahi *et al.* (127); Ece Solmaz *et al.* (132)
							BBS8/TTC8	Splice-site, insertion–deletion, missense	Ansley *et al.* (138); Chen *et al.* (129); Smaoui *et al.* (139)
							BBS9/PTHB1	Frameshift, splice-site, deletion	Nishimura *et al.* (70); Fattahi *et al.* (127); Khan *et al.* (140)
							BBS10	Missense, nonsense, frameshift, deletion, splice-site	Stoetzel *et al.* (141); Khan *et al.* (142); Billingsley *et al.* (143)
							BBS11/ TRIM32	Frameshift, missense mutations	Chiang *et al.* (68); Cossée *et al.* (144)
							BBS12	Nonsense, deletion, missense, frameshift	Stoetzel *et al.* (72)
							BBS13/MKS1	Missense	Leitch *et al.* (145)
							BBS14/ CEP290	Nonsense (loss of function)	Leitch *et al.* (145)
							BBS15/ WDPCP	Splice-site	Cui *et al.* (146)
							*BBS16/ SDCCAG8/ NPHP10**	Nonsense, splice-site	Schaefer *et al.* (147)
							BBS17/ LZTFL1	Missense, nonsense	Marion *et al.* (148)
							BBS18/BBIP1	Stop mutations (null)	Scheidecker *et al.* (149)
							*BBS19/IFT27**	Splice-site (loss of function)	Aldahmesh *et al.* (150)
							BBS20/ IFT172	Splice-site mutations	Schaefer *et al.* (151)
							BBS21/ C8ORF37	Missense mutations	Khan *et al.* (152)
Börjeson-Forssman-Lehmann Syndrome (OMIM #301900)	Unknown	Severe intellectual disability, epilepsy, microcephaly, short stature, obesity,	No	No	Yes	X-linked	*PHF6*	Missense and truncating mutations	Lower *et al.* (153)

(*Continues*)

Table 1 (Continued)

Name(s) of the syndrome/ gene and OMIM number	Prevalence	Clinical features	Is the obesity feature mandatory?	Wide clinical heterogeneity	Is it fully genetically elucidated?	Type of inheritance	Likely causal gene/ chromosomal area	Examples of genetic defects	References
		hypogonadism and gynecomastia							
Carpenter syndrome/ acrocephalopolysyndactyly type II (OMIM #201000)	1 in 1 million Victorine *et al.* (154)	Acrocephaly, soft tissue syndactyly, brachy- or agenesis mesophalangy of the hands and feet, preaxial polydactyly, congenital heart disease, mental retardation, hypogenitalism, obesity and umbilical hernia	Yes	No	Yes	Autosomal recessive	*RAB23*	Truncating, missense, nonsense	Jenkins *et al.* (155); Cohen *et al.* (22)
CHOPS syndrome*	Unknown	Cognitive impairment, coarse facies, heart defects, obesity, pulmonary involvement, short stature and skeletal dysplasia	Yes	No	Yes	Autosomal dominant	*AFF4*	Loss of function: deletions, duplications, missense or splice-site mutations	Izumi *et al.* (156)
Chudley–Lowry syndrome (OMIM #309580)	Unknown	Mental retardation, short stature, mild obesity, hypogonadism and distinctive facial features	Yes	No	Yes	X-linked recessive	*XNP/ATR-X**	Loss of function mutations	Abidi *et al.* (157); Chudley *et al.* (158)
Coffin–Lowry syndrome (OMIM #303600)	1 in 50,000–100,000 Pereira *et al.* (159)	Severe to profound intellectual disability in males, normal to profound intellectual impairment in females, characteristic facial features, hand structural anomalies, short height, microcephaly and cardiac abnormalities	No	Yes	Yes	X-linked	*RSK2/ RPS6KA3*	Missense mutations, nonsense mutations, splicing errors, short insertion-deletions	Delaunoy *et al.* (160)
Cohen syndrome (OMIM #216550)	Irish travelers: 1 in 565 to 2000 Murphy *et al.* (25)	Mental retardation, facial dysmorphism, microcephaly, retinal dystrophy, truncal obesity, joint laxity and intermittent neutropenia	No	Yes	Yes	Autosomal recessive	*VPS13B/ COH1*	CNV changes, deletions, missense, nonsense, point mutations, duplications	Kolehmainen *et al.* (161); Seifert *et al.* (162)
Cornelia de Lange syndrome/Brachmann-de Lange-syndrome (OMIM #122470)	1 in 10,000 Mei *et al.* (163)	Intellectual disability, distinctive facial features, prenatal and postnatal growth retardation, hirsutism and non-obligatory obesity	No	Yes	No	Autosomal dominant	*NIPBL*	Frameshift, missense, nonsense, splice-site mutations, truncating	Tonkin *et al.* (164); Deardorff *et al.* (165); Gillis *et al.* (166)
						Autosomal dominant	*RAD21*	Loss of function, missense	Deardorff *et al.* (165)

(*Continues*)

Table 1 (Continued)

Name(s) of the syndrome/ gene and OMIM number	Prevalence	Clinical features	Is the obesity feature mandatory?	Wide clinical heterogeneity	Is it fully genetically elucidated?	Type of inheritance	Likely causal gene/ chromosomal area	Examples of genetic defects	References
						X-linked	*SMC1A*	Missense, deletion	Musio *et al.* (167); Deardorff *et al.* (168)
						NA	*SMC3*	Deletion	Deardorff *et al.* (168)
						X-linked	*HDAC8*	Loss of function: *de novo* missense, nonsense mutations	Deardorff *et al.* (165)
Kabuki syndrome/Niikawa–Kuroki syndrome (OMIM #147920)	1 in 32,000 Bokinni (169)	Facial gestalt, intellectual disability, visceral and skeletal malformations and, postnatal short stature with overweight	No	Yes	No	Autosomal dominant	*KMT2D/ MLL2/ALR/ KABUK1*	Nonsense substitution, frameshift, deletion	Ng *et al.* (170)
						X-linked dominant	*KDM6A/ UTX/ KABUK2*	Deletions, point mutations	Lederer *et al.* (171); Miyake *et al.* (172)
Kallmann syndrome/ hypogonadotropic hypogonadism with anosmia (OMIM #308700)	1 in 8,000–70,000 Abujbara *et al.* (173)	Anosmia or hyposmia and hypogonadotropic hypogonadism	No	Yes	No	Autosomal dominant	*FGFR1*	Loss of function mutations: nonsense, frameshift, splice-site, missense	Dodé *et al.* (174)
						X-linked	*KAL1*	Frameshift stop mutations, deletions, missense	Hardelin *et al.* (175); Dodé *et al.* (176)
						Autosomal recessive	*PROK2*	Point mutations: missense, frameshift, single nucleotide substitution	Dodé *et al.* (176)
						Autosomal recessive	*PROKR2*	Point mutations: frameshift, missense	Dodé *et al.* (176)
						Autosomal recessive	*SOX10*	Loss of function: missense	Pingault *et al.* (177); Suzuki *et al.* (178)
Kleefstra syndrome/9q34.3 deletion syndrome	Unknown	Mental retardation, obesity, hypotonia, brachycephaly, characteristic facial features and cardiac abnormalities	No	Yes	No	Autosomal dominant	*EHMT1*	Deletions, frameshift, nonsense, *de novo* mutations	Kleefstra *et al.* (179); Cormier-Daire *et al.* (180); Neas *et al.* (181)
Laron syndrome/growth hormone receptor deficiency (OMIM #262500)	Unknown	Short stature, reduced muscle strength and endurance, obesity, hypoglycemia in infancy, small genitals, delayed puberty, thin and fragile hair and dental abnormalities	Yes	Yes	Yes	Autosomal recessive	*GHR*	Nonsense, splice-junction, frameshift mutations	Guevara-Aguirre *et al.* (182); Berg *et al.* (183)
MORM (mental retardation, truncal obesity, retinal dystrophy and micropenis) syndrome	Unknown	Static moderate mental retardation, truncal obesity, congenital non-progressive retinal dystrophy and micropenis	Yes	No	No	Autosomal recessive	*INPP5E**	Loss of function mutations: nonsense	Hampshire *et al.* (184); Jacoby *et al.* (185)
	1 in 20,000		Yes	Yes	No	Variable		Imprinting defects	Jong *et al.* (187)

