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CORRELATION BETWEEN GENETIC VARIATIONAND RECURRENT SPONTANEOUS ABORTION

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Abstract

Abortion is defined as the excretion of the fetus outside the uterus before it reaches the stage of viability in which it is able to survive. The viability is defined as the period (23-23) weeks of gestational age, which represent the supposed age of the fetus to survive after birth. The international health organization has defined abortion as the loss of pregnancy or the fetus with a weight less than 500 grams and the age range between (20-22) weeks of pregnancy.

Keywords: *Abortion, Excretion, Fetus, Uterus, Pregnancy*

The genetic basis for recurrent abortion is poorly known, and single gene mutations, polygenic and cytogenetic factors are all associated with recurrent abortion. Analysis of single nucleotide polymorphisms in enzyme-coding genes with a regulatory role in essential metabolic pathways (MTHFR enzyme), coagulation factors (leiden factor V and prothrombi)and hormones and receptor for hormone like progesterone receptor. The genetic variation of the MTHFR gene is generally associated with the hyperhomocystinemia and the recurrent abortion, and the most common gene variant is the A1298C transformation which result in the change of Glutamine to Alanine amino acids in the catalytic pathway of MTHFR, this condition makes the abnormality enzyme and defect in its function. The oxytocin hormone also play an important psychology role during pregnancy, studies have shown that the polymorphism (rs53576) of the oxytocin receptor gene is associated with two main social processes related to emotional interaction and stress.

RECURRENT SPONTANOUSE ABORTION

Recurrent Spontanouse Abortion It is also called recurrent pregnancy loss (RLP) It is defined as the loss of a pregnancy three or more times with a lifetime of less than 20 weeks From the period of pregnancy, The incidence of recurrent miscarriage has been estimated 1-3% around the world [1].

There are multiple reasons that lead to recurrent miscarriage Including hereditary reasons As the occurrence of chromosomal impairment, or it may be for immune reasons, or defect in metabolism and endocrine glands, or anatomical reasons as abnormalities in the womb, However, progress in identifying the causative agents of recurrent miscarriage is very slow, This indicates the presence of other underlying causes that have not yet been diagnosed, And at the present time the disorders of blood clotting and the occurrence of blood clots and impaired coagulation pathway It is one of the most important reasons that lead to recurrent miscarriage and Thrombophilia is one of the most common disorders leading to recurrent miscarriage [2,3].

GENETIC DISORDERS WHICH CAUSES THE RECURRENT ABORTION

Several studies have confirmed that he FVL gene mutation its present in Caucasian society and that prevalence of the genotypic GA variant is (13.2%), in addition to that there is a rare extremism between the societies of Africans, China, Japan, and south Asians, and the prothrombin gene mutation affected (1.3%) of Caucasian society and this mutation do not have identified among patients in the Asian community and this indicated for these mutation considered rare in Asian population. Other study found the mutation of FVL and Prothrombin genes approximately appear in (3-6%) of Caucasian women, in the united kingdom these mutation are associated with (25%) of cases for blood clotting[4,5].

FOLATE, VITAMIN B12 AND HOMOCYSTINE IN GENETIC EVOLUTION

The pregnant women with low level of folate have significant risk factors for fetal infection with neural tube defect NTD and the folate supplementation protect against this injury as the partial disturbances and that lead to NTD are unknown but it may include the inadequate metabolism of the developing fetus and disruption and distortion during proliferation of nerve cells and also programmed death, these events are essential and may also reduce the vitality of the fetus, recent study have shown an increase in the risk of early spontaneous abortion among pregnant women with low folate level in the blood an lack of Vitamin B12 during pregnant and increase in the level of homocystine in the fetus therefore increase the risk factors on NTD infection, in addition the inherited transcobilamine deficiency result in sever nervous abnormality and mental retardation[6,7,8].

Folate and Vitamin B12,These effect may be significant specially at early stage of folate development when cells undergo rapid proliferation and differentiation[9].

