

## The Study of Genetic Mutations in Genes AGPAT2, LMNA, PPARG, PLIN1, AKT2, CIDEC in Köbberling–Dunnigan Syndrome

Shahin Asadi<sup>1\*</sup> and Samaneh Sadeh Dell<sup>2</sup>

<sup>1</sup>Master of molecular genetics, Director of the Division of Medical Genetics and Molecular Research, Iran

<sup>2</sup>Molecular Biology Genetics, Elite Club, Tabriz Branch, Islamic Azad University, Tabriz, Iran

### \*Corresponding author:

Dr. Shahin Asadi, Medical Genetics-IRAN-TABRIZ, Director of the Division of Medical Genetics and Molecular Research, Iran, Tel:+989379923364; Email: shahin.asadi1985@gmail.com

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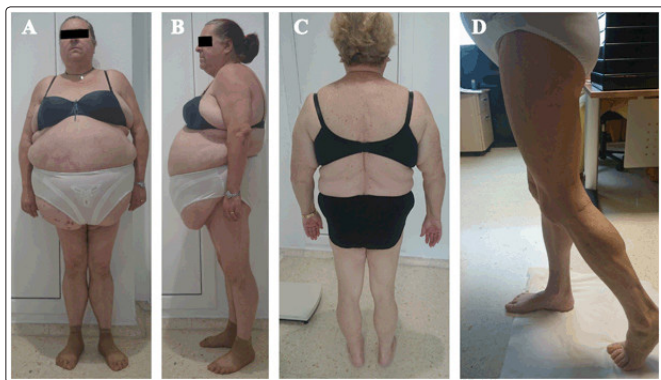
### Abstract

Köbberling-Dunnigan syndrome, also known as partial familial lip dystrophy, is a rare genetic disorder characterized by abnormal distribution of adipose tissue. Many people with Köbberling-Dunnigan syndrome develop insulin resistance, a condition in which body tissues cannot adequately respond to insulin hormone. Insulin hormone is a hormone that helps regulate the level of your blood glucose. Köbberling-Dunnigan syndrome can be due to mutations in several different genes. However, type 2 Köbberling-Dunnigan syndrome is caused by the mutation of the LMNA gene, which is based on the long arm of chromosome 1 as 1q22.

**Keywords:** : Kubberling-Dunnigan syndrome, AGPAT2, LMNA, PPARG, PLIN1, AKT2 and CIDEC Genes, Metabolic Disorder

### Generalizations of Köbberling-Dunnigan Syndrome

Köbberling-Dunnigan syndrome, also known as partial familial lip dystrophy, is a rare genetic disorder characterized by abnormal distribution of adipose tissue. Adipose tissue is usually seen in many under skin around the internal organs [1].



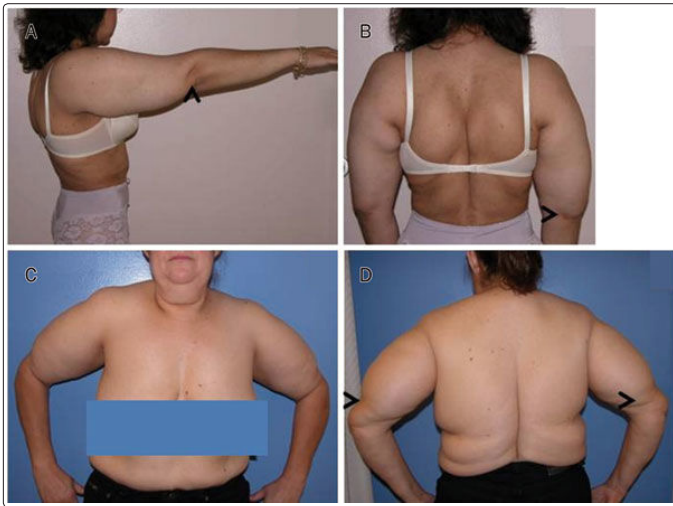
**Figure 1:** Images of a Woman with Köbberling-Dunnigan syndrome with Related Disorders



**Figure 2:** A woman with Köbberling-Dunnigan syndrome (left) and a male with this syndrome (right side) with abnormal distribution of adipose tissue (adipose)

The adipose tissue is stored as an energy source in the body and is used whenever necessary. In people with Köbberling-Dunnigan syndrome, fat tissue is lost from the arms, legs, and pelvis and these parts of the body appear muscular. Therefore, fat not stored in the

organs is created around the face and neck and inside the abdomen. Excessive fat in these areas gives people an appearance similar to those in Cushing's disease. This abnormal fat distribution may begin at any time from childhood to adolescence [2].



