

Review Article

TMPRSS6- Mutation in iron deficiency anemia -A review

Running title: TMPRSS6- mutation in iron deficiency anemia

Abstract:

Introduction:

Iron is one of the metals involved in a variety of physiological reactions, including the construction of haemoglobin, which transports oxygen to the tissues. Chronic blood loss or insufficient food intake are the most common causes of iron insufficiency. It demonstrates that iron insufficiency exists. A germline mutation in TMPRSS6, which encodes type two transmembrane serine protease generated by the liver and helps regulate the expression of systemic iron, can induce anaemia that is resistant to oral iron treatment.

Structure:

The plasma membrane is cleaved by TMPRSS6 *in vitro*. The signalling mechanism required for iron-dependent hepcidin transcription regulation is thought to be downregulated by TMPRSS6. They also investigated whether the robust physiologic inducer of hepcidin, iron, can affect TMPRSS6 mRNA levels *in vivo*, as one of the most important activators of hepcidin expression *in vitro* and *in vivo*.

Role of TMPRSS6

Overexpression of normal TMPRSS6 protein reduces Hamp promoter activity, and the TMPRSS6 cytoplasmic domain mediates Hamp suppression via the proximal promoter element. TMPRSS6 polymorphisms are more common than mutations and have been linked to variations in iron and hematologic markers.

Conclusion:

Because TMPRSS6 is linked to haematological factors, it is essential for maintaining iron homeostasis and proper erythropoiesis. Overproduction of hepcidin is caused by the TMPRSS6 mutation, which contributes to poor iron absorption and utilisation. Patients with poor transferrin

saturation, normal ferritin levels, high amounts of hepcidin molecules, and a family history of iron deficiency anemia should be aware of TMPRSS6 gene mutations.

Keywords: TMPRSS6, hepcidin, protein, iron deficiency, innovative technique and Eco friendly, innovative technique.

Introduction

Iron is one of the metals involved in a variety of physiological reactions, including the construction of haemoglobin, which transports oxygen to the tissues. It reveals that iron deficiency is frequently linked to chronic blood loss or insufficient food intake. Anemia resistant to oral iron therapy can be caused by a germline mutation in TMPRSS6, a type two transmembrane serine protease generated by the liver that aids in the regulation of systemic iron expression. TMPRSS6 is essential for human systemic iron homeostasis.(1)Hepcidin's discovery revealed the control of iron metabolism, and investigations on animals over the last few years have revealed its critical function in iron metabolism regulation. Hepcidin, which governs iron absorption and recycling, is one of several genes that regulates body iron metabolism.(2) The TMPRSS family contains sixteen genes, and mutations in TMPRSS 1, 2, 3, and 5 are linked to nonsyndromic deafness and cancer aetiology. Hepcidin levels that are too high inhibit duodenal iron absorption as well as macrophage heme iron recycling.(3-5)

The first gene-regulating hepcidin, TMPRSS6, encodes a negative regulator of hepcidin expression, a mutation that causes chronic iron deficiency anemia. Hepcidin expression is influenced by iron, hypoxia, inflammatory signals, and erythropoietic demand. Iron administration usually increases hepcidin expression; however, the TMPRSS6 mutation results in excessive hepcidin production and, as a result, insufficient iron absorption. It's uncertain whether TMPRSS6 mutations create excessively high levels of hepcidin. The most straightforward explanation is that TMPRSS6 ordinarily cleaves a protein that inhibits hepcidin synthesis, secretion, or clearance in oron hepatocytes.(6) Mutations in the TMPRSS6 gene are the root cause of the disease. Normally, the TMPRSS6 gene produces matriptase-2, a

transmembrane serine protease that inhibits the formation of hepcidin iron regulatory protein. Ferroportin, the main iron source, is equalised by hepcidin. Matriptase-2 protein cannot be generated when the TMPRSS6 gene is mutated. As a result, hepcidin levels rise, inhibiting ferroportin. Despite the existence of iron storage, the iron that is unable to enter the systemic circulation causes iron deficiency anemia, which is resistant to oral iron therapy.(7)