(*Continues*)

Table 1 (Continued)

Name(s) of the syndrome/ gene and OMIM number	Prevalence	Clinical features	Is the obesity feature mandatory?	Wide clinical heterogeneity	Is it fully genetically elucidated?	Type of inheritance	Likely causal gene/ chromosomal area	Examples of genetic defects	References
Prader–Willi syndrome/ Prader–Labhart–Willi syndrome (OMIM #176270)	Reinhardt *et al.* (186)	Failure to thrive and feeding difficulties during infancy, obesity and hyperphagia beginning in childhood, muscular hypotonia, genital hypoplasia, developmental delay, growth hormone deficiency, short stature, small hands and feet, behavioural problems					*MKRN3/ ZNF127 MAGEL2*	Truncating mutations of paternal allele	Schaaf *et al.* (188)
							NDN	Deletions	MacDonald *et al.* (189)
							NPAP1/ C15orf2	Loss of function	Färber *et al.* (190)
							SNURF-SNRPN	Loss of function of paternal copy	Sahoo *et al.* (191)
Multiple small nucleolar RNAs, specifically *SNORD115/HBII-52* and *SNORD116/HBII-85*	Inactivation and deletion	de los Santos *et al.* (192); Sahoo *et al.* (191)							
paternally inherited chromosome 15q11–q13 abnormalities	Deletion, maternal uniparental disomy chromosome 15, imprinting defects	Donlon *et al.* (193)							
Prader–Willi-like phenotype	Unknown	Mental, psychomotor and developmental delay, obesity, hypotonia and short extremities	Yes	Yes	No	Autosomal dominant	*SIM1*	Loss of function mutations – missense mutations	Villa *et al.* (194); Bonaglia *et al.* (195); Bonnefond *et al.* (73); Ramachandrappa *et al.* (196)
						Autosomal dominant	*MRAP2*	Loss of function mutations	Geets *et al.* (197)
						X-linked dominant	*FMR1*	Loss of function mutations	De Vries *et al.* (198)
						Autosomal dominant	6q16.3q23.3	Duplications	Desch *et al.* (199)
Proximal 16p11.2 deletion syndrome	Unknown	Obesity, autism, intellectual disability, congenital anomalies and developmental delay	Yes	Yes	No	Autosomal dominant	*SH2B1*	Deletions	Bachmann-Gagescu *et al.* (200); Yu *et al.* (201)
							KCTD13	Deletions	Golzio *et al.* (202)

(*Continues*)

Table 1 (Continued)

Name(s) of the syndrome/ gene and OMIM number	Prevalence	Clinical features	Is the obesity feature mandatory?	Wide clinical heterogeneity	Is it fully genetically elucidated?	Type of inheritance	Likely causal gene/ chromosomal area	Examples of genetic defects	References
Rubinstein–Taybi syndrome	1 in 125,000 to 700,000 Kamenarova *et al.* (203)	Short stature, obesity, visual difficulties, keloids, eating problems, spine curvature and joint problems	No	Yes	No	Autosomal dominant	*CREBBP*	Nonsense, frameshift, missense, splice-site, deletions, point mutations	Stevens *et al.* (204); Petrij *et al.* (205)
							EP300	Frameshift mutations	Woods *et al.* (206)
Smith–Magenis syndrome (OMIM #182290)	1 in 15,000–25,000 Carmon a-Mora *et al.* (207)	Intellectual disability, delayed speech and language skills, distinctive facial features, sleep disturbances, obesity, and behavioural problems	Yes	Yes	Yes	De-novo or autosomal dominant	*RAI1*	Haploinsufficiency: deletions, frameshift, nonsense	Slager *et al.* (208); Dubourg *et al.* (209)
WAGRO	Unknown	Aniridia, wilms tumour, genitourinary abnormalities, obesity and growth, and mental retardation	Yes	No	Yes	Autosomal dominant	*BDNF*	Deletions	Han *et al.* (38)
Unnamed 1	Unknown	Severe early-onset obesity, hyperphagia, developmental delay and defects in higher neurological function	Yes	No	Yes	*De novo*	*NTRK2**	Missense mutation	Yeo *et al.* (210)
Unnanmed 2	Unknown	Delayed puberty, hypogonadism, macrocephaly, moderate short stature, central obesity, unprovoked aggressive outbursts, fine intention tremor, pes cavus and abnormalities of the toes	Yes	No	Yes	X-linked	*CUL4B**	Missense mutations	Tarpey *et al.* (211)
Unnamed 3	Unknown	Mental retardation, hair whorls, characteristic facial features, short and broad neck, low posterior hairline, widely spaced nipples, small penis, small and flat feet, hirsutism, myxedematous appearance and dry skin	Yes	Yes	Yes	X-linked	*UBE2A/HR6A*	Deletions, missense and truncating mutations	Nascimento *et al.* (21); Budny *et al.* (212)
Unnamed 4	Unknown	Hyperphagia and severe obesity, developmental delay, impaired cognitive function and hyperactivity	Yes	No	Yes	Autosomal dominant	*BDNF*	Chromosomal inversion, microdeletions	Gray *et al.* (213); Shinawi *et al.* (214)
Unnamed 5	Unknown		Yes	No	Yes		*SH2B1**		Doche *et al.* (215)

(*Continues*)

Table 1 (Continued)

Name(s) of the syndrome/ gene and OMIM number	Prevalence	Clinical features	Is the obesity feature mandatory?	Wide clinical heterogeneity	Is it fully genetically elucidated?	Type of inheritance	Likely causal gene/ chromosomal area	Examples of genetic defects	References
		Severe early-onset obesity, hyperphagia, disproportionate insulin resistance, behavioural abnormalities and reduced final adult height				Autosomal dominant		Loss of function mutations: Frameshift, missense mutations	
Unnamed 6	Unknown	Deteriorating vision, obesity, normal glucose, cholesterol, triacylglycerols levels	Yes	No	Yes	Autosomal recessive	*TUB**	Loss of function: frameshift	Borman *et al.* (216)
Unnamed 7	Unknown	Moderate intellectual disability, behavioural disorder with aggressive and/or autistic features, epilepsy, scoliosis and truncal obesity	Yes	No	No	Autosomal dominant	*CHD2* and *RGMA**	Microdeletions	Courage *et al.* (217)

*The gene has not been replicated or confirmed by a second independent study.
WAGRO, Wilm's tumour, aniridia, genitourinary abnormalities, mental retardation, and obesity.

Table 2 Genetically non-elucidated syndromes identified by our systematic search of literature

Name(s) of the syndrome/gene and OMIM number	Clinical features	Is the obesity feature mandatory?	Clinical heterogeneity	Type of inheritance	Genetic cause	Examples of genetic defects	References
Camera-Marugo-Cohen syndrome (OMIM #604257)	Short stature, mental deficiency, obesity, hypogonadism, micropenis, contractures of the fingers and body asymmetry	Yes	No	Unknown	Unknown	Unknown	Camera *et al.* (218); Lambert *et al.* (219)
Clark and Baraitser XLMR syndrome (OMIM #300602)	Mental retardation, macrocephaly, characteristic facial features and obesity	Yes	No	X-linked	Unknown	Unknown	Baraitser *et al.* (220)
DiGeorge, velocardiofacial and conotruncal anomaly face syndromes (DGS/VCFS/CTAF)/22q11.2 deletion syndrome	Obesity, hyperphagia, parathyroid and thyroid hypoplasia, palatal abnormalities, cardiac malformations and psychiatric symptoms such as aggressive behaviour	No	Yes	Autosomal dominant	22q11.2	Deletions	D'Angelo *et al.* (221)
Distal 16p11.2 deletion syndrome	Developmental delay, behavioural problems, unusual facial morphology and obesity	No	No	Autosomal dominant	16p11.2	Microdeletions	Barge-Schaapveld *et al.* (222)
MEHMO (mental retardation, epileptic seizures, hypogonadism and -genitalism, microcephaly, obesity) syndrome (OMIM #300148)	Mental retardation, epileptic seizures, hypogonadism, microcephaly and obesity	Yes	No	X-linked mitochondrial	Xp21.1–p22.13	Unknown	Steinmüller *et al.* (102); Leshinsky-Silver *et al.* (223); Delozier-Blanchet *et al.* (101)
MOMES (mental retardation, obesity, mandibular prognathism with eye and skin anomalies) syndrome (OMIM #606772)	Mental retardation, delayed speech, obesity, craniofacial manifestations and ocular anomalies	Yes	No	Autosomal recessive	4q35.1 del and/or 5p14.3 dup	Deletions/duplications	Kantaputra *et al.* (224); van Haelst *et al.* (225)
MOMO (macrosomia, obesity, macrocephaly and ocular abnormalities) syndrome (OMIM #157980)	Macrocrania, obesity, ocular abnormalities (retinal coloboma and nystagmus), downward slant of palpebral fissures, mental retardation and delayed bone maturation	Yes	Yes	Autosomal dominant	Unknown	Unknown	Vu *et al.* (96); Moretti-Ferreira *et al.* (226)
Morgagni-Stewart-Morel syndrome/hyperostosis frontalis interna (OMIM #144800)	Advanced hyperostosis frontalis interna, obesity, shortness and cognitive impairment	No	Yes	Autosomal or X-linked dominant	Unknown	Unknown	Koller *et al.* (227)
Ring chromosome 4	Mild developmental delay, deafness, short stature, obesity and the onset of type 2 diabetes in adolescence	No	No	Unknown	Distal 4p	Ring chromosome deletions	Blackett *et al.* (228)
Ring chromosome 11	Ocular anomalies, skeletal, muscular and articular defects, obesity,	Yes	No	Unknown	r (11) (p15.5–q25]	Ring chromosome	Daniele *et al.* (229)