**Figure 3:** Another view of adipose tissue disorder in patients with Köbberling-Dunnigan syndrome

### Symptoms of Köbberling-Dunnigan Syndrome

Abnormal storage of fat in the body can lead to health problems in adulthood. Many people with Köbberling-Dunnigan syndrome develop insulin resistance, a condition in which body tissues cannot adequately respond to insulin hormone. Insulin hormone is a hormone that helps regulate the level of your blood glucose. Insulin resistance may get worse to become more seriously called diabetes. Some people with Köbberling-Dunnigan syndrome, an abnormality of acanthosis, have a skin condition associated with high insulin levels in the bloodstream. Acanthosis nigricans causes skin scaling, wrinkling, and thickening, darkening and tightening of the skin [3].



**Figure 4:** Another view of a man with Köbberling-Dunnigan syndrome associated with the related disorder

Often people with Köbberling-Dunnigan syndrome also have high levels of fat called circulating triglycerides in the bloodstream (hypertriglyceridemia) which can lead to pancreatitis (inflammation of the pancreatitis) [4].

In addition, abnormal accumulation of fat in the liver (fatty liver), which can lead to liver enlargement (hepatomegaly), which can lead to impaired liver function, may also occur in the Köbberling-Dunnigan syndrome. Some women with Köbberling-Dunnigan syndrome after puberty may experience multiple cysts in the ovary, increased body hair growth (hirsutism), and inability to fertility (infertile), possibly related to hormonal changes [5].

The researchers have described six forms of Köbberling-Dunnigan syndrome, whose genetic cause has been identified. Among them, Type 2 Köbberling-Dunnigan syndrome is the most common form, also known as Dunnigan disease. In addition, some people with Köbberling-Dunnigan syndrome may have myelopathic disorder, heart muscle impairment (cardiomyopathy), and impaired cardiac conduction [5].

Familial partial lipodystrophy is a rare condition characterized by an abnormal distribution of fatty (adipose) tissue. Adipose tissue is normally found in many parts of the body, including beneath the skin and surrounding the internal organs. It stores fat as a source of energy and also provides cushioning. In people with familial partial lipodystrophy, adipose tissue is lost from the arms, legs, and hips, giving these parts of the body a very muscular appearance. The fat that cannot be stored in the limbs builds up around the face and neck, and inside the abdomen. Excess fat in these areas gives individuals an appearance described as "cushingoid," because it resembles the physical features associated with a hormonal disorder called Cushing disease. This abnormal fat distribution can begin anytime from childhood to adulthood [5].



**Figure 5:** Images of adipose tissue disorder in patients with Köbberling-Dunnigan syndrome

Abnormal storage of fat in the body can lead to health problems in adulthood. Many people with familial partial lipodystrophy develop insulin resistance, a condition in which the body's tissues cannot adequately respond to insulin, which is a hormone that normally helps to regulate blood sugar levels. Insulin resistance may worsen to become a more serious disease called diabetes mellitus. Some people with familial partial lipodystrophy develop acanthosis nigricans, a skin condition related to high levels of insulin in the bloodstream. Acanthosis nigricans causes the skin in body folds and creases to

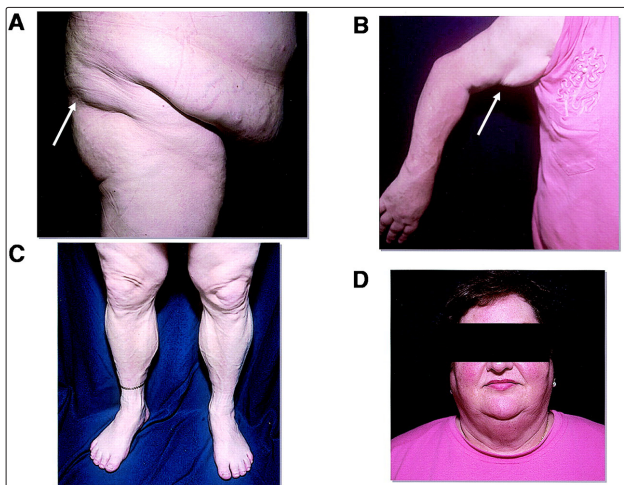
become thick, dark, and velvety [5].

