

## A founder RAB27A variant causes Griscelli syndrome type 2 with phenotypic heterogeneity in Qatari families

Reem Al-Sulaiman, Amna Othman, Karen El-Akouri, Shehab Fareed, Hajer AlMulla, Aseel Sukik, Mariam Al-Mureikhi, Noora Shahbeck, Rehab Ali, Fatma Al-Mesaifri, Sara Musa, Mariam Al-Mulla, Khalid Ibrahim, Khalid Mohamed, Maryam Ali Al-Nesef, Mohammad Ehlayel, Tawfeg Ben-Omran

### Item type

Journal Contribution

### Terms of use

This work is licensed under a [CC BY 4.0](#) license

### This version is available at

[https://manara.qnl.qa/articles/journal\\_contribution/A\\_founder\\_RAB27A\\_variant\\_causes\\_Griscelli\\_syndrome\\_type\\_2\\_with\\_phenoty](https://manara.qnl.qa/articles/journal_contribution/A_founder_RAB27A_variant_causes_Griscelli_syndrome_type_2_with_phenoty)














Access the item on Manara for more information about usage details and recommended citation.

Posted on Manara – Qatar Research Repository on

2020-08-28

## ORIGINAL ARTICLE

## A founder RAB27A variant causes Griscelli syndrome type 2 with phenotypic heterogeneity in Qatari families

Reem Al-Sulaiman<sup>1,2</sup> | Amna Othman<sup>1,3</sup>  | Karen El-Akouri<sup>1,3</sup>  |  
 Shehab Fareed<sup>2</sup>  | Hajer AlMulla<sup>1,2</sup>  | Aseel Sukik<sup>4</sup>  | Mariam Al-Mureikhi<sup>1,3</sup> |  
 Noora Shahbeck<sup>1,3</sup>  | Rehab Ali<sup>1,3</sup>  | Fatma Al-Mesaifri<sup>1,3</sup>  | Sara Musa<sup>1</sup>  |  
 Mariam Al-Mulla<sup>1,3</sup> | Khalid Ibrahim<sup>5</sup>  | Khalid Mohamed<sup>5</sup>  |  
 Maryam Ali Al-Nesef<sup>6</sup>  | Mohammad Ehlayel<sup>7,8</sup>  | Tawfeg Ben-Omran<sup>1,3,8</sup> 

<sup>1</sup>Department of Medical Genetics, Hamad Medical Corporation, Doha, Qatar

<sup>2</sup>Department of Adult Hematology/Oncology, Hamad Medical Corporation, Doha, Qatar

<sup>3</sup>Division of Genetic and Genomic Medicine, Sidra Medicine, Doha, Qatar

<sup>4</sup>Department of Internal Medicine, Hamad Medical Corporation, Doha, Qatar

<sup>5</sup>Division of Pediatric Neurology, Sidra Medicine, Doha, Qatar

<sup>6</sup>Department of Medicine, Hamad Medical Corporation, Doha, Qatar

<sup>7</sup>Department of Pediatrics, Hamad Medical Corporation, Doha, Qatar

<sup>8</sup>Weill Cornell Medical College, Doha, Qatar

## Correspondence

Tawfeg Ben-Omran, MD, FRCPC, FCCMG, Senior Consultant, Clinical and Metabolic Genetics, Associate Professor, Weill Cornell Medical College, Department of Medical Genetics, Hamad Medical Corporation, PO BOX 3050, Doha, Qatar.  
 Email: tawben11@hotmail.com, tomran@hamad.qa

## Abstract

Griscelli syndrome type 2 (GS2) is a rare autosomal recessive disorder caused by pathogenic variants in the *RAB27A* gene and characterized by partial albinism, immunodeficiency, and occasional hematological and neurological involvement. We reviewed and analyzed the medical records of 12 individuals with GS2 from six families belonging to a highly consanguineous Qatari tribe and with a recurrent pathogenic variant in the *RAB27A* gene (NM\_004580.4: c.244C > T, p.Arg82Cys). Detailed demographic, clinical, and molecular data were collected. Cutaneous manifestations were the most common presentation (42%), followed by neurological abnormalities (33%) and immunodeficiency (25%). The most severe manifestation was HLH (33%). Among the 12 patients, three patients (25%) underwent HSCT, and four (33%) died. The cause of death in all four patients was deemed HLH, providing evidence for this complication's fatal nature. Interestingly, two affected patients (16%) were asymptomatic. This report highlights the broad spectrum of clinical presentations of GS2 associated with a founder variant in the *RAB27A* gene (c.244C > T, p.Arg82Cys). Early suspicion of GS2 among Qatari patients with cutaneous manifestations, neurological findings, immunodeficiency, and HLH would shorten the diagnostic odyssey, guide early and appropriate treatment, and prevent fatal outcomes.

## KEYWORDS

founder effect, GS2, HLH, Qatari, *RAB27A*

**Abbreviations:** DD, developmental delay; GS2, Griscelli syndrome type 2; HLH, hemophagocytic lymphohistiocytosis; HSCT, hematopoietic stem cell transplantation; ID, intellectual disability.

This is an open access article under the terms of the Creative Commons Attribution License, which permits use, distribution and reproduction in any medium, provided the original work is properly cited.

© 2020 The Authors. *American Journal of Medical Genetics Part A* published by Wiley Periodicals LLC.

## 1 | INTRODUCTION

Griscelli syndrome (GS) is a rare autosomal recessive disorder first described in 1978 as a disorder of partial albinism associated with immunodeficiency (Griscelli et al., 1978). Symptoms of GS overlap

with Chediak-Higashi syndrome: partial albinism, variable neurological deficit, and lower body immunity that may lead to recurrent infections and, subsequently, hemophagocytic lymphohistiocytosis (HLH) (Henter et al., 2007). HLH, usually triggered by viruses and manifested by unremitting fever, cytopenia, and organomegaly, is a life-threatening complication unless treated with hematopoietic stem cell transplantation (HSCT).