(*Continues*)

Table 2 (Continued)

Name(s) of the syndrome/gene and OMIM number	Clinical features	Is the obesity feature mandatory?	Clinical heterogeneity	Type of inheritance	Genetic cause	Examples of genetic defects	References
	cryptorchidism and mild mental retardation						
ROHHAD	Rapid-onset obesity with hypothalamic dysfunction, hypoventilation and autonomic dysregulation	Yes	No	Unknown	Unknown	Unknown	Ize-Ludlow *et al.* (230)
ROHHADNET	Rapid-onset obesity, hypothalamic dysfunction, hypoventilation and autonomic dysregulation associated with a neural tumour	Yes	No	Unknown	Unknown	Unknown	Bougnères *et al.* (60); Abaci *et al.* (231)
Shashi XLMR syndrome	Mental retardation, coarse face, prominent lower lip, large testes and obesity	Yes	No	X-linked	Xq26–Xq27	Unknown	Castro *et al.* (32); Shashi *et al.* (33)
Unnamed 1	Hypotonia and developmental delay, growth abnormalities, obesity and craniofacial dysmorphism	Yes	No	Unknown	1p36	Deletions	Slavotinek *et al.* (232)
Unnamed 2	Early-onset obesity, hyperphagia, intellectual deficiency and behavioural difficulties	Yes	No	Unknown	2p25	Deletions-paternal	Doco-Fenzy *et al.* (233); Rio *et al.* (234)
Unnamed 3*	Pervasive developmental disorder, delayed speech and rapid onset of obesity	Yes	NA	Unknown	3p25–p26.2	Duplications	Bittel *et al.* (235)
Unnamed 4	Mild dysmorphic features, late presentation of learning difficulties and behaviour problems, obesity, breast hypertrophy and bilateral slipped capital femoral epiphysis	Yes	No	Unknown	4q32.1q32.3	Deletions	Aladhami *et al.* (236)
Unnamed 5	Impaired intelligence, minor dysmorphisms, obesity and genital hypoplasia	Yes	No	Unknown	t(4;14)(q12; q13)	Translocations	Cooke *et al.* (237)
Unnamed 6*	Mental retardation, short stature, obesity, microcephaly, brachycephaly, a short smooth philtrum, central hair whorl, simian creases, 5th finger brachydactyly and skeletal disproportion	Yes	NA	Unknown	6q14–q16	Duplications	Roland *et al.*, 1993 (238)
Unnamed 7*	Intellectual delay, short stature, small hands and feet, eye abnormality, small mouth and obesity	Yes	NA	Unknown	Paternal 6q24.3–q27	Duplications	Smith *et al.* (18)
Unnamed 8	Developmental abnormalities, dysmorphic features, psychomotor delay and truncal obesity	No	No	Unknown	9q34	Duplications	Gawlik-Kuklinska *et al.* (239)
Unnamed 9		Yes	No	Unknown	11p15.4	Microduplications	

(*Continues*)

Table 2 (Continued)

Name(s) of the syndrome/gene and OMIM number	Clinical features	Is the obesity feature mandatory?	Clinical heterogeneity	Type of inheritance	Genetic cause	Examples of genetic defects	References
	Intellectual disability, obesity, overgrowth and dysmorphic features						Sofos *et al.* (240)
Unnamed 10	Distinctive facial dysmorphisms, short stature with small extremities, keratoconus, overweight and intellectual disability	No	No	NA	11q24.1	Microtriplications	Beneteau *et al.* (241)
Unnamed 11	Mental retardation, obesity, variable dysmorphic features and food seeking behavior	Yes	Yes	Unknown	12q subtelomere	Deletions	Niyazov *et al.* (242)
Unnamed 12	Intellectual disability, seizures, obesity and diabetes mellitus	Yes	No	Unknown	17p13.1–p13.2	Duplications	Kuroda *et al.* (243)
Unnamed 13	Intellectual disability, speech delay, truncal obesity, seizures, hearing loss and a particular facial gestalt	Yes	No	Unknown	17q24.2	Microdeletions	Vergult *et al.* (244)
Unnamed 14*	Bilateral periventricular nodular heterotopia, severe learning disability, obesity and epilepsy	Yes	NA	Unknown	der (19) t(X;19) (q11.1–11.2; p13.3)	Translocations	Balci *et al.* (245)
Unnamed 15	Obesity, short stature, hypertrichosis and facial dysmorphism	Yes	No	Unknown	19p13.12	Microdeletions	Van der Aa *et al.* (246)
Unnamed 16	Macrocephaly, obesity, mental retardation and behavior problems	No	No	Unknown	19p13.3	Deletions	de Smith *et al.* (247)
Unnamed 17	Developmental delay, dysmorphic facies, macrocephaly, mental retardation and obesity	Yes	No	Unknown	19q11.05–q13.2 (variable size)	Trisomy/ duplications	Davidsson *et al.* (248); Quack *et al.* (249); Hall *et al.* (250); Zung *et al.* (251)
Unnamed 18	Mental retardation, developmental delay, selective mutism, distinctive facial features, sensorineural hearing loss, single right kidney, uterine didelphys and obesity	No	No	Unknown	Duplication of 20p11.2–p13 and deletion of 20p13.pter	Deletions/ duplications	Trachoo *et al.* (252)
Unnamed 19*	Severe psychomotor delay, behavioural problems, no speech, microcephaly, feeding problems with frequent regurgitation, idiopathic thrombocytopenia, obesity, deep set eyes, down turned corners of the mouth, dysplastic ears and small chin	Yes	NA	Unknown	21q22	Microdeletions	Oegema *et al.* (253)

(*Continues*)

Table 2 (Continued)

