Review Article

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The genetic elucidation of monogenic obesity in the Arab world: a systematic review

Abstract

Background: Investigation of monogenic obesity (MO), a rare condition caused by a single gene variant(s), especially in consanguineous populations, is a powerful approach for obtaining novel insights into the genetic alterations involved. Here, we present a systematic review of the genetics of MO in the 22 Arab countries and apply protein modeling *in silico* to the missense variants reported.
Methods: We searched four literature databases (PubMed, Web of Science, Science Direct and Scopus) from the time of their first creation until December 2020, utilizing broad search terms to capture all genetic studies related to MO in the Arab countries. Only articles published in peer-reviewed journals involving subjects from at least one of the 22 Arab countries and dealing with genetic variants related to MO were included. Protein modelling of the variants identified was performed using PyMOL.
Results: The 30 cases with severe early-onset obesity identified in 13 studies carried 14 variants in five genes (*LEP, LEPR, POMC, MC4R and CPE*). All of these variants were pathogenic, homozygous and carried by members of consanguineous families.
Conclusion: Despite the elevated presence of consanguinity in the Arab countries, the genetic origins of MO remain largely unexplained and require additional studies, both of a genetic and functional character.

Introduction

Childhood obesity is a major global health problem, with more than 340 million cases worldwide in 2017 [1]. In Arab countries, the prevalence of childhood obesity has been increasing dramatically due to the sedentary lifestyle and increased consumption of food rich in fat associated with improvements in living standards [2]. In addition, genetic predisposition exerts a considerable impact on susceptibility to obesity in these countries, as shown by early twin studies and the discovery of rare monogenic forms of obesity [3, 4].

Monogenic obesity (MO) resulting from a single gene variant(s) leads to severe obesity with onset usually before the age of 5 [5, 6]. Many of the genes which predispose for the development of MO encode proteins related to the leptin-melanocortin pathway responsible for food intake and energy expenditure, including leptin (*LEP*), the leptin receptor (*LEPR*), preopiomelanocortin (*POMC*), prohormone convertase 1 (*PCSK1*) and the melanocortin 4 receptor (*MC4R*) [7]. In addition to the new knowledge attained, the discovery of genes and variants that predispose for obesity facilitates clinical diagnosis and management of this disease, as well as the development of pharmacological therapy for certain forms [3, 8].

Studies on consanguineous populations have provided invaluable insights into the genes and variants thereof that are involved in the development of MO, especially those inherited in autosomal recessive fashion. For example, the first MO gene in humans (the *LEP* gene) was identified in consanguineous families from Pakistan [9, 10]. The extensive prevalence of consanguinity in Arab countries, due to sociocultural and religious factors, has motivated investigations of this nature in these countries and, here, we present a systematic review of such reports published to date.

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Methods

Search strategy

From the timepoint of their creation until December 2020, four databases (PubMed, Science Direct, Web of Science and Scopus) were searched systematically for articles concerning monogenic obesity with study subjects from an Arab country. The 22 Arab countries include Algeria, Bahrain, the Comoros Islands, Djibouti, Egypt, Iraq, Jordan, Kuwait, Lebanon, Libya, Mauritania, Morocco, Oman, Palestine, Qatar, Syria, Saudi Arabia, Somalia, Sudan, Tunisia, United Arab Emirates and Yemen. The profile of English key terms employed in this search included "monogenic obesity" OR "early-onset obesity" OR "childhood obesity" OR "bariatric" OR "pediatric" OR "melanocortin" in combination, one at a time, with the names of the 22 Arab countries. To broaden the search, the names of the eight well-established MO genes (*ADCY3*,

LEP, LEPR, MC3R, MC4R, MRAP2, NTRK2 and POMC) were also used as search terms. All of the articles thus obtained were subjected to initial screening based on their titles and abstracts and those that met the inclusion criteria (see further below) were analyzed (see Figure 1).

Inclusion criteria

Only research papers that fulfilled the following inclusion criteria were subjected to complete assessment: (1) publication in a peer-reviewed journal; (2) involving subjects from at least one of the 22 Arab countries; and (3) including discussion of genetic variants related to monogenic obesity.

