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REVIEW ARTICLE

Genetic basis of obesity: a review

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ABSTRACT

Obesity is a state of "positive" energy balance when energy intake in is much greater than energy expenditure. The familial aggregation of body size was first published by Sir Francis Galton in 1889, which become a well-established risk factor for childhood obesity. Obesity is often allied with insulin resistance, dyslipidemia and cardiovascular disease.

Monogenic obesity includes the involvements of Leptin (LEP) gene, leptin receptor(LEPR), Proopiomelanocortin (POMC), Melanocortin-4 receptor (MC4R), single-minded gene 1 (SIM 1), Proprotein convertase subtilisin/ kexin type 1 (PCSK1), Neuropeptide Y (NPY). Polygenic obesity is due to Adrenoceptor beta 1 (ADRB1), ADRB2, ADRB3, Uncoupling protein 1(UCP1), UCP2, UCP3. Monogenic and polygenic obesity; pleiotropic syndromes, chromosomal rearrangement are different types of obesity with genetic cause. Surprisingly all "obesity genes" carriers do not become overweight, and exercise, maintaining healthy routine is a significant contributing factor to nullify genetic prediposition.

Background:

Obesity is a state of "positive" energy balance when energy intake in is much greater than energy expenditure. Obesity occurs when excess body fat accumulates. It is a well known fact that obesity is associated with cardiovascular disorder (CVD), type 2 diabetes, and cancer. Although environment contributes for the development of obesity, but genetics also plays a crucial role (40% - 70%). The familial aggregation of body size was first published by Sir Francis Galton in 1889, which become a well-established risk factor for childhood obesity. The search for human obesity genes started long back. The search was intensified by the advances in the molecular biology techniques. Genetics influence the normal physiology, embryonic development, adaptation, and obesity. Still the research in "genetic environment interactions" is in the early stage [1, 2].

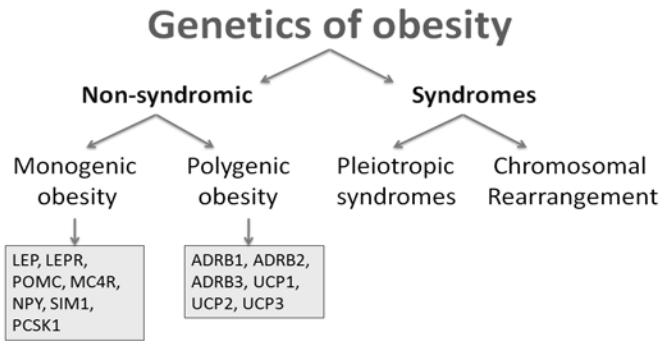

Figure – 1 Role of genes in obesity

Monogenic obesity includes the involvements of Leptin (LEP) gene , leptin receptor(LEPR), Proopiomelanocortin (POMC), Melanocortin-4 receptor (MC4R), single-minded gene 1 (SIM 1), Proprotein convertase subtilisin/ kexin type 1 (PCSK1), Neuropeptide Y (NPY). Polygenic obesity is due to Adrenoceptor beta 1 (ADRB1), ADRB2, ADRB3, Uncoupling protein 1(UCP1), UCP2, UCP3. Monogenic obesity occurs due to spontaneous mutations in a single gene, which is relatively rare and on the other side, endocrine disorders are responsible for severe early-onset obesity. Genes control appetite, intake of food, and energy equilibrium in the body. Genes code for hormone leptin, leptin receptor, melanocortin-4 receptor, pro-opiomelanocortin, Melanocortin-4 receptor, Single-minded gene 1, PCSK1 - Proprotein convertase subtilisin/ kexin type 1 [3, 4].

Role of Leptin

The LEP gene produce hormone leptin from adipocytes, regulates body weight. Leptin binds to leptin receptor, found in many organs including hypothalamus, which controls hunger and thirst. Leptin binds with receptor and acts via Janus Kinases-start activators of transcription (JAK-STAT) signaling pathways.