Name(s) of the syndrome/gene and OMIM number	Clinical features	Is the obesity feature mandatory?	Clinical heterogeneity	Type of inheritance	Genetic cause	Examples of genetic defects	References
Unnamed 20	Mental retardation, severe macrocephaly, obesity, characteristic face, big hands and feet, advanced bone age and brain abnormalities including frontal cortical atrophy	Yes	No	Unknown	22q13	Deletions	Tabolacci *et al.* (254)
Unnamed 21	Macrocephaly, normal or near normal birth weight and length with subsequent relative obesity, variable developmental delay and typical face, characterised by a square outline with frontal bossing, a 'dished-out' mid-face, biparietal narrowing and long philtrum	Yes	No	Autosomal dominant	Unknown	Unknown	Cole *et al.* (255)
Unnamed 22	Growth retardation, obesity and various physical anomalies such as inguinal or umbilical hernias, cryptorchism, tapering fingers, contractures, deeply rooted thumbs and club-feet	Yes	No	X-linked	Unknown	Unknown	Deshaies *et al.* (256)
Unnamed 23	Obesity, coxa-epiphysiolysis, mental retardation and bilateral thumb ankylosis	Yes	No	Unknown	Unknown	Unknown	Piussan *et al.* (257)
Unnamed 24	Short stature, obesity, minor anomalies including a sloping, narrow forehead, small ears, a narrow nose with prominent bridge and long septum, short upper lip, receding mandible, and short limbs with brachydactyly, and clinodactyly of little fingers	Yes	No	Autosomal recessive	Unknown	Unknown	Schinzel *et al.* (258)
Unnamed 25	Congenital hydrocephalus, mental retardation, short stature, obesity and hypogenitalism	Yes	No	X-linked recessive	Unknown	Unknown	Sengers *et al.* (259)
Unnamed 26	Short stature, obesity, 'bulbous' nasal tip, microretrognathism, brachydactyly, joint hyperlaxity and dislocation and mental retardation	Yes	No	Unknown	Unknown	Unknown	Mégarbané *et al.* (260)
Unnamed 27	Juvenile autoimmune hypothyroidism, pituitary enlargement, obesity and insulin resistance	Yes	No	Unknown	Unknown	Unknown	Reutrakul *et al.* (261)
Unnamed 28		No	Yes		Unknown	Unknown	

(*Continues*)

Table 2 (Continued)

Name(s) of the syndrome/gene and OMIM number	Clinical features	Is the obesity feature mandatory?	Clinical heterogeneity	Type of inheritance	Genetic cause	Examples of genetic defects	References
	Pigmentary retinopathy, hypogonadism, mental retardation, nerve deafness, glucose intolerance and obesity			Autosomal recessive			Edwards *et al.* (262)
Unnamed 29	Colobomatous microphthalmia, obesity, hypogonadism and mental retardation	No	Yes	Autosomal dominant	Unknown	Unknown	Verloes *et al.* (263)
Unnamed 30*	Peculiar facies, obesity, cleft lip and palate, growth hormone deficiency and mental retardation	Yes	NA	Unknown	Unknown	Unknown	Gabrielli *et al.* (264)
Unnamed 31	Craniofacial dysmorphism, short stature, relative obesity, sensorineural deafness, multiple pigmented naevi and severe mental retardation	Yes	No	Unknown	Unknown	Unknown	Sinnerbrink *et al.* (265)
Unnamed 32	Hypogonadism, gynecomastia, mental retardation, obesity and short stature	Yes	No	X-linked	Unknown	Unknown	Vasquez *et al.* (266)
Unnamed 33	Moderate mental retardation, mildly dysmorphic facial features, obesity, hypermetropia and additional hair anomalies	No	No	Unknown	Unknown	Unknown	Thienpont *et al.* (267)
Unnamed 34	Intellectual disability, unusual facial morphology, hand anomalies, microcephaly, short stature and obesity	No	No	Autosomal recessive	Unknown	Unknown	Sousa *et al.* (268)
Unnamed 35*	Mental retardation, shortness of stature, multiple minor anomalies, obesity, and speech deficit	Yes	NA	Unknown	Unknown	Unknown	al-Attia *et al.* (269)
Unnamed 36	Obesity, congenital hypothyroidism, neonatal colitis, cardiac biventricular hypertrophy, craniosynostosis and developmental delay	Yes	No	Unknown	Unknown	Unknown	Tan *et al.* (270)

*Unique syndrome – the syndrome has only been reported in one patient.
ROHHAD, rapid-onset obesity with hypothalamic dysfunction, hypoventilation and autonomic dysregulation; ROHHADNET, rapid-onset obesity with hypothalamic dysfunction, hypoventilation, autonomic dysregulation and neural crest tumour; XLMR, X-linked mental retardation.

The two factors that lead to a higher frequency of autosomal recessive syndromes in certain geographical areas are (i) limited number of ancestors and unique founder mutations in isolated areas such as islands and (ii) consanguineous mating systems (26,27). Hjortshøj *et al.* identified a novel *BBS1* mutation in 10 Bardet–Biedl syndrome (BBS) patients from the Faroe Islands in northern Europe (26). Nine patients were homozygous for the novel splice-site mutation, c.1091 + 3G > C, and one patient was compound heterozygous (26). A founder mutation was concluded to be the most probable cause of this observation as the Faroe Islands are believed to be isolated both historically and genetically (26). Given the relatively higher prevalence of BBS in the province of Newfoundland, Canada, Woods

et al. conducted a genetic survey on 17 BBS families from an isolated island region of Newfoundland (28). Scattered distribution of BBS across Newfoundland was observed, despite the isolation of communities before the construction of roads. They concluded that a single founder effect event was likely not responsible for the observation in all families studied, and that multiple events could have occurred several generations ago (28). The prevalence of BBS among northern European populations has been estimated to be 1 in 160,000, whereas in isolated regions of Kuwait, it is 1 in 13,500 (29). The marked difference between the two can be attributed to the high level of consanguinity in Kuwaiti populations (30).

In the case of sporadic syndromes that are caused by chromosomal segregation errors and by *de novo* genetic and epigenetic events (such as Prader–Willi syndrome [PWS]), the prevalence is not influenced by consanguinity or founder effects. Clinical features of X-linked syndromes are more prevalent among males, although the prevalence of the mutated gene/chromosomal abnormality itself is typically higher among females. Because of X-inactivation, female carriers of pathogenic mutations on the X chromosome display a range of phenotypes, from no clinical features through subtle manifestations to full features of the syndrome (31). Wherever possible, careful phenotyping of carrier mothers should be undertaken and reported along with the phenotype of their sons. For instance, all nine patients reported to have the Shashi XLMR syndrome are males, though maternal body weights were not reported (32,33).

Additionally, the amount of research conducted and case reports published varies geographically, further skewing the apparent geographical prevalence of syndromes.

'Non-mandatory' obesity

Classification of rare genetic syndromes has traditionally relied on clinical observations made by paediatricians and other subspecialists, including efforts to describe subsets of clinical findings that were both necessary and sufficient for diagnosis. Of the 79 syndromes identified in this systematic review, obesity was considered to be a mandatory feature in 55 of them. For the other 24 syndromes, although the prevalence of obesity was higher than that in the general population, obesity was not considered a cardinal clinical feature. For instance, according to a clinical spectrum of Kabuki syndrome patients, 57% of the patients were observed to be overweight or obese (23).

The increasing prevalence of overweight and obesity in the general population poses a difficulty in delineating between correlational and coincidental obesity (3,34). Microtriplication of 11q24.1 has been reported as a highly recognizable phenotype, with a possibility of being an obesity syndrome (35). However, only one of the two patients reported displayed obesity, whereas the other presented with overweight (35). Despite the uncertainty about whether this is an obesity syndrome or not, it was included in our review for completeness. Such ambiguity is pronounced in cases where only one patient is reported. For instance, Blackett *et al.* described a unique case of a patient with a ring chromosome 4 displaying early-onset T2D, deafness, developmental delay, short stature and obesity (36). Although the combination of these clinical features could be used to classify this patient as having a unique form of syndromic obesity, obesity could also be coincidental (36).

The difficulty in classifying case reports as syndromic forms of obesity can be decreased by comparing the prevalence of obesity in the general population with that of the patient population. A clinical spectrum of 110 adult Angelman syndrome (AS) patients found that 32% of the patients were overweight or obese, with a disproportionally higher prevalence in females (37). In such cases, where the prevalence of obesity in the general population is close to that in the patient population, identification of the genetic cause behind the obesity feature or the syndrome is beneficial for determining whether or not obesity is a clinical feature of the syndrome. For instance, approximately 48% of Wilm's tumour, aniridia, genitourinary abnormalities and mental retardation (WAGR) syndrome patients were found to display obesity (38). A bimodal distribution of BMI was observed, and molecular evidence showed that all patients with a deletion including the *BDNF* locus are obese, resulting in the delineation of the Wilm's tumour, aniridia, genitourinary abnormalities, mental retardation and obesity (WAGRO) syndrome (38).

