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The Role of Genetic Mutations in Genes WNK1, WNK4, CUL3, KLHL3 in Gordon's Syndrome

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ABSTRACT

Gordon's syndrome, also known as Pseudohypoaldosteronism, that is type II (PHAII), is a genetic disorder that affects the amount of sodium and potassium in the body. People with Gordon syndrome have high blood pressure (hypertension) and high levels of potassium in the blood (hyperkalemia), despite having normal kidney function. The Gordon syndrome is based on the mutation of the WNK1,WNK4, CUL3, KLHL3 genes.

Keywords: *Gordon's syndrome, genetic mutations, WNK1,WNK4,CUL3,KLHL3 genes.*

GENERALIZATIONS OF GORDON'S SYNDROME

Gordon's syndrome, also known as PHAII, is a genetic disorder that affects the amount of sodium and potassium in the body. Potassium and potassium are important in controlling blood pressure, and their adjustment mainly occurs in the kidneys[1].

Signs and Symptoms of Gordon's Syndrome

People with Gordon's syndrome have high blood pressure (hypertension) and high levels of potassium in the blood (hyperkalemia), despite having normal kidney function. The age of the onset of Gordon's syndrome varies, so that some people find signs of illness in childhood and others in adulthood.[2]Hyperkalemia usually occur in early life and high blood pressure is then created in life. In addition, people who are affected by Gordon syndrome have high blood calcium levels (hypercalcemia) and acid (metabolic

acidosis), also known as hyperchloremic metabolic acidosis. It is worth noting that people with hyperkalemia, hyperchloraemia, and metabolic acidosis can have nonspecific symptoms such as nausea, vomiting, severe fatigue, and muscle weakness. People with Gordon's syndrome may also have high levels of calcium in the urine (hypercalciuria)[3].

Etiology of Gordon's Syndrome

The Gordon's syndrome is based on the mutation of the WNK1 gene in the short arm of chromosome 12 as 12p13.33, the WNK4 gene, which is based on 17q21.2 in the long arm of chromosome 17, is the CUL3 gene in the long arm of chromosome number 2 as 2q36.2 The KLHL3 gene, which is based on the long arm of chromosome number 5, is based on 5q31.2. These genes are involved in regulating blood pressure4.

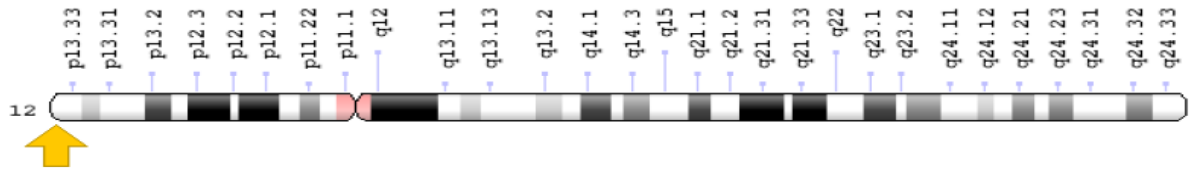

Figure1. *Schematic view of chromosome 12, in which the WNK1 gene is based on the short arm of this chromosome 12p13.33*

The proteins produced by the WNK1 and WNK4 genes control the amount of sodium and potassium in the body by regulating the canals in the cell membrane, which carry the transport

of sodium or potassium into and out of the cell. This process occurs mainly in the kidneys. The mutation in each of these genes disrupts the control of these canals, leading to a decrease in the concentration of sodium and potassium in the body. As a result, people with Gordon's syndrome have high blood pressure and hyperkalemia[5].