Individuals with or without other predisposed factors may be affected by TMPRSS6 mutations, which can lead to iron deficiency anemia. In humans, TMPRSS6 modulates hepcidin levels and could be useful in the treatment of iron problems. Inhibition of TMPRSS6's putative protease activity, for example, could be used to treat illnesses in which hepcidin levels are abnormally low, such as primary hemochromatosis and iron loading anemias. (8,9)the use of hepcidin as a biomarker for iron metabolism regulation Expression of hepcidin is triggered by inflammation. This may be due in part to a host defense mechanism designed to protect against infection and cancer by limiting the iron available, with hepcidin predominantly in the liver. In addition, hepcidin expression is triggered by inflammation. This may be due in part to a host defense mechanism designed to protect against infections and cancer by limiting the iron available. Downregulation of hepcidin requires the presence of the TMPRSS6 gene.(10). Our team has extensive knowledge and research experience that has translated into high quality publications (11).(12–25),(26–30), The aim of this study is TMPRSS6- Mutation in iron deficiency anemia.

STRUCTURE

TMRSS6 cleaves hemojuvelin from the plasma membrane in vitro. The signalling mechanism required for iron-dependent hepcidin transcription regulation is hypothesised to be down-regulated by TMPRSS6. In addition to determining if one of the most important activators of hepcidin expression, iron, can affect TMPRSS6 mRNA levels in vivo, they also investigated whether iron, a robust physiologic inducer of hepcidin, can modulate TMPRSS6 mRNA levels in vitro and in vivo(8).The matriptase-2 protein is made using instructions from the TMPRSS6 gene. This protein is a component of a signalling system that regulates the amounts of hepcidin, a crucial regulator of iron balance in the body.(31)

The TMPRSS6 gene encodes matriptase-2, a type II transmembrane serine protease. Matriptase-2 is structurally and functionally identical to matriptase-1, a protein linked to cancer

progression. Matriptase-2 was discovered to be responsible for iron homeostasis after phenotypes of iron-refractory iron deficiency anemia were discovered in mice models.(32,33),

ROLE OF TMPRSS6

Polymorphisms in the TMPRSS6 gene are more common than mutations, and they've been linked to differences in iron and hematologic factors.(34,35)The cytoplasmic domain of TMPRSS6 regulates Hamp inhibition via the proximal promoter region, and overexpression of the normal TMPRSS6 protein reduces Hamp activation. TMPRSS6 is an important component of the system that detects iron deficiency and inhibits hamp transcription, enabling better absorption of iron in the diet.(36).

Mutations in the TMPRSS6 gene, which encodes Matriptase2, a negative regulator of hepcidin transcription, induce iron resistant iron deficiency anaemia (IRIDA). IronRefractory Iron Deficiency Anemia and Microcytic Anemia are both classified as TMPRSS6. The extracellular matrix degradation and the Hfe effect on hepcidin synthesis are two linked mechanisms. Hepcidin binds to ferroportin and causes its internalisation and degradation, making it a key regulator of iron homeostasis. Hepcidin levels that are too high inhibit duodenal iron absorption as well as macrophage heme iron recycling(37).

TMPRSS6 is found primarily in the liver and suppresses hepcidin, a systemic iron-regulating hormone. The TMPRSS6 (Transmembrane Serine Protease 6) gene encodes matryptase 2, a hepcidin regulator that is involved in iron homeostasis and may be involved in breast cancer susceptibility. Increased expression of the TMPRSS6 gene in cancer tissues suggests that tryptase 2 is effective in the cancer process. As a result, TMPRSS6 gene polymorphisms can affect disease processes by altering patient blood parameters.(36,38)

DEMERITS:

Patients with a tendency to iron deficiency, such as celiac disease patients and fertile women, may be at risk for TMPRSS6 polymorphisms.