Most people with familial partial lipodystrophy also have high levels of fats called triglycerides circulating in the bloodstream (hypertriglyceridemia), which can lead to inflammation of the pancreas (pancreatitis). Familial partial lipodystrophy can also cause an abnormal buildup of fats in the liver (hepatic steatosis), which can result in an enlarged liver (hepatomegaly) and abnormal liver function. After puberty, some affected females develop multiple cysts on the ovaries, an increased amount of body hair (hirsutism), and an inability to conceive (infertility), which are likely related to hormonal changes [5].

Researchers have described at least six forms of familial partial lipodystrophy, which are distinguished by their genetic cause. The most common form of familial partial lipodystrophy is type 2, also called Dunnigan disease. In addition to the signs and symptoms described above, some people with this type of the disorder develop muscle weakness (myopathy), abnormalities of the heart muscle (cardiomyopathy), a form of heart disease called coronary artery disease, and problems with the electrical system that coordinates the heartbeat (the conduction system) [5].



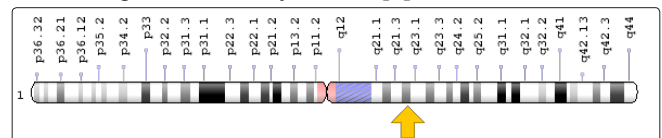
**Figure 6:** Images of related disorders in women with Köbberling-Dunnigan syndrome



**Figure 7:** Other Implications of Disorders in Köbberling-Dunnigan syndrome

### Etiology of Köbberling-Dunnigan Syndrome

Köbberling-Dunnigan syndrome can be due to mutations in several different genes. However, type 2 Köbberling-Dunnigan syndrome is caused by the mutation of the LMNA gene, which is based on the long arm of chromosome 1 as 1q22. The LMNA gene provides instructions for the synthesis of proteins that contain a variety of cell functions, including fat storage. In particular, these proteins play an important role in the development and functioning of adipocytes, which are fat storage cells in fatty tissues. The mutation in any of the genes associated with Köbberling-Dunnigan syndrome reduces or eliminates the function of the relevant proteins, which reduces the growth of the structure or function of the adipocytes, and as a result, the body can maintain and use lipids in Positions are not suitable. These disorders of the adipose tissue produce hormones and affect many organs of the body. However, it is not clear why these changes make fat stored in some parts of the body and disappear in some others. It is worth noting that no mutation has been identified in some patients with Köbberling-Dunnigan syndrome, and researchers believe that genetic or other epigenetic changes may also be involved in the development of this syndrome [6].



**Figure 8:** Schematic view of chromosome number 1, where the LMNA gene is located in the long arm of this chromosome as 1q22

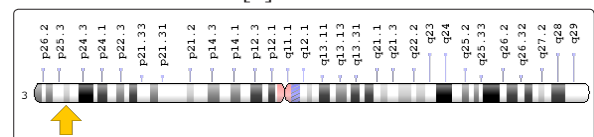
Often cases, Köbberling-Dunnigan type 2 syndromes follow the dominant autosomal inheritance pattern. Therefore, in order to produce this syndrome, a mutated version of the LMNA gene (parent or parent) is required and the chance of having a child with Köbberling-Dunnigan syndrome in the dominant autosomal state is 50% for each pregnancy [6].