The exclusion criteria were as follows: (1) epidemiological studies on obesity; (2) focusing on common/polygenic obesity (such as Genome Wide Association Studies [GWAS]); (3) investigations on syndromic forms of obesity (such as Prader–Willi syndrome); (4)
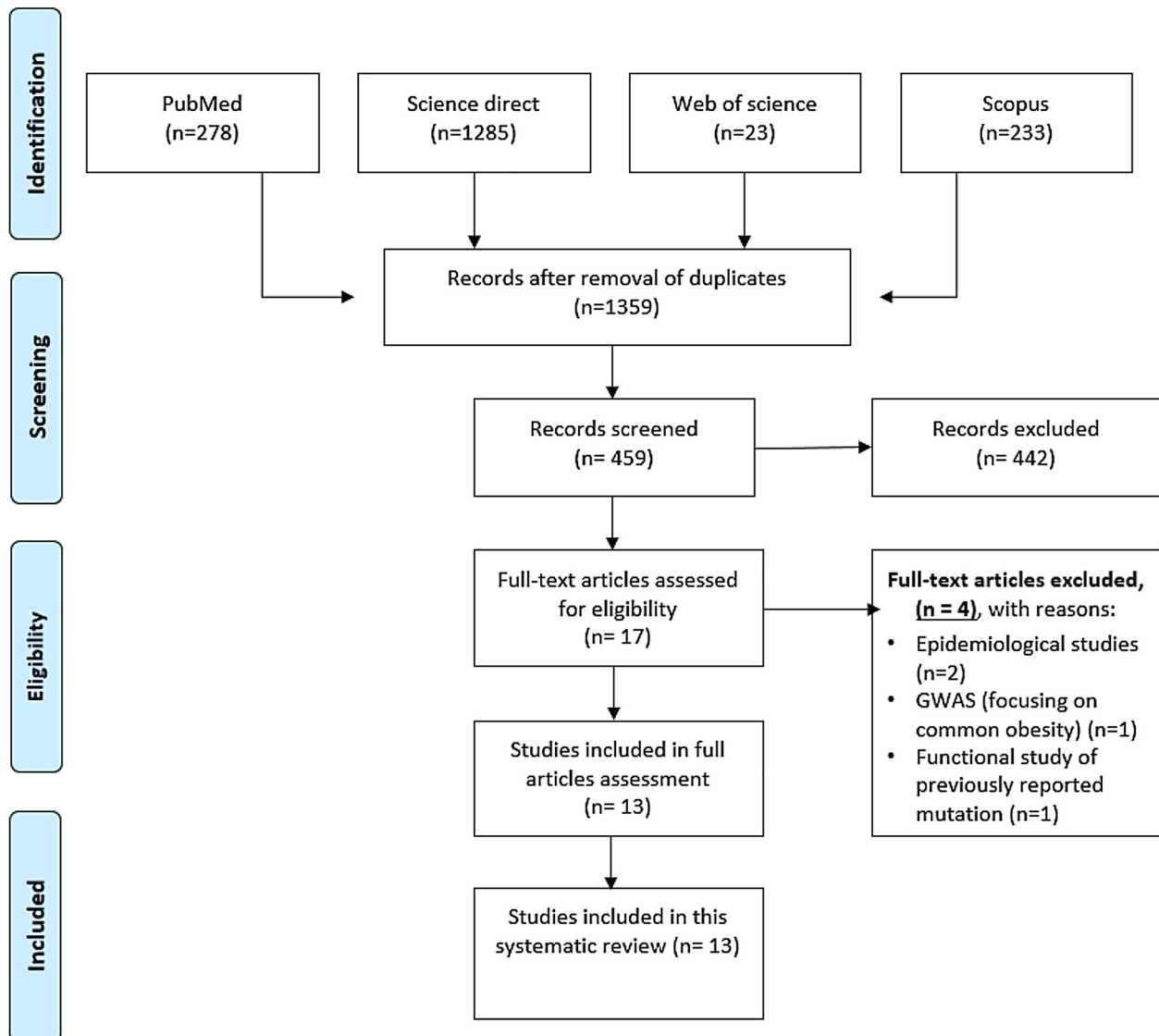

Figure 1: Flow chart illustrating the search strategy.

functional studies on MO variants; and (5) studies that do not involve subjects from at least one of the 22 Arab countries.

