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LITERATURE REVIEW: THE MODULATION OF TMPRSS6 POLYMORPHISM ON THE IRON-RELATED MARKERS: REVIEW STUDY CENTERED ON HEMOGLOBIN, SERUM FERRITIN, HEPCIDIN, AND SOLUBLE TRANSFERRIN RECEPTOR

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ABSTRACT

Anemia is a global health problem that occurs both in developed and developing countries. About 1.2 million people in the world are affected with Anemia, especially iron deficient (ID). Iron refractory iron deficiency anemia (IRIDA) is one of genetic recessive, characterized by refractory anemia from oral iron therapy but partially responsive to parenteral therapy. A transmembrane protease serine 6 (TMPRSS6) is a gene providing hepcidin suppression and is a regular iron metabolism. This gene allows for the compensatory mechanism of iron absorption. Hemoglobin has an association with TMPRSS6 which detected at a low level and it's may be due to an iron imbalance of homeostasis. On the other hand, polymorphism of the SNP gen TMPRSS6 rs855791 and rs4820268 also iron intake had an association both with the iron status, particularly in Serum Ferritin (SF) concentration. TMPRSS6 is encoding a Matriptase-2 which plays an essential role in hepcidin. Down-regulation of hepcidin levels is associated with matriptase-2, which means a regulator key for iron hemostasis. A mutation in TMPRSS6 pathogenically may uninhibit the hepcidin production, causing IRIDA. Soluble transferrin receptor (sTfR) is also associated with the TMPRSS6 gene which is caused by fractional iron absorption as one of many factors induced by IRIDA. TMPRSS6 has an important role in IRIDA condition. A mutation may affect the hepcidin levels and lead to iron deficiency. Hepcidin levels together with hemoglobin, serum ferritin and sTfR affected by this TMPRSS6 gene mutation. SNPs of TMPRSS6 also has a different role in IRIDA. Although, it is very limited information about this gene and its association with IRIDA, further research in larger population with including races and ethnics are needed

INTRODUCTION

Anemia is a blood disorder with many etiologies, such as genetic mutations, infectious diseases, nutritional or absorption deficiencies, and excessive menstrual blood. The most common cause of anemia is iron deficiency anemia (IDA) which is more prevalent in females and a universal clinical problem worldwide.[1] About 3,7% of maternal deaths during pregnancy and childbirth in Africa are caused by Anemia.[2] More than 50% of reproductive-age women (15-49 years) have been reported as anemic.[3]

Iron Deficiency (ID) is a global nutritional disorder that may affect both developing and developed countries, this may have a significant impact on human health. Absolute and functional ID condition is predominant to be the cause of anemia and may threat to health also quality of life. About 1.2 million people in the world are affected by ID, becoming the top 5 causes of the years that lead to disability. ID is a result of insufficient iron stores, inadequate iron mobilization, or a combination.[4,5] One of many strategies to prevent and treat iron deficiency is iron supplementation. Now, the genetic recessive form of iron refractory iron deficiency anemia (IRIDA) is identified. This type of anemia is refractory to oral iron therapy but partially responsive to parenteral iron administration. IRIDA is a rare autosomal recessive disorder hallmarked by anemia microcytic hypochromic, in conjunction with low plasma iron, low transferrin saturation, and ferritin in a normal range.[6]

The transmembrane protease serine 6 (TMPRSS6) gene provide tonic suppression of hepcidin, the regulator of iron metabolism. Studies in mutant mice showed the TMPRSS6 genes caused the loss of the catalytic domain of matriptase-2 that concurrently increased hepcidin levels in the liver. Single nucleotide polymorphisms (SNP) can decrease the function or inactivation of matriptase-2, releasing tonic suppression of hepcidin (HAMP) gene expression. The TMPRSS6 gene's function is essential in iron deficiency to allow the compensatory mechanism of increased iron absorption. Patients with IRIDA gave high hepcidin, as the result of defective negative control by TMPRSS6, limitation in duodenal absorption, and heme iron recycling by macrophages, which may lead to the severity of anemia.[7,8] Human TMPRSS6 is located on chromosome 22 (22q12.3) and expressed as 7 different transcripts, only 4 of them have a well-supported annotation and are predicted as proteins. It is known as a type II serine protease mainly expressed at the cell surface. [9] IRIDA is also characterized by congenital microcytic, hypocromic anemia with low mean corpuscular volume erythrocyte, low transferrin saturation and defects in iron absorption also utilization. Figure 1 shows the TMPRSS6 gene structure and its mutation with representation of Matriptase-2 mutations in IRIDA patients.[10]