Three distinct types of GS have been described based on molecular analysis. GS type 1 (GS1) (OMIM: 214450) is caused by pathogenic variants in the *MYO5A* gene and presents with hypopigmentation and primary neurological deficit with an intact immune system (Pastural et al., 1997). GS type 2 (GS2) (OMIM: 607624) is caused by pathogenic variants in the *RAB27A* gene and manifests with partial albinism that can be subtle and immunodeficiency that mainly affects T lymphocytes and natural killer (NK) cells, with complications ranging from frequent pyogenic infections of the skin and internal organs to HLH. Neurological impairment, which is a well-recognized feature of GS1 at birth, is increasingly reported in GS2 as a spectrum of neuropathology that develops at a later stage after birth and includes seizures, strabismus, nystagmus, ataxia, hemiparesis, facial palsy, and impairment of cognitive functions (Anikster et al., 2002; Rajadhyax et al., 2007). GS type 3 (GS3) (OMIM: 609227) is caused by pathogenic variants in the *MELANOPHILIN* gene and is characterized by unusually light skin and silvery-gray hair. Unlike the other forms of GS, the central nervous system (CNS) and the immune system are not involved in GS3 (Ménasché et al., 2003).

In GS2, the *RAB27A* gene that encodes a GTPase called Rab27a is disrupted and affects a melanosome-anchoring complex in melanocytes as well as exocytosis of cytolytic granules from T lymphocytes and NK cells, thus increasing the susceptibility to recurrent infections and culminating in life-threatening HLH (Bahadoran et al., 2003; Marsh, 2018; Zhang et al., 2016). Ashen mice with a loss of function variant in the *RAB27A* gene provide a mouse model for GS and demonstrate defects in melanosomes, which abnormally cluster in the perinuclear region of melanocytes, and lytic granules within cytotoxic T lymphocytes (CTLs), which prevents CTLs from killing target cells (Barral et al., 2002; Haddad et al., 2001; Hume et al., 2001; Stinchcombe et al., 2001; Wilson et al., 2000; Wu et al., 2001). The Rab27a protein, a member of the Rab family, has been identified in different cell types, including oligodendrocytes, as a potential positive regulator of exosome release and proteolipid trafficking (Shen et al., 2016). Meeths et al. (2010) suggested that GS's neurological abnormalities could be associated with the inflammatory HLH state and lymphohistiocytic infiltration of the brain rather than a result of the Rab27a deficiency itself. However, another theory proposed that neurological abnormalities could be part of the underlying disease, directly related to the defective Rab27a protein, and occurring in the absence of immunodeficiency (Panigrahi et al., 2015)

## 2 | OBJECTIVE

This case series aims to describe the broad spectrum of clinical presentations of GS2 in Qatari families in association with a recurring *RAB27A* pathogenic variant (NM\_004580.4: c.244C > T, p.Arg82Cys) ranging from asymptomatic healthy individuals to patients with

isolated dermatosis and skin manifestations, to patients with more severe neurological and immunological complications, including fatal HLH. In this article, we refer to this *RAB27A* variant as p.R82C.

## 3 | MATERIALS AND METHODS

In this case series, we report on 12 individuals from six Qatari families diagnosed with GS2 at the Medical Genetics Department at Hamad Medical Corporation, Doha, Qatar, between 2002 and 2019. We conducted a thorough review of patient medical records and collected detailed demographic and clinical data: age at presentation, age at diagnosis, gender, family history, clinical presentation, diagnostic workup (hematological, immunological, neuroimaging, and molecular genetic), management, and disease outcome. Medical data were stratified based on the most common systems involved, including neurological (e.g., seizures, strabismus, nystagmus, hemiparesis, developmental delay, intellectual disability, and abnormal brain imaging), hematological (e.g., HLH), dermatological, and immunological.

Clinical exome sequencing (CES) (XomeDx) was performed on all probands at GeneDx, USA. DNA was extracted from submitted specimens, enriched for most genes of the human genome using a proprietary capture system developed by GeneDx for next-generation sequencing with copy number variant (CNV) calling (NGS-CNV), and sequenced with paired-end reads on an Illumina platform (GeneDx, n.d.). Bi-directional sequence reads were assembled and aligned to reference sequences based on NCBI RefSeq transcripts and human genome build GRCh37/UCSC hg19 (GeneDx, n.d.). A custom-developed analysis tool (XomeAnalyzer) was used to filter and analyze the data to identify the sequence and copy number variants (Retterer et al., 2016). Reported clinically significant variants were confirmed by an appropriate orthogonal method. Sequence variants were reported according to the Human Genome Variation Society (HGVS) (GeneDx, n.d.).

CES (XomeDx) covered 100% of the coding region of the *RAB27A* gene (NM\_004580.4) at a minimum of 10x. All probands and their family members, male and female, identified to harbor the *RAB27A* p.R82C variant were included in this study. Non-Qatari patients and patients with pathogenic *RAB27A* variants different from p.R82C were excluded.

The study was conducted under the Declaration of Helsinki, and the protocol was approved by the Institutional Review Board (IRB) at Hamad Medical Corporation.