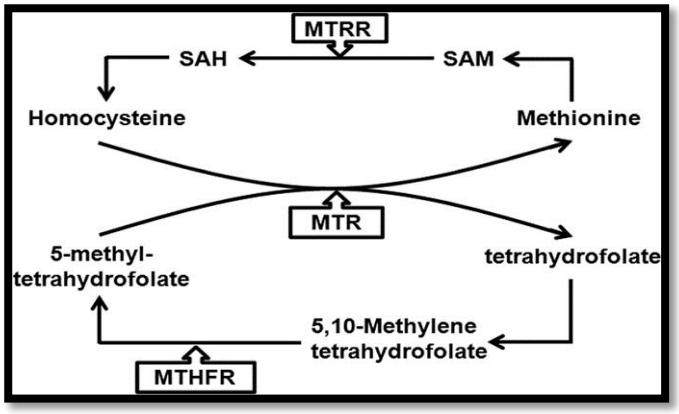
MTHFR GENE AND HEREDITARY VARIATION OF TRANSCOBALAMINE GENE IN SPONTANEOUS ABORTION

many study give evidence through disorders of the metabolism pathway of folate and others pathway dependent on vitamin B12, the variation in the MTHFR and Transcobalamine genes are considered as primary risk factor for many disorders during genetic growth and development such as NTD an down syndrome, another studies found strong correlation between the MTHFR (A1298C)mutation and the high concentration of homocystine in the amniotic fluid and the most state of hyperhomocystonemia is a risk factor for recurrent abortion. The common apparent effect of MTHFR and TC genes is a decrease in the bioavailability of folate and vitamin B12 and also increase level of homocystine in the blood [10,11].

The MTHFR gene is responsible for the formation of the enzyme (methylenetetrahydroflate reeducates enzyme) it is a basic enzyme that catalyze conversion (5,10-methylenetetrahydroflate) to (5-methylenetetrahydroflate), the genetic variation of MTHFR gene is generally associated with hyperhomocystinemia in pregnant women, and this is one of the risk factors for anural tube defect and recurrent miscarriage abortion [12].

There are several studies that recognize the correlation between increasing the level of homocystine and therefore losing the fetus, and there are two type of genetic variation in MTHFR gene, the first is C677T its responsible to transformation the amino acid alanin to amino acid valin in the catalytic pathway of the MTHFR enzyme, and this condition make defect enzyme and reduce the activity of the anzyme, The second common mutation of MTHFR gene is

A1298C its result from change of amino acid Glutamin to Alanin in the sequence of MTHFR enzyme, and this mutation causes reduce activity of MTHFR enzyme [13,14].



The second common variation of MTHFR gene its convert the C to A nucleotide on site 1298 which result from it change amino acid glutamine ti alanine amino acid, and that mutation (C1298A) registered on it decrease the activity of MTHFR enzyme and there for increase in the level of homocystein and decrease the level of folate in the blood and this difference its considers one of the main causes of miscarriage[15].

FACTOR V LEIDEN AND PROTHROMBIN GENES WITH ABORTION

The FV Leiden gene mutations considered is the most common causes of hereditary thrombosis in different population and also a reason for the occurrence of deep venous thrombosis and pulmonary blood clots and active protein resistance, Numerous studies give evidence show where about (7.3%) of Caucasian peoples carry heterozygous pattern to FVL gene, as they have increase risk factor of development of a venous thrombosis, while people with homozygous mutant pattern of FVL gene face an (80%) greater risk factor of getting venous thrombosis [16, 17].