**Table 1: Name of effective genes in various types of Köbberling-Dunnigan syndrome with chromosomal position**

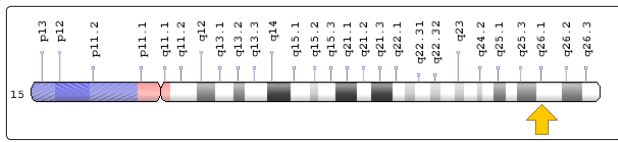
Gene	Chromosome position	Syndrome Type
AGPAT2	9q34.3	1
LMNA	1q22	2
PPARG	3p25.2	3
PLIN1	15q26.1	4
AKT2	19q13.2	5
CIDEA	3p25.3	6

### Frequency of Köbberling-Dunnigan Syndrome

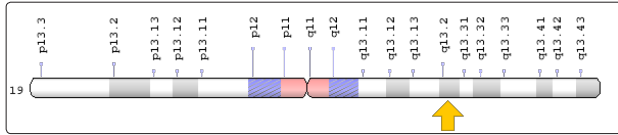
Köbberling-Dunnigan syndrome is a rare genetic disorder with an estimated 1 in 1 million live births in the world. Type 2 Köbberling-Dunnigan syndromes is the most common form of this disorder, and so far, more than 500 cases have been reported from all over the world in medical literature [7].



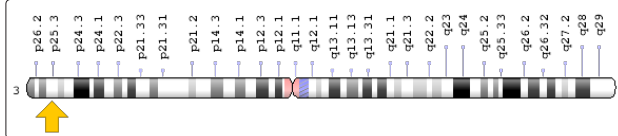
**Figure 9:** Schematic view of chromosome number 3, where the PPARG gene is located in the short arm of this chromosome as 3p25.2



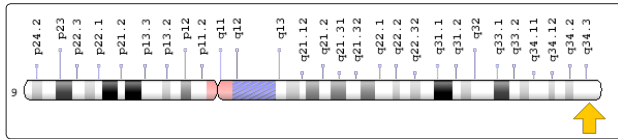
**Figure 10:** Schematic view of chromosome number 15, where the PLIN1 gene is located in the long arm of this chromosome as 15q26.1



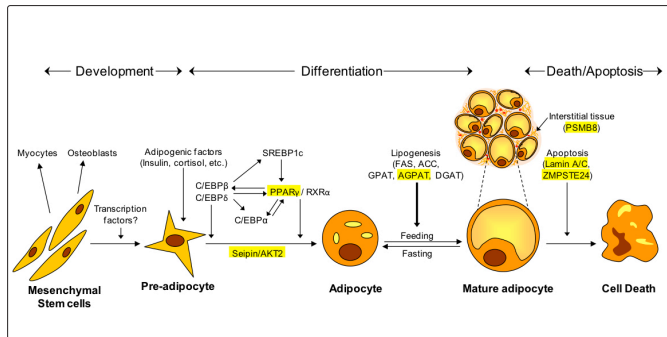
**Figure 11:** Schematic view of chromosome number 19, where the AKT2 gene is located in the long arm of this chromosome as 19q13.2



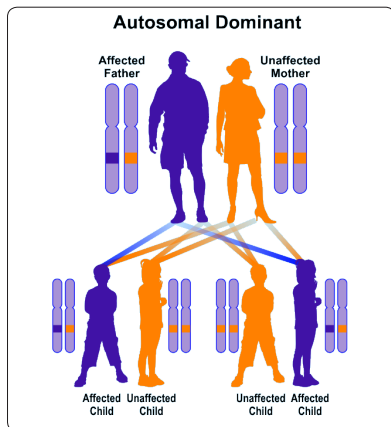
**Figure 12:** Schematic view of chromosome number 3, where the CIDEC gene is located in the long arm of this chromosome as 3p25.3



**Figure 13:** Schematic view of chromosome number 9, where the AGPAT2 gene is located in the long arm of this chromosome as 9q34.3



**Figure 14:** Schematic of the molecular pathway of genes inducing Köbberling-Dunnigan syndrome in cell differentiation of adipose tissue, apoptosis and tissue development