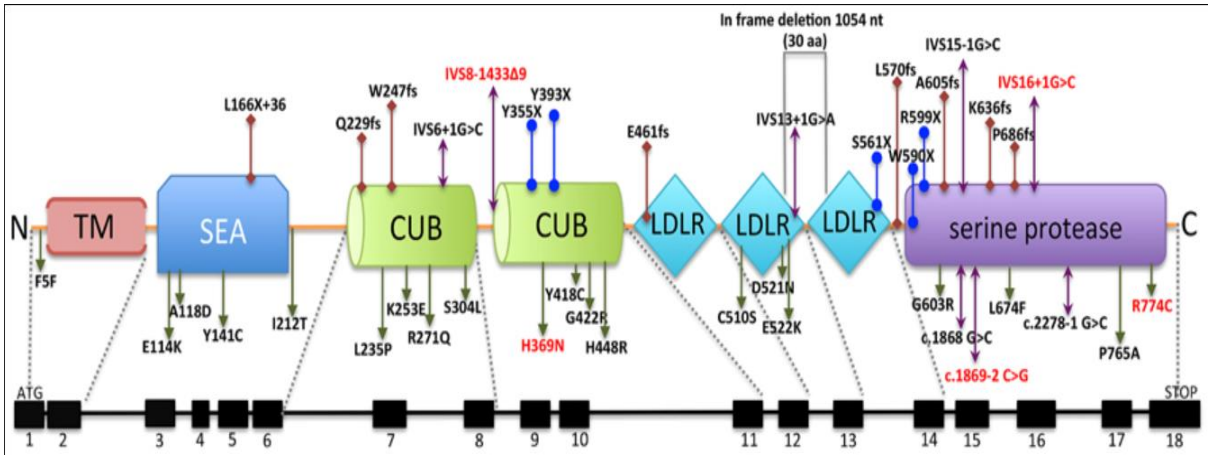

Figure 1. TMPRSS6 gene structure and its mutation corresponding with Matriptase-2 in IRIDA patients. The green, blue, red, and purple arrows show the missense, nonsense, frameshift and splice junction mutations respectively.[10]

Iron-refractory Iron Deficiency Anemia (IRIDA) is a recessive form genetically identified because of constitutively high hepcidin levels. This type of anemia is refractory but has a good response in parenteral iron administration. A common mutation in the TMPRSS6 gene especially rs855791 may influence hepcidin. The product from this gene is matriptase-2, as the regulator of iron homeostasis. Matriptase-2 protein provides a tonic suppression in hepcidin. Hepcidin blocks intracellular releasing iron by downregulating ferroportin, known as mammalian protein transporter iron cellular. Any single nucleotide polymorphism (SNP) in TMPRSS6 may lead to decreased function or inactivation of matriptase-2. This condition may contribute to inappropriately elevated hepcidin levels, blocking iron absorption and recycling, and promoting iron deficiency and anemia.[5,11,12] This study aims to know how the TMPRSS6 gene plays a role in IRIDA and its influence on iron deficiency, focusing on hemoglobin, serum ferritin, hepcidin, and soluble transferrin receptor.