Clinical heterogeneity

Theoretically, clinical heterogeneity within a syndrome can be attributed to genetic or allelic heterogeneity, ancestral differences, environmental impacts including interventions/medical treatments, and epigenetics. Gene–environment and gene–gene interactions, two topics that have yet remained largely unexplored in this field, could also play a role. Genetic heterogeneity can also be due to structural variants such as insertions, deletions, inversions and complex rearrangements.

Our systematic review of literature indicates that 23 obesity syndromes display wide phenotypic heterogeneity. However, because clinical heterogeneity is common within syndromes, and there is a limited number of syndromic obesity patients, studying phenotypic heterogeneity is challenging, and there might be more syndromes presenting with phenotypic heterogeneity.

Genetic/allelic heterogeneity

Carmi *et al.* compared the clinical manifestations of BBS patients from three unrelated Arab-Bedouin kindreds and

observed differences in the limb distribution of the postaxial polydactyly and the extent and age of onset for obesity (39). *BBS4* abnormalities, located on chromosome 15, were associated with early-onset morbid obesity, whereas patients with *BBS2* abnormalities, located on chromosome 16, displayed a milder form of obesity (39).

Cornelia de Lange syndrome (CdLS) can be caused by mutations in *NIPBL*, *RAD21*, *SMC1A*, *SMC3* and *HDAC8* (40). Typical *NIPBL* abnormalities include small intragenic alterations such as missense, nonsense, splice-site, regulatory mutations and deletions/insertions/duplications, resulting in a partially or non-functional truncated protein (40). A CdLS patient mosaic for the c.2827delA mutation in *NIPBL* demonstrated growth and psychomotor retardation, characteristic of the severe form of CdLS (41). However, he did not display severe limb reduction defects and other major malformations observed with typical CdLS *NIPBL* mutations, suggesting a mild form of the syndrome (41). This case was also the first evidence of somatic mosaicism in CdLS, explaining the unique collection of clinical features as the mutation was shown to be present in about 10–33% of DNA samples from peripheral blood and buccal smears (41). On the other hand, microduplications in *NIPBL* result in the 5p13 microduplication syndrome, characterized by developmental delay, autistic behaviour, obesity, lymphedema, hypertension and macrocephaly (41,42). Thus, genetic and allelic heterogeneity can result in clinical heterogeneity within a syndrome and also in the delineation of two different syndromes due to considerably diverse phenotypes.

Bardet–Biedl syndrome is an excellent example of genetic heterogeneity, because 21 genes have been identified that can contribute to BBS (43–45). *BBS1* to *BBS20* code for proteins is involved in the production or functioning of the BBSome complex, which controls cilium function (44). The involvement of *BBS21* with the BBSome is still being studied (43). Compared with the wide range of genetic heterogeneity in BBS, the clinical features seem to be fairly homogeneous. Similarly, Kallmann syndrome can result from mutations in *FGFR1*, *KAL1*, *PROK2* and *PROKR2* (46).

Methylation-specific multiplex ligation-dependent probe amplification (MS-MLPA) was used to detect unique deletions within the 15q11.2 and 15q13.3 regions in seven PWS patients with distinct phenotypic features (47). Although the chromosomal region was the same as the typical PWS region, the deletions were either smaller (~2.46 Mb) or larger (~9.31 Mb) than the typical deletions (5.3–6 Mb) (47).

Alström syndrome is a ciliopathy caused by mutations in *ALMS1* (48). Marshall *et al.* conducted a mutation spectrum of *ALMS1* in 239 Alström syndrome patients. They identified 109 novel mutations, which increased the total number of *ALMS1* mutations identified by that time to 239 (48). The majority of the mutations were nonsense and frameshift (insertions or deletions). Splice-site mutations, an *Alu* transposon insertion and a balanced translocation have also been reported, as have larger deletions that remove entire exons. (49–52).

Ethnic differences

Ethnic differences can also result in a varying presentation of clinical features. Atypical presentation of the clinical features of PWS in African–Americans has been reported. For instance, in the 10 African–American PWS patients assessed by Hudgins *et al.*, growth was less affected, hand and foot lengths were usually normal and facies were atypical in comparison with PWS Caucasian patients (53). This phenotypic difference between Caucasian and African–American populations can result in the under-diagnosis of PWS in African–Americans (53). Butler *et al.* suggested that this under-reporting can be due to the less characteristic appearance and absence of acromicria (54).

Medical interventions

Treatment can also be a modifying factor in the clinical presentation of syndromes with obesity. Improvements in physical parameters with growth hormone therapy in PWS patients have been reported by multiple studies. Whitman *et al.* studied the impacts of growth hormone treatment in children and adolescents with PWS over a 2-year period and found physical and small behavioural improvements in the patients (55). Physical improvements include improved muscle tone, strength and endurance. Children undergoing growth hormone therapy showed a decrease in parent-reported symptoms of depression (55).

Epigenetics

Epigenetics is an emerging field in human diseases, and its role in the development of various disorders, such as obesity, is still being studied. Patwari *et al.* reported on monozygotic twins discordant for the rapid-onset obesity with hypothalamic dysfunction, hypoventilation and autonomic dysregulation (ROHHAD) phenotype, where only one twin manifested the typical clinical features of ROHHAD syndrome (56). ROHHAD syndrome has not yet been genetically elucidated. Alternative etiologies such as autoimmune or epigenetic influences and a combination of genetic predisposition and acquired precipitant have been suggested (56).

Overlap of clinical features and diagnostic difficulties

Clinical features among the 79 identified syndromes often overlap. For instance, at least 52 obesity syndromes display some form of mental retardation, seven syndromes present with macrocephaly and seven syndromes with microcephaly.

Non-obligatory obesity, clinical heterogeneity and overlap of clinical features between syndromes all contribute towards difficulties experienced by clinicians in effectively diagnosing syndromic obesity (57). Milani *et al*. reported on a patient who was initially diagnosed with BBS when she was 8 years old. However, at the age of 14, an updated clinical and genetic analysis was used to correctly diagnose the patient as having Alström syndrome. Alström syndrome and BBS are ciliopathies and despite being genetically distinct, display clinical overlap of features such as retinal degeneration and obesity (57).

Evolution of clinical features of syndromes with new reports

Clinical spectra based on large series of patients and reports of additional patients play a critical role in refining the description of syndromes, but both methods have limitations.

In a clinical study of seven patients with Kabuki syndrome, three patients had ocular anomalies (58). This novel finding was added to the list of Kabuki syndrome clinical features and encouraged detailed ophthalmologic examination of patients for better diagnosis and treatment options (58). Macrocephaly, obesity, mental (intellectual) disability and ocular abnormalities (MOMO) syndrome was initially defined as macrosomia, obesity, macrocephaly and ocular abnormalities syndrome (59). However, after reporting the clinical features of two additional MOMO syndrome patients, it was suggested that macrosomia be excluded from the syndrome name as only four features (macrocephaly, obesity, mental disability and ocular abnormalities) are unique to this syndrome and should be used as the major diagnostic criteria (59). The difficulty associated with such clinical spectra is the lack of a large series of patients due to the extremely low prevalence of certain obesity syndromes.

The endocrine manifestations of rapid-onset obesity with hypothalamic dysfunction, hypoventilation, autonomic dysregulation and neural crest tumour (ROHHADNET) syndrome in six patients were studied by Bougnères *et al*. (60). They found a wide range of hypothalamic–pituitary endocrine dysfunctions and concluded that the possible diagnosis of ROHHADNET should be considered in all cases involving isolated, rapid and early-onset obesity (60). Deep phenotyping collects information beyond what is usually recorded in medical charts and requires not only expertise but also additional time (61).

Uniting and subdividing obesity syndromes

Progress in the genetic elucidation and continuous evolution of the cardinal features of a syndrome with clinical spectrums and reports of additional patients has enabled the subdivision and unification of syndromes for improved scientific nosology and diagnosis. Before the advent of genetic technologies, diagnoses relied heavily on patients' phenotypic features. For instance, researchers have proposed uniting Carpenter, Goodman and Summit syndromes into one syndrome due to the overlap of clinical features such as obesity, syndactyly and acrocephaly (22). The difference in the features of these three syndromes can be attributed to clinical heterogeneity and is not significant enough to classify them as unique syndromes (22). Recently, DNA-level evidence obtained through genetic tests has been used to improve diagnostic criteria. WAGR syndrome can be subdivided into two syndromes, WAGR and WAGRO. In addition to the typical features of WAGR, WAGRO patients also display obesity (62). This subdivision of WAGR has been confirmed by molecular evidence because all WAGR patients presenting with deletions in *BDNF* have obesity (38).