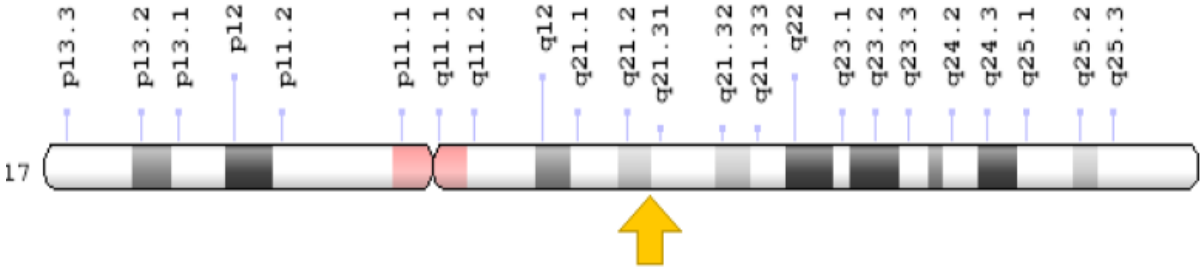

Figure2. *Schematic view of Chromosome No. 17 in which the WNK4 gene is located in the long arm of this chromosome as 17q21.2.*

The proteins produced from the CUL3 gene (called Cullin-3) and the KLHL3 gene control the amount of available WNK1 and WNK4 proteins. The Cullin-3 and KLHL3 proteins are two pieces of the E3-complex of ubiquitin-ligase, which labels some other proteins with a molecule called ubiquitin. This molecule is broken down as a signal for the protein labeled when it is no longer needed. The E3, the ubiquitin-ligase containing Cullin-3 and KLHL3, capable of tagging the WNK1 and WNK4 proteins with the ubiquitin molecule, leads to their breakdown. The mutation in the CUL3 or KLHL3 gene results in the degradation of the WNK4 protein. (The effect of this mutation in the WNK1 protein is unknown.) Increased excess of WNK4 is likely to interfere with sodium and potassium levels, which leads to high blood pressure and hyperkalemia[6].

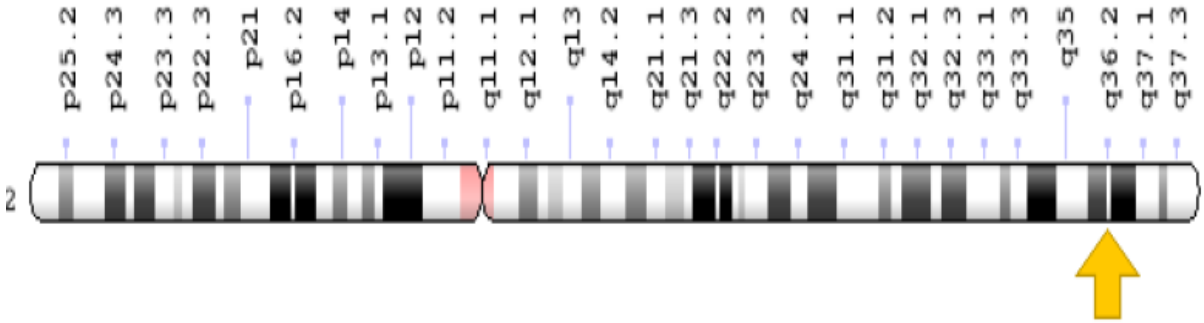

Figure3. *Schematic view of chromosome number 2 where the CUL3 gene is located at 236.2 in the long arm of this chromosome*

Gordon's syndrome often follows the dominant autosomal inheritance pattern. Therefore, in order to create this syndrome, a copy of the mutated genes WNK1, WNK4, CUL3, KLHL3 (parent or parent) is needed and the chance of having a child with this syndrome in the dominant autosomal state is 50% for each pregnancy[7].

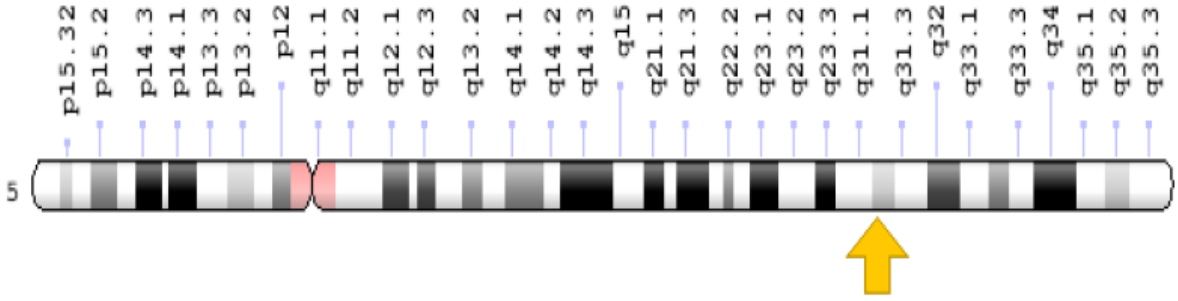

Figure4. *Schematic view of chromosome number 5, where the KLHL3 gene is located in the long arm of this chromosome as 5q31.2*

