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Review Article

The Role of Mutations on Genes PLAGL1 & ZEP57 in 6q24-Related Transient Neonatal Diabetes Mellitus Syndrome

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Abstract

6q24 Transient Infant Diabetes Syndrome is a type of diabetes that occurs in infants. This form of diabetes is characterized by high blood sugar levels (hyperglycemia) caused by a lack of the hormone insulin. 6q24 neonatal transient diabetes syndrome is caused by the overactivity (overexpression) of certain genes in an area of the long arm (q) of chromosome 6 called 6q24. Humans inherit two copies of their genes, one from the mother and the other from the father.

Keywords: 6q24 associated neonatal transient diabetes syndrome; PLAGL1; ZEP57 genes; Genetic Mutation

Overview of 6q24 Associated Neonatal Transient Diabetes Syndrome

6q24 Transient Infant Diabetes Syndrome is a type of diabetes that occurs in infants. This form of diabetes is characterized by high blood sugar levels (hyperglycemia) caused by a lack of the hormone insulin. Insulin controls the conversion of glucose (a type of sugar) from the blood to the cell for conversion into energy [1]y.

Clinical signs and symptoms of transient neonatal diabetes syndrome associated with 6q24

People with 6q24 transient neonatal diabetes syndrome experience very slow growth before birth (severe intrauterine growth retardation). Babies with high blood sugar and hypothyroidism (dehydration) usually begin in the first week of life. The signs and symptoms of this form of diabetes are transient, meaning that they gradually decrease over time and generally disappear between the ages of 3 months and 18 months. However, diabetes can recur, especially during childhood or pregnancy. Up to half of people with transient diabetes in 6q24 infants develop permanent diabetes after life [1,2].

Other features of transient neonatal diabetes mellitus related to 6q24 that occur in some affected individuals include abnormally large tongue (macroglossia). In addition, abdominal hernias, brain, heart or kidney abnormalities, poor muscle tone (hypotension), deafness, and developmental delays are other symptoms of transient neonatal diabetes associated with 6q24 [1,2].

Etiology of neonatal transient diabetes syndrome associated with 6q24

6q24 neonatal transient diabetes syndrome is caused by the overactivity (overexpression) of certain genes in an area of the long arm (q) of chromosome 6 called 6q24. Humans inherit two copies of their genes, one from the mother and the other from the father. Usually both copies of each gene are activated or turned on in the cell [1,3].

However, in some cases, only one of the two versions is clear. Which version is active depends on the parents of origin: Some genes are usually active only when inherited from the person's father. Others are active only when inherited from the person's mother. This phenomenon is known as genomic marking [1,3].

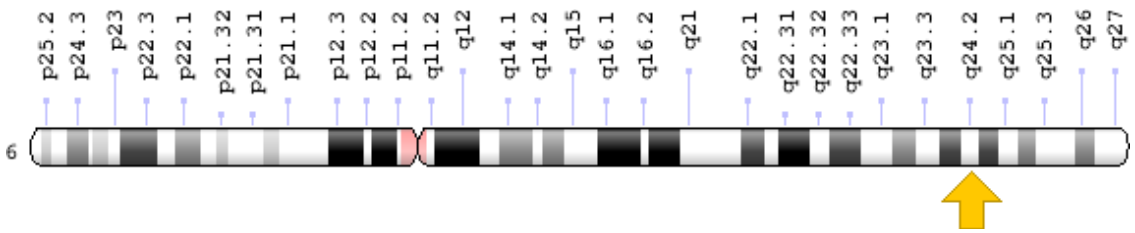

Figure 1: *Schematic view of chromosome 6 where the PLAGL1 gene is located in the long arm of this chromosome as 6q24 [1].*

The genes made in region 6q24 are of the paternal inherited pattern, meaning that usually only a copy of each gene obtained from the father is active. Copy of each gene obtained from the mother is inactivated by a mechanism called methylation [1,4] .

The hyperactivity of one of the genes made with the paternal hereditary pattern expressed in this region is called the PLAGL1 gene, and is believed to cause transient neonatal diabetes mellitus related to 6q24. Other genes made with the paternal hereditary pattern in the region, some of which have not been identified, may also play a role in the disorder]1,4[.

There are three ways in which overexpression of intact genes in the 6q24 region may occur. About 40% of cases of transient neonatal diabetes mellitus related to 6q24 are due to a genetic mutation known as paternal monozygosity (UPD) of chromosome 6. From each parent, the paternal UPD causes individuals to have two active copies of the genes made by the paternal inherited pattern, instead of one active copy from the father and one inactive copy from the mother [1,5].

