EUROPEAN ACADEMIC RESEARCH
Vol. VII, Issue 3/ June 2019

Impact Factor: 3.4546 (UIF)
DRJI Value: 5.9 (B+)

ISSN 2286-4822
www.euacademic.org

Common Beta-Thalassemia Mutation and virological study of Beta -thalassemic patients. Review Article

NAZO RAHIM
Institute of Biochemistry, University of Balochistan
Quetta, Pakistan
MUHAMMAD USMAN
Bolan Medical University and Health Sciences Quetta, Pakistan
MUHAMMAD AKHTER SHAH
Bolan Medical University and Health Sciences Quetta, Pakistan
BAKHT ZAREEN RAHIM
Department of Botany, University of Balochistan Quetta, Pakistan
SHEIKH AHMED
Institute of Biochemistry, University of Balochistan Quetta, Pakistan
Bolan Medical University and Health Sciences Quetta, Pakistan

Abstract

Beta-thalassemia is a group of inherited blood disorder characterize by compact or absent beta globin chain synthesis, resulting in chronic hemolytic anemia and unproductive erythropoiesis. Persons with β-thalassemia have commonly variable clinical manifestations, extending from nearly asymptomatic to severe anemia requiring lifetime regular blood transfusions and convoluted by multiple organ damage. Chronic transfusions inevitably lead to iron overload which necessitate iron chelation therapy. Current overview about the disease clinical picture, method of diagnosis, complications and principles of management is going to be discussed in brief.

Key words: Thalassemia. Anemia. Infections. Blood transfusion. Mutation.

Thalassemia

Thalassemia is part of hereditary hematologic disorders characterize by the onset of anemia cause, which results due to concentrated rate of separation of one or more globin kinesis caused by mutations of the globin chain(Rund & Rachmilewitz, 2005)

The commonest monogenic syndrome is thalassemia that is characterized by low assembly of one or the other polypeptide chains resulting by decreased microcytosis & hypochromia. Due to persistent usual making of unaltered globin chain the unnecessary globin chain amalgamation results in to the growth of uneven collections of these unpaired globin chains resulting into oxidative membrane break & early demolition of erythrocytes in the peripheral circulation & also at previous levels of maturation. It results in the decreased the level of hemoglobin in the blood & O_2 transport ability of RBCs. Thalassemias can be classified into α-, ß-, γ δ ß thalassemia which depends on the type of the effected globin chain, thalassemias can be classified into α-,ß-, γ δ ß thalassemia(Benz Jr & Forget, 1975)

Two main types are described beta Thalassemia in which no ß globin chain is produced & ß+ thalassemia in which some ß- globin chains are produced. Less sever forms of ß thalassemia are sometimes designated ß++ to indicate that the defect in ß- chain production is particularly mild(Weatherall, 2004)

Majority of ß – thalassemias are caused by point mutations. Almost 200 ß – thalassemia alleles have now been characterized. Studies on the molecular genetics of thalassemia in various ethnic groups have shown that each group tends to have its own set of common mutations(Weatherall, 2004)

Symptomatic ß – thalassemia have been identified due to mutations inherited in the dominant fashion. Exon III of ß globin is involved in many of them gene & include complex rearrangements leading to elongation of ß globin gen & frame shift premature termination mutation & globin gene products Such mutations have been identified(Gunion & Haber, 1986)

GAA→TAA is the most common which changes at codon 121 resulting to nonfunctional protein. ß – "Globin chain In the heterozygous state dominant thalassemia mutations form hyper unstable hemoglobin variants that precipitate in the erythroid cells & cause thalassemia Intermedia(Baysal & Carver, 1995)

Some typical ß – thalassemias are observed without any detectable mutation in the ß – "globin gene or its immediate flanking regions Compound heterozygosis for two new mutations in the beta-globin gene (Semenza et al., 1984)

With normal Hemoglobin A_2 a number of forms of beta– thalassemia in heterozygous state are recognized. Amount which some are due to "silent" ß– thalassemia alleles while others reflect the co-inheritance of beta and alpha Thalassemia gene(Taher, Musallam, Cappellini, & Weatherall, 2011)

Thalassemia is a genetic blood disorder. People with Thalassemia disease are not able to make enough hemoglobin, which causes severe anemia. Hemoglobin is found in red blood cells and carries oxygen to all parts of the body. When there is not enough hemoglobin in the red blood cells, oxygen cannot get to all parts of the body. Organs then become starved for oxygen and are unable to function properly(Inati, Noureldine, Mansour, & Abbas, 2015)

