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LITERATURE REVIEW

A Literature Review : The Role of Genetics in Women of Reproductive Age with Anemia

Ida Rahmah Burhan[1], Delmi Sulastri[2]

1. *Department of Public Health, Faculty of Medicine, Andalas University, Padang;*
2. *Department of Nutrition, Faculty of Medicine, Andalas University, Padang*

Correspondence: Ida Rahmah Burhan, email: idarahmahburhan@med.unand.ac.id, phone: 0811660401

Abstract

One of the main nutritional problems in Indonesia is anemia. Iron deficiency anemia can occur due to the interaction of two factors, namely iron intake itself and the role of genetics. The genes in humans and animals involved in iron mechanism is Transmembrane Protease Serine 6 (TMPRSS6). The purpose of this literature review is to determine the role of genetics in reproductive age women with anemia. The search was conducted with Google School database and Pubmed database looking for articles of the last 10 years from 2012 - 2022. From the number of articles found, only about 10 articles had full criteria.

Keywords: *Anemia, Genetic, Iron deficiency, TMPRSS 6, female, age of reproduction.*

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INTRODUCTION

Anemia is one of the main nutritional problems in Indonesia. This condition occurs because the level of red blood cells that bind oxygen or the level of hemoglobin (Hb) in the blood is lower than normal.[1] The incidence of anemia in Indonesia is still quite high, namely 48.9%. [2] Measurement of the normal value of hemoglobin levels for men > 13.5 g/dl, whereas in women > 12 g/dL, if this condition is less than the normal value there will be several signs that can be observed or felt by the person in the form of 5L (weak, tired, lethargic, lethargic, limp), dizziness, dizzy eyes, irregular heartbeat, shortness of breath, and pale face.[3]

World Health Organization (WHO) data in the Worldwide Prevalence of Anemia reports that the world's population suffering from anemia is 1.62 billion people with a prevalence of more than 50% of women of reproductive age worldwide suffering from anemia. Almost 38% of pregnant women, 29% of non-pregnant women have anemia. The impact of anemia on maternal health during pregnancy has an effect, especially in iron supplementation that is not successful, so preparations are needed long before pregnancy which can be given to teenage girls and women of childbearing age.[4]

Factors that cause anemia are the lack of levels of iron, vitamin B12, folic acid and protein in the body. This can directly occur as a result of quite a lot of blood loss due to acute or chronic conditions and imperfect maturation of red blood cells in the body so that the production of red blood cells is reduced.[5]

Iron also plays a very important role in neurocognitive and neurobehavioral. Iron has a role in the formation of the myelin sheath and as a cofactor for several enzymes that play a role in the formation of neurotransmitters such as serotonin and norepinephrine and dopamine. The role of iron in neurotransmitter function is supported by the distribution of iron in the brain which is also related to the distribution of some of these neurotransmitters.[6]

Iron deficiency can occur due to the interaction of two factors, namely iron intake itself and also the role of genetics. One of the genes in the human and animal bodies involved in the iron mechanism is Transmembrane Protease Serine 6 (TMPRSS6) or also known as Matriptase-2. Polymorphism in the Matriptase-2 domain will affect the translation process which can produce different proteins that interfere with the hemojuvelin binding process and lose the catalytic domain which results in an excess amount of hepcidin in the liver. This condition can reduce the ability to absorb iron and have an impact on the occurrence of iron deficiency anemia.[7]

Matriptage-2 will prevent excess hepcidin in the blood by breaking down hemojuvelin which is a substrate of the Matriptase-2 enzyme, so that hemojuvelin will dissolve and enter cells and will not activate Hepcidin Antimicobial Peptide (HAMP) and will control hepcidin production. If hemojuvelin is not successfully broken down, hepcidin will bind to Bone Morphogenic Protein (BMP) and will activate HAMP so that there will be an increase in hepcidin release. The high amount of hepcidin in the body can inhibit the absorption, release and recycling of iron, because hepcidin will bind to ferroportin and cause internalization and

breakdown of ferroportin in lysosomes, so that ferroportin will not be carried from intracellular to plasma and will cause a decrease in one's iron status. [7]