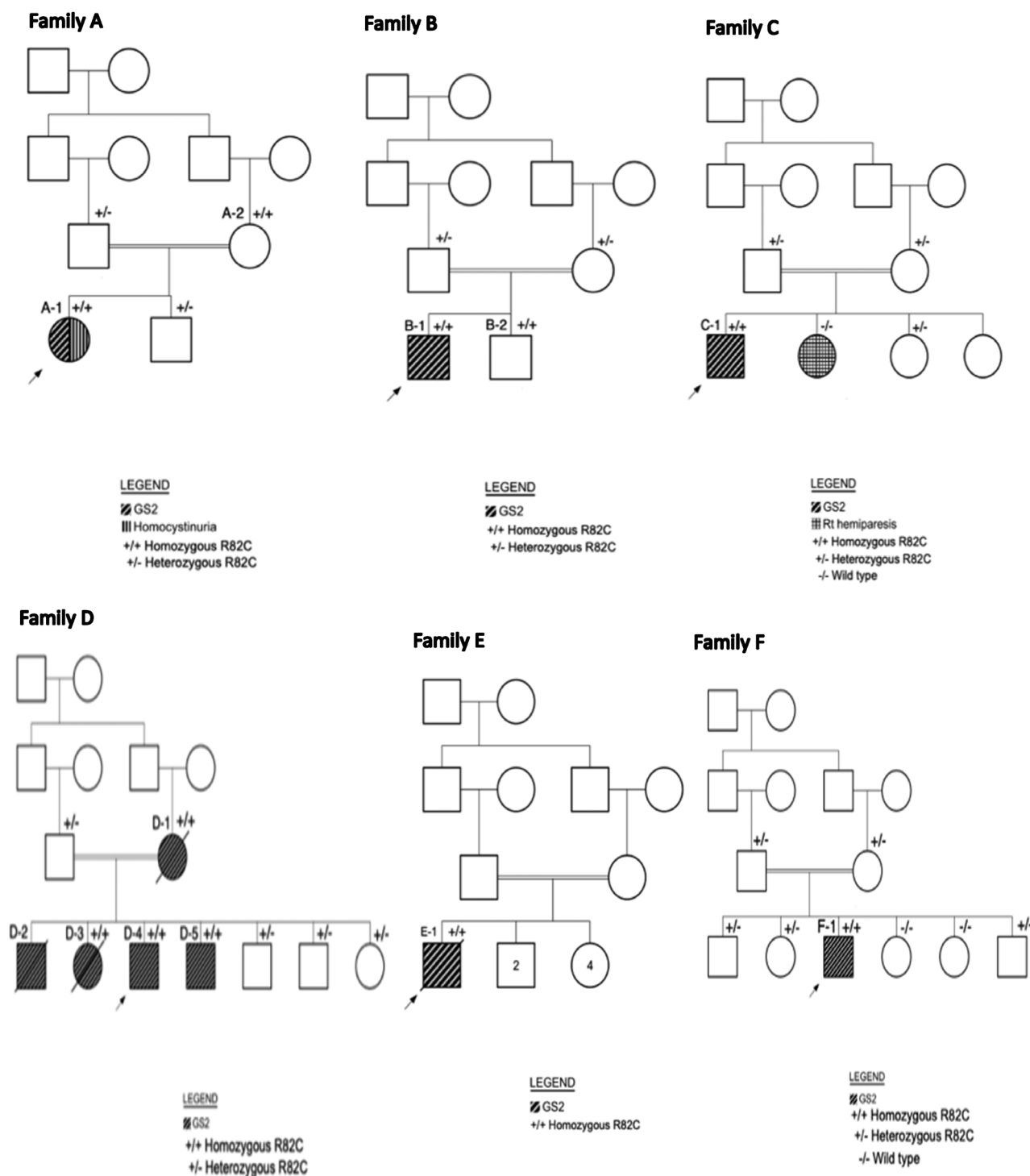
## 4 | RESULTS

### 4.1 | Cases presentations

Families are presented in Figure 1a–f.

#### 4.1.1 | Family A

The index patient A-1 is a 13-year-old female. She was the product of a full-term normal vaginal delivery with a birth weight of



**FIGURE 1** Family Pedigree (A-F)

3,200 g, a length of 51 cm, and a head circumference of 35 cm (Figure 1a). Apgar score was 9 at 1 min and 10 at 5 min. She was diagnosed with classical homocystinuria through the Qatar National Expanded Metabolic Newborn Screening Program and was immediately started on treatment with a good outcome. Her parents are first cousins, and she has an older brother, all reported to be healthy.

At the age of 1 year, the patient started to develop a progressive skin rash (eczematous patches/granulomatous), mainly on the face and limbs. Different dermatologists evaluated her over several years without reaching a final diagnosis. At the age of 12 years, CES was performed and showed a homozygous pathogenic variant p.R82C in the *RAB27A* gene. Interestingly, trio analysis of the exome sequencing data revealed that the mother A-2, who is asymptomatic, was

homozygous for the same *RAB27A* pathogenic variant, while the father and brother were heterozygous.

#### 4.1.2 | Family B

The index patient B-1 is a previously healthy 4-year-old male who presented with a non-paralytic squint, imbalanced gait, slurred speech for 2 weeks, abnormal brain magnetic resonance imaging (MRI), and three hypopigmented macules on the trunk (Figure 1b). Subsequently, his condition acutely deteriorated with progressive encephalopathy, impaired consciousness, peripheral hypotonia, bilateral facial palsy and weakness, and bulbar palsy. The patient was the product of a full-term normal vaginal delivery with a birth weight of 3,120 g, a length of 50 cm, and a head circumference of 33 cm. Apgar score was 9 at 1 min and 10 at 5 min. His parents are first cousins, and he has a younger brother B-2 who is apparently healthy and developing normally. There is a positive family history of hypopigmentation in a few family members.

Initial investigations included an electroencephalogram (EEG) that showed slow background but no specific epileptic findings and an initial metabolic screen that revealed normal lactate, ammonia, and amino acids. All testing for bacterial and viral pathogens, as well as immunological workup and cerebrospinal fluid (CSF) analysis, were negative. Urine organic acids and CSF neurotransmitters were also normal. A repeated brain MRI showed bilateral symmetrical basal ganglia high signal with adjacent cortical and subcortical involvement. A provisional diagnosis of biotin-thiamine-responsive basal ganglia disease was then proposed, and the patient was started empirically on biotin and thiamine. However, there was no improvement, and molecular genetic testing of the *SLC19A3* gene was negative. He was also started on methylprednisolone because of the initial concern about a possible immune disorder. CES was performed and showed a homozygous pathogenic variant p.R82C in the *RAB27A* gene. Interestingly, his asymptomatic brother B-2 was also found to be homozygous for the same *RAB27A* pathogenic variant. B-1 underwent HSCT without significant complications. He has no neurological complications post-transplant. B-2 underwent preemptive HSCT. It was paternally derived bone marrow transplant with subsequent graft failure and poor engraftment. Thereafter, he received two DLI (Donor lymphocyte infusion). However, he remained neurologically stable.