Extraction of data and *in-silico* analysis

The papers included were screened fully for relevant data concerning MO variants and cases. This was performed by two different authors in order to ensure complete and accurate extraction of data.

Subsequently, the variants thus identified were subjected to *in-silico* analysis employing SIFT [11], PolyPhen2 [12], CADD score [13], Mutation Taster [14], SNPs&go [15] and PyMol (v.2.4.1) [16]. The crystal structure of MC4R was obtained from the Protein Data Bank (PDB) [17] (ID: 6w25) [18]. The crystal structures of LEP and LEPR are not available and were therefore predicted using I-TASSER [19].

Results

Selection of articles for analysis

Following the inclusion criteria (described in methods), we initially identified 1,819 eligible articles, of which 1,359 remained after removal of duplicates. Based on our exclusion criteria (described in methods), 442 articles were removed and only 17 appeared eligible. After full assessment of these 17 articles, four were removed because they met one or more of the exclusion criteria, leaving a total of 13 eligible articles for analysis.

Variants identified

A total of 30 cases were identified with a total of 14 variants in five MO genes. The 14 variants were reported in Algeria

(1 variant), Egypt (6), Iraq (2), Kuwait (1), Morocco (1), Saudi Arabia (1), Sudan (2) and the United Arab Emirates (UAE) (1) (Figure 2). Six of these variants were in the *LEP* gene (46%), 3 in *LEPR* (23%), 3 in *MC4R* (21%), 1 in *POMC* (7%) and 1 in *CPE* (7%), all were in homozygous state.

Table 1 summarizes the variants identified, along with the associated phenotype and clinical information. All 14 variants are reported to be pathogenic in ClinVar [20]. These variants were subjected to further analysis utilizing SIFT, PolyPhen2, SNPs&go, Mutation taster, the CADD score, the American College of Medical genetics (ACMG) [21] classification (Table 1) and PyMOL.

PyMOL analysis

PyMOL analysis of the five missense variants identified revealed that of the five rotamers, three (i.e., LEP; p.R105W, LEPR; p.P316T, MC4R; p.I69R) were predicted to clash with neighboring residues, which could potentially result in steric hindrance and subsequent destabilization of the protein structure (Figure 3C–E). Moreover, loss of polar contacts that could also lead to destabilization of the protein structure was predicted to occur in LEP; p.R105W and MC4R; T162I (Figure 3C and F); whereas gain of polar contacts that could make the protein more rigid was predicted to occur in the case of MC4R; p.I69R (Figure 3E). Finally, in certain of the variants, including LEP; p.R105W, LEPR; p.P316T and MC4R; p.I69R, the mutant amino acid residue was much larger than the native residue, which might result in hindrance and destabilization (Figure 3C–E).
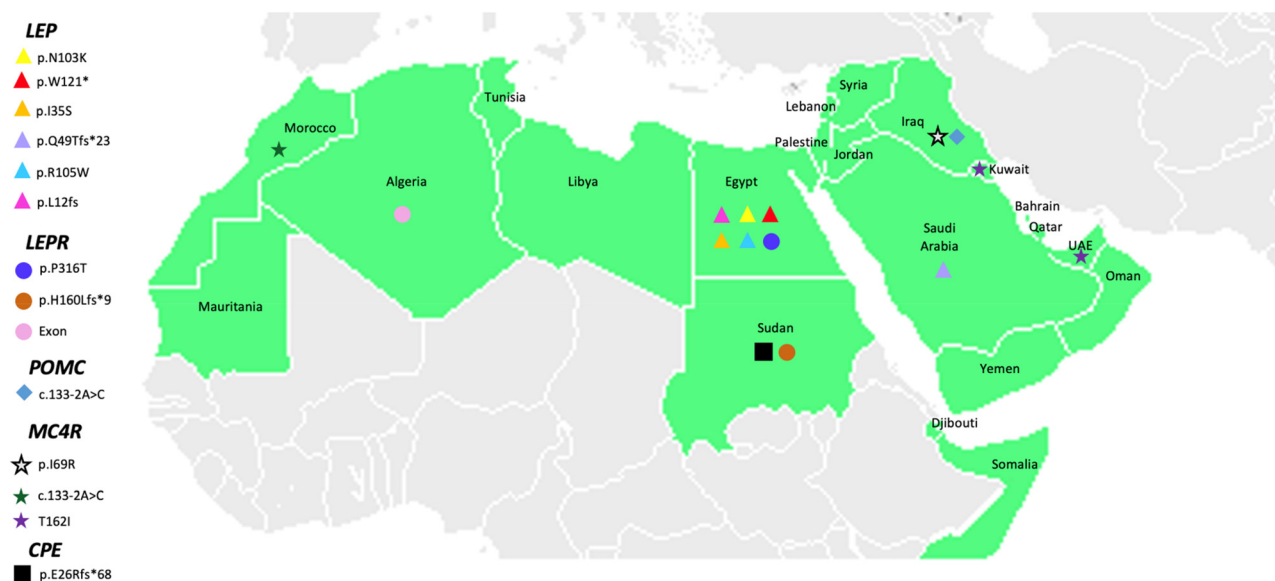