Gene identification techniques

Analysis of our search results shows that only 30 out of 79 obesity syndromes have been partially or fully genetically elucidated, and the chromosomal location of the causal gene is assumed to be accurate for 27 non-elucidated syndromes. Genetic elucidation of syndromes is critical, because it provides a clue to the molecular mechanisms associated with the development of the disorder, improving the diagnostic criteria, care and treatment plans. Cytogenetics, linkage, homozygosity mapping, candidate gene, functional genomics and whole-exome sequencing (WES) studies have been employed for the identification of obesity syndrome critical chromosomal regions and genes. BBS is an excellent illustration because the 21 BBS genes have been identified using diverse methods (43–45).

Genetic and chromosomal abnormality detection started with karyotyping. Over time, technological advances enabled mutation identification techniques such as cytogenetics in order to identify large chromosomal abnormalities (63). A combination of multiplex ligation-dependent probe amplification (MLPA), fluorescence in situ hybridization (FISH) and array comparative genomic hybridzation (aCGH) analyses were used to detect a large (>80 kb) mosaic deletion in *NIPBL* in a Cornelia de Lange patient (64). For smaller sized deletions, microduplications and copy number variations (CNVs), the use of genome-wide single nucleotide polymorphism (SNP) array in combination with CNV analysis can be used to identify the disease-causing CNV. For instance, Walters *et al*. identified the 16p11.2 deletion syndrome by using a combination of aCGH, genotyping arrays, quantitative polymerase chain reaction and MLPA (65). Capturing such rare variants or recurring CNVs can be difficult when using SNP tagging, and a combination of strategies might be needed to identify the variant (65).

When the genetic cause is not a structural abnormality, alternative techniques to identify mutations have been developed. Linkage mapping has been the standard means of detecting the chromosomal location of a disease gene for most of the 20th century (66). Compared with mapping complex diseases, it has proven to be more successful for mapping genes contributing to monogenic rare diseases (66). Kwitek-Black *et al.* performed a genome-wide search for linkage to map *BBS2* to chromosome 16q (67). SNP microarray genotyping for homozygosity mapping in a small consanguineous Israeli Bedouin family with BBS was used to identify a candidate region. Mutation analysis of the candidate region identified a mutation in *TRIM32*. Functional analysis of *TRIM32* in zebrafish and expression correlation analysis among other BBS genes were used to show that *TRIM32* is the BBS11 gene (68). Chiang *et al.* used comparative genomic analysis to identify *ARL6* as the *BBS3* gene (69). Similarly, a combination of comparative genomic analysis, gene expression studies using BBS knockout mouse models and homozygosity mapping was used to identify parathyroid hormone-responsive gene B1 as the BBS9 gene (70). Through linkage analysis in an Isreali Bedouin kindred, *BBS3* had been earlier mapped to chromosome 3 (71). In order to identify the best candidate genes, it was hypothesized that the genomes of model organisms that contained orthologues to previously known BBS genes could also contain an orthologue for *BBS3* (69). DNA from the Bedouin kindred was then sequenced. The results showed that all affected individuals carried a homozygous stop mutation in the same candidate gene *ARL6*, demonstrating that *ARL6* is *BBS3* (69). Using a similar functional genomic approach with *FLJ35630* as a candidate gene, Stoetzel *et al.* identified the *BBS12* gene as they found pathogenic homozygous mutations in two Gypsy families and 14 families of various ethnic backgrounds (72).

Sim1 haploinsufficiency in mice induces hyperphagic obesity and developmental abnormalities in the brain (73). Bonnefond *et al.* observed that deletions of the 6q16 region in humans had been reported in some obese children with Prader–Willi like syndrome (PWLS), and *SIM1* is located within this region (73). A unique approach was then used to confirm a link between *SIM1* and obesity in humans. *SIM1* was sequenced in four subject groups as (i) children with PWLS features, (ii) children with severe early-onset obesity, (iii) morbidly obese adults and (iv) controls. After conducting genetic and functional studies, a firm link between *SIM1* loss-of-function mutations and the presence of PWLS was established (73).

More recently, WES has been used to identify disease genes. Mapping of rare monogenic diseases has been revolutionized by the development of next-generation sequencing. WES limits the capture and sequencing to gene exons, and is well suited for rare Mendelian disorders. Bee *et al.* utilized this approach to identify a novel mutation (p.Y644X) in the *BBS2* gene (74).

Obesity syndromes may show complex patterns of inheritance

Increasing genetic elucidation of obesity syndromes has provided an insight into the intricate nature of their inheritance. Kallmann syndrome has been attributed to autosomal or X-linked mutations (75). The autosomal mutations can be located in *FGFR1*, *PROKR2* or *PROK2*, and the X-linked mutations are located in *KAL1* (75). Dodé *et al.* analysed these mutations in a cohort of 192 patients using a candidate gene strategy. *PROK2* mutations were found in the heterozygous state, whereas *PROKR2* mutations were present in the heterozygous, homozygous or compound heterozygous states (75). One of the patients heterozygous for the *PROKR2* mutation was also carrying a missense mutation in *KAL1*, providing a possibility of digenic inheritance for Kallmann syndrome (75).

Triallelic inheritance has been suggested for BBS. After screening a cohort of 163 BBS families for mutations in *BBS2* and *BBS6*, it was proposed that BBS may not be a single-gene recessive disease, but rather a complex disorder requiring three mutant alleles for full disease penetrance (76). Genetic evidence for involvement of another locus was found in at least nine of the 19 families with *BBS2* mutations and three of the eight *BBS6* pedigrees (76). *BBS4*, a minor contributor to BBS, has also been proposed to participate in this triallelic inheritance model (77). However, further studies testing for triallelism in BBS did not find convincing evidence for this model of inheritance, and it can be considered a rare phenomenon (78,79).

The pathogenesis of CdLS can be influenced by modifying genes. Pié *et al.* conducted a molecular characterization of 30 unrelated CdLS patients (80). Despite sharing the same mutation in *NIPBL* (p.R827GfsX2), several patients displayed variable phenotypes, indicating the influence of modifiers and the possibility of oligogenic inheritance (80).

A unique case of mosaicism was observed in monozygotic twins with discordant phenotypes (81). Twin 1 exhibited syndromic obesity features such as developmental delay and overweight, whereas twin 2 had an autistic spectrum disorder. Molecular karyotyping showed that twin 1 had a 2p25.3 deletion (81). On the other hand, twin 2 had that deletion in one-third of the cells, displayed a 2p25.3 duplication in one-third of the cells, with the remaining one-third being normal (81). This complex pattern could be a result of mitotic non-allelic recombination during blastomeric divisions of a normal zygote (81).

In another rare case, a female patient with unaffected parents was diagnosed with Börjeson-Forssman-Lehman Syndrome, an X-linked syndrome (82). Skewed X inactivation, with a high proportion of cells in which the normal X

chromosome was inactivated, was considered to be the most likely explanation for this observation (82).

There has been a recent increase in the search for modifying genes and SNPs in single gene disorders (83). Obesity predisposing SNPs can potentially modify the severity of obesity in syndromes, leading to complex patterns of monogenic and polygenic inheritance. However, we did not find any studies related to the impact of SNPs on the presentation of syndromic forms of obesity, which can be attributed to the rarity of the syndromes.

A contiguous gene syndrome requires the deletion/duplication of multiple adjacent gene loci for the presentation of the cardinal features of a syndrome (84). For instance, PWS results from deletion of paternal chromosome 15q11–13 and WAGR syndrome is caused by 11p13 deletions (38,85). The genetic elucidation of such syndromes is further complicated as not all genes within the deleted/duplicated region might be causal (85).

Quality of evidence

Quality of evidence has been defined as the extent to which one can be confident that an estimate of effect is correct (86). Assessment of the quality of evidence of the clinical and genetic properties of syndromes is important for clinicians to know how much confidence can be placed in recommendations of scientific reports.

