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The Role of Genetic Mutations in Gene NBEAL2 in Gray Platelet Syndrome

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Abstract: *Gray platelet syndrome (GPS) is a rare inherited bleeding disorder characterized by macro thrombocytopenia, myelofibrosis, splenomegaly and typical gray appearance of platelets on Wright stained peripheral blood smear. GPS is caused by mutations in the* NBEAL2 *gene. Absence or marked reduction of alpha-granules in platelets underlies the disorder. Alpha-granules are the most abundant vesicles in platelets and store proteins that promote platelet adhesiveness and wound healing when secreted during platelet activation.*

Keywords: *Gray Platelet Syndrome, Hematology Disorder, NBEAL2 gene.*

1. Overview of Gray Platelet Syndrome

Gray platelet syndrome is a bleeding disorder associated with abnormal platelets that are involved in blood clotting. The skin of people with this syndrome is easily bruised and may increase the risk of nasal bleeding [1].

2. Clinical Signs and Symptoms of Gray Platelet Syndrome

Patients with GD may also experience abnormal or severe bleeding after surgery, dental work or minor skin damage. Women with gray platelet syndrome often experience irregular periods (menorrhagia) of menstruation. These bleeding problems are usually mild to moderate, but in some people they can be life threatening [1, 2].

Another common feature of gray platelet syndrome is a condition called myelofibrosis, where scar tissue (fibrosis) occurs in the bone marrow. Bone marrow is the spongy tissue at the center of the long bone that contains most of the blood cells needed by the body, including platelets. Wounds associated with myelofibrosis can damage the bone marrow and prevent the production of sufficient blood cells. Other organs, especially the spleen, begin to produce more blood cells to compensate, and this process often results in enlargement of the spleen (splenomegaly) [1, 3]

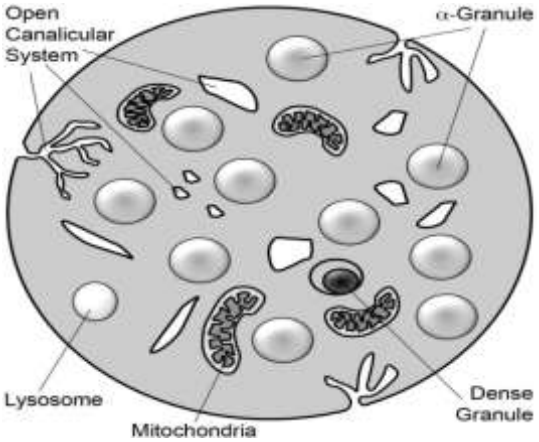

Figure1: *Schematic view of the cellular structure of blood platelets*

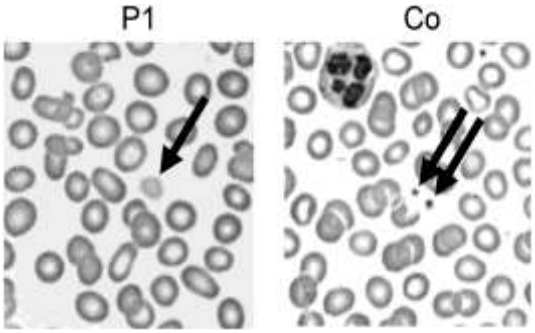

Figure2: *Microscopic view of gray platelets in the range of blood samples with gray platelet syndrome*

3. Etiology of Gray Platelet Syndrome

Gray platelet syndrome is caused by the mutation of the NBEAL2 gene located on the

short arm of chromosome 3 at 3p21.31. This gene provides the necessary guidance for protein synthesis; so far little information has been identified. NBEAL2 protein appears to play an important role in the formation of alpha granules. Alpha granules are contained in sacs that contain other growth factors and proteins and are important for blood clotting and wound healing. In response to injuries that cause bleeding, proteins stored in the granules help platelets form a plug that repels blood vessel damage and prevents further bleeding [1, 4].

