



## Obesity and Leanness Caused by Mutations in the Leptin Gene: Already 6 Pathogenic Mutations Reported in this Gene

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### Abstract

Obesity and leanness are the medical conditions in which excess and deficient body fat present respectively. It may have an adverse effect on health, leading to reduced life expectancy and increased health problems. Environmental factors, especially increased consumption of high caloric diet, are considered responsible for the obesity epidemic, although genetic factors also contribute dysregulation of food consumption. Leptin gene may have an effect on the obesity and leanness because six pathogenic mutations already reported in leptin gene. Leptin gene mutations have a vital role to cause different types of cancers.

**Keywords:** Leptin gene; Body mass index; Melanocortin Hormone (MCH); Genetics and environmental factors

### Introduction

Leptin is taken from the Greek word leptos which means thin. It is 16-kDa circulating hormone in the body. It is a protein consisting of 167 amino acids and mainly originated from white adipose tissue [1]. First of all leptin gene was discovered in mice in 1994 [2]. It is involved in the development of brain and modulation of carbohydrate metabolism [3]. Leptin is released mainly by adipose tissue in both obese and lean individuals, but the obese individuals have higher level of leptin concentration as compared to lean individuals due to presence of greater amount of fat [4]. Whether a person is obese or lean is determined by Body Mass Index (BMI). If BMI of a person exceeds from 30 kg/m<sup>2</sup> then person is considered obese, lean when BMI is less than 18 kg/m<sup>2</sup> [5].

### Important Pathways in Leptin Gene

Main channel of the leptin gene is JAK/STAT. It is the chief transduction signaling channel that leptin uses to perform its effects or functions. Abbreviation of JAK/STAT is Janus kinase and signal transducer and activator of transcription, respectively. This channel takes signal from exterior of the cell. In DNA transcription and cell activity, signals transfer to the cell nucleus by passing through cell membrane, activate the promoters and these promoters interact with the DNA [6]. JAK-STAT Pathway has great importance in leptin signaling. Studies indicated that leptin specifically activated STAT3 pathway. Comparison of STAT3 mRNA level in lean and obese mice were performed, which showed that level of STAT3 mRNA was very low in the arcuate nucleus as compared to control mice [7]. Neuropeptide Y promoted feeding behavior in the body. Mice reduced body weight due to MCH-deficiency and revealed the phenotype of leanness due to hypophagia. So MCH was a regulator of energy balance and feeding but the deletion in this gene could result in leanness [8].

### Pathogenic Mutations in Leptin Gene

Until now 6 pathogenic mutations reported in the leptin gene that are associated with congenital leptin deficiency. These mutations are; (the first homozygous mutation was (p.Gly133fsX145) detected in two Pakistani cousins [9], second mutation (R105W) was identified in 4 members of a Turkish family [10], third (N103K) in 2 Egyptian children [11], fourth (L72S) in an Austrian female child [12], fifth and sixth mutations were (p.Leu161fsX170 and c.104\_106delTCA) in obese children of Pakistan [4,13]. These mutations are basically reported in obese individuals.

### Mutations in Leptin Receptors (LEPR)

Leptin Receptor (LEPR) belongs to gp130 family of cytokine receptors. LEPR exists in at least six isoforms (Ob Ra to Ob Rf), one of which is called 'long form' that is Ob Rb if there is a change then this change cause obesity. It is reported in a single family a harmful mutation in the LEPR was detected. LEPR was sequenced in 300 subjects; all these subjects were obese due to hyperphagia. Out of 300, 8 subjects had nonsense or missense LEPR mutations. Out of 8 subjects, 7 carried homozygous mutations and 1 was heterozygote [14].

### Leptin is Involved in Obesity and Leanness

It is reported that dose-response relationship with weight and fat loss was observed in obese and lean individuals. Scientists done experiments to find out that leptin gene is involved in obesity and leanness. In the experiments scientist gave subcutaneous recombinant leptin injections in both lean and obese subjects. According to this study it is concluded that, exogenous leptin appears to induce weight loss in some obese subjects with elevated endogenous serum leptin concentrations [15]. Another study in rodents about reduction in leptin level during weight loss signals to the brain to increase feeding and decrease energy expenditure. Leptin levels fell during weight loss and increased brain activity in areas involved in emotional, cognitive, and sensory control of food intake. Restoration of leptin levels maintained weight loss and reversed the changes in brain activity. Thus, leptin is a critical factor linking reduced energy stores to eating

behavior. Potentially, leptin therapy could sustain weight loss by overriding the tendency toward energy conservation [16]. In the above it is mentioned that six pathogenic mutations were found in leptin gene that's showed leptin gene involved in the obesity and leanness [13].

### Side Effect of Obesity and Leanness

Diseases which are associated with obesity involved; certain types of cancers, type II diabetes, heart diseases, obstructive sleep apnea, osteoarthritis and many more [17]. Leanness causes certain types of cancer, anorexia nervosa and reduced self-esteem. Anorexia Nervosa (AN) is an eating disorder in which at least 15% of expected body weight loss. Anorexia nervosa is life-threatening as well as psychological disturbance. Reduced self-esteem is a condition which is caused by AN [18]. It is reported that muscle weakened by computed tomography as compare to whole body fat and increases with testosterone [19]. In another article it is reported that leptin has a vital role to cause different types of cancers [20].

### Conclusion

Obesity and leanness are the medical conditions in which excess and deficient body fat present respectively. It may have an adverse effect on health, leading to reduced life expectancy and increased health problems. Environmental factors, especially increased consumption of high caloric diet, are considered responsible for the obesity epidemic, although genetic factors also contribute dysregulation of food consumption. Leptin gene may have an effect on the obesity and leanness because six pathogenic mutations already reported in leptin gene. Leptin gene mutations have a vital role to cause different types of cancers.

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