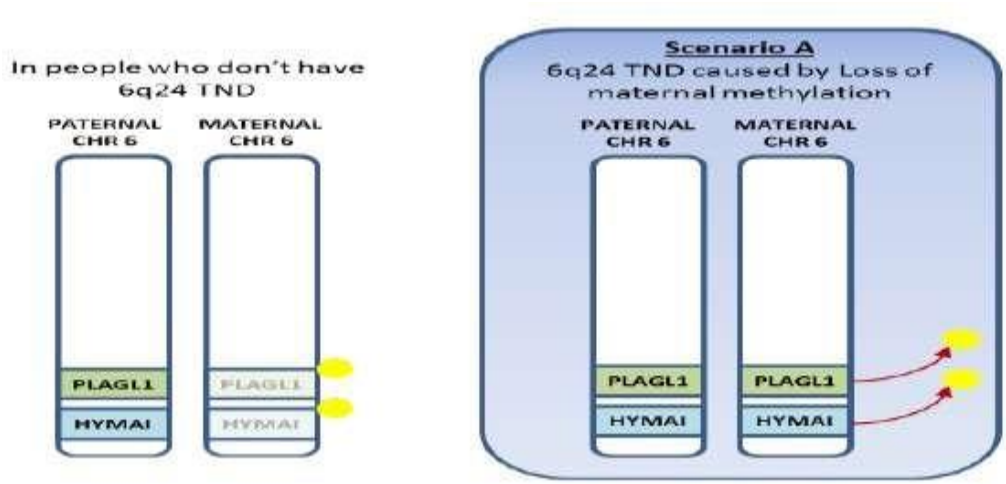

Figure 2: *Schematic of abnormal maternal methylation function in the long arm of maternal chromosome 6 in region 6q24 [1].*

Another 40 percent of cases of 6q24 transient neonatal diabetes syndrome occur when the parent-derived version of chromosome 6 has amplified genetic material, including genes made from the paternal hereditary pattern in the 6q24 region [1,6].

The third mechanism, which indicates overexpression of genes in region 6q24, is disruption of the maternal version of the genes (maternal hypomethylation). Approximately 20% of cases of transient neonatal diabetes related to 6q24 are due to maternal hypomethylation. Some people with this condition have a genetic change in the native version of the 6q24 region that prevents the genes in that region from being turned off. Other people with the disorder have a gene silencing that is targeted in many areas, known as penetrating site hypothalamus (HIL) [1,6].