The polymorphism that occurs at point (SNP) rs855791 is G → A which will change the Valine protein to Alanine and occurs in exon 17 which is the strongest association with a decrease in Hemoglobin (Hb) 0.13 g/dL, a decrease in Serum Ferritin (SF) 3.71µg/L , and an increase in Transferrin Receptor (TfR) of 0.02 mg/L per A allele. 7 In Gan's study, a similar result was obtained. Polymorphism in the TMPRSS6 SNP rs855791 gene was significantly associated with a decrease in Hb concentration (P≤0.0013), plasma ferritin (p ≤ 0.0058).[8] In another study it was found that the polymorphism in the TMPRSS6 gene was not only directly associated with iron levels in the blood but also had a direct relationship (border line significant, p = 0.054) with the intelligence function of children.[9] Mutations in the TMPRSS6 gene can affect intelligence function because apart from being dominant in the liver, it is also found in the kidneys, brain, lymph glands, uterus and testes.[10]

METHOD

This research is a literature review that examines and analyzes research results related to the role of genetics in anemia through a literature search both nationally and internationally using the PubMed database and Google Scholar (Google Scholar).

The initial stage of searching for journal articles with a range of 2012-2022, obtained 1640 articles using the keywords "Genetics, anemia", 34 articles using the keywords "TMPRSS6, Genetics, anemia, iron, women, reproductive age". Of these only about 10 articles have full criteria. The results showed that TMPRSS6 is associated with iron deficiency anemia.

RESULTS

Identification results from search methods on Google Schoolar and Pubmed where the title contains one or more keywords being searched for, from these articles 34 articles can be excluded with appropriate titles and 10 data are obtained from the review results. The process of screening the search results data obtained the results of data types that have similarities in the research theme. The eligibility stage is carried out to determine which articles are included in the inclusion and exclusion criteria based on the suitability of the title and content of the article. Furthermore, the include stage is the suitability of the occupation with the inclusion criteria, namely articles with a time limit of the last ten years that have been set by the author in the form of a study on genetic influences on anemia, free full text, articles 2012-2022. The results that have been obtained from the study are then screened and then included so that the data obtained matches the required criteria. From the results of this synthesis, 10 article documents were obtained which would then be carried out critical thinking. The results of a literature review study found that TMPRSS6 genetics is related to iron deficiency anemia.

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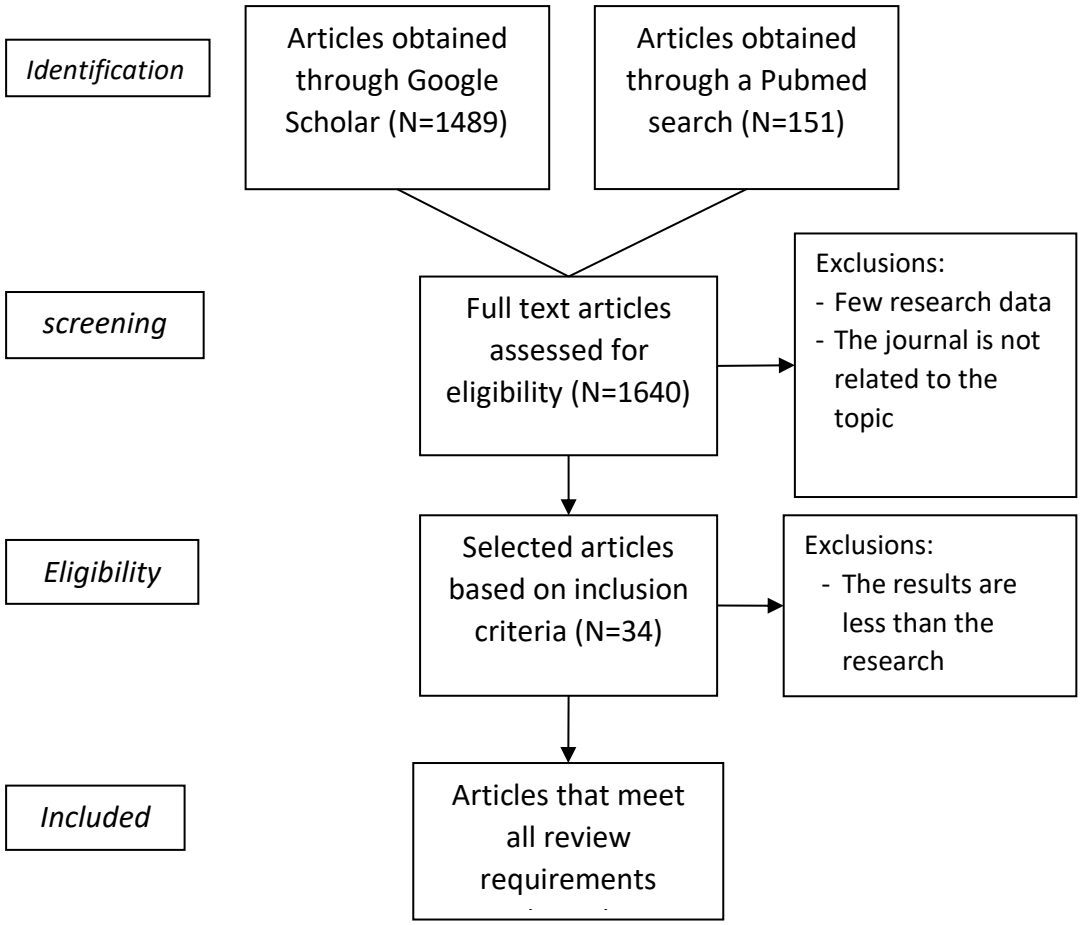

