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Case Report

A Novel Homozygous RAB27A Mutation is Associated with Griscelli Syndrom Type II and Less Severe Presentations

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Abstract

Griscelli syndrome type II is a primary immunodeficiency disorder caused by a RAB27A gene mutation. It is inherited in an autosomal recessive manner and is characterized by oculocutaneous hypopigmentation and various cellular immune system deficiencies.

Herein, we report a 5-year-old girl with silvery-gray hair, eyebrows, and eyelashes who was referred to our primary immune deficiency clinic because of recurrent oral thrush. Further investigations were performed to uncover the probable underlying genetic disorder. Whole-exome sequencing revealed a novel mutation in the RAB27A gene (c.137T>G) and confirmed the diagnosis of Griscelli syndrome type 2.

Due to the poor prognosis nature of this disorder and also its need for differential diagnosis with some other conditions with hypopigmentation, prompt diagnosis, genetic analysis, and proper treatment are necessary for avoiding serious complications.

Keywords: Griscelli Syndrome Type II; Novel Mutation; Primary Immunodeficiency Disorder; RAB27A Gene

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Introduction

Griscelli syndrome (GS) type 2 is a rare autosomal recessive disorder that is classified as primary immunodeficiency disorder in the class of immune dysregulation diseases1. In addition to immune defects, hypopigmentation of hair, skin, and eyes are common manifestations of this disorder. Silver-gray hair is seen in most of the patients, and some of those experienced neurological symptoms 2-5.

Griscelli syndrome type 2 is caused by the mutations in the RAB27A gene, which is located on 25q21 and responsible for encoding small GTPase protein 6, 7. RAB27A expression in cytotoxic T lymphocytes and natural killer cells plays an important role in granzyme and perforin-containing granule exocytosis8.Primary immunodeficiency manifestations of Griscelli syndrome type 2 consist of frequent pyogenic infection, fever, neutropenia, and thrombocytopenia9, 10. Hemophagocytic lymphohistiocytosis (HLH) is a state of hyperinflammation caused by the uncontrolled proliferation of lymphocytes and histocytes. Approximately all patients with Griscelli syndrome type 2 may experience HLH crises, which are life-threatening and increase the mortality rate in these patients 11-13. It seems that the best way to cure HLH and increase survival in GS type effectively 2 patients is hematopoietic stem cell transplantation 13, 14.

Here, we report a case of Griscelli syndrome in an Iranian child with a new mutation in the RAB27A gene.

Case Presentation

A 5-year-old female was born from consanguineous parents (first cousins) and referred to our PID clinic with silvery-gray hair, eyebrows, and eyelashes **(Figure 1)**. On the physical examination, there was a limited oral thrush compatible with candidiasis. Her parents were apparently healthy, and interestingly, there are 2 other family members with the same hair color, which never presented symptoms of immunodeficiencies. She had never experienced hospitalization and neurological symptoms, and the only abnormal infection was oral candidiasis. The patient family pedigree is shown in **Figure 2**.

The initial laboratory investigations showed no abnormal results **(Table 1)**. The peripheral smear showed 4% atypical lymphocytes, but there is no evidence of giant lymphocytes. Pathologic examination of the hair shaft revealed abnormal pigmentation, compatible with Griscelli syndrome.

Whole Exome Sequencing (WES) was performed for the patient. Agilent V6+UTR library preparation and an Illumine NextSeq 500 sequencing platform were used. The bioinformatics analysis pipeline uses Burrows-Wheeler Aligner (BWA 0.7.15), Genome Analysis ToolKit (GATK 3.6), Variant Effect Predictor (VEP 89) and frequency filters with public and house databases (e.g., ExAC, GnomaAD, and GME).