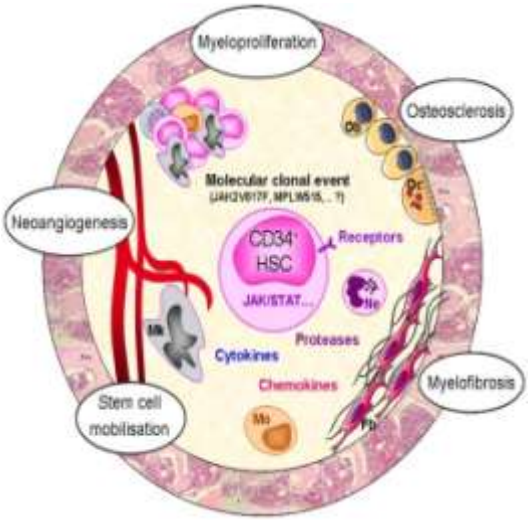

Figure3: *Schematic of the molecular pathway in blood cell differentiation*

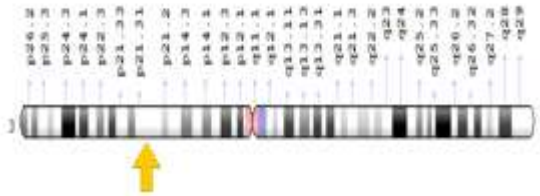

Figure4: *Schematic overview of chromosome 3 where the NBEAL2 gene is located in the short arm of chromosome 3p21.31*

Mutation in the NBEAL2 gene disrupts the normal production of alpha granules. Without alpha granules, platelets are abnormally large and less than normal (macrotrombocytopenia). Abnormal platelets, when viewed under a microscope, appear gray, which is a hallmark of gray platelet syndrome. Deficiency of alpha granules reduces the normal activity of platelets during blood clotting and increases the risk of abnormal bleeding. Myelofibrosis appears to occur due to growth factors and other proteins that are normally transferred to alpha granules in bone marrow. Therefore, proteins lead to fibrosis, which affects the ability of the bone marrow to create new blood cells. It is worth noting that some people with gray platelet syndrome do not have a mutation in the NBEAL2 gene and the cause of their disease is unknown [1, 5].

Gray platelet syndrome follows an autosomal recessive inheritance pattern if it is caused by a NBEAL2 gene mutation. Therefore, two copies of the mutated NBEAL2 gene (one from the father and the other from the mother) are needed to cause this syndrome and the chance of having a child with gray platelet syndrome in this case is 25% for each possible pregnancy [1,5].

If gray platelet syndrome is caused by mutations in other genes that have not yet been identified, it will follow an autosomal dominant inheritance pattern. Therefore, a version of the unknown mutant gene (whether parent or parent) is required for this syndrome and the chance of having a child with autosomal dominant gray platelet syndrome is 50% for each possible pregnancy. [1, 5]

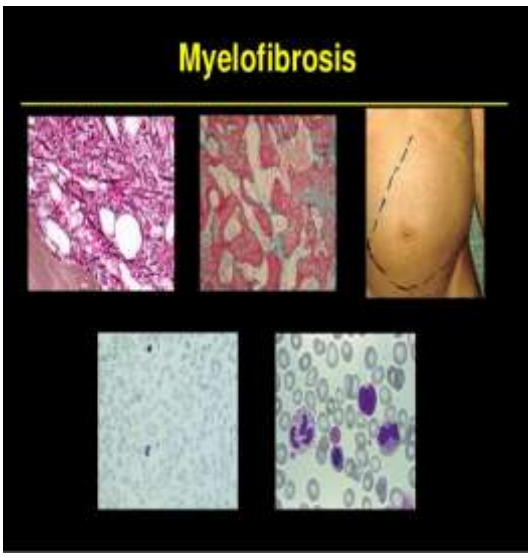

Figure5: *Images of myelofibrosis in patients with gray platelet syndrome*

4. Frequency of Gray Platelet Syndrome

Gray platelet syndrome is a rare hematogenetic disorder that has so far been reported in 60 medical cases worldwide [1, 6].

5. Diagnosis of Gray Platelet Syndrome

Gray platelet syndrome is diagnosed based on clinical findings of patients and pathological tests. Blood tests and platelet counts under a microscope are helpful to diagnose this syndrome. The most definitive method for the diagnosis of gray platelet syndrome is molecular genetic testing for the NBEAL2 gene to detect possible mutations [1, 6].