Figure 2: Map of the specific MO gene variants detected in the different Arab countries.

Table 1: Summary of the genetic MO variants identified in the Arab countries, including clinical presentation and *in-silico* prediction.

Gene	Transcript ID	rsID	Change in cDNA	AA[1] change	Method of Detection	Country	No. of subjects	No. of cases with the mutation	Age of mutation carriers (Years)	Clinical Phenotype
CPE	ENST00000402744.4	-	c.76_98del	p.E26Rfs*68	WES	Sudan	1	1	20	Hyperphagia Intellectual disability T2DM Hypogonadotrophic Hypogonadism
LEP	ENST00000308868.4	rs28954113	c.309C>A	p.N103K	Targeted gene panel	Egypt	30	2	3-7	Severe hyperphagia Repeated infections Hypogonadism Developmental Delay Hyperinsulinism Hypotonia Hepatomegaly
		-	c.223G>A	p.W121*	Targeted gene panel	Egypt	30	4	-	Severe hyperphagia Repeated infections Delayed puberty
		-	c.144indel TAC	p.Q49Tfs*23	Targeted gene panel	Saudi Arabia	1	1	2.5	Bronchial asthma Rapid Weight Gain
		-	c.104T>G	p.I35S	Targeted gene panel	Egypt	80	1	7 Months	Rapid weight gain High blood Pressure Hyperphagia
		-	c.34delC	p.L12fs				1	10	
		rs104894023	c.313C>T	p.R105W				1	3	
LEPR	ENST00000349533.6	rs754897895	c.946C>A	p.P316T	Targeted gene panel	Egypt	32	4	2	Severe hyperphagia Repeated infections
		rs1557670990	c.479delA	p.H160LfsX9	WES	Sudan	5	2	12, 14	Sleep apnea Impaired glucose tolerance Acanthosis nigricans Developmental delay
		-	c.2213-2G>A	-	Targeted gene panel	Algeria	3	3 (3 siblings 2 of which passed away)	19	Emotional liability Social disability Amenorrhea
MC4R	ENST00000299766.3	-	c.346-347del AG	-	Targeted gene panel	Morocco	1	1	3	Hyperphagia Progressive weight gain Endocrine abnormalities
		rs751160202	c.206T>G	p.I69R	Targeted gene panel	Iraq	1	1	5	Progressive weight gain Fatty liver Mild hepatomegaly Hyperphagia
		rs1555691402	c.485C>T	p.T162I	Targeted gene panel	UAE	4	3	4-14	Hyperphagia Morbid obesity Acanthosis nigricans Diabetes Hypertension Obstructive sleep apnea Mild insulin resistance
						Kuwait	4	1	8.5	Obstructive sleep apnea Hypertension Asthma nocturia
POMC	ENST00000395826.2	rs1553400259	c.133-2A>C	-	Targeted gene panel	Iraq	2	2	9, 1	Fair Skin Light brown hair Hyperphagia Overgrowth