#### 4.1.3 | Family C

The index patient C-1 is a 7-year-old male with a seizure disorder, global developmental delay, white matter abnormalities, and fair skin and hair compared to his parents and siblings (Figure 1c). Fetal life was complicated by gestational diabetes, intrauterine growth restriction (IUGR), oligohydramnios, and positive group B streptococcus. The patient was the product of a cesarean section for fetal distress with a birth weight of 2,200 g, a length of 46 cm, and a head circumference of 31 cm (all parameters at the 10th percentile). He was admitted to

the neonatal intensive care unit (NICU) for 4 days for suspected sepsis, resolving thrombocytopenia and hyperbilirubinemia, and a brief jerky movement of the left upper limb. He was re-admitted at the age of 10 days with a history of abnormal jerky movements of the left upper and lower limbs associated with facial twisting, and he was treated with phenobarbitone. His parents are first cousins, he has a younger sister with right hemiparesis and MRI finding of leukodystrophy, and he has a paternal uncle with intellectual disability.

On physical exam, there was spasticity with scissoring gait, brisk reflexes, and sustained clonus. Besides, three hypopigmented macules were noted. The patient had an extensive workup including lactate, ammonia, plasma amino acids, urine organic acids, urine for purines and pyrimidines, congenital disorders of glycosylation (CDG) and peroxisomal studies, and chromosomal microarray analysis, which were all normal. Brain MRI revealed significant interval resolution of intraparenchymal hemorrhage with residual hemosiderin deposition in the right high parietal and left occipital lobes, diffuse white matter volume loss with periventricular and centrum semi-ovale representing hypoxic/ischemic changes, diffuse thinning of the corpus callosum, and mild dilatation of ventricular system. Magnetic resonance spectroscopy showed a lactate peak and areas of mildly elevated choline. CES was done and revealed a homozygous pathogenic variant p.R82C in the *RAB27A* gene.

#### 4.1.4 | Family D

The index patient D-4 is a 19-year-old male with no previous remarkable medical history diagnosed with primary immunodeficiency with NK cell dysfunction at the age of 16 years (Figure 1d). His parents are consanguineous, and there is an extensive family history of primary immunodeficiency and HLH. His sibling, D-5, is a 17-year-old male diagnosed with primary immunodeficiency with NK dysfunction at the age of 14 years. Two older siblings D-2 and D-3 were diagnosed with familial HLH and passed away at the ages of 11 and 12 years, respectively.

D-2 presented at the age of 10 years with acute encephalitis, neutropenia, and thrombocytopenia. At the age of 11 years, he developed a progressive course of pancytopenia, multiple intracranial hemorrhagic lesions, intractable seizures, demyelinating sensorimotor neuropathy, and viral infection. He died of HLH.

D-3 presented at the age of 9 years with lateral gaze nystagmus, ataxic gait, generalized hypotonia, bilateral tremors, and head titubation with abnormal brain MRI. Three café au lait spots (1 × 1 cm each) were noted on her right leg during the physical exam. She later developed a viral infection and died of HLH.

The mother D-1 was also diagnosed with HLH with a prior Epstein-Barr virus (EBV) infection and died at the age of 39 years.

CES performed on this family revealed that D-1, D-3, D-4, and D-5 are homozygous for a pathogenic variant p.R82C in the *RAB27A* gene. D-1 was diagnosed with GS2 postmortem using previously banked DNA. The father and the three remaining siblings were found to be heterozygous for the familial pathogenic *RAB27A* variant p.R82C in

the gene and remain asymptomatic. This family was previously published (Netter et al., 2016).

4.1.5 | Family E

The index patient E-1 is a 22-year-old male with no previous remarkable medical history. He has no significant family history besides consanguineous parents (Figure 1e). He was admitted with generalized weakness, night sweats, and weight loss of 15 kg in 6 months. On examination, he was found to have small palpable lymph nodes. Laboratory investigations showed pancytopenia and a picture of disseminated intravascular coagulopathy (DIC). Pan computed tomography (CT) revealed sub-centimetric cervical lymph node, intra-abdominal enlarged lymph nodes, and hepatosplenomegaly. Bone marrow examination suggested hypercellular with trilineage hemopoiesis and atypical lymphoid infiltrate. The patient traveled abroad and lost follow-up. Four months later, he was admitted to the intensive care unit (ICU) with a decreased level of consciousness. MRI of the brain showed demyelination features, and lumbar puncture (LP) was unremarkable. A second bone marrow exam showed a picture of significant hemophagocytic activity in addition to increasing triglyceride and ferritin levels, which led to a diagnosis of HLH. He was started on HLH protocol; however, pancytopenia worsened daily with a picture of DIC and multiple organ failure. He was kept on supportive transfusions until he died at the age of 22 years. CES was performed and revealed a homozygous pathogenic variant p.R82C in the *RAB27A* gene.