Thalassemia is a genetic blood disorder. People with Thalassemia disease are not able to make enough hemoglobin, which causes severe anemia. Hemoglobin is found in red blood cells and carries oxygen to all parts of the body. When there is not enough hemoglobin in the red blood cells, oxygen cannot get to all parts of the body. Organs then become starved for oxygen and are unable to function properly (Inati et al., 2015)

There are two primary types of Thalassemia disease: Alpha Thalassemia disease and Beta Thalassemia disease. Beta Thalassemia Major (also called Cooley's anemia) is a serious illness. Symptoms appear in the first two years of life and include paleness of the skin, poor appetite, irritability, and failure to grow. Proper treatment includes routine blood transfusions and other therapies. (Danjou, Anni, & Galanello, 2011)

Alpha Thalassemia

There are two main types of Alpha Thalassemia disease. Alpha Thalassemia Major is a very serious disease in which severe anemia begins even before birth. Pregnant women carrying affected fetuses are themselves at risk for serious pregnancy and delivery complications. Another type of Alpha Thalassemia is Hemoglobin H disease. There are varying degrees of Hemoglobin H disease. Alpha

Thalassemia is the result of lacking or absent synthesis of Alpha globin chains (Danjou et al., 2011)

Two genes located on chromosome 16 are responsible of alpha globin gene production Alpha globin gene deficiency is always cause by deletion of one or more gene Alpha thalassemia is silent carrier status, is caused by single gene deletion which is asymptomatic and normal hematologic (Danjou et al., 2011)

Minor thalassemia is caused by two gene deletion with usually no anemia. Hemoglobin H is caused by three gene deletion causes microcytic anemia, hemolysis and Hemoglobin Bart's (HbH Bart's) is caused by four-gene deletion. This is usually known as alpha thalassemias major with HbH Bart's usually result in fatal hydrops fetalis Splenomegaly(Whipple & Bradford, 1936)

Thalassemia is a complex group of diseases that are relatively rare in worldwide but common in Mediterranean regions and South and Southeast Asia. Worldwide, there are 350,000 births per year with serious hemoglobinopathy (blood disorders). In Pakistan as a consequence of immigration patterns, occurrence of thalassemia disorders is increasing.

Beta Thalassemia

It is caused by absent synthesis of beta globin chains produces more alpha chains. Chromosomes handle beta globin g production (Rund & Rachmilewitz, 2005).

200 point mutation cause beta thalassemia and two genes are deleted (ELENA)

Minor beta thalassemia trait is caused by one gene defect, leading to asymptomatic and results micro cytosis and mild anemia. If production of both genes are severely reduce or absent a person affected with beta thalassemia major, also known as cooly anemia (Falk, 2017)

There are hundreds of mutations within the beta globin gene, but approximately 20 different alleles comprise 80% of the mutations found worldwide. Within each geographic population there are unique mutations. Individuals who have beta thalassemia major are usually homozygous for one of the common mutations, or heterozygous for one of the common mutations and one of the geographically-unique mutations. Both lead to absence of beta globin chain production.

Thalassemia in Pakistan

Carrier frequency of approximately 5.6% for beta-thalassemia in Pakistan has a population of more than 160 million people. Due to 50% of the population, Punjab is the largest province of the country. Due to low literacy in South Punjab rate the state of beta-thalassemia is alarming as consanguinity rate is very high (>81%). in this part of Pakistan, thalassemia impediment program is very essential. Hazara division of Pakistan had beta-thalassemia trait has 58% of the siblings of beta-thalassemia major children(ANJUM, TAQYYAB, SHAH, & CHAUDHRY, 2001)

β-Thalassemia Mutation Prevalence in Pakistan

Mutations can be checked by using Polymerase Chain Reaction (PCR) techniques. There are many types of mutations found in Pakistan. Identification of mutations helps for further treatment. Have checked the prevalence of different mutations in different districts of Punjab and balochistan. B-Thalassemia is one of the most frequent inherited hemoglobin disorders in Pakistan. The transporter incidence is probable to be 5.5%. To conclude the continuum of ß-globin gene defect causing ß-thalassemia, we have analyzed an envoy sample of 602 alleles from six national groups in Pakistan; 99.1% alleles were characterized, although 0.9% remains unknown. The field of mutations is heterogeneous and we have established 18 different mutations in all tribal groups. The four most frequent mutations, IVS-I-5 (G→C) (37.7%), codon 8/9 (+G) (21.1%), the 619 bp deletion (12.4%), and IVS-I-1 (G→T) (9.5%), account for 80.7% of the alleles. There is difference among the national groups and also among provinces. In the four provinces of Pakistan, the IVS-I-5 (G→C) mutation is more prevalent in Balochistan and as well as also in Sindh, while the codon 8/9 (+G) mutation is more common in the kpk and also in Punjab(Ansari et al., 2011)