Table 1: (continued)

SIFT	PolyPhen2	CADD	SNPs&go	Mutation Taster	gnomAD AF[2]	GME[3] AF	ACMG Manual**	ACMG Auto	Reference
-	-	-	-	Disease Causing	-	-	-	-	[34]
Deleterious	Probably Damaging	18.06	Disease	Disease Causing	0.00002	0.005	PM2	Uncertain Significance (Cool)	**[23, 28]**
-	-	-	-	Polymorphism	-	-	-	-	[23]
-	-	-	-	Polymorphism	-	-	-	-	[35]
-	Probably Damaging		Disease	Polymorphism	-	-	PM2	Uncertain Significance (Cool)	**[22]**
-	-	-	-	Polymorphism	-	-	-	-	[22]
Deleterious	Probably Damaging	26	Disease	Polymorphism	-	-	PM2/ PP5	Uncertain Significance (Tepid)	**[22]**
Deleterious	Benign	22.2	Neutral	Disease Causing	0.000032	-	PM1/ PM2	Uncertain Significance (Warm)	**[23, 36]**
-	-	-	-	Disease Causing	-	-	-	-	[37]
-	-	-	-	-	-	-	-	-	[6]
-	-	-	-	Polymorphism	-	-	-	-	[38]
Deleterious	Probably Damaging	26.1	Neutral	Polymorphism	0.000004	-	PM1/ PM2/ PM5	Likely Pathogenic	**[39]**
Deleterious	Probably Damaging	27.1	Disease	Disease Causing	-	-	PM1/ PP3	Uncertain Significance (Warm)	**[27]**
-	-	33	-	-	-	-	-	-	[40]