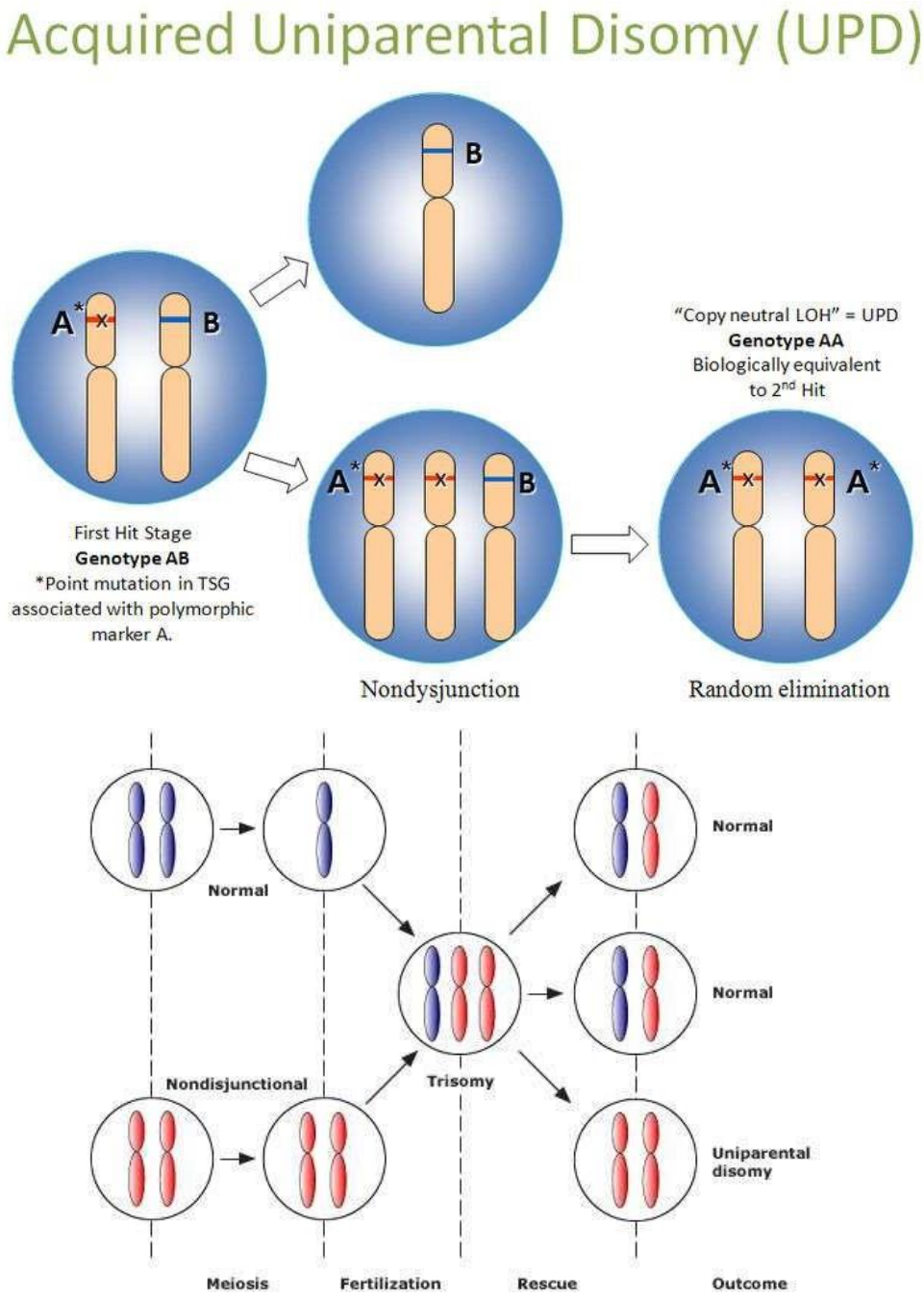

Figure 3: *Schematic of a single parent [1].*

About half the time of hypomethylation, HIL is caused by a mutation in the ZFP57 gene, which is located in the short arm of chromosome 6 at 6p22.1. Studies show that the protein produced by this gene is important in creating and maintaining gene silencing. Other causes of HIL are unknown. Because HIL can overexpress many genes, this mechanism may lead to other health problems in some people with transient neonatal diabetes related to 6q24 [1,7].

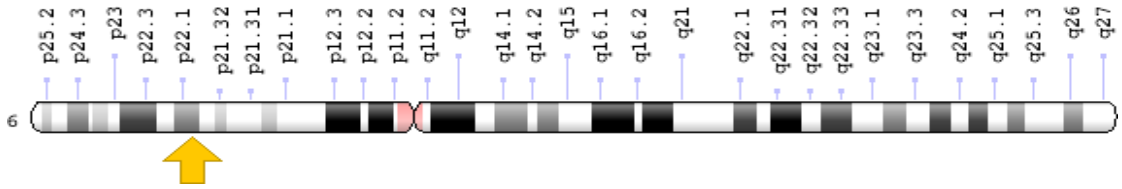

Figure 4: *Schematic view of chromosome 6 where the ZFP57 gene is located in the short arm of this chromosome as 6p22.1 [1].*

It is not yet well understood how overexpression of the PLAGL1 gene and other genes in region 6q24 causes transient neonatal diabetes mellitus associated with 6q24, and why the disease resolves after infancy. The protein produced by the PLAGL1 gene helps control another protein called the pituitary adenylate cyclase activating polypeptide receptor (PACAP1), and one of its functions is to stimulate insulin secretion by beta cells in the pancreas. In addition, overexpression of PLAGL1 protein has been shown to stop the cell division cycle and lead to cell self-destruction (apoptosis). Researchers suggest that overexpression of the PLAGL1 gene may reduce the number of insulin-secreting beta cells or impair their function in infected individuals [1,8].

Adequate insulin deficiency leads to the signs and symptoms of diabetes.

In people with transient neonatal diabetes mellitus related to 6q24, these signs and symptoms are more likely to occur during times of physiological stress, including the rapid growth of infants, childhood illnesses, and pregnancy. Because insulin acts as a growth factor in the early stages of growth, a deficiency of this hormone may cause intrauterine growth retardation in 6q24 transient neonatal diabetes [1,9].

Most cases of transient neonatal diabetes mellitus related to 6q24 are not inherited, especially those caused by paternal and maternal dysmosis. In these cases, genetic changes occur as random events during the formation of reproductive cells (eggs and sperm) or in the early stages of embryonic development. Affected people usually do not have a family history of the disorder [1,9].