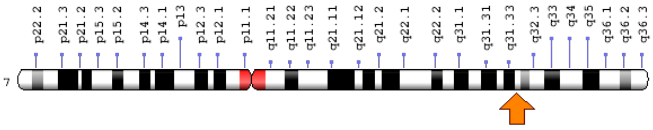

Figure – 2 Chromosome location: Leptin gene

It is downstream signaling pathways, inhibit feeding & promote energy expenditure i.e. producing a feeling of fullness (satiety) [5]. The chromosome for leptin is located in 7q32.1, long (q) arm of chromosome 7 at the position 32.1 [6]. leptin gene and regulatory regions mutation cause severe morbid obesity associated with Hypo gonadism [7]. Subcutaneous injection of leptin is clinically recommended in LEP deficient children and adults. It decreases food intake and slower rate of eating which leads to weight loss and decrease in fat mass.

Table – 1 Rare monogenic forms of human obesity

Gene	Mutation type	obesity	Associated phenotypes
Leptin (LEP)	Homozygous mutation	Severe, from the first days of life	Gonadotropic and thyrotropic insufficiency
Leptin receptor (LEPR)	Homozygous mutation	Severe, from the first day of life	Gonadotropic, thyrotropic and somatotropic insufficiency
Proopiomelano-cortin (POMC)	Homozygous or compound heterozygous mutation	Severe, from the first months of life	ACTH insufficiency Mild hypothyroidism and ginger hairs if the mutation leads to the absence of POMC production
Proprotein convertase subtilisin/ kexin type 1 (PCSK 1)	Homozygous or compound heterozygous mutation	Severe obesity occurring in childhood	Adrenal, gonadotropic, somatotropic and thyrotropic insufficiency Postparandial hypoglycemic malaises Central diabetes insipidus
Single-minded 1 (SIM1)	Translocation between chr1p22.1 and 6q16.2 in the SIM 1 gene	Severe obesity occurring in childhood	Inconstantly, neurobehavioral abnormalities (including emotional labiality or autism- like behavior)

Table 1 reveals that rare monogenic forms of human obesity involving Leptin, Leptin receptor, Proopiomelano-cortin, Proprotein convertase subtilisin/ kexin type 1, Single-minded 1 [8].

Obesity and Melanocortin 4 receptor (MC4R)

MC4R gene encodes MC4R protein, controls feeding behaviour, metabolism, sexual behaviour, and erectile function in males [9, 10]. In 2009, two very large genome-wide association studies of BMI confirmed the association of variants with insulin resistance, obesity. 2 - 3% of adult and child obesity is associated with MC4R [11-13]. Normally α melanocyte-stimulating hormone plays a vital role on MC4R, which reduces food intake [14].

It is well documented that mutations or failure in the function of proopiomelanocortin gene causes obesity in experimental models like mice and humans. Carriers of MC4R gene variant (22% of the general population) have both appetite & satiety. Remarkable behavioural changes include eating larger amounts of food, frequent intake of snacks, and more attractions towards fatty foods are common. Research evidences suggests each copy of the variant is responsible for a BMI (Body Mass Index) 0.22 which risks obesity by 8% [15-17].

Polygenic obesity "common obesity" mutations in multiple genes

Majority (>95% of cases) of the obesity is polygenic obesity, in clinical situations. Each susceptibility gene, contributes a little on weight gain. 'obesogenic lifestyle' increases the risk for cumulative effect from these genes. Obesogenic lifestyle factors includes overfeeding, Sedentariness and stress [8].

Ample evidence available from animal models, human linkage studies, monozygotic and dizygotic twins, and association research works of large populations shows significant contributions in common obesity. Twin studies unfolded the genetics of common obesity. Data obtained from 25,000 twin pairs and 50,000 biological and adoptive family members, showed that mean correlations for BMI (estimated) were 0.74 for monozygotic twins, where as 0.32 was for dizygotic twins [13].

Researchs showed that genes played a significant contribution for BMI of monozygotic twins but in shared genes the effect is relatively less. However, the study assumed that both twins grown up same degree of sahred environment.

Syndromic obesity

Genetic syndromes also contributes obesity. Significantly impaired intellectual and adaptive functioning, dysmorphic features, anomalies in the development is most commonly observed in severe obesity.