Bold text indicates missense variants. Genome build GRCh37. [a]AA: amino acid. [b]AF, allele frequency; [c]GME, Great Middle East. [d]ACMG classification Key: Criteria for pathogenicity. PM1 (Moderate): Located in a mutational hot spot and/or critical and well-established functional domain (e.g., active site of an enzyme) without benign variation. PM2 (Moderate): Absent from controls (or at extremely low frequency if recessive) in Exome Sequencing Project, 1000 Genomes Project, or Exome Aggregation Consortium. PP3 (Supporting): Multiple lines of computational evidence support a deleterious effect on the gene or gene product (conservation, evolutionary, splicing impact, etc.).
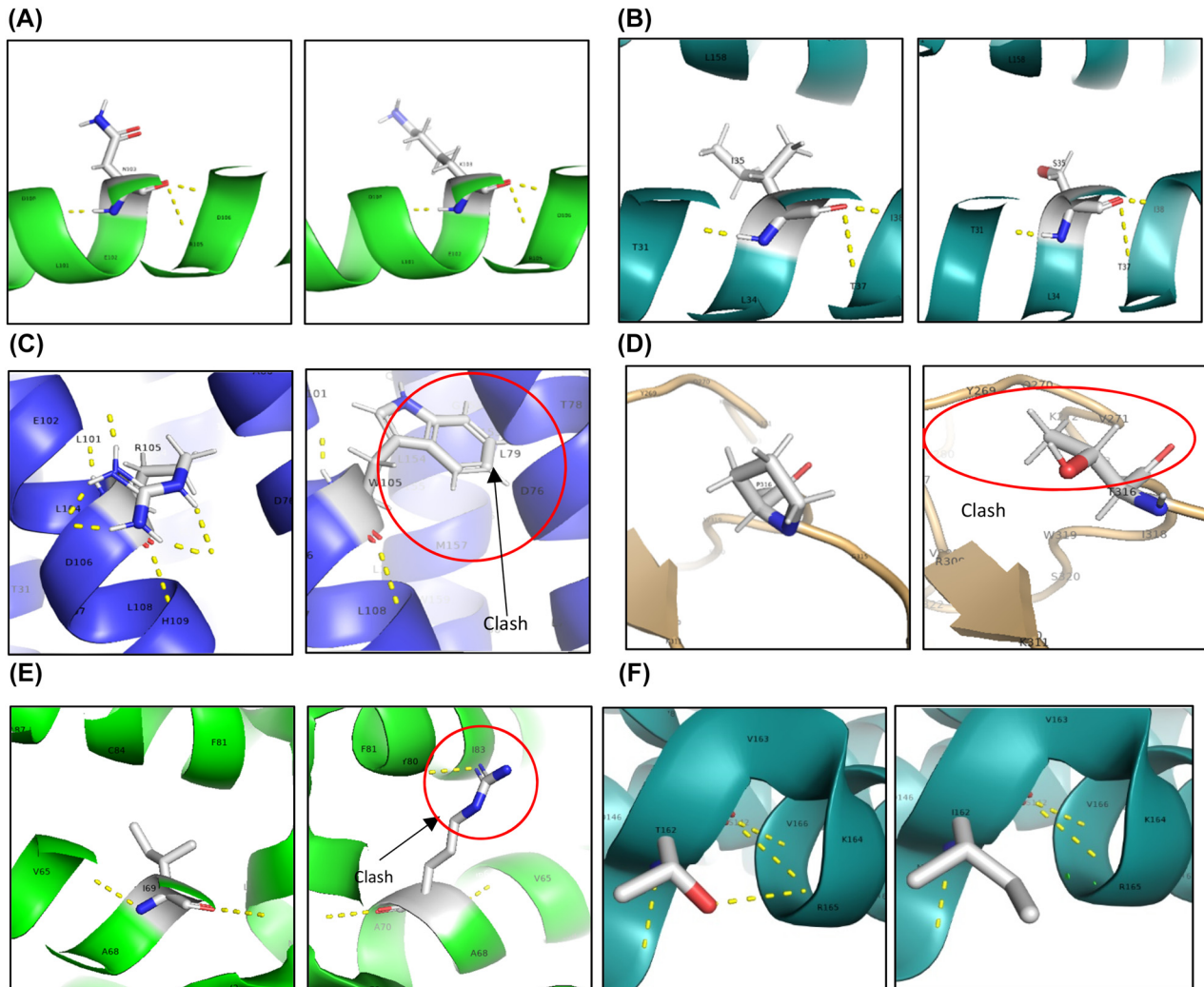
Figure 3: Visualization of the molecular structures of the proteins encoded by the various genetic variants. Points where the variant residue is predicted to interfere with neighboring residues are indicated by an arrow and encircled.
(A) In the case of LEP; p.N103K, no interference was predicted. (B) In LEP; p.I35S, it was predicted that loss or gain of polar contacts would occur. (C) The structure predicted for LEP; p.R105W indicates major interference with the neighboring residue L79. (D) The structure predicted for LEPR; p.P316T indicates major interference with neighboring residues, including Y269, O270, V271, but no gain or loss of polar contacts. (E) MC4R; p.I69R was predicted to gain a polar contact, as well as show minor interference with the neighboring residue I83. (F) For MC4R; p.T162I loss of polar contact with R165 was predicted.

Discussion

To our knowledge, this is the first systematic review focusing on the genetic basis of monogenic obesity in the Arab countries, where the prevalence of obesity, in general, and of childhood obesity, in particular, is high. We identified only 13 relevant articles describing investigations in eight of the 22 Arab countries considered, which highlights the need for research of this type in this geographical region, especially since the high level of consanguinity in Arab populations can render such efforts especially rewarding.

Ten of the 13 (67%) genetic MO variants identified among Arabs were novel, which emphasizes the necessity of examining distinct individual populations in this manner. At the same time, none of the studies revealed genes not previously known to be involved in MO, which was to be expected, since in 9 cases, gene panels of known MO genes were employed. Quite possibly, whole exome/genome approaches would reveal novel MO genes, especially those inherited in an autosomal recessive fashion.

Most of the studies included in this review were cases studies confirming MO in suspected cases with severe early onset obesity, while two studies involved large screenings

for MO using targeted gene panel. One of these two studies was conducted by ElSaeed and colleagues [22], and included 80 subjects who had severe early-onset obesity. The detection rate was 3.75% (3 out of 80 subjects had MO variants). The second study by El-Gammal and colleagues [23] screened 30 subjects also with severe early-onset obesity, and the detection rate was 26.7% (8 out of 30 subjects had MO variants).