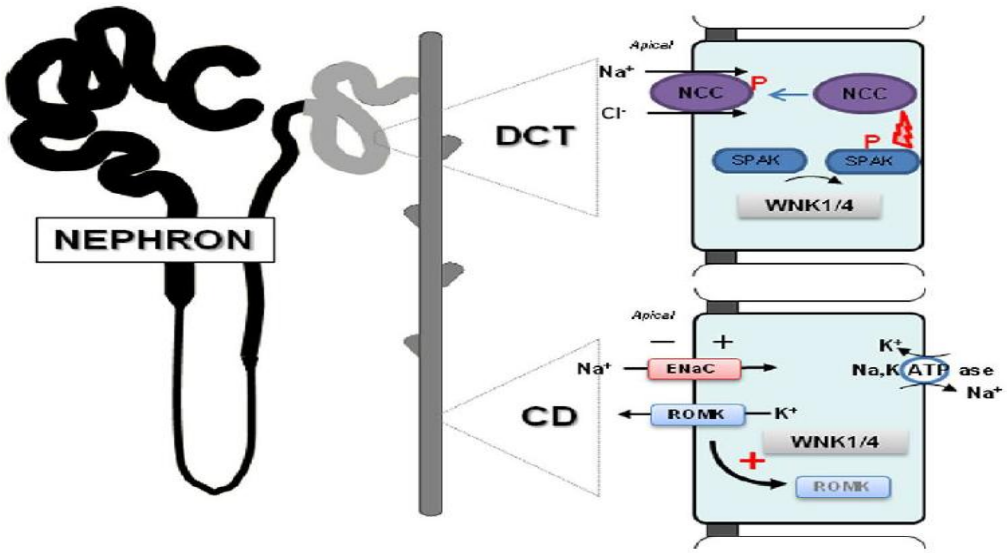

Figure5. *Schematic of the role of WNK1 and WNK4 genes in nephron tissue*

In some cases, Gordon's syndrome follows mutation in the KLHL3 gene from an autosomal recessive hereditary pattern. Therefore, in order to produce this syndrome, two versions of the mutated gene of KLHL3 (one parent and one of the mother) are needed, and the chance of having a child with this syndrome in an autosomal recessive state is 25% for each pregnancy[7].

Frequency of Gordon's Syndrome

Gordon's syndrome is a rare genetic disorder whose frequency is not known in the world. So far, more than 40 cases of this syndrome have been reported from medical literature throughout the world[8].