Pleiotropic syndromes

Obesity as a clinical feature is observed in 30 Mendelian disorders [18]. Pleiotropic syndromes occurs when one gene influences two or more apparently unrelated phenotypic traits. Some of the common examples are Albright's hereditary osteodystrophy syndrome, Alström syndrome, Bardet-Biedl syndrome, Borjeson, Forssman and Lehmann syndrome, Cohen syndrome, Fragile X syndrome, Mehmo syndrome, Simpson-Golabi-Behmel syndrome, Ulnar-mammary syndrome, Wilson–Turner syndrome. Chromosomal rearrangements involves obesity include Prader-Willi syndrome, Sim-1 [single-minded (Sim) gene], WAGR syndrome[4].

"Fat mass and obesity-associated" (FTO) gene

It is located in chromosome 16. This gene is associated with appetite in humans. "High-risk" FTO variants are the most susceptible with an increase in age. There is an 20-30% increase obesity risk for the varients. A specific high-risk variant is rs1421085. Fat mass and obesity-associated protein is an enzyme (encoded by the FTO gene), identified in 2007 [12, 13]. It has been observed that high-fat food is a preferable choice for its carriers. They become obese with advance in age [19].

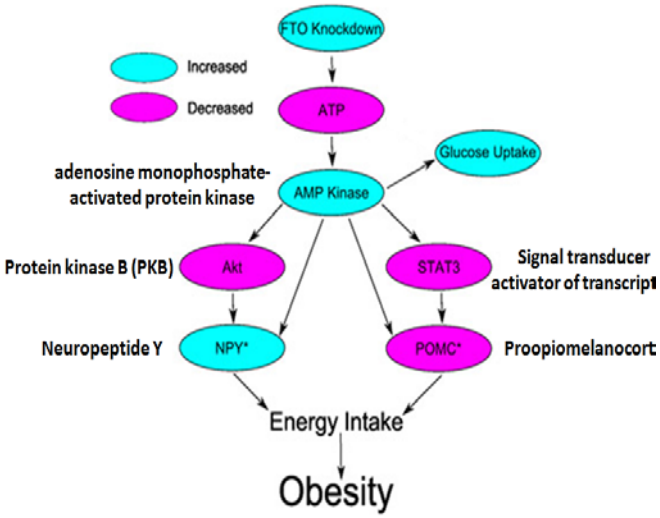

Figure - 3 Proposed mechanism of action of FTO in controlling obesity

Although human genes have not changed more but rising obesity cases may be a result of changed environmental factors - physical, social, political, economic surroundings. These factors determines our physical activity, food habbit and eating behavior causes the recent surge of overweight and obesity [18]. Research showed physically active individuals can counterbalance the effects of one obesity-promoting gene (FTO varient) [20, 21].

Conclusion

Genes control obesity. Monogenic and polygenic obesity; pleiotropic syndromes, chromosomal rearrangement are different types. Surprisingly all "obesity genes" carriers do not become overweight, and exercise, maintaining healthy routine is a significant contributing factor to nullify genetic prediposition. Some people have single gene disorders of obesity (rare forms; <1% of the obesity cases). In the same environment different people have different risk of obesity including genetic influences on food preference, food addiction, pleasurable feelings from food and exercise. So according to scientist Veerman, "genes may co-determine who becomes obese, but our environment determines how many become obese."

Competing interests

None declared.

Authors' contribution

BR and SG drafted the manuscript. BS and IB critically revised, incorporated necessary changes. Final manuscript is is approved by all authors.

Abbreviations

Adrenoceptor beta 1 (ADRB1), cardiovascular disorder (CVD), Janus Kinases-start activators(JAK-STAT), Leptin (LEP) gene, leptin receptor(LEPR), Melanocortin-4 receptor (MC4R), Neuropeptide Y (NPY), Proopiomelanocortin (POMC), Proprotein convertase subtilisin/ kexin type 1 (PCSK1), single-minded gene 1 (SIM 1), Uncoupling protein 1(UCP1).

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