All of the 30 MO cases reviewed were members of families that were consanguineous to different extents. Of the 30 cases, the parents of 17 were first cousins and the parents of 3 were second cousins, while the degree of consanguinity was not specified for the remaining 10. Moreover, all variants reported were homozygous, which probably reflects autozygosity.

All of the cases exhibited hyperphagia and rapid early-onset weight gain due to disruption of the leptin-melanocortin pathway. Interestingly, certain variants were associated with other clinical characteristics as well. For example, the variant (c.76_98del; p.E26Rfs*68) in *CPE* carried by a Sudanese individual was associated with intellectual disability. Similarly, a homozygous nonsense variant in *CPE* (c.405C>A; p.Y135*) caused intellectual disability in three siblings from Turkey [24].

MO variants in the *MC4R* gene usually exhibit autosomal dominant inheritance [25]. Birla and colleagues [22] observed the homozygous *MC4R* variant (c.206T>G; p.I69R) in a 5-year-old Iraqi male whose parents were first cousins and who had gained weight progressively, as well as developing fatty liver. This same variant was identified previously in a heterozygous state in a Norwegian girl who exhibited progressive weight gain early in life [26], indicating the advantage of such research on consanguineous populations with respect to identifying recessive variants. Moreover, this same mutation in HEK293 cells completely eliminates cyclic AMP-dependent signaling by MC4R [24].

Another homozygous *MC4R* variant (c.485C>T; p.T162I) was detected in four cases in Kuwait and the UAE (including two siblings), all of whom were severely obese and diabetic, with obstructive sleep apnea and hypertension [25]. Their parents, who were all heterozygous for this variant, exhibited normal BMI. The presence of this same rare variant in four children from different Arab countries might possibly indicate common Arab ancestry. This same study revealed that bariatric surgery was an effective means of treating three of these patients, although such surgery may not always be as effective and targeted treatment with pharmacological chaperons might give better results in some cases [27].

Twelve of the cases of MO analyzed here were due to variants in the *LEP* gene and second most common were variants in *LEPR* (9 cases). The most common phenotype of these 21 cases involved hyperphagia at an early age in combination with repeated infections. Multiple functional studies have been conducted in mice in attempt to understand how mutations in these genes could lead to hyperphagia, amenorrhea, insulin resistance, developmental delay and immunological disturbances [9].

To date, the only variant studied functionally is the p.N103K variant in the *LEP* gene, carried homozygously by two severely obese Egyptian children who demonstrated a very low serum levels of leptin (1.1 and 1.3 ng/mL), as published in two papers by the same group in [23, 28]. Niv-Spector and colleagues demonstrated that this mutation did not alter the folding of the protein, which was, nonetheless, completely inactive [29], concluding that obese phenotype reported in the Egyptian cases originated not only from low serum leptin levels but from the almost total lack of leptin activity. In 2015, Wabitch and colleauges [30] identified the p.N103K variant in homozygous state in two siblings with severe early-onset obesity and hyperphagia, while the circulating leptin levels in these individuals were high (>50 ng/mL), which contradicts the leptin levels described in the studies from Egypt. The *in vitro* investigations confirmed the biological inactivity of the p.N103K leptin, which in alignment with what has been addressed earlier by Niv-Spector and colleagues [29], concluding that p.N103K causes functional leptin deficiency. Clearly, investigations of this nature are essential to understanding the functional consequences of MO variants and their role in the pathogenesis of obesity and other phenotypic changes.

Currently, the Food and Drug Administration (FDA) has approved treatments for certain types of MO, including IMCIVREE™ (setmelanotide) for patients with a deficiency in POMC, PCSK1 [31] and/or LEPR and Myalep™ (recombinant leptin) for patients with LEP deficiency [32, 33]. However, none of the 13 articles analyzed here discussed potential use of these treatments.

Conclusions

To date, we could identify only 13 studies on monogenic obesity in the Arab world. In light of the high prevalence of this disease, as well as the high degree of consanguinity in Arab countries, more investigations of this nature are clearly warranted.

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