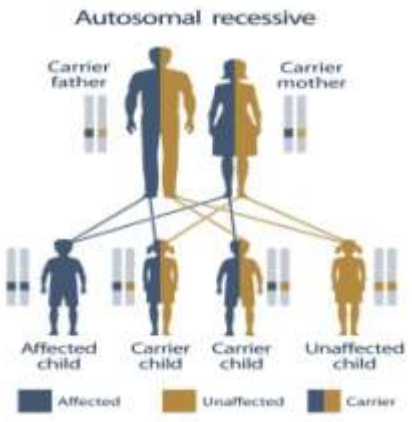

Figure6: *Schematic view of the autosomal recessive inheritance pattern that follows the pattern of gray platelet syndrome with NBEAL2 gene mutation*

6. Gray Platelet Syndrome Treatment Pathways

The strategy of treatment and management of gray platelet syndrome is symptomatic and supportive. Treatment may be provided with the efforts and coordination of a team of specialists including hematology (hematology), molecular genetics genetics, immunology specialist and other health care professionals if needed. No definitive treatment for gray platelet syndrome has been identified. Genetic counseling is also important for all parents who want a healthy baby [1, 6].

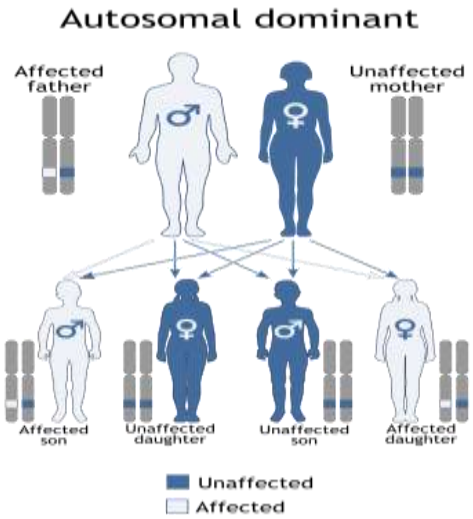

Figure7: *Schematic overview of the dominant autosomal inherited pattern that gray platelet syndrome can mutate with other genes*

7. History of Gray Platelet Syndrome

The first case of Gray Platelet Syndrome was first reported by Raccuglia in 1971 and then described in 1980 by Gerrard et al [1, 6].

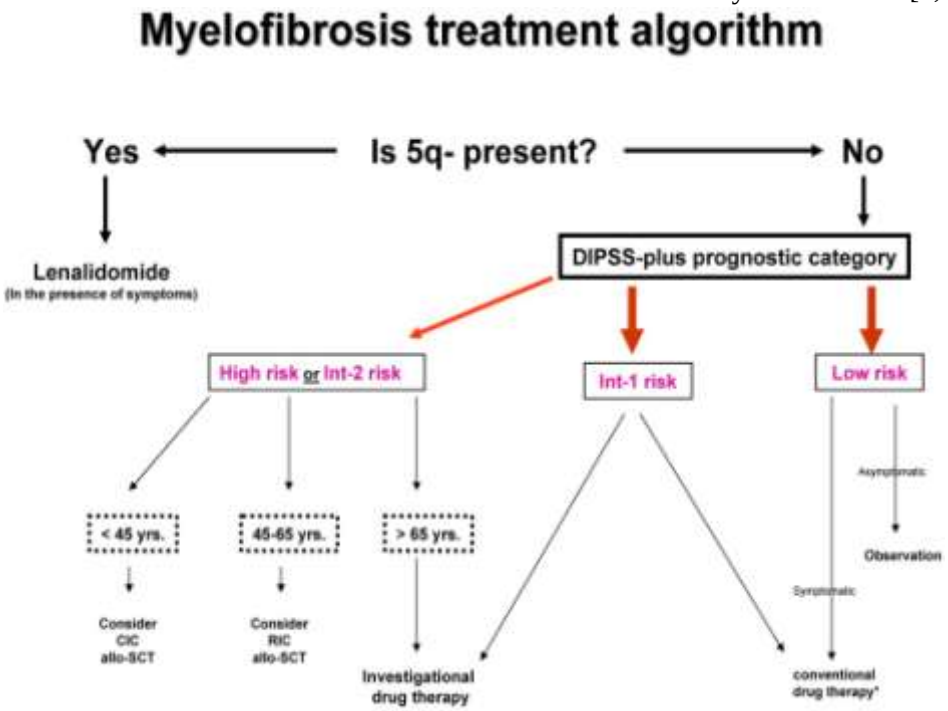

Figure8: *Schematic of myelofibrosis treatment algorithm*

8. Discussion and Conclusion

Gray platelet syndrome (GPS), or platelet alpha-granule deficiency, is a rare congenital autosomal recessive bleeding disorder caused by a reduction or absence of alpha-granules in blood platelets, and the release of proteins normally contained in these granules into the marrow, causing myelofibrosis. [1-6]