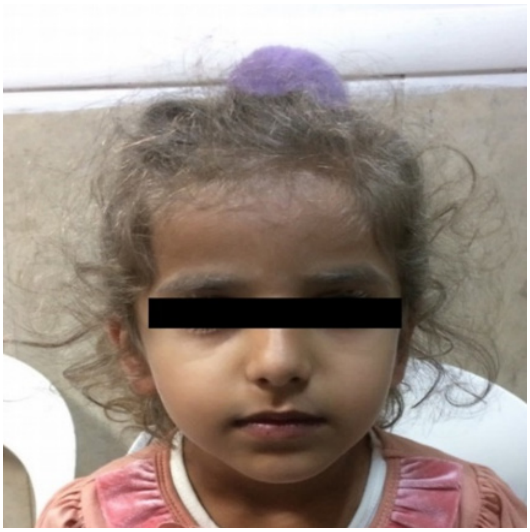

Figure 1. silvery gray hair, eyebrow and eyelashes

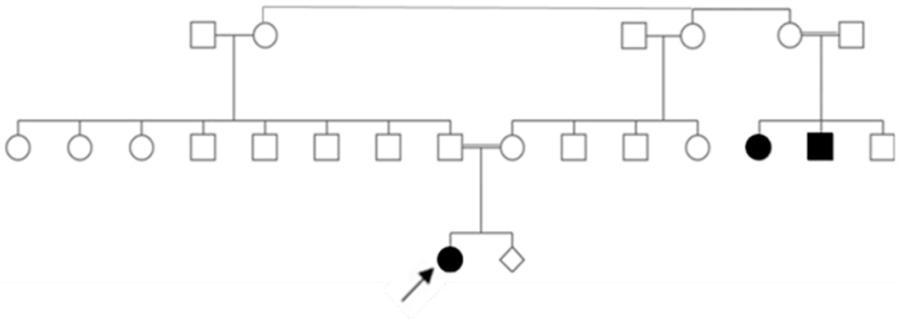

Figure 2. Patient Family Pedigree

Table1. Summary of laboratory evaluation of patient

Blood	Patient	Normal range
WBC (*10^9/L)	7.12	4-10
Neutrophil%	33.9	50-70
Lymphocyte%	49.7	20-40
RBC (*10^12/L)	4.83	3.5-5.5
Hb (g/dl)	12.5	11-16
MCV (fL)	75.4	80-100
Plat (*10^9/L)	254	150-450
LDH (IU/L)	471	5-615
Fcrritin (micg/L)	42	30-220
Vitamin B 12 (pg/ml)	604	201-804
Immunoglobulin levels		
IgG (mg/dl)	669	386-1470
IgM (mg/dl)	133	37-224
IgA (mg/dl)	74	25-154
IgE (IU/dl)	0.6	<68

A homozygous missense variant was detected in the RAB27A gene (LRG_96t1: c.137T>G; p.Phe46Cys). The parents were the heterozygous carriers of this variant. This missense variant in RAB27A was not described before, but similar variants (e.g., p.Trp7GLy or Ala87Pro) have been shown to cause autosomal recessive type 2 Griscelli syndrome. Also, the computer algorithms PolyPhen and SIFT suggested the variant to be probably damaging and deleterious, respectively.

Discussion

Griscelli syndrome was first reported by Griscelli et al. in 1978 in two unrelated patients15. It is a rare autosomal recessive disorder that manifests with the dilution of skin and hair color and the irregular accumulation of large pigmented granules in the hair shaft, leading to silver-gray hair and may also be accompanied by neurologic defects and immune deficiency 16. GS is classified into 3 groups based on the mutations in three genes: MyoVa, RAB27A, and MLPH, all of which manifest with similar pigment dilution17. Type 1 is associated with the myosin5a (MyoVa) gene mutation and is more likely to develop neurological disorders, but in type 3, which is associated with the melamophilin (MLPH) gene mutation, only a hair and skin hypopigmentation occur. Type 2 is associated with RAS-related protein RAB27A mutations, and symptoms of immunodeficiency are more common in this group of patients 6, 18, 19. In addition to immunodeficiency, hepatosplenomegaly, recurrent infections, hypomelanosis, and silvery gray hair can also be seen in this type19.

In the case of hypopigmentation with immunodeficiency, some differential diagnosis should be considered. Chediac-Higashi syndrome (caused by a mutation in the LYST gene with regular melanin granules in the hair shaft and giant azurophilic granular inclusions in peripheral blood leukocytes), Hermansky-Pudlak syndrome type 2 (caused by a mutation in the AP3B1 gene), p14 deficiency (caused by a mutation in the MAPBPIP gene) and griscelli syndrome type 2 (caused by a mutation in RAB27A and large irregular melanin granules in microscopic investigations of the hair shaft) 3, 5.

In our case, we performed whole-exome sequencing, and for the patient, we identified a homozygous variant mutation in RAB27A, which was not reported before. The amino acid Phe46

is part of the putative GEF (Guanine nucleotide exchange factor) interaction site (amino acids 39,43..50,67,69; CDD:206700). GEFs are RAB activators by stimulating the release of GDP (Guanosine diphosphate) and facilitating the GTP (Guanosine triphosphate) binding. Activated RAB-GTP have an essential role in cell traffic through binding with effector proteins20.

However, GS type II is associated with severe clinical manifestation in most cases; it is suggested that the severity of the disease could be impressed by the type of mutations in the gene. Regarding the general condition, the patient is doing well now without neurological signs and infection, although there have been episodes of gastroenteritis and lung infection in the past, and bone marrow transplantation is planned to be done for her.

Conclusion

The prognosis of Griscelli syndrome is poor, and most patients die in early childhood due to complications such as HLH unless they undergo hematopoietic stem cell transplantation 21. Although this is the only way to effectively treat patients with Griscelli syndrome, the best condition for transplantation is provided when HLH is first treated and partial recovery is achieved 22, 23.

The rate of autosomal recessive disorders, including primary immunodeficiency diseases in consanguineous families is high, unlike the general population 24. The high percentage of consanguinity in our region 25 is a reason for the higher prevalence of rare immunodeficiency diseases. For this reason, genetic counseling before marriage and prenatal care, as well as educational programs, can have a great impact on reducing the burden of genetic disorders on society.