4.1.6 | Family F

The index patient F-1 is a six-year-old male (Figure 1f). He was the product of a full-term normal vaginal delivery with a birth weight of 3,000 g. He was admitted to the NICU for 1 week after birth due to fever to rule out sepsis. At the age of 2 months, he started to have eczema. Recurrent cough and breathing difficulties led to a diagnosis of reactive airway disease (RAD) with findings on chest X-ray. At the age of 12 months, he was admitted to the pediatric intensive care unit (PICU) due to fever, respiratory distress, abdominal distention, decreased activity, and decreased oral intake. He was found to have bronchiolitis due to respiratory syncytial virus (RSV) and past infection with both EBV and cytomegalovirus (CMV). Neck ultrasound (US) and abdomen US revealed generalized lymphadenopathy, significant hepatosplenomegaly, and umbilical hernia. He was evaluated by different specialties to rule out various etiologies for his symptoms, but no final diagnosis was reached. An immunological workup at the age of 18 months showed neutropenia and immune dysregulation with elevated IgE, IgA, and IgG in the context of recurrent infections, which led to the suspicion of primary immunodeficiency.

CES was performed and revealed a homozygous pathogenic variant p.R82C in the *RAB27A* gene, consistent with a diagnosis of autosomal recessive GS2. His parents are first cousins and heterozygous carriers of the familial *RAB27A* p.R82C variant.

At the age of 28 months, F-1 had an allogeneic bone marrow transplant (BMT) from a fully matched sister. There were no significant neurological complications post-transplant. He was then diagnosed with scaphocephaly at the age of 5 years. Currently, he has normal developmental milestones. He is in a generally fair condition with mild eczema, mild astigmatism, and allergic rhinitis.

4.2 | Clinical stratifications

4.2.1 | Demographics

Data were collected from six families labeled from A to F. Clinical details of the patients selected from these families are mentioned in a separate section in this report. Among the 12 individuals identified, five belonged to one family (family D). The gender distribution was unequal, with eight males (66%). While the age at presentation ranged from less than 1 year to 21 years with a median of 9.5 years of age, we found the age at diagnosis to differ significantly, ranging from 3 to 42 years with a median of 11.5 years of age. Consanguinity was present in 100% of the patients. All families were found to belong to the same Qatari tribe. There was a positive family history for 10 out of 12 (83%) patients (Table 1).

4.2.2 | Clinical findings and outcomes

The most common clinical manifestations found in patients were the cutaneous ones that were identified in 5 out of 12 patients (42%):

TABLE 1 Summary of demographic and clinical characteristics of the 12 Qatari patients with GS2

Variable	N = 12
Male: Female	2:1
Consanguinity (n, %)	12 (100%)
Family history (n, %)	10 (83.3%)
Clinical features	
Presentation age in years median (IQR) <sup>a</sup>	9.5 (1.75–15.5)
Diagnosis age in years median (IQR) <sup>a</sup>	11.5 (4.7–21.25)
Neurological presentations (n, %)	4 (33%)
Cutaneous manifestations (n, %)	5 (42%)
Diagnostic features	
Immunological abnormalities (n, %)	3 (25%)
Viral infections/viremia (n, %)	5 (42%)
Brain MRI abnormalities (n, %)	4 (33.3%)
Molecular ( <i>RAB27A</i> c.244C > T) variant (n, %)	11 (91.6%)
Treatment/outcome	
HLH complication (n, %)	4 (33%)
HSCT (n, %)	3 (25%)
Alive (n, %)	1. (66.7%)

<sup>a</sup>A2 and D1 outliers.



four out of five patients (80%) had albinism, and one out of five patients (20%) had hypopigmentation. The second most frequent manifestations were the neurological abnormalities in 4 out of 12 patients (33%), all of which had an abnormal brain MRI (100%). Among the four patients with neurological involvement, two had seizures (50%), two had strabismus (50%), two had hemiparesis (50%), two had a developmental delay (50%), and two had an intellectual disability (50%). The most severe manifestation identified in our patients was HLH, which was found in four individuals (33%), three of which belong to the same family (family D). Most (75%) of the patients who had HLH had a viral infection before HLH: one had EBV, and two had CMV. The immunodeficiency was also found in three patients (25%), two of which belong to one family (family D). A total of two patients (16%) were completely asymptomatic. Three patients (25%) underwent HSCT. Out of 12 patients, four (33%) died, and eight (66%) remained alive. The cause of death among the four deceased patients was deemed HLH, which provides evidence for the fatality of this complication of GS2 (Table 2).

### 4.3 | Molecular findings

CES on families A to F revealed the same homozygous pathogenic variant p.R82C in exon 4 in the *RAB27A* gene (NM\_004580.4). The p.R82C variant is a non-conservative amino acid substitution, which is likely to impact secondary protein structure as these residues differ in polarity, charge, size, and/or other properties. This substitution occurs at a position that is conserved across species. In silico analysis, which includes protein predictors and evolutionary conservation, supports a deleterious effect. Published functional studies demonstrate the *RAB27A* p.R82C variant impairs NK cell-mediated cytotoxicity and impairs the functional activity of the Rab27a protein (Netter et al., 2016).

To prove the founder effect of R82C in the Qatari families, common haplotype analysis on this variant was conducted as described by Burns et al. (2018). The largest shared runs of homozygosity was hg19 chr15:55497988–55,881,111 (383,123 bp), which equals 0.180 cM (sex-averaged). Remembering that a cM is defined as the distance for which the expected average number of intervening chromosomal crossovers in a single generation is 0.01, this works out to the mutation having occurred approximately 555 generations ago (at 25 years/generation that means ~14,000 years ago). Variants for analysis were limited to single-nucleotide polymorphisms with read depth >10x and genotype qualities (GQ) > 30.

## 5 | DISCUSSION

GS2 is a rare autosomal recessive disorder caused by pathogenic variants in the *RAB27A* gene and manifested with partial albinism and immunodeficiency, with or without neurological and hematological involvement. In this case series, we report 12 patients with GS2 from six Qatari families with extreme intrafamilial and interfamilial

phenotypic variability despite harboring the same pathogenic variant p.R82C in the *RAB27A* gene. How this clinical variability occurs is unclear; however, modifier genes or epigenetics may be contributing. The analysis of our patients' data highlights the broad spectrum of clinical presentations in terms of age of onset, speed of disease progression, the extent of involvement of different systems, and life expectancy. The phenotype of GS2 ranges from asymptomatic healthy individuals to patients with isolated dermatosis and cutaneous manifestations, to patients with more severe neurological and immunological complications, including fatal HLH.