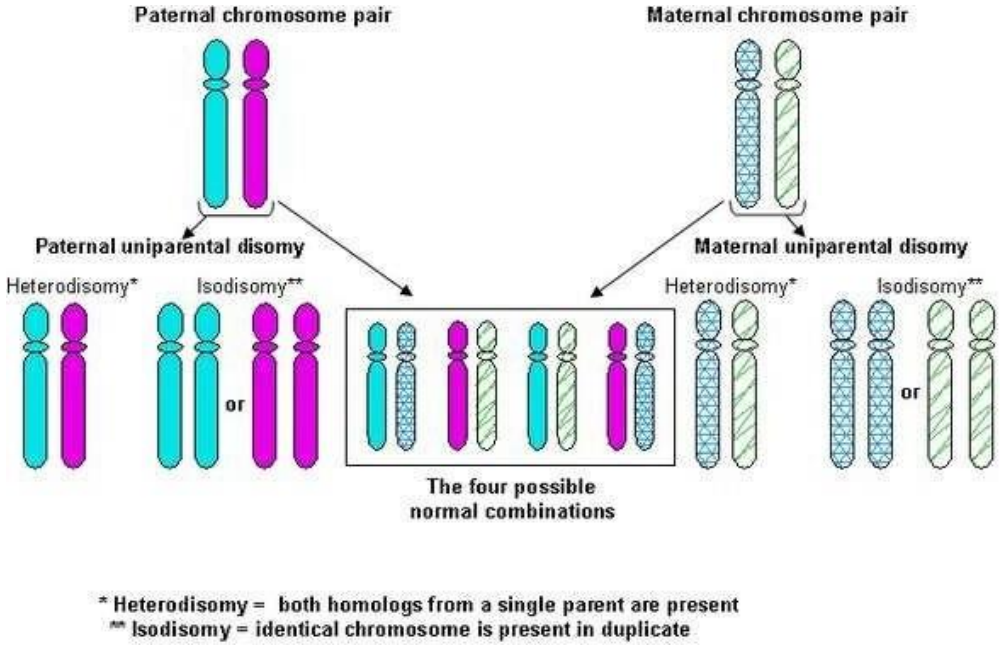

Figure 5: *Schematic of the mechanism of dysplasia functioning of paternal (left) and maternal (right) [1].*

Occasionally, a genetic mutation associated with 6q24 in transient neonatal diabetes syndrome is inherited. For example, the replication of genetic material on paternal chromosome 6 can be passed down from generation to generation [1,10].

When 6q24 transient neonatal diabetes syndrome is related to mutations in the ZFP57 gene, it is inherited in an autosomal recessive pattern. Therefore, two copies of the ZFP57 mutant gene (one from the father and the other from the mother) are required to cause the disease, and the chance of having a child with the autosomal recessive disease for each possible pregnancy is 25%. The parents of a person with autosomal recessive disease each carry a copy of the mutated gene, but usually do not show any signs or symptoms of the disease [1,10].

Frequency of neonatal transient diabetes syndrome associated with 6q24

Between 1 in 215,000 and 1 in 400,000 babies are born with diabetes. About half of these babies have transient diabetes. Researchers estimate that approximately 70% of transient diabetes in infants is due to genetic changes in 6q24 [1,10].