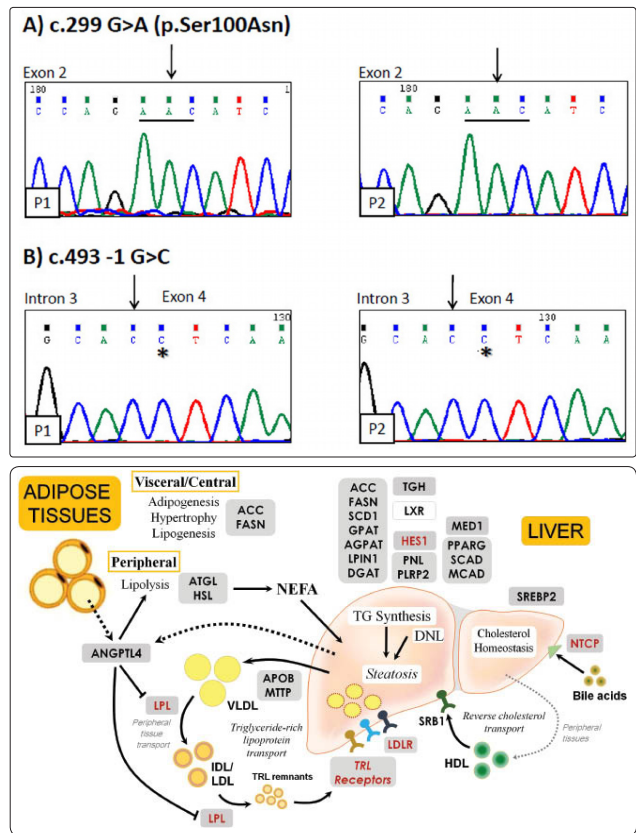
**Figure 15:** Schematic view of the dominant autosomal inheritance pattern that follows the Köbberling-Dunnigan syndrome

### Diagnosis of Köbberling-Dunnigan Syndrome

Köbberling-Dunnigan syndrome is diagnosed based on the clinical and physical findings of the patients and some pathological examinations. The best way to diagnose this syndrome is to test for at least the genetic gene of LMNA to investigate the presence of possible mutations [8].

### Therapeutic routes for Köbberling-Dunnigan Syndrome

The Köbberling-Dunnigan syndrome treatment and management strategy is symptomatic and supportive. Treatment may be done by a team of experts, including gastroenterologist, liver specialist, clinical biochemist and other healthcare professionals. There is no standard treatment for this syndrome and all clinical measures are needed to reduce the suffering of the infected person. Genetic counseling is also a special place for all parents who want a healthy baby [8].

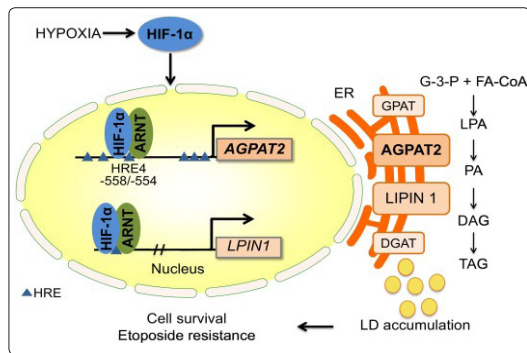


**Figure 16:** Schematic of types of AGPAT2 mutations in Köbberling-Dunnigan syndrome and molecular genetic pathway of genes that are effective in creating this syndrome in the liver and adipose tissue

### Discussion and conclusion

Köbberling-Dunnigan syndrome, also known as partial familial lip dystrophy, is a rare genetic disorder characterized by abnormal distribution of adipose tissue. Many people with Köbberling-Dunnigan syndrome develop insulin resistance, a condition in which body tissues cannot adequately respond to insulin hormone. Insulin hormone is a hormone that helps regulate the level of your blood glucose. Köbberling-Dunnigan syndrome can be due to mutations in several different genes. However, type 2 Köbberling-Dunnigan syndrome is caused by the mutation of the LMNA gene, which is based on the long arm of chromosome 1 as 1q22. Köbberling-Dunnigan syndrome is a rare genetic disorder with an estimated 1 in 1 million live births in the world. There is no standard treatment

for this syndrome and all clinical measures are needed to reduce the suffering of the infected person [9].



**Figure 17:** Schematic of molecular genetic pathway AGPAT2 gene in Köbberling-Dunnigan syndrome and effective in Cell survival

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