In this case series, all patients (100%) belonged to highly consanguineous families, similar to patients with GS2 reported in the literature from the Middle East, and reflective of the unique Middle Eastern culture characterized by a high consanguinity rate. In this case series, we identified a recurring pathogenic variant p.R82C in the *RAB27A* gene across all 12 patients who belong to the same tribe, suggesting the p.R82C variant is a founder pathogenic variant in this Qatari tribe. Supporting evidence using haplotype analysis on this variant revealed that this variant has occurred approximately 555 generations ago (at 25 years/generation that means ~14,000 years ago) suggesting that p.R82C is an ancient and founder variant in our population. Knowing that the reported tribe extends to neighboring countries, the founder *RAB27A* pathogenic variant p.R82C might be a recurring founder variant in the Gulf region.

There is a significant gap in the literature in regards to genotype-phenotype correlations in GS2 and the presence of founder effect, specifically in the Middle East. The majority of previously reported Middle Eastern patients with GS2 were from consanguineous families. They presented with partial albinism and irregularly distributed small and large clumps of melanin pigment found by light microscopy examination of the hair shaft. Patients developed fever, organomegaly, immunodeficiency, neurological complications, and HLH as part of their accelerated phase. In contrast, a few others were reported to develop neurological deterioration without bone marrow evidence of hemophagocytosis. Types of reported pathogenic variants include missense, nonsense, and frameshift pathogenic variants (Aksu et al., 2003; Ashrafi et al., 2006; Harfi et al., 1992; Mamishi et al., 2008; Masri et al., 2008; Mishra et al., 2014; Ohbayashi et al., 2010; Patiroglu et al., 2016; Shamsian et al., 2010). Three of the 35 patients reported by Al-Mofareh et al. (2020) had the same *RAB27A* pathogenic variant p.R82C as our patients. Jin et al. (2018) also reported the same *RAB27A* variant. More details on the previously reported GS2 genotypes and phenotypes are illustrated in the supplementary Table S1.

In this case series, we reported neurological manifestations during the disease in 33% of patients compared to 46% among patients with GS2 reported in the reviewed literature, highlighting the importance of considering GS2 in patients presenting with progressive neurological impairment. In GS2, neurological symptoms could be primary when occurring in the absence of immunodeficiency, and likely related to the defective Rab27a protein (Panigrahi et al., 2015). Alternatively, neurological abnormalities could be secondary to cellular infiltration of the nervous system when HLH develops (Marsh, 2018). There are

Clinical/Diagnostic Item	N = 12															
No. of families	A	B				C		D		E				F		
Patient #	A-1	A-2	B-1	B-2	C-1	D-1	D-2	D-3	D-4	D-5	E-1	F-1				
Family history	+	+	+	+	+	+	+	+	+	+	-	-				
Consanguinity	+	+	+	+	+	+	+	+	+	+	+	+				
Gender	F	F	M	M	M	F	M	F	M	M	M	M				
Age at presentation	12 months	N/A	4 years	N/A	10 days	N/A	10 years	9 years	16 years	14 years	21 years	12 months				
Age at diagnosis	12 years	42 years	4 years	17 months	6 years	39 years	11 years	11 years	19 years	17 years	22 years	22 months				
Neurological manifestations	Seizures	-	+	-	+	-	-	-	-	-	-	-				
	Strabismus	-	+	-	-	-	-	-	-	-	+	-				
	Nystagmus	-	-	-	-	-	-	-	-	-	-	-				
	Hemiparesis	-	+	+	+	-	-	-	-	-	-	-				
	DD <sup>a</sup>	-	+	-	+	-	-	-	-	-	-	-				
	ID <sup>b</sup>	-	-	-	+	-	-	-	-	-	+	-				
Abnormal brain MRI	N/A	N/A	+	N/A	+	N/A	+	N/A	-	-	+	N/A				
HLH <sup>c</sup>	-	-	-	-	-	+	+	+	-	-	+	-				
Immune deficiency	-	-	-	-	-	-	-	-	+	+	-	+				
Viral infection/viremia	-	-	-	-	-	EBV	CMV	EBV	-	EBV	-	EBV				
Cutaneous manifestation	+	-	+	-	+	-	-	+	-	-	-	+				
HSCT <sup>d</sup>	-	-	+	+	-	-	-	-	-	-	-	+				
Outcome	Alive	Alive	Alive	Alive	Alive	Deceased	Deceased	Deceased	Alive	Alive	Deceased	Alive				
RAB27A pathogenic variant	p.R82C	p.R82C	p.R82C	p.R82C	p.R82C	p.R82C	N/A	p.R82C	p.R82C	p.R82C	p.R82C	p.R82C				

<sup>d</sup>Hematopoietic stem cell transplantation (HSCT).



no extensive studies delineating the rate or age at diagnosis of primary neurological abnormalities. Moreover, there is a gap in the medical literature regarding studies that examine the association between the specific type of pathogenic variant in GS2 and the occurrence of different types of primary abnormalities. These two facts could be attributed to the rarity of GS2, a disease where most publications consist of case reports of one to two patients or small cohorts (Al-Ahmari et al., 2010; Bindu et al., 2015; Meeths et al., 2010; Rajyalakshmi & Chakrapani, 2016; Sarper et al., 2002). The presentation of progressive unexplainable neurological diseases such as seizures, strabismus, nystagmus, hemiparesis, developmental delay, or intellectual disability in children who were previously healthy should raise suspicion of GS2, regardless of the simultaneous presence of cutaneous or immunological abnormalities. Considering GS2 as a primary differential diagnosis in such cases would enable early detection, prompt initiation of appropriate and effective treatment, and avoid the fatal outcome of HLH.