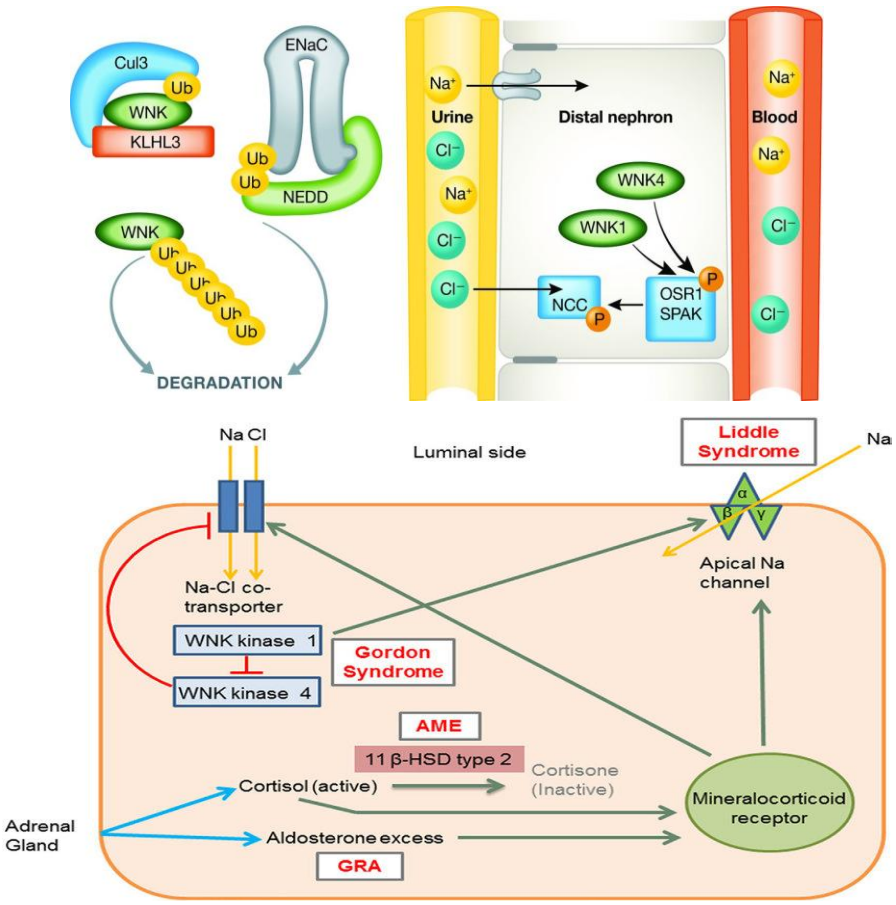

Figure6. *Schematic of the mechanisms of action of WNK1 and WNK4 genes, and CUL3 and KLHL3 in regulating the amount of sodium and chlorine in the adrenal gland*

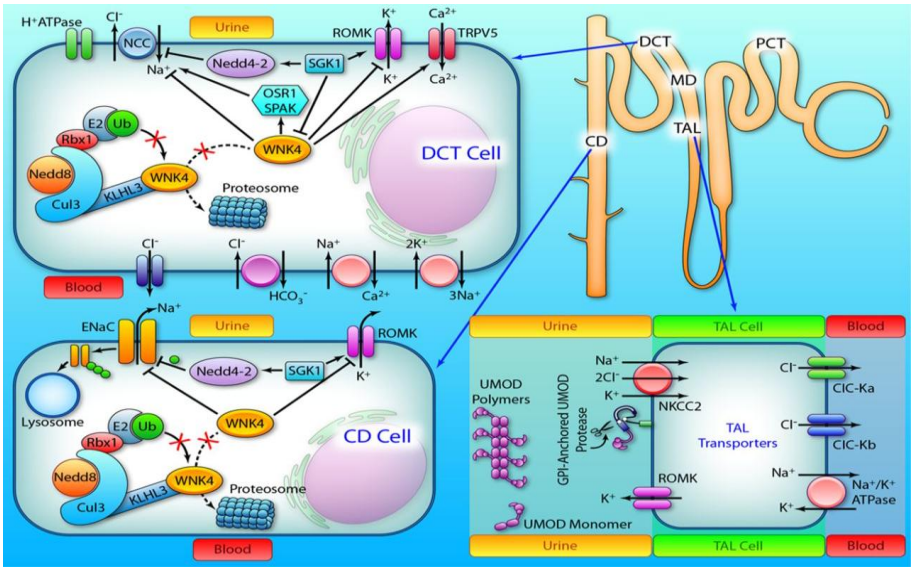

Figure7. *Schematic of the molecular pathway of the WNK1, WNK4, CLU3, and KLHL3 genes*

Gordon's Syndrome Diagnosis

Gordon's syndrome is diagnosed based on the clinical and clinical findings of the patients and some pathological tests. The most accurate method for detecting this syndrome is the molecular genetic testing of WNK1, WNK4, CUL3, and KLHL3 genes to investigate the presence of possible mutations[8].