CONCLUSION:

Because TMPRSS6 is linked to haematological factors, it is essential for maintaining iron homeostasis and proper erythropoiesis. Overproduction of hepcidin is caused by the TMPRSS6 mutation, which contributes to poor iron absorption and utilisation. Patients with poor transferrin saturation, normal ferritin levels, high amounts of hepcidin molecules, and a family history of iron deficiency anemia should be aware of TMPRSS6 gene mutations.

Reference:

1. Kloss-Brandstätter A, Erhart G, Lamina C, Meister B, Haun M, Coassin S, et al. Candidate Gene Sequencing of SLC11A2 and TMPRSS6 in a Family with Severe Anaemia: Common SNPs, Rare Haplotypes, No Causative Mutation [Internet]. Vol. 7, PLoS ONE. 2012. p. e35015. Available from: <http://dx.doi.org/10.1371/journal.pone.0035015>
2. Cau M, Melis MA, Congiu R, Galanello R. Iron-deficiency anemia secondary to mutations in genes controlling hepcidin [Internet]. Vol. 3, Expert Review of Hematology. 2010. p. 205–16. Available from: <http://dx.doi.org/10.1586/ehm.10.2>
3. Camaschella C, Poggiali E. Inherited disorders of iron metabolism [Internet]. Vol. 23, Current Opinion in Pediatrics. 2011. p. 14–20. Available from: <http://dx.doi.org/10.1097/mop.0b013e3283425591>
4. Brundha MP. A Comparative Study-The Role of Skin and Nerve Biopsy in Hansen's Disease. Res J Pharm BiolChem Sci. 2015;7(10):837.
5. Timothy CN, Samyuktha PS, Brundha MP. Dental pulp Stem Cells in Regenerative Medicine--A Literature Review. Research Journal of Pharmacy and Technology. 2019;12(8):4052–6.
6. Killip S, Bennett JM, Chambers MD. Iron deficiency anemia. Am Fam Physician. 2007 Mar 1;75(5):671–8.
7. Ardicoglu AY, Gulnaz K, Hüseyin O, Ferda Ö, Nejat A. First Observation of Two

- TMPRSS6 Gene Mutations (G603R and K636AFSX17) in Turkish Population [Internet]. Vol. 6, International Journal of Blood Research and Disorders. 2019. Available from: <http://dx.doi.org/10.23937/2469-5696/1410046>
8. Finberg KE, Heeney MM, Campagna DR, Aydinok Y, Pearson HA, Hartman KR, et al. Mutations in TMPRSS6 cause iron-refractory iron deficiency anemia (IRIDA) [Internet]. Vol. 40, Nature Genetics. 2008. p. 569–71. Available from: <http://dx.doi.org/10.1038/ng.130>
 9. McGovern G. Address in the American Society for Parenteral and Enteral Nutrition for the third clinical congress [Internet]. Vol. 3, Journal of Parenteral and Enteral Nutrition. 1979. p. 137–8. Available from: <http://dx.doi.org/10.1177/0148607179003003137>
 10. Enawgaw B, Birhanie M, Terefe B, Asrie F. Prevalence of Anemia and Iron Deficiency Among Pregnant Women Attending Antenatal Care Service at University of Gondar Hospital, Northwest Ethiopia [Internet]. Vol. 65, Clinical Laboratory. 2019. Available from: <http://dx.doi.org/10.7754/clin.lab.2018.180822>
 11. Anita R, Paramasivam A, Priyadharsini JV, Chitra S. The m6A readers YTHDF1 and YTHDF3 aberrations associated with metastasis and predict poor prognosis in breast cancer patients. *Am J Cancer Res.* 2020 Aug 1;10(8):2546–54.
 12. Jayaseelan VP, Paramasivam A. Emerging role of NET inhibitors in cardiovascular diseases. *Hypertens Res.* 2020 Dec;43(12):1459–61.
 13. Sivakumar S, SmilineGirija AS, VijayashreePriyadharsini J. Evaluation of the inhibitory effect of caffeic acid and gallic acid on tetR and tetM efflux pumps mediating tetracycline resistance in *Streptococcus* sp., using computational approach. *Journal of King Saud University - Science.* 2020 Jan 1;32(1):904–9.
 14. SmilineGirija AS. Delineating the Immuno-Dominant Antigenic Vaccine Peptides Against gacS-Sensor Kinase in *Acinetobacterbaumannii*: An in silico Investigational Approach. *Front Microbiol.* 2020 Sep 8;11:2078.
 15. IswaryaJaisankar A, SmilineGirija AS, Gunasekaran S, VijayashreePriyadharsini J.