Although we reported a lower frequency of HLH (33%) in our patients compared to previously reported cases (71%), it is still crucial to consider and suspect GS2 in the above-described pediatric group given the high fatality rate of HLH and the limited availability of HSCT that can improve overall survival. In this case series, almost half of the patients had a viral infection, mainly EBV, and three out of four patients with fatal HLH complications (75%) had a viral infection, 50% of which were EBV-related. HLH-related EBV infection is the most common viral infection in children (Kogawa et al., 2014). Although the pre-transplant viral infection was documented in 42% of our patients, HLH was noticeably less frequent than previously described. Kuskonmaz et al. (2017) studied 10 children with GS2 who received HSCT and reported EBV infection in all of them. A plausible explanation for this difference might be related to the pathogenic *RAB27A* variant p.R82C conferring less susceptibility to EBV infections.

Although partial albinism or hypopigmentation is still considered a characteristic feature of GS2 (Cetica et al., 2015; Netter et al., 2016; Tesi et al., 2018), the p.R82C variant is known to present only with cytotoxic defect, sparing pigmentary dilution (Netter et al., 2016). Therefore, it was predicted that all of the affected patients should have normal pigmentation; however, 4 out of 12 patients in this series had partial albinism. It is unclear how the p.R82C variant is causing pigmentary dilution in some patients while retaining it in others. It is suggested that the presence of modifier genes or epigenetic factors may explain the pigmentary dilution in the four patients in our cohort.

In this case series, we have observed a significant gap of 2 years (median) between the age at presentation and the age at diagnosis. This delay in diagnosis poses a real challenge and could be attributed to the type of clinical features the patients presented with. The majority of patients did not have cutaneous pigmentary changes, and their primary neurological symptoms were related to the disease itself rather than HLH. The delay in diagnosis maybe even longer than 2 years in practice. However, this was not reflected by our study, where several patients were diagnosed shortly after their clinical presentation due to the high diagnostic yield of CES and our previous

knowledge of GS2 in our patient population, notably in a specific Qatari tribe.

This study provides evidence that CES is a valuable diagnostic tool for evaluating conditions with broad phenotypic variability such as GS2, which can present as late as the fifth decade of life, therefore, limiting the diagnostic odyssey. It is thus recommended that the *RAB27A* gene to be added to the list of genes, which secondary (incidental) findings should be reported as recommended by the American College of Medical Genetics (ACMG). Furthermore, the study highlights the importance of testing apparently asymptomatic family members especially in the absence of pigment dilution who may be homozygous for a pathogenic variant and at risk of disease. These individuals could then be monitored for signs and symptoms of GS2 that may develop throughout their life and be considered for prophylactic interventions such as HSCT. Targeted testing of asymptomatic family members who are in the reproductive age is also essential to accurately assess the risk of GS2 in their offspring and to provide genetic counseling and guidance regarding available reproductive options.

## 6 | CONCLUSIONS

In conclusion, all of the patients with GS2 in our cohort were homozygous for the same founder pathogenic variant p.R82C in the *RAB27A* gene; albeit striking phenotypic variability was noted among them. We recommend that GS2 should be considered in the differential diagnosis of acutely deteriorating patients with immune dysregulation, HLH, or CNS involvement, especially among consanguineous Qatari families, to shorten the diagnostic odyssey, guide early and appropriate treatment, and prevent possible fatal outcomes. We also recommend targeted testing of this founder *RAB27A* variant p.R82C in the identified Qatari tribes to identify asymptomatic carriers and asymptomatic homozygotes who may benefit from preventative measures and genetic counseling in the premarital, preconceptional, or prenatal period.

## ACKNOWLEDGMENTS

We acknowledge Hamad Medical Corporation, Medical Research Centre for approving our case series (MRC-04-20-325).

We acknowledge our partner laboratory GeneDx, USA for running the CES on our patients and for conducting bioinformatics analyses to study the age of the p.R82C variant in our population.

## CONFLICT OF INTEREST

There are no commercial associations that might pose a conflict of interest. We wish to confirm that there are no known conflicts of interest associated with this publication, and there has been no significant financial support for this work that could have influenced its outcome. We confirm that the manuscript has been read and approved by all named authors and that there are no other persons who satisfied the criteria for authorship but are not listed. We further confirm that the order of the authors listed in the manuscript has been

approved by all of the authors. We confirm that we have given due consideration to the protection of intellectual property associated with this work and that there are no impediments to publication, including the timing of publication, with respect to intellectual property. In doing so, we confirm that we have followed the regulations of our institutions concerning intellectual property. We further confirm that any aspect of the work covered in this manuscript that has involved either experimental animals or human patients has been conducted with the ethical approval of all relevant bodies and that such approvals are acknowledged within the manuscript. We understand that the corresponding author is the sole contact for the editorial process (including the editorial manager and direct communications with the office). He/She is responsible for communicating with the other authors about the progress, submission of revisions, and the final approval of proofs. We confirm that we have provided a current, correct email address that is accessible by the corresponding author.