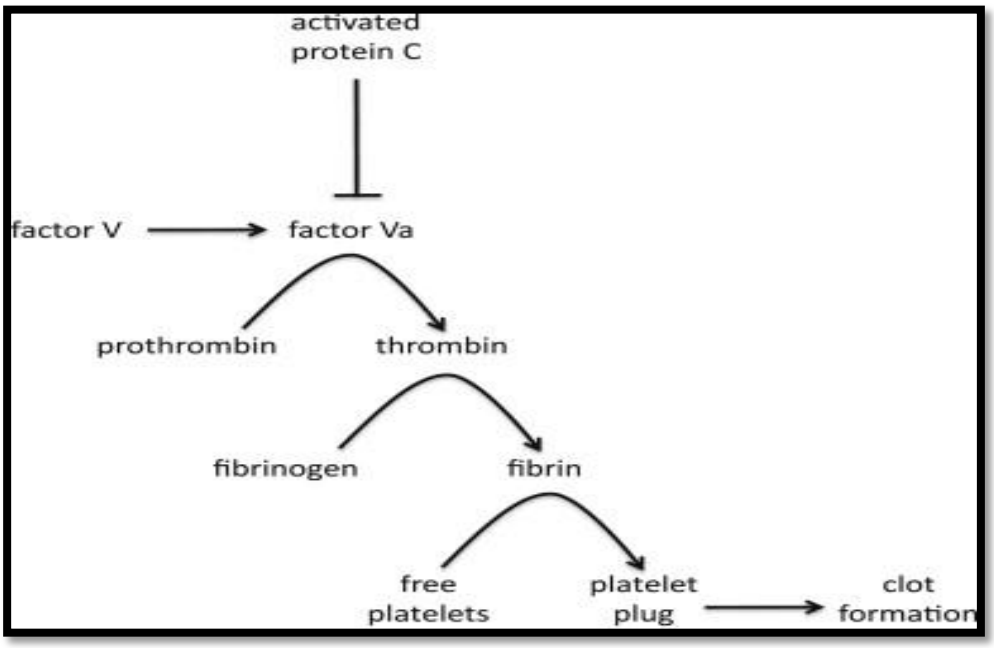
FVL gene mutation is the most common cause of hereditary thrombosis in Caucasian societies and is also a reason for the occurrence of deep venous thrombosis and pulmonary blood clots. FVL gene mutation leads to resistance to protein C activation, and these mutation involves changing the nitrogenous base G to A in the site of 1691 nucleotide of the FVL gene, which is located in the exon 10 and this change in the nitrogen base leads to a change of the amino acid Argenine to Glutamine amino acid, at the site 506 of the protein which is one of the three basic natural fission sites of the protein C moleculs [18,19].

There is another mutation called prothrombin (G20210A) mutation, thus was recently considered as one of the most important risk factors for blood clotting, this mutation increase the concentration of prothrombin in the plasma and also increase the risk of thrombopolic disease by two to four times and the genetic variation of the prothrombin gene is appoint mutation that result in the change of G to A nucleotide at the site 20210 in the prothrombin gene, The prothrombin gene mutation (G20210A) was recently considered to be one of the most important risk factors for coagulation, this mutation increase the concentration of prothrombin in the plasma and also increase the prospect having thromboebolic disease two to four times [20,21].

The gene responsible for encoding prothrombin consist of 21000 bp, which include 14 Exons and 13 Introns, and is located near the cenromer of chromosome number 11, and this mutation

is closely related o high levels of prothrombin in the blood, and the peoples who carry the heterozygous genotype of the prothrombin gene have twice the rate of deep venous thrombosis, while the people who carry homozygous mutant type increase the risk factor 15-20 times to venous thrombosis [20].

In addition many studies has found that PT and FVL genes mutation may be considered a major risk factor for the incidence of newborn stroke cases in Saudi Arabic population, the study recommended that FVL (G1691A) mutation and PT (G2010A) mutation are important causes for several genetic disorders [18].



OXYTOCIN RECEPTOR GENE WITH ABORTION

Oxytocin is a peptide of nine amino acids that are produced in the thalamus gland and released in both brain and blood stream, it was discovered by the Italian scientist in 1835. It is a peptide that act as both neurotransmitter and has wide effect on, and play an important role in social motional treatment throughout the body and it is have well-known function in the uterus outer action and milk generation, the oxytocin has a major effective bond between the child and her mother and giving confidence to people and maintaining eye contact in communication during the conversation [23,24].

Studies have shown that the polymorphism (rs53576) of oxytocin receptor gene (G allele) is associated with two main social process related to emotional interaction and stress compared with people carrying homozygous wild type of alleles, this study also showed that people who carry one or two copies of the allele A (AG\AA) have less sympathetic and moody compression, as measured by the mind reading test by eyes and other sympathetic scales [25].

Moreover persons with the (AG\AA) genotype showed higher physical and mood fatigue efficacy than GG persons, determined by the heart rate response and emotional interaction scale, In human the SNP polymorphism of adenine (A) or guanine (G) of oxytocin in site (rs53576) has been associated with autism, it is a disorders characterized by duplication of social interaction and communication [26,27].

This genetic variation has also been associated with the parenting relationship parents

demonstrate toward their children. Thus, people who have one or two copies of allele A, when compared with homozygote people for (G) allele, have an increased likelihood of diagnosis autism and displaying less parental sensitivity [25].

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