Cohen syndrome is characterized by non-progressive psychomotor retardation, microcephaly, characteristic facial features, retinal dystrophy and intermittent neutropenia (87). Carey *et al*. described four patients with Cohen syndrome, and one of them was of normal intelligence. They concluded that mental deficiency should not be considered a mandatory feature of Cohen syndrome (88). However, subsequent clinical spectrums with more patients confirmed that psychomotor retardation was a cardinal feature of the syndrome (89). This observation points to the need for critical appraisal of literature. Unique case reports refer to the syndromes for which only one patient has been reported in literature. Seven of the syndromes identified by our search are unique case reports. Because these syndromes have not been confirmed by additional reports, it can result in poor quality of evidence. None of the unique reports used the Case Report (CARE) guidelines, or another form of reporting assessment, in order to increase the quality of evidence (90).

Of the 68 disease genes identified through our search, 59 have been replicated and confirmed in independent studies, increasing the confidence in the results. The quality of evidence can also be elevated by avoiding the reporting of initial false positive results (91). Chromosome 8p22–8p23.1 duplication was reported to lead to Kabuki syndrome by studying six unrelated Kabuki syndrome patients (92). This finding was soon proven false by other research teams after unsuccessful replication attempts (93,94). A re-examination of this region by Milunsky *et al*. confirmed that the original study published was a false positive (95). A homozygous balanced reciprocal translocation (16;20)(q21;p11.2) suggested *LINC00237* to be a candidate gene for MOMO syndrome (96). However, due to the lack of a confirmatory study, this finding could not be verified, and the genetic aetiology of MOMO syndrome is still debated. Replication studies are required to identify false positive results and confirm novel findings.

Discussion

Gaps in our knowledge and classification of syndromic obesity

Previous reviews on the genetics of obesity have described 20 to 30 syndromes (6,12,97–99). In this systematic review, we describe 79 syndromes associated with obesity, which highlights the importance of the present knowledge synthesis effort.

Naming of obesity syndromes

Our results demonstrated that 43 syndromes have not been assigned a name, and 11 syndromes have more than one name. Such inconsistencies can hinder the search for relevant scientific literature, efficient diagnosis and further scientific research on the syndrome. Naming discrepancies found through our literature search emphasize the need for systematic and straightforward naming guidelines for syndromes. For instance, the WAGR/WAGRO and ROHHAD/ROHHADNET syndromes may be seen as unique syndromes with mandatory and non-mandatory clinical features (38,60,62,100). Rather than multiplying the description of new syndromes with close clinical features, clinical heterogeneity within an established syndrome should be acknowledged.

Instead of naming syndromes after their clinical features or genetic regions, they should be named using the last names of the first author and last author of the first research team that described the syndrome for consistency. In cases where more than one research team describes a new syndrome at the same time, or if there is shared first authorship, a maximum of three last names could be used to name the syndrome. If a research team described more than one syndrome, alternative names should be used to name the syndrome to avoid confusion in the field. Two brothers displaying the features of the mental retardation, epileptic seizures, hypogenitalism, microcephaly and obesity (MEHMO) syndrome were first reported in the French language in the year 1989, but the authors did not provide a name for this new syndrome at the time (101). Nine years later, Steinmuller *et al*. described additional patients, considered it to be a novel syndrome and named it as MEHMO (102). This is an example of a naming discrepancy caused

due to language barriers, stressing the importance of reporting novel syndromes in the universal English language. Obesity syndromes often have overlapping clinical features, and acronyms will not suffice as they can result in very similar names (e.g. MEHMO and MOMO). Moreover, because the cardinal features of a syndrome can evolve with new reports, naming a syndrome using this method might result in the name being irrelevant after a revision of the cardinal features. Assigning the gene or region of chromosomal abnormality as the name of the syndrome is also not the preferred method as the same gene or chromosomal region can result in more than one syndrome. Additionally, genetic elucidation of syndromes can advance, and more than one gene causing the same syndrome can be identified, rendering the name of the syndrome irrelevant or inaccurate. The World Health Organization recently developed a report outlining the best practices for naming new human infectious diseases, and similar guidelines should be developed for a systematic approach to naming pleiotropic syndromes (103).

Classification of obesity syndromes

One of the difficulties noted in this field was identifying whether the obesity feature in a syndrome is coincidental or correlational. For instance, BMI has been shown to be negatively correlated with intelligence quotient, making it more likely to find obesity in syndromic patients with mental retardation (104,105). Thus, even if obesity is highly prevalent in a syndrome, it could be due to a random association. In AS and the 22q11.2 deletion syndrome, obesity tends to develop later in life, and it is unclear whether the obesity phenotype is associated with the genetic defects or with other clinical features such as intellectual disability and difficulty walking (37,106).

A suggestion for developing guidelines to classify a syndrome as an obesity syndrome is ensuring that the prevalence of obesity in the patient population is higher than that in the general population. We suggest using obesity (BMI > 30 kg m^{-2} in adults or >95th percentile in children) as a cut-off for identifying an obesity syndrome as obesity is more severe than overweight and is less likely to occur coincidentally. Numerous obesity syndromes display early-onset obesity. When diagnosing obesity in the paediatric age group, proper comparison to age-matched and ancestry-matched controls would enable better delineation of the quantitative effect size of rare alleles that contribute to obesity in these syndromes. It is likely that not all alleles will shift the BMI *Z*-score by 2 standard deviations or more. In some patient groups, such as those for 16p11.2 deletion syndrome, obesity is fully penetrant in adults, whereas not all children reach the obesity cut-off (65). Thus, the analysis of parental BMI, along with their genotypic analysis, can help establish the effect size of an individual rare allele across different age groups and better diagnose the obesity syndrome in the paediatric age group.

The average prevalence of obesity in a syndrome can be close to that in the general population, such as that for AS (37). An innovative way to overcome such a challenge is to test for a bimodal distribution of BMI, as it can indicate whether the obesity feature is related to specific disease genes/genetic abnormalities. This decreases ambiguity as to whether the prevalence of obesity is significant enough for the syndrome to be considered an obesity syndrome or not. Han *et al*. studied the relationship between BMI and genotype in 33 WAGR/WAGRO patients and found an association between BDNF haploinsufficiency and BMI (38). Obesity was more prevalent in cases where chromosome 11p deletions, resulting in the WAGRO syndrome, encompassed *BDNF* (38). Such assessment of bimodal distribution requires a sufficient number of patients and some knowledge of the disease gene or chromosomal abnormalities. Thus, the DNA-level difference can be used to predict the phenotype and better classify a syndrome as an obesity syndrome.

With advanced clinical and genetic knowledge of obesity syndromes, we have a better understanding of the clinical and genetic overlap between syndromes, clinical heterogeneity within a syndrome and evolution of clinical features with the description of more patients. The current classification of syndromes, developed majorly on the basis of cardinal features, may be outdated. Using genetic testing and molecular information to classify syndromes may prove to be more efficient. For instance, on a molecular level, all ciliopathies (e.g. BBS and Alström syndrome) affect ciliary function, which could be used to classify them all as the same disease with extensive clinical and genetic heterogeneity (107). Diabetes is an example of a disease that has numerous sub-classifications based on molecular and clinical features (108,109). Developing a similar organizational structure for ciliopathies will enhance classification of syndromes that are also ciliopathies, improving the process of diagnosing, managing and treating syndromic obesity.

Very few syndromes have a perfect 1:1 correlation between an individual mutation and a unique set of clinical manifestations. If different pathogenic mutations in the same gene can lead to a syndrome, then the syndrome manifests allelic heterogeneity. If, in addition, pathogenic mutations in different genes can lead to the same syndrome, then the syndrome also manifests genetic heterogeneity.

Clinical guidelines for diagnosing syndromes have been formulated (19). However, updating these guidelines with scientific advancements is required to reach the correct diagnosis. Diagnosis can be made based on clinical and genetic analysis. Testing for clinical features is not as accurate because of its qualitative nature and clinical heterogeneity within syndromes. Thus, once a syndrome is genetically elucidated, clinical description combined with genetic testing is an optimal diagnostic approach.