Molecular characterisation of *csgA* gene among ESBL strains of *A. baumannii* and targeting with essential oil compounds from *Azadirachta indica*. *Journal of King Saud University - Science*. 2020 Dec 1;32(8):3380–7.

16. Girija ASS. Fox3+ CD25+ CD4+ T-regulatory cells may transform the nCoV's final destiny to CNS! *J Med Virol* [Internet]. 2020 Sep 3; Available from: <http://dx.doi.org/10.1002/jmv.26482>
17. Jayaseelan VP, Ramesh A, Arumugam P. Breast cancer and DDT: putative interactions, associated gene alterations, and molecular pathways. *Environ Sci Pollut Res Int*. 2021 Jun;28(21):27162–73.
18. Arumugam P, George R, Jayaseelan VP. Aberrations of m6A regulators are associated with tumorigenesis and metastasis in head and neck squamous cell carcinoma. *Arch Oral Biol*. 2021 Feb;122:105030.
19. Kumar SP, Girija ASS, Priyadharsini JV. Targeting NM23-H1-mediated inhibition of tumour metastasis in viral hepatitis with bioactive compounds from *Ganoderma lucidum*: A computational study. *pharmaceutical-sciences* [Internet]. 2020;82(2). Available from: <https://www.ijpsonline.com/articles/targeting-nm23h1-mediated-inhibition-of-tumour-metastasis-in-viral-hepatitis-with-bioactive-compounds-from-ganoderma-lucidum-a-comp-3883.html>
20. Girija SA, Priyadharsini JV, Paramasivam A. Prevalence of carbapenem-hydrolyzing OXA-type β -lactamases among *Acinetobacter baumannii* in patients with severe urinary tract infection. *Acta Microbiol Immunol Hung*. 2019 Dec 9;67(1):49–55.
21. Priyadharsini JV, Paramasivam A. RNA editors: key regulators of viral response in cancer patients. *Epigenomics*. 2021 Feb;13(3):165–7.
22. Mathivadani V, Smiline AS, Priyadharsini JV. Targeting Epstein-Barr virus nuclear antigen 1 (EBNA-1) with *Murrayakoengii* bio-compounds: An in-silico approach. *Acta Virol*. 2020;64(1):93–9.
23. Girija As S, Priyadharsini J V, A P. Prevalence of Acb and non-Acb complex in elderly