Figure 1. Flow chart for selecting research articles.

Table 1. Research results.

No.	Researcher	Title	Research methods	Results
1.	Nasira et al., 2021	*Role of TMPRSS6 rs855791 (T>C) polymorphism in reproductive age women with iron deficiency anemia from Lahore, Pakistan*	*Case control*	The TMPRSS rs855791 (TC) polymorphism is closely related to iron deficiency anemia. (P < 0.05, OR: 1.5 and 95% CI: 0.9, 2.6, P < 0.05, OR: 0.5 and 95% CI: 0.2, 0.9 respectively)

2.	Dewi et al., 2019	*The Association of TMPRSS6 Gene Polymorphism and Iron Intake with Iron Status among Under-Two-Year-Old Children in Lombok, Indonesia*	*Randomized Clinical trials*	TMPRSS6 decreased serum ferritin (SF) by 4.50 g/L per minor allele copy (A) of rs855791 (p = 0.08) and 5.00 µg/L per minor allele copy (G) of rs4820268 (p = 0.044).
3.	Sudarshan, et al., 2021	*The Role of Gene Variants in the Iron Metabolism of Anemic Adolescent Girls*	*Case Control*	The genotype frequencies of GG and GA at rs602662 and GG, GT, and TT at rs11568350 are associated with low iron status in anemic patients.
4.	Farah, et al., 2022	*TMPRSS6 gene polymorphisms associated with iron deficiency anemia among the global population*	*Case Control*	Several genetic variants of transmembrane protease serine 6 (TMPRSS6) associated with different iron parameters, especially the which contributes to elevated hepcidin levels, low blood pressure, and iron status.
5.	Yuliana, et al., 2013	Polymorphism of the Trans Membrane	*Case Control*	In this study, polymorphism

		Protease Serine 6 (TMPRSS6) Gene as a Risk Factor for Iron Deficiency Anemia in Pregnant Women		rs855791 TMPRSS6 gene is a risk factor for iron deficiency anemia. Genotyping with the T allele affects the increase in serum hepcidin and has an impact on decreasing the erythrocyte index as an ADB parameter.
6.	Putu, et al., 2017	Genetic Variation of the TMPRSS6 Gene at SNP rs855791, Iron Intake, Nutritional Status and Environmental Factors as a Determinant of Intelligence Function in Elementary School Children Aged 7-10 Years in Kupang City	*Cross-sectional*	The frequency of the TMPRSS6 SNP rs855791 gene is 49.4% heterozygote (AG), 6.8% homozygote dominant (GG), and 43.8% variant homozygote (AA)
7.	Titi, et al., 2023	TMPRSS 6 Gene Mutation on Hemoglobin Levels in Rice Farmers Exposed to Pesticides in Tanggondipo Village, Uepai District, Konawe Regency	*Cross-sectional*	The results of the TMPRSS 6 gene mutation study in farmers who had low hemoglobin levels at the Uepai Health Center were CC genotype (0%). The CT genotype (57%) was found in samples 1, 2, 3

				and 7 marked by the appearance of bands measuring 331 bp, 225 bp and 151 bp. The TT genotype (42.85%) was found in samples 4, 5 and 6 which were indicated by the appearance of bands of 331 and 151 bp.
8.	Peng, et al., 2012	*TMPRSS6, but not TF, TFR2 or BMP2 variants are associated with an increased risk of iron-deficiency anemia*	*Case Control*	The results showed that the TF, TFR2 and TMPRSS6 polymorphisms were significantly associated with reduced iron status, but only the variants in TMPRSS6 were a genetic risk factor for iron deficiency.
9.	Habib, et al., 2018	*Prevalence and determinants of iron deficiency anemia among nonpregnant women of reproductive age in Pakistan*	*Secondary analysis pre-structured instrument*	A total of 7491 non-pregnant women aged between 15-49 years were included in the analysis. The prevalence of iron deficiency anemia is 18.1%.
10.	Pei, et al., 2014	*TMPRSS6 rs855791 polymorphism*	*Case Control*	The results showed that homozygosity for

	influences the susceptibility to iron deficiency anemia in women at reproductive age	the TMPRSS6 rs855791 C genotype has a protective role against iron deficiency anemia in women of reproductive age, especially those with menorrhagia.