TMPRSS6 Polymorphism and Hemoglobin

Red blood cells (RBC) or erythrocytes contain hemoglobin, which is an iron-rich tetramer, composed of two alpha-globin and beta-globin chains. RBC indices include hemoglobin (Hb), hematocrit (HCT), mean corpuscular hemoglobin (MCH), mean corpuscular hemoglobin concentration (MCHC), mean corpuscular volume (MCV), and red blood cell width (RDW). Several common TMPRSS6 variants have been associated with multiple RBC traits. Mutations in TMPRSS6 are associated with IRIDA, characterized by anemia microcytic and hypochromic with low transferrin saturation.[13]

The TMPRSS6 736(V) allele is associated with high hepcidin serum levels comparatively in Caucasians and Asians, low level of serum iron, transferrin saturation, MCV, and Hb (average difference between homozygote 0,2 g/dL). A study from Danquah et al. found that southern highlands of Rwanda every fourth child with anemia has iron deficiency and the Hb difference between iron deficiency and others is in the range of 1 g/dL.[14]

A study with menstrual women as the samples showed that women with the TX genotype have inversely correlated Hb with the pictorial blood-loss assessment chart (PBAC) scores. In

contrast, the correlation was statistically not significant with C homozygote (R^2=0.062, p = 0.15). In menstrual loss, it would be greater in iron loss and after IDA, generally compatible with the concept. A population-based study shows that rs855791, the variants genetic of TMPRSS6 are associated with IDA susceptibility in elderly women.[15]

In an Iraq population study, adult IDA patients have a TMPRSS6 gene with rs855791 mutation and are found significantly associated with IDA. The frequency of the mutant (TT) genotype of TMPRSS6 rs855791 polymorphism was higher in IDA patients. TMPRSS6 C/T polymorphism genotypes and risk of IDA have an association statistically significant (P≤0.038). Other results found that the means of Hb, MCV, MCH, and MCHC in IDA patients were significantly lower than their means in the control (P≤0.00). Low concentration of Hb, MCV, MCH, and MCHC due to an imbalance in iron homeostasis (low heam decreases Hb synthesis) which leads to IRIDA.[16]

The two SNPs TMPRSS6 shows less severe changes in association with serum iron or hemoglobin, they are rs855791 and rs4820286. These findings confirmed with subsequent study, showed rs855791 and rs4820286 had significant effect in iron-related hematologic parameters. A meta-analysis study in African populations showed the minor alleles A of rs2413450 were associated with lower Hb. The rs5756506 was found strongly associated with Hb levels.[1]

Ferritin Serum levels associated with TMPRSS6 Polymorphism

In young children, a study conducted by Shinta et al. found that TMPRSS6 genes have an association with the hemoglobin and iron status where IDA is prevalent. Polymorphism of the SNP gen TMPRSS6 rs855791 and rs4820268 also iron intake had an association both with the iron status, particularly in SF concentration. Serum ferritin is the indicator of iron status, which is sensitive to the early stage of iron deficiency and can be shown as the iron depletion stage. The minor allele frequency of SNP rs855791 and rs4820268 tend to be lower in African than European and Asian populations. The iron intake had a more significant polymorphism of rs855791 and rs4820268 with SF concentration. From that result, both gene and intake had an association with iron status, more significantly in the human status of iron.[8]

In addition, sex manifested its effect on SF levels, which may mainly be caused by the instability and sensitivity of SF. Another study shows that menstruation is a risk factor for ID and even in IDA women.[17] In Rwanda, about 17.5% population was iron deficient, and ferritin levels were low for children ≤ 2 years (mean, 67.1; 95% CI, 56.4-77.8 ng/ml). Also, it is more common in ≤ 2 years (22.6%) than in the older children (13.6%, P = 0.001).[14]

About 14% of black female South Africans had a low SF concentration and the homozygous wild type presented a significantly lower level of SF concentration (P = 0.02).[2] Other studies in Gambian adults, from 251 individuals, found 31.9% were anemia and 37.5% of them were iron deficient (IDA).[7]