Statement of Ethics

The patient's parents provided their written informed consent to participate in this study.

Conflict of interests

There is no conflict of interest.

References

1. Al-Herz W, Bousfiha A, Casanova J-L, et al. Corrigendum: Primary immunodeficiency diseases: An update on the classification from the International Union of Immunological Societies Expert Committee for primary immunodeficiency. Front immunol 2014;5:460.
2. Tomita Y and Suzuki T. Genetics of pigmentary disorders. Am J Med Genet C Semin Med Genet 2004;131C:75-81.
3. Rezaei N, Moazzami K, Aghamohammadi A, et al. Neutropenia and primary immunodeficiency diseases. Int Rev Immunol 2009;28:335-366.
4. Klein C, Philippe N, Le Deist F, et al. Partial albinism with immunodeficiency (Griscelli syndrome). J Pediatr 1994;125:886-895.
5. Rezaei N, Aghamohammadi A, Notarangelo LD. Primary Immunodeficiency Diseases: Definition, Diagnosis, and Management. 1st ed. Velag Berlin Heidelberg: Springer, 2016.
6. Menasche G, Pastural E, Feldmann J, et al. Mutations in RAB27A cause Griscelli syndrome associated with haemophagocytic syndrome. Nat Genet 2000;25:173-176.
7. Wilson SM, Yip R, Swing DA, et al. A mutation in Rab27a causes the vesicle transport defects observed in ashen mice. Proc Natl Acad Sci U S A 2000;97:7933-7938.
8. Ménasché G, Fischer A, de Saint Basile G. Griscelli syndrome types 1 and 2. Am J Hum Genet2002;71:1237-1238.
9. Kharkar V, Pande S, Mahajan S, et al. Griscelli syndrome: a new phenotype with circumscribed pigment loss? Dermatol Online J 2007;13:17.
10. Meeths M, Bryceson YT, Rudd E, et al. Clinical presentation of Griscelli syndrome type 2 and spectrum of RAB27A mutations. Pediatr Blood Cancer 2010;54:563-572.
11. Filipovich AH. Hemophagocytic lymphohistiocytosis (HLH) and related disorders. Hematology Am Soc Hematol Educ Program 2009;1:127-131.
12. Filipovich AH. Life‐threatening hemophagocytic syndromes: Current outcomes with hematopoietic stem cell transplantation. Pediatr Transplantat 2009;9:87-91.
13. Henter JI, Horne A, Aricó M, et al. HLH‐2004: diagnostic and therapeutic guidelines for hemophagocytic lymphohistiocytosis. Pediatr Blood Cancer 2007;48:124-131.
14. Hamidieh AA, Pourpak Z, Yari K, et al. Hematopoietic stem cell transplantation with a reduced‐intensity conditioning regimen in pediatric patients with G riscelli syndrome type 2. Pediatr Transplantat 2013;17:487-491.
15. Griscelli C, Durandy A, Guy-Grand D, et al. A syndrome associating partial albinism and immu-

nodeficiency. Am J Med 1978;65:691-702.
16. Szczawinska-Poplonyk A, Kycler Z, Breborowicz A, et al. Pulmonary lymphomatoid granulomatosis in Griscelli syndrome type 2. Viral Immunol 2011;24:471-473.
17. Durmaz A, Ozkinay F, Onay H, et al. Molecular analysis and clinical findings of Griscelli syndrome patients. J Pediatr Hematol Oncol 2012;34:541-544.
18. Pastural E, Ersoy F, Yalman N, et al. Two genes are responsible for Griscelli syndrome at the same 15q21 locus. Genomics 2000;63:299-306.
19. Singh A, Garg A, Kapoor S, et al. An Indian boy with griscelli syndrome type 2: case report and review of literature. Indian J Dermatol 2014;59:394-397.
20. Figueiredo AC, Wasmeier C, Tarafder AK, et al. Rab3GEP is the non-redundant guanine nucleotide exchange factor for Rab27a in melanocytes. J Biol Chem 2008;283:23209-23216.
21. Mamishi S, Modarressi MH, Pourakbari B, et al. Analysis of RAB27A gene in griscelli syndrome type 2: novel mutations including a deletion hotspot. J Clin Immunol 2008;28:384-389.
22. Henter JI, Horne A, Arico M, et al. HLH-2004: Diagnostic and therapeutic guidelines for hemophagocytic lymphohistiocytosis. Pediatr Blood Cancer 2007;48:124-131.
23. Janka GE. Familial and acquired hemophagocytic lymphohistiocytosis. Eur J Pediatr 2007;166:95-109.
24. Shamsian BS, Norbakhsh K, Rezaei N, et al. A novel RAB27A mutation in a patient with Griscelli syndrome type 2. J Investig Allergol Clin Immunol 2010;20:612-615.
25. Rezaei N, Pourpak Z, Aghamohammadi A, et al. Consanguinity in primary immunodeficiency disorders; the report from Iranian Primary Immunodeficiency Registry. Am J Reprod Immunol 2006;56:145-151.