- population with urinary tract infection (UTI). *ActaClin Belg.* 2021 Apr;76(2):106–12.
24. Anchana SR, Girija SAS, Gunasekaran S, Priyadharsini VJ. Detection of *csgA* gene in carbapenem-resistant *Acinetobacterbaumannii* strains and targeting with *Ocimum sanctum* biocompounds. *Iran J Basic Med Sci.* 2021 May;24(5):690–8.
 25. Girija ASS, Shoba G, Priyadharsini JV. Accessing the T-Cell and B-Cell Immuno-Dominant Peptides from *A.baumannii* Biofilm Associated Protein (*bap*) as Vaccine Candidates: A Computational Approach. *Int J Pept Res Ther.* 2021 Mar 1;27(1):37–45.
 26. Arvind P TR, Jain RK. Skeletally anchored forsus fatigue resistant device for correction of Class II malocclusions-A systematic review and meta-analysis. *OrthodCraniofac Res.* 2021 Feb;24(1):52–61.
 27. Venugopal A, Vaid N, Bowman SJ. Outstanding, yet redundant? After all, you may be another Choluteca Bridge! *SeminOrthod.* 2021 Mar 1;27(1):53–6.
 28. Ramadurai N, Gurunathan D, Samuel AV, Subramanian E, Rodrigues SJL. Effectiveness of 2% Articaine as an anesthetic agent in children: randomized controlled trial. *Clin Oral Investig.* 2019 Sep;23(9):3543–50.
 29. Varghese SS, Ramesh A, Veeraiyan DN. Blended Module-Based Teaching in Biostatistics and Research Methodology: A Retrospective Study with Postgraduate Dental Students. *J Dent Educ.* 2019 Apr;83(4):445–50.
 30. Mathew MG, Samuel SR, Soni AJ, Roopa KB. Evaluation of adhesion of *Streptococcus mutans*, plaque accumulation on zirconia and stainless steel crowns, and surrounding gingival inflammation in primary molars: randomized controlled trial [Internet]. Vol. 24, *Clinical Oral Investigations.* 2020. p. 3275–80. Available from: <http://dx.doi.org/10.1007/s00784-020-03204-9>
 31. Khuong-Quang D-A, Schwartzentruber J, Westerman M, Lepage P, Finberg KE, Majewski J, et al. Iron refractory iron deficiency anemia: presentation with hyperferritinemia and response to oral iron therapy. *Pediatrics.* 2013 Feb;131(2):e620–5.

32. Ahmad KA, Ahmann JR, Migas MC, Waheed A, Britton RS, Bacon BR, et al. Decreased Liver Hcpidin Expression in the Hfe Knockout Mouse [Internet]. Vol. 29, Blood Cells, Molecules, and Diseases. 2002. p. 361–6. Available from: <http://dx.doi.org/10.1006/bcmd.2002.0575>
33. Brundha MP, Pathmashri VP, Sundari S. Quantitative Changes of Red Blood cells in Cancer Patients under Palliative Radiotherapy-A Retrospective Study. Research Journal of Pharmacy and Technology. 2019;12(2):687–92.
34. Sato T, Iyama S, Murase K, Kamihara Y, Ono K, Kikuchi S, et al. Novel missense mutation in the TMPRSS6 gene in a Japanese female with iron-refractory iron deficiency anemia [Internet]. Vol. 94, International Journal of Hematology. 2011. p. 101–3. Available from: <http://dx.doi.org/10.1007/s12185-011-0881-0>
35. Hannah R, Ramani P, Brundha MP, Sherlin HJ, Ranjith G, Ramasubramanian A, et al. Liquid Paraffin as a Rehydrant for Air Dried Buccal Smear. Research Journal of Pharmacy and Technology. 2019;12(3):1197–200.
36. An P, Wu Q, Wang H, Guan Y, Mu M, Liao Y, et al. TMPRSS6, but not TF, TFR2 or BMP2 variants are associated with increased risk of iron-deficiency anemia [Internet]. Vol. 21, Human Molecular Genetics. 2012. p. 2124–31. Available from: <http://dx.doi.org/10.1093/hmg/dds028>
37. Heeney MM, Campagna DR, Westerman M, Fleming MD. The Clinical and Genetic Spectrum of TMPRSS6 Mutations Leading to Inappropriate Hcpidin Expression and Iron Refractory Iron Deficiency Anemia (IRIDA) [Internet]. Vol. 114, Blood. 2009. p. 629–629. Available from: <http://dx.doi.org/10.1182/blood.v114.22.629.629>
38. Poggiali E, Andreozzi F, Nava I, Consonni D, Graziadei G, Cappellini MD. The role of TMPRSS6 polymorphisms in iron deficiency anemia partially responsive to oral iron treatment [Internet]. Vol. 90, American Journal of Hematology. 2015. p. 306–9. Available from: <http://dx.doi.org/10.1002/ajh.23929>