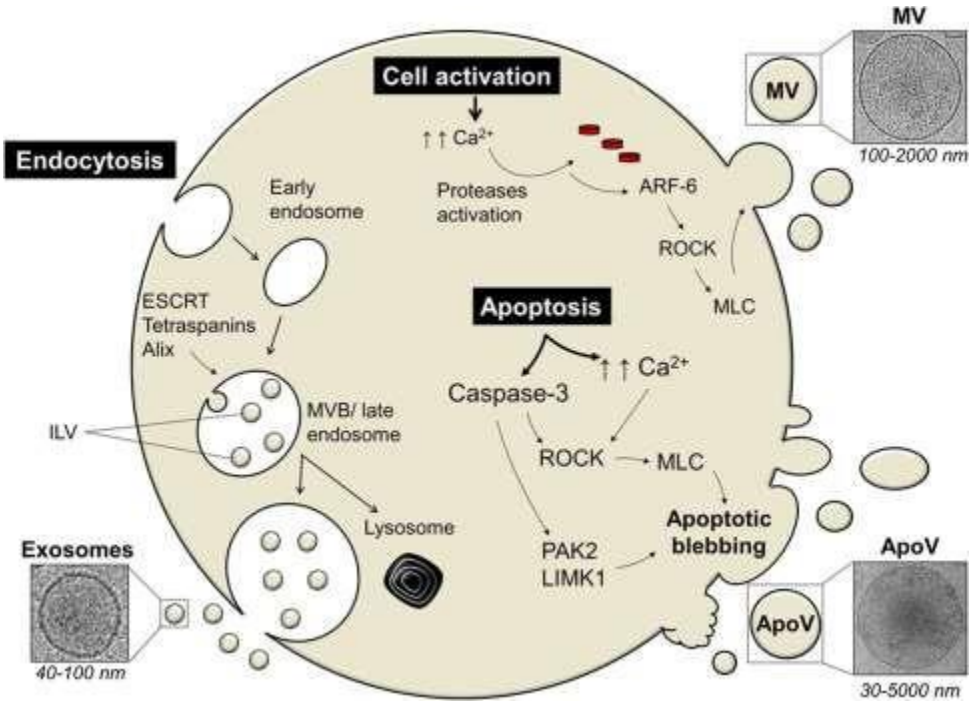

Figure 6: *Schematic of the biochemical mechanism of physiological cell death (apoptosis) [1].*

Diagnosis of transient neonatal diabetes syndrome associated with 6q24

Transient neonatal diabetes syndrome associated with 6q24 can be diagnosed based on the clinical findings of some patients and some pathological tests. The most accurate way to diagnose this type of diabetes is to test the molecular genetics for the target genes on the long arm of chromosome 6 at 6q24, to check for possible changes [1-11].

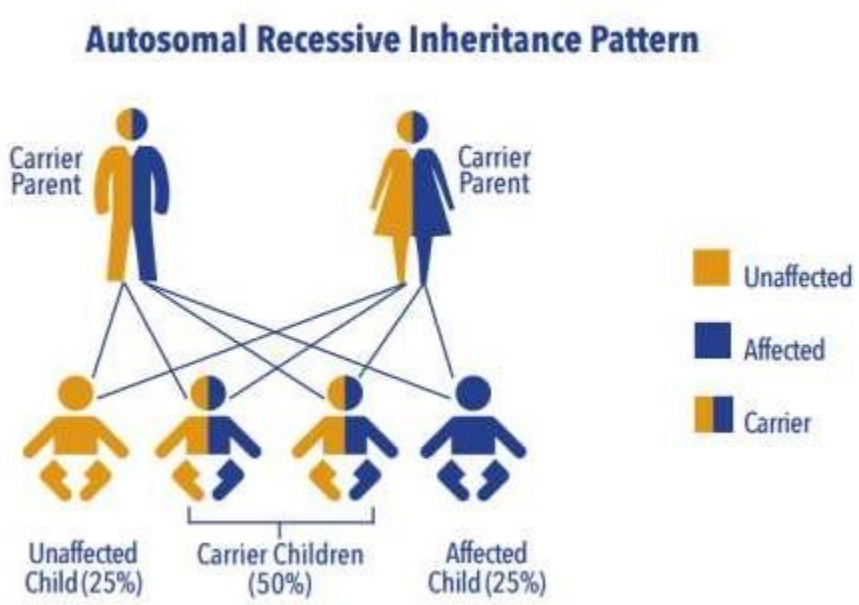

Figure 7: *Schematic of the autosomal recessive inherited pattern followed by 6q24-associated neonatal transient diabetes syndrome [1].*

Treatment routes for transient neonatal diabetes syndrome associated with 6q24

The treatment strategy and management of transient neonatal diabetes syndrome associated with 6q24 is symptomatic and supportive. Treatment is performed with the efforts and coordination of a team of specialists including pediatricians, neonatal nutritionists, endocrinologists and other health care professionals. Genetic counseling is also very important for having a healthy child [1,11].

Discussion and Conclusion

People with 6q24 transient neonatal diabetes syndrome experience very slow growth before birth (severe intrauterine growth retardation). Babies with high blood sugar and hypothyroidism (dehydration) usually begin in the first week of life. The signs and symptoms of this form of diabetes are transient, meaning that they gradually decrease over time and generally disappear between the ages of 3 months and 18 months. However, diabetes can recur, especially during childhood or pregnancy. Transient neonatal diabetes syndrome associated with 6q24 can be diagnosed based

on the clinical findings of some patients and some pathological tests. The treatment strategy and management of transient neonatal diabetes syndrome associated with 6q24 is symptomatic and supportive [1-11].

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