Hepcidin levels and TMPRSS6 influence

TMPRSS6 is encoding a Matriptase-2 which plays an essential role in hepcidin. Down-regulation of hepcidin levels is associated with matriptase-2, which means a regulator key for

iron hemostasis. A mutation in TMPRSS6 pathogenically may uninhibit the hepcidin production, causing IRIDA. A Dutch case series study of 21 IRIDA patients and their relatives, found that bi-allelic genetic with severe genotype defects are more severe in IRIDA phenotypes. Transferrin saturation (TSAT)/hepcidin ratio was found to be lower in bi-allelic IRIDA patients than in mono-allelic ($P < 0.05$).[6]

In study with IRIDA and IDA populations, found that hepcidin levels were significantly higher in IRIDA patients than IDA as the control. Also, a higher ability of TSAT/hepcidin ratio to discriminate between IRIDA and TMPRSS6-unrelated IDA. TSAT/hepcidin ratio is distinguished lower in IRIDA patients from IDA patients as control with specificity and sensitivity is 100% (95%CI 91-100% and 84-100%, respectively).[18] Another study by Al-Jamea et al., the mean hepcidin levels were higher IRIDA group and it is higher in the post- than pretreatment stage and the difference was not significant ($P = 0.75$). The mean TMPRSS6 RNA level was low in IDA and IRIDA patients compared to the control and it is highly significant ($P < 0.001$).[5]

The association of SNPs in the TMPRSS6 gene with iron and parameters in IDA patients is statistically significant with a positive correlation in hepcidin levels (r-0.418; $P<0.0001$).[1] Matriptase-2 together with TMPRSS6 are a member of familial enzymes of cell surface protein defined as type II transmembrane serine protease. An evidence suggest that in the absence of TMPRSS6 may increased hepcidin concentration degrade intestinal ferroprotein and interfere with normal iron absorption. Hepcidin overproduction is expected to cause iron trapping in enterocytes and in macrophage. The resulting of IDA is hypoferremia as the consequences of the reduced absorption and recycling of iron which diminish the amount of available for hemoglobin synthesis and red cell production.[19]

TMPRSS6 polymorphism and Soluble Transferrin Receptor

Transferrin receptor has their own role in hepcidin synthetizing in response to increasing body iron. A study shows that the TMPRSS6 rs855791 TT variant is associated with low iron absorption in all model controlling. Soluble Transferrin Receptor (sTfR) has been associated with fractional iron absorption (FIA) as one of several factors together with Hepcidin, Hb, and Transferrin serum in TT variants, with 38% of the variability iron absorption.[20]

SNP in TMPRSS6 and several genes have been reported to have a positive association with the status of SF, iron store (IS), sTfR, Hb, total iron-binding capacity, unsaturated iron-binding capacity, hemochromatosis (HFE), and ferroportin. Each iron status biomarker has advantages and limitations, Hb is used for screening biomarker ID but unsuitable for assessing iron status, SF remains for the optimal indicator of IS in the absence of infection or inflammation, and sTfR to measure cellular iron deficiency, directed by iron-deficient erythropoiesis and its not strongly affected by concurrent infection and inflammation.[17]

In a South African study, focusing on black females found that 61% of the population had a high sTfR concentration (>8.3 mg/L). About 30 SNPs were investigated, and the association was found to be significant in TF gene and SF, sTfR, and BI. The heterozygous genotype class of rs1799852 significantly higher sTfR concentration ($P = 0.03$) than the homozygous wild-type genotype class. Multiple linear regression models of rs1799852 and rs3811647 explained

about 13% of the variation in sTfR concentration after adjustment of age, area of residence, and proportion of heme iron intake.[2]

Conclusion

TMPRSS6 has an important role in IRIDA condition. A mutation may affect the hepcidin levels and lead to iron deficiency. Hepcidin levels together with hemoglobin, serum ferritin and sTfR affected by this TMPRSS6 gene mutation. SNPs of TMPRSS6 also has a different role in IRIDA. Although, it is very limited information about this gene and its association with IRIDA, further research in larger population with including races and ethnics are needed.

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