ß- Thalassemia trait is significant two forms of hypo chromic microcytic anemia. Iron deficiency and ß -thalassemia trait is common in Pakistan. In one of the studies Hazara division of Pakistan had beta-thalassemia trait. Iron deficiency was found in 9% while ß -thalassemia was seen in 3% in the study carried out "Ratio between the percentages of microcytic hypo chromic cells as a screening test is an easy, reliable and sensitive index which can be used for mass

screening of ß-thalassemia trait mostly in a population where iron deficiency is also common(Puthenveetil et al., 2004)

11% of the Pakistani population hold thalassemia trait. In Punjabis prevalence rate is 3.26% while it is 7.96% in Pathans. And majority of the patients are due to cousin marriage and it's now important to control so it need serious attention to do something agents this alarming problems(Ahmed et al., 2000)

Infections due to Blood Transfusions to Thalassemic Patients

Universal from 0.3% to 5.7% of thalassemia patients are hepatitis B (HBsAg)–positive and from 4.4% to 85.4% are positive for Hepatitis C antibodies. The prevalence of HBV chronic infection is higher in Asia and Southeast Asia countries, whereas HCV chronic infection is common all over the world. Among HCV-infected thalassemia patients(Mirmomen et al., 2006)

Other hepatotropic viruses, such as GB virus C and transfusion transmitted (TT) virus, are also widespread between thalassemia patients but have not been create to donate to chronic hepatocellular break HCV transmission can take place during blood transfusion. The occurrence of chronic hepatitis C was senior among thalassemia patients transfused before 1990, when screening of blood donors was still not obtainable. Nowadays broadcast of HBV and HCV by transfusion is uncommon because of obligatory screening of blood yield. HBV transmission by mother to infant, sexual contact, or household speaks to is still common in the intermediate or high Endemic area. Finally, the intravenous drug use with infected needles is another common cause of both HBV and HCV infection(Ocak, Kaya, Cetin, Gali, & Ozturk, 2006)

Blood transfusions are secure in residential country. Since the introduction of blood donor screening for HBV and HCV infection, the residual risk has essentially been inadequate to blood units composed during the "window period, the period stuck between the time of infection and the time when antibodies against the virus C are noticeable in the serum To reduce even this remaining possibility, some national health organizations have supplementary purpose of HBV-DNA and HCV RNA by PCR technology of screening tests(Yugi, Hino, Satake, & Tadodoro, 2005) The test is performed on plasma mini-pools of different blood donors. The current risk of transfusion-

transmitted viral infection is estimated to be less than 2.5 per 1 million donations in the Asia, and several European countries. The situation differs in developing countries that have not yet incorporated the key requirements for a modern blood transfusion system. Most of these countries are in Asia and Africa. Vaccination against HBV infection is a key intervention in prevents the transmission of HBV and is a dangerous policy in dropping the worldwide morbidity and mortality. Persons immunize beside HBV like long-term fortification, and countries that have implement worldwide hepatitis B vaccination have knowledgeable a considerable decrease in HBV connected diseases(Prati, 2006)

Cardiac Complications

Cardiac failure and severe arrhythmias are the main causes of life-threatening morbidity and mortality in iron overload patients. Earlier than the accessibility of chelation therapy, cardiac disease was predictable for the duration of the second decade and still occurs in older patients or those who are poorly compliant with chelation therapy. consequently, cardiac function is monitor yearly inauguration at seven or eight years of age by electrocardiogram, echocardiogram, 24- hour Holter monitor, and recently by cardiac T2* MRI, which can notice preclinical cardiac iron accumulation(Kirk et al., 2009)

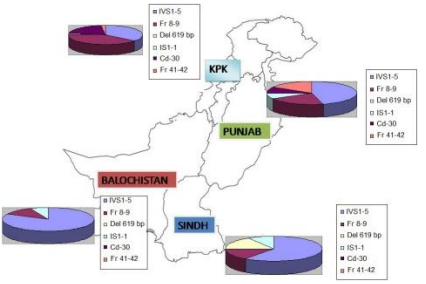

Figure 1. Distribution of different genetic mutations in different provinces of Pakistan.(Khan & Riazuddin, 1998)