RESULTS

Based on the results of a review of a number of articles, anemia that occurs is a public health problem with a prevalence of 21.7%. [11] This micronutrient deficiency already covers one third of the world's population with iron deficiency and is one of the main causes of anemia in the world. [12]

Putu's research, et al stated the role of the related TMPRSS6 gene in the mechanism of iron absorption. Mutations in the TMPRSS6 gene will affect the control of hepcidin expenditure in the liver, reduce iron absorption and increase the risk of developing Iron Refractory Deficiency Anemia (IRIDA). Low iron levels, especially in infants, will affect brain structure and will affect cognitive function in the future. This study found a decrease in hemoglobin levels in respondents who had the alele A.[13]

According to Dian Purwanto's research, the main regulator of iron metabolism is hepcidin. Hepcidin synthesis is controlled by bone marrow erythropoietic activity, iron storage and the presence of inflammation in the body. Excessive hepcidin production is affected by the mutation of the TMPRSS 6 gene.[14]

TMPRSS 6 mutations in humans cause refractory iron deficiency anemia (IRIDA) that is unresponsive to oral iron therapy. IRIDA is also characterized by congenital hypochromic, microcytic anemia, low red cell volume and low transferrin saturation.[15]

Recently TMPRSS 6 has been identified as an iron homeostatic modifier because it regulates the expression of the systemic iron regulatory hormone hepcidin and inhibits hepcidin activation by cleaving the hemojuvelin membrane. Hepcidin controls iron absorption by binding to a cellular iron export protein known as ferroportin, causing degradation of ferroportin and blockage of iron circulation from erythrocytes. In addition, hepcidin blocks the transfer of iron from macrophages into the circulation which is the main source of iron for cryptopoiesis after erythrophagocytosis and redeployment of blood cells.[15]

Previous studies have been conducted by Nasira et.al., 2021 has conducted research on the Role of TMPRSS6 rs855791 (T > C) polymorphism in reproductive age women with iron deficiency anemia from Lahore, Pakistan obtained TMPRSS 6 rs855791 (TC) polymorphism results related closely related to IDA sufferers in women of childbearing age as has been observed in the codominant and recessive models, in addition to that Maria et.al., 2008 A mutation in the TMPRSS6 gene, encoding a transmembrane serine protease that suppresses hepcidin production, in familial iron deficiency anemia refractory to oral iron showed that the observed TMPRSS6 mutation causes excessive hepcidin production and leads to impaired absorption and utilization of iron.[16,17]

In a study by Habib et.al., reported that the prevalence of women of reproductive age experiencing iron deficiency anemia is high globally. The relationship between TMPPRSS6 and the pathogenesis of iron deficiency anemia is significant in menstruating women. Increased gynecological problems related to pregnancy, postpartum bleeding and menorrhagia cause women of reproductive age to experience anemia at a higher rate. [18] A study conducted by Pei et.al. reported that elderly women who are menstruating have a higher susceptibility to deficiency anemia iron due to loss of blood a lot.[19]

CONCLUSION

Iron deficiency anemia is still the most common cause of anemia and is a global public health problem that affects a large number of people worldwide. Iron deficiency can occur due to the interaction of two factors, namely iron intake itself and also the role of genetics. One of the genes in the human and animal bodies involved in the iron mechanism is Transmembrane Protease Serine 6 (TMPRSS6) or also known as Matriptase-2. The main regulator of iron metabolism is hepcidin, excessive hepcidin production is affected by mutations in the TMPRSS 6 gene and causes impaired absorption and utilization of iron. This condition can reduce the ability to absorb iron and have an impact on the occurrence of iron deficiency anemia. The relationship between TMPPRSS6 and the pathogenesis of iron deficiency anemia is significant in menstruating women. An increase in gynecological problems related to pregnancy, postpartum hemorrhage and menorrhagia causes women of reproductive age to experience anemia at a higher rate.

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