Gordon's Syndrome Treatment Routes

The Gordon's syndrome treatment and management strategy is symptomatic and supportive. Treatment may be done by a team of experts, including a specialist in physiology, clinical specialist, gastroenterologist, nephrologists, and other health care 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 needed for parents who want a healthy baby[8].

Discussion And Conclusion

The age of the onset of Gordon's syndrome varies, so that some people find signs of illness in childhood and others in adulthood. Hypercalemia usually occurs in early life and high blood pressure is then created in life. There is no standard treatment for this syndrome and all clinical measures are needed to reduce the suffering of the infected person.

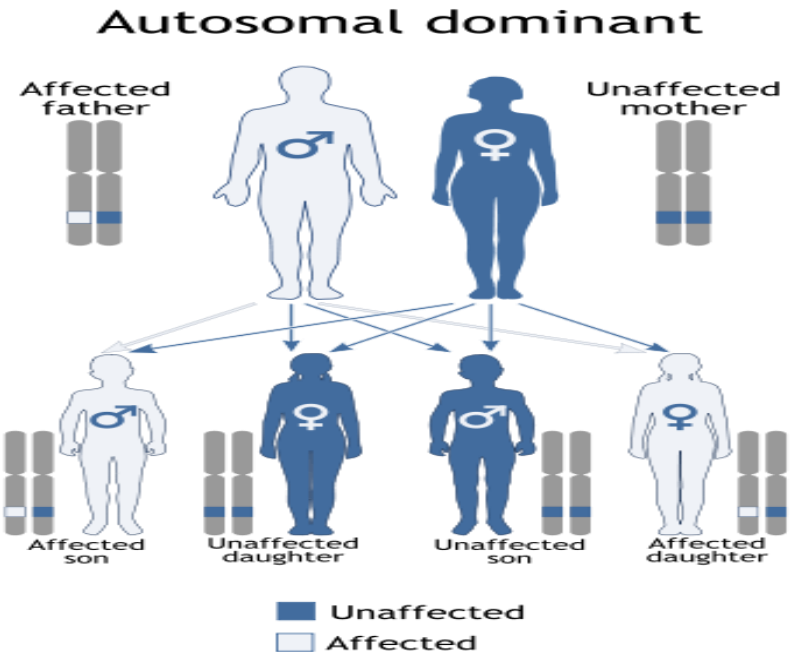

Figure 8. *Schematic view of the dominant autosomal inheritance pattern that Gordon syndrome often follows from this pattern*

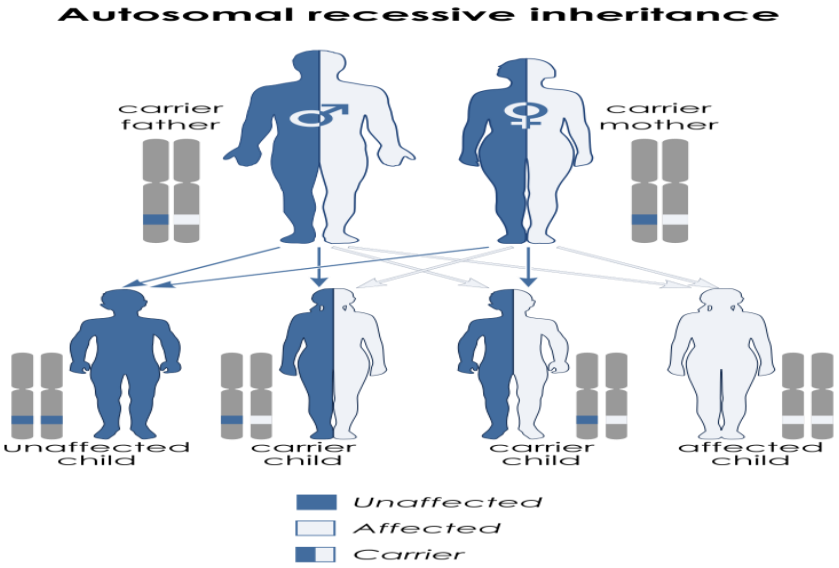

Figure9. *Schematic view of an autosomal recessive hereditary pattern that Gordon syndrome in some cases follows the mutation in the KLHL3 gene*

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