Diagnosis

Microcytic hypochromic anemia is detected in CBC. Target cells and nucleated red blood cells in blood film. Hemoglobin electrophoresis or high-performance liquid chromatography (HPLC) can be diagnostic

with predominant HbF, low or absent HbA, and elevated HbA2. Familial and DNA studies may be required to confirm the diagnosis and for genetic counseling Investigation of hematological parameters as well as of genetic mutations to the α, ß and γ genes are essential steps, both in confirming a diagnosis of thalassemia and in deciding treatment.(Bain, 2011)

Symptoms

The most severe form of alpha thalassemia major causes stillbirth (death of the unborn baby during birth or the late stages of pregnancy). Children born with TM are normal at birth, but major symptoms in early childhood are anemia and mild jaundice. There is always some degree of hepato Splenomegaly, bone changes are variable and range from none to severe deformity, identical to that seen in ß-homozygous thalassemia.(Patne, Hisalkar, Gaikwad, & Patil, 2012)

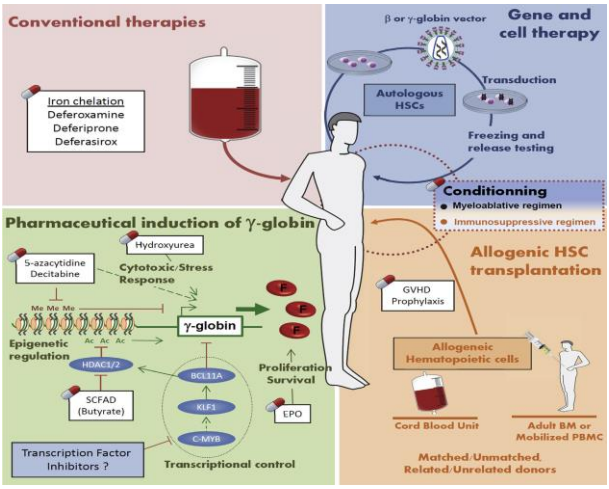

Fig. 2 Current and future therapies for beta-thalassemia major. Hemoglobin disorders account for almost 5% of deaths in children under the age of five years. For a minority of patients, mostly in high-income countries, current therapies include lifelong.(de Dreuzy, Bhukhai, Leboulch, & Payen, 2016)

Prevention

It is important to nervous tension that the most important advance in the field of thalassemia is its prevention. This has been very productively achieved in Mediterranean countries i.e., Italy, Greece,

Cyprus and Sardinia. There are four important aspect of prevention like Awareness, detection of carrier, useful counseling and prenatal diagnosis. Over last two decades, the programmed has been successfully concerned in the world. However, the desired goal of zero birth rate of thalassemia has remained a distant goal. Pakistan needs such programmed to prevent thalassemia and to reach the desired goal. However, in the absence of a national thalassemia prevention programmed, this still remains a difficult but extremely desirable goal(Sarker, Ghosh, Saha, & Shahriar, 2014)

CONCLUSION

Provided that in order to patients in comprehensible and correct conditions about the scenery of the disease, the need for treatment, the new medical protocol, has helpful possessions both on the result of thalassemia and sadness. Information deficits may result in needless sadness condition of in sequence should be individualized and proper to the age, developmental period, emotional development, individuality and family surroundings.

Thalassemia patients need lifetime mental support for preclusion of mental health issues. The final goal of completion emotional programs for thalassemia patients is to fight happiness by attractive their combination into the community conventional, minimizing information deficits and as long as help to plan and actualize their learning, individual and profession goals thus leading satisfying life.

References

1. Ahmed, S., Saleem, M., Sultana, N., Raashid, Y., Waqar, A., Anwar, M., Petrou, M. (2000). Prenatal diagnosis of beta- thalassaemia in Pakistan: experience in a Muslim country. *Prenatal diagnosis, 20*(5), 378-383.
2. ANJUM, S., TAQYYAB, M., SHAH, S. H., & CHAUDHRY, N. (2001). DETECTION OF ß-THALASSAEMIA TRAIT: ASTI DY OF FIFTY FEMALES. *Journal of Ayub Medical College Abbottabad, 13*(2).
3. Ansari, S. H., Shamsi, T. S., Ashraf, M., Bohray, M., Farzana, T., Khan, M. T., . . . Nadeem, M. (2011). Molecular epidemiology of ß-

thalassemia in Pakistan: far reaching implications. *International Journal of Molecular Epidemiology and Genetics, 2*(4), 403.