GPS is primarily inherited in an autosomal recessive manner, and the gene that is mutated in GPS has recently been mapped to chromosome 3p and identified as *NBEAL2*. *NBEAL2* encodes a

protein containing a BEACH domain that is predicted to be involved in vesicular trafficking. It is expressed in platelets and megakaryocytes and is required for the development of platelet alpha-granules. *NBEAL2* expression is also required for the development of thrombocytes in zebrafish. [1-6]

GPS is characterized by "thrombocytopenia, and abnormally large agranular platelets in peripheral blood smears. The defect in GPS is the failure of megakaryocytes to package secretory proteins into alpha-granules. Patients with the GPS are affected by mild to moderate bleeding tendencies. Usually these are not major bleeds but there has been some life threatening cases. Affected women will tend to have heavy, irregular periods. Myelofibrosis is a condition that usually comes with GPS [1-6].

REFERENCES

[1] Asadi S, Jamali M, Bagheri R, Book of Pathology in Medical Genetics vol 3, Amidi Publications, 2018, Iran.

[2] Albers CA, Cvejic A, Favier R, Bouwmans EE, Alessi MC, Bertone P, Jordan G, Kettleborough RN, Kiddle G, Kostadima M, Read RJ, Sipos B, Sivapalaratnam S, Smethurst PA, Stephens J, Voss K, Nurden A, Rendon A, Nurden P, Ouwehand WH. Exome sequencing identifies NBEAL2 as the causative gene for gray platelet syndrome. Nat Genet. 2011 Jul 17; 43(8):735-7. doi: 10.1038/ng.885.

[3] Bottega R, Pecci A, De Candia E, Pujol-Moix N, Heller PG, Noris P, De Rocco D, Podda GM, Glembotsky AC, Cattaneo M, Balduini CL, Savoia A. Correlation between platelet phenotype and NBEAL2 genotype in patients with congenital thrombocytopenia and α-granule deficiency. Haematologica. 2013 Jun; 98(6):868-74. doi: 10.3324/haematol.2012.075861. Epub 2012 Oct 25.

[4] Gunay-Aygun M, Falik-Zaccai TC, Vilboux T, Zivony-Elboum Y, Gumruk F, Cetin M, Khayat M, Boerkoel CF, Kfir N, Huang Y, Maynard D, Dorward H, Berger K, Kleta R, Anikster Y, Arat M, Freiberg AS, Kehrel BE, Jurk K, Cruz P, Mullikin JC, White JG, Huizing M, Gahl WA. NBEAL2 is mutated in gray platelet syndrome and is required for biogenesis of platelet α-granules. Nat Genet. 2011 Jul 17; 43(8):732-4. doi: 10.1038/ng.883.

[5] Gunay-Aygun M, Zivony-Elboum Y, Gumruk F, Geiger D, Cetin M, Khayat M, Kleta R, Kfir N, Anikster Y, Chezar J, Arcos-Burgos M, Shalata A, Stanescu H, Manaster J, Arat M, Edwards H, Freiberg AS, Hart PS, Riney LC, Patzel K, Tanpaiboon P, Markello T, Huizing M, Maric I, Horne M, Kehrel BE, Jurk K, Hansen NF, Cherukuri PF, Jones M, Cruz P, Mullikin JC, Nurden A, White JG, Gahl WA, Falik-Zaccai T. Gray platelet syndrome: natural history of a large patient cohort and locus assignment to chromosome 3p. Blood. 2010 Dec 2; 116(23):4990-5001. doi: 10.1182/blood-2010-05-286534. Epub 2010 Aug 13.

[6] Kahr WH, Hinckley J, Li L, Schwertz H, Christensen H, Rowley JW, Pluthero FG, Urban D, Fabbro S, Nixon B, Gadzinski R, Storck M, Wang K, Ryu GY, Jobe SM, Schutte BC, Moseley J, Loughran NB, Parkinson J, Weyrich AS, Di Paola J. Mutations in NBEAL2, encoding a BEACH protein, cause gray platelet syndrome. Nat Genet. 2011 Jul 17; 43(8):738-40. doi: 10.1038/ng.884.

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