Genetic elucidation of obesity syndromes

Only 24.1% of obesity syndromes have been fully elucidated and 13.9% have been partially elucidated. No disease genes for the remaining 62% have yet been identified, pointing towards a need for increased effort in elucidating the genetic basis of obesity syndromes. A limited number of patients, funding constraints and complex patterns of inheritance (modifying genes, mosaicism, epigenetics) can obstruct advancements in genetic elucidation of obesity syndromes.

The quality of genetic elucidation can be improved through methodological, technological and organizational changes. The elucidation of Mendelian and more complex patterns of inheritance has been limited in the past because of technical constraints. However, with the development of new tools such as WES and WGS, more syndromes may be genetically elucidated. Whole genome sequencing (WGS) has significantly contributed towards the identification of genetic variants. WGS in 2,657 European individuals and exome sequencing in 12,940 individuals from five ancestry groups was used to study variants associated with T2D. Genetic variants (26.7 million) such as single nucleotide variations (SNVs) and point mutations, in addition to indels and large deletions, were detected. Compared with GWAS, this technique allows a more thorough study of disease-related SNVs and indels (108). Thus, in order to significantly advance genetic identification, WGS should be the next step as it has the capability to identify point mutations, indels, microdeletions, CNVs and large chromosomal abnormalities.

In order to fully understand the genetics and inheritance of obesity syndromes, we need to increasingly analyse digenic and multigenic inheritance and gene–gene and gene–environment interactions. Genetic diseases can be a result of complex combinations of variant alleles at multiple loci. Assessments of the genome beyond single-locus analysis, placing more emphasis on rare and common SNVs and CNVs, should be conducted (110). A digenic pattern of inheritance has been observed in diseases such as facioscapulohumeral muscular dystrophy and retinitis pigmentosa, showing that Mendelian patterns are not always responsible for the inheritance of monogenic diseases (110). Similarly, epigenetics is an emerging field in human diseases, and its role in the development of various disorders, such as obesity, is still being studied. Organizational changes include the development of international consortia, such as the ones developed for complex polygenic diseases. For instance, the Genetic Investigation of ANthropometric Traits (GIANT) consortium is an international collaboration developed for studying the genetics of polygenic obesity and measured traits such as BMI, height and waist circumference. Data from the GIANT consortium have been used to identify numerous genetic loci associated with traits such as BMI and risk of obesity (111,112). Such consortia on an international level may increase the quality and quantity of genetic elucidation for obesity syndromes and identification of clinical features and molecular determinants of a disease. Tools such as GeneMatcher may also help connect researchers and clinicians working on the genetic elucidation of rare obesity syndromes (113).

It is noteworthy that common genetic variants in/near genes involved in obesity syndromes (e.g. *BBS4*, *BDNF, NTRK2, SDCCAG8*, *SH2B1* and *TUB*) have been conclusively associated with BMI variation/common obesity in children and adults through GWAS (98). Thus, investigation of syndromic obesity genes can benefit to the identification of gene loci associated with polygenic obesity (98).

Quality of evidence

Implementation of high scientific standards in research designs ensures the accuracy of results and prevents potential negative clinical consequences, such as the administration of improper treatments. Nine of the 68 disease genes identified by our search have not been replicated or confirmed by independent studies, which points to the need for an increased effort in confirming candidate genes and replicating novel results. Considering the extent of genetic variability among humans, the co-occurrence of a genetic alteration with a syndrome can be coincidental rather than causal in the absence of replication.

A high quality of evidence is required to increase clinicians' confidence in the results and attain the efficient diagnostic and treatment criteria for syndromes. Quality metrics need to be developed and implemented in order to assess the quality of evidence in scientific literature pertaining to syndromic obesity. We recently developed Q-Genie, a methodological tool for assessment of the quality of polygenic association studies (114). Similar quality metrics for Mendelian diseases can be used to increase the reliability and quality of syndromic obesity studies. The CARE guidelines for assessment of case reports and the strengthening the reporting of genetic association studies (STREGA) for assessment of polygenic diseases have been developed (90,115,116). However, tools specifically built for assessing quality of evidence for case reports and genetic elucidation of syndromic monogenic obesity are still lacking. The rare occurrence of obesity syndromes can be a challenge in achieving a high quality of evidence.

Strengths and limitations

Our study is the first systematic review of literature on obesity syndromes and their genetic elucidation. A systematic review ensures the analysis and reporting of all reports found through a broad literature search. The inclusive nature of our report is evident from the initial number of references (13,719) retrieved through our literature search of

seven different databases. Because of the exhaustive and systematic nature of our review, we identified 79 obesity syndromes. We recognized challenges faced by researchers and clinicians in the field of syndromic obesity and provide suggestions for improvements in this field. These suggestions have the potential to serve as a framework for the formulation of rigorous guidelines.

The first limitation of our review is that we found it difficult to draw a strict distinction between monogenic syndromic and monogenic non-syndromic forms of obesity. The leptin–melanocortin pathway involves genes such as *LEP*, *LEPR*, *SH2B1*, *POMC*, *PCSK1*, *MC4R* and *MC3R* (98). Abnormalities in these genes mainly result in monogenic (homozygous/heterozygous compound mutation carriers) and oligogenic (heterozygous mutation carriers) obesity through their influence on food intake and energy expenditure (98). Other than obesity, clinical features associated with genetic abnormalities in the leptin–melanocortin pathway include hypogonadotrophic hypogonadism, low blood pressure, behavioural abnormalities, cholestasis and seizures (98). These pleiotropic clinical features fit with the definition of syndromic obesity. For the purposes of this review, we did not consider them as syndromic as they have traditionally been defined as monogenic non-syndromic forms of obesity. A detailed review of syndromic and non-syndromic classification of monogenic obesity is required to update the criteria used to classify monogenic obesity.

The second limitation is that the prevalence of some syndromes was not available because of their extremely rare nature. Because the apparent prevalence also depends on the frequency of case reports published in various geographical areas, the reported prevalence might not be generalizable globally. Additionally, founder effects and non-random mating can increase the apparent prevalence of autosomal recessive syndromes. We found that 23 obesity syndromes display wide clinical heterogeneity. The reporting of whether a syndrome displays clinical heterogeneity or not is based on the limited number of case reports available in literature, decreasing the reliability of this information. Additionally, the clinical heterogeneity for the seven unique case reports could not be assessed as they have only been reported in one patient so far.

The final limitation of our review is the inability to assess the quality of evidence provided by the included case reports, due to the lack of specific guidelines for assessing syndromic obesity case reports, case series and genetic elucidation studies.

Conclusion

The compilation of obesity syndromes summarized in our systematic review provides a comprehensive update on the current status of literature on syndromic obesity. We suggest ways in which the existing knowledge gap can be overcome. With technological advancements in the field of genetics, improved genetic elucidation can potentially identify disease genes for the partially elucidated and non-elucidated obesity syndromes. Enhanced clinical research through international collaborations and development of consortia will advance our understanding of the genetic bases and inheritance of syndromic obesity and the biology of human obesity. In the long run, a revision of the classification of syndromes based on molecular evidence, increased organization and systematic assessment of quality of evidence in the field of syndromic obesity can potentially improve prenatal and post-natal diagnosis, management and treatment of obesity syndromes. We hope that our systematic review of literature on syndromic obesity encourages and stimulates progress to advance our understanding of the clinical and genetic aspects of syndromic forms of monogenic obesity.

Conflict of interest statement

No conflict of interest was declared.

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Author contributions

R. J. d.S. and D. M. contributed to the study conception and design. Y. K., R. J. d.S. and D. M. designed and implemented the literature search. Y. K., R. J. d.S. and D. M. acquired the data. Y. K. and D. M. conducted the data analysis and interpretation. Y. K., R. J. d.S. and D. M. conducted the statistical analysis. Y. K. and D. M. drafted the manuscript. R. J. d.S. and W.G. conducted the critical revision of the manuscript for intellectual content. D. M. provided administrative, technical or logistical support and supervised the project. All authors approved the final version of the manuscript.

Supporting information

Additional Supporting Information may be found online in the supporting information tab for this article. http://dx.doi.org/10.1111/obr.12531

Table S1: Search queries used in systematic review for the seven databases.

Table S2: Search queries (Pubmed) for types of genetic defects for syndromes and their associated genes.
Table S3: Relevant animal studies included in our review but not captured by our search.
Table S4: Key references identified by a subject matter expert not captured by the literature search.

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