4. Bain, B. J. (2011). Haemoglobinopathy diagnosis: algorithms, lessons and pitfalls. *Blood reviews, 25*(5), 205-213.
5. Baysal, E., & Carver, M. (1995). The ß-and δ-thalassemia repository. *Hemoglobin, 19*(3-4), 213-236.
6. Benz Jr, E. J., & Forget, B. (1975). The molecular genetics of the thalassemia syndromes. *Prog Hematol, 9*, 107-155.
7. Danjou, F., Anni, F., & Galanello, R. (2011). Beta-thalassemia: from genotype to phenotype: Haematologica.
8. de Dreuzy, E., Bhukhai, K., Leboulch, P., & Payen, E. (2016). Current and future alternative therapies for beta-thalassemia major. *biomedical journal, 39*(1), 24-38.
9. ELENA, F. C. Ph. D. THESIS Beta-thalassemia trait-epidemiological and clinical aspects in children in Constanta County.
10. Falk, R. (2017). The Inagathering of Exiles *Zionism and the Biology of Jews* (pp. 143-174): Springer.
11. Gunion, J. F., & Haber, H. E. (1986). Higgs bosons in supersymmetric models (I). *Nuclear Physics B, 272*(1), 1-76.
12. Inati, A., Noureldine, M. A., Mansour, A., & Abbas, H. A. (2015). Endocrine and bone complications in ß-thalassemia intermedia: Current understanding and treatment. *BioMed research international, 2015*.
13. Khan, S., & Riazuddin, S. (1998). Molecular characterization of ß-thalassemia in Pakistan. *Hemoglobin, 22*(4), 333-345.
14. Kirk, P., Roughton, M., Porter, J. B., Walker, J. M., Tanner, M. A., Patel, J., . . . Anderson, L. J. (2009). Cardiac T2* magnetic resonance for prediction of cardiac complications in thalassemia major. *Journal of Cardiovascular Magnetic Resonance, 11*(1), O2.
15. Mirmomen, S., Alavian, S.-M., Hajarizadeh, B., Kafaee, J., Yektaparast, B., Zahedi, M.-J., . . . Faridi, A.-R. (2006). Epidemiology of hepatitis B, hepatitis C, and human immunodeficiency virus infecions in patients with beta-thalassemia in Iran: a multicenter study. *Arch Iran Med, 9*(4), 319-323.
16. Ocak, S., Kaya, H., Cetin, M., Gali, E., & Ozturk, M. (2006). Seroprevalence of hepatitis B and hepatitis C in patients with thalassemia and sickle cell anemia in a long-term follow-up. *Archives of medical research, 37*(7), 895-898.
17. Patne, A., Hisalkar, P., Gaikwad, S., & Patil, S. (2012). Alterations in antioxidant enzyme status with lipid peroxidation in ß thalassemia major patients. *Int J Pharm Life Sci, 3*, 2003-2006.

18. Prati, D. (2006). Transmission of hepatitis C virus by blood transfusions and other medical procedures: a global review. *Journal of hepatology, 45*(4), 607-616.
19. Puthenveetil, G., Scholes, J., Carbonell, D., Qureshi, N., Xia, P., Zeng, L., . . . Yee, J.-K. (2004). Successful correction of the human ß-thalassemia major phenotype using a lentiviral vector. *Blood, 104*(12), 3445-3453.
20. Rund, D., & Rachmilewitz, E. (2005). ß-Thalassemia. *New England Journal of Medicine, 353*(11), 1135-1146.
21. Sarker, N. R., Ghosh, A. K., Saha, S. K., & Shahriar, A. (2014). Recent advances in the management of Thalassaemia: A Review Update. *Journal of Shaheed Suhrawardy Medical College, 6*(1), 31-37.
22. Taher, A. T., Musallam, K. M., Cappellini, M. D., & Weatherall, D. J. (2011). Optimal management of ß thalassaemia intermedia. *British journal of haematology, 152*(5), 512-523.
23. Weatherall, D. (2004). The thalassemias: the role of molecular genetics in an evolving global health problem. *The American Journal of Human Genetics, 74*(3), 385-392.
24. Whipple, G. H., & Bradford, W. L. (1936). Mediterranean disease-thalassemia (erythroblastic anemia of Cooley): associated pigment abnormalities simulating hemochromatosis. *The Journal of Pediatrics, 9*(3), 279-311.
25. Yugi, H., Hino, S., Satake, M., & Tadodoro, K. (2005). Implementation of donor screening for infectious agents transmitted by blood by nucleic acid technology in Japan. *Vox sanguinis, 89*(4), 265-265.