## AUTHOR CONTRIBUTIONS

**Reem Al-Sulaiman:** Concepts; design; definition of intellectual content; literature search; clinical studies; data acquisition; data analysis; statistical analysis; manuscript preparation; manuscript editing; manuscript review and approval. **Amna Othman:** Concepts; design; definition of intellectual content; literature search; clinical studies; manuscript preparation; manuscript editing; manuscript review and approval. **Karen El-Akouri:** Concepts; design; definition of intellectual content; literature search; clinical studies; data acquisition; manuscript preparation; manuscript editing; manuscript review and approval. **Shehab Fareed:** Concepts; design; definition of intellectual content; clinical studies; data acquisition; data analysis; manuscript preparation; manuscript review and approval. **Hajer AlMulla:** Concepts; design; data acquisition; manuscript preparation; manuscript review and approval. **Aseel Sukik:** Data acquisition; data analysis; manuscript review and approval. **Mariam Al-Mureikhi:** Concepts; definition of intellectual content; manuscript review and approval. **Noora Shahbeck:** Concepts; definition of intellectual content; manuscript review and approval. **Rehab Ali:** Concepts; definition of intellectual content; manuscript review and approval. **Fatma Al-Mesaifri:** Concepts; definition of intellectual content; manuscript review and approval. **Sara Musa:** Concepts; definition of intellectual content; manuscript review and approval. **Mariam Al-Mulla:** Concepts; definition of intellectual content; manuscript review and approval. **Khalid Ibrahim:** Concepts; data acquisition; manuscript preparation; manuscript review and approval. **Khalid Mohamed:** Concepts; data acquisition; manuscript preparation; manuscript review and approval. **Maryam Ali Al-Nesef:** Concepts; design; definition of intellectual content; manuscript editing; manuscript review and approval. **Mohammad Ehlayel:** Concepts; design; definition of intellectual content; literature search; data analysis; statistical analysis; manuscript editing; manuscript review and approval. **Tawfeg Ben-Omran:** Concepts; design; definition of intellectual content; literature search; clinical studies; data acquisition; data analysis; statistical analysis; manuscript preparation; manuscript editing; manuscript review and approval.















## ETHICS STATEMENT

The study was approved by the Ethical Committee of the Hamad Medical Corporation, Doha, Qatar (MRC-04-20-325). All clinical investigations were conducted according to the principles expressed in the 1964 Helsinki declaration and its recent amendments.

## DATA AVAILABILITY STATEMENT

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

## ORCID

**Amna Othman**  <https://orcid.org/0000-0001-7309-7243>  
**Karen El-Akouri**  <https://orcid.org/0000-0003-1476-3490>  
**Shehab Fareed**  <https://orcid.org/0000-0001-6118-3988>  
**Hajer AlMulla**  <https://orcid.org/0000-0001-8797-8025>  
**Aseel Sukik**  <https://orcid.org/0000-0002-3725-9281>  
**Noora Shahbeck**  <https://orcid.org/0000-0002-4534-3731>  
**Rehab Ali**  <https://orcid.org/0000-0002-4346-3887>  
**Fatma Al-Mesaifri**  <https://orcid.org/0000-0003-4744-5114>  
**Sara Musa**  <https://orcid.org/0000-0001-5165-4109>  
**Khalid Ibrahim**  <https://orcid.org/0000-0002-2668-0804>  
**Khalid Mohamed**  <https://orcid.org/0000-0001-6656-2792>  
**Maryam Ali Al-Nesef**  <https://orcid.org/0000-0001-9354-0214>  
**Mohammad Ehlayel**  <https://orcid.org/0000-0002-6872-2451>  
**Tawfeg Ben-Omran**  <https://orcid.org/0000-0001-8522-7738>

## REFERENCES

- Aksu, G., Kütükçüler, N., Genel, F., Vergin, C., & Omowaire, B. (2003). Griscelli syndrome without hemophagocytosis in an eleven-year-old girl: Expanding the phenotypic spectrum of Rab27A mutations in humans. *American Journal of Medical Genetics. Part A*, 116A(4), 329–333. <https://doi.org/10.1002/ajmg.a.10836>
- Al-Ahmari, A., Al-Ghoniaim, A., Al-Mansoori, M., Hawwari, A., Eldali, A., Ayas, M., ... El-Solh, H. (2010). Hematopoietic SCT in children with Griscelli syndrome: A single-center experience. *Bone Marrow Transplantation*, 45(8), 1294–1299. <https://doi.org/10.1038/bmt.2009.358>
- Al-Mofareh, M., Ayas, M., Al-Seraihy, A., Siddiqui, K., Al-Jefri, A., Ghemlas, I., ... Al-Ahmari, A. (2020). Hematopoietic stem cell transplantation in children with Griscelli syndrome type 2: A single-center report on 35 patients. *Bone Marrow Transplantation*. <https://doi.org/10.1038/s41409-020-0885-6>
- Anikster, Y., Huizing, M., Anderson, P. D., Fitzpatrick, D. L., Klar, A., Gross-Kieselstein, E., ... Hurvitz, H. (2002). Evidence that Griscelli syndrome with neurological involvement is caused by mutations in RAB27A, not MYO5A. *The American Journal of Human Genetics*, 71(2), 407–414. <https://doi.org/10.1086/341606>
- Ashrafi, M. R., Mohseni, M., Yazdani, S., Alizadeh, H., Ramyar, A., Aghamohammadi, A., ... Heris, J. A. (2006). Bilateral basal ganglia involvement in a patient with Griscelli syndrome. *European Journal of Paediatric Neurology*, 10(4), 207–209. <https://doi.org/10.1016/j.ejpn.2006.07.005>
- Bahadoran, P., Busca, R., Chiaverini, C., Westbroek, W., Lambert, J., Bille, K., ... Ballotti, R. (2003). Characterization of the molecular defects in Rab27a, caused by RAB27A missense mutations found in patients with Griscelli syndrome. *The Journal of Biological Chemistry*, 278(13), 11386–11392. <https://doi.org/10.1074/jbc.M211996200>
- Barral, D. C., Ramalho, J. S., Anders, R., Hume, A. N., Knapton, H. J., Tolmachova, T., ... Seabra, M. C. (2002). Functional redundancy of

- Rab27 proteins and the pathogenesis of Griscelli syndrome. *The Journal of Clinical Investigation*, 110(2), 247–257. <https://doi.org/10.1172/JCI15058>
- Bindu, P., Mahadevan, A., Taly, A., Chickabasaviah, Y., Bharath, R., Nagappa, M., & Sinha, S. (2015). Neuroimaging findings in Griscelli syndrome type 2 with primary neurological presentation. *Journal of Pediatric Neuroradiology*, 03(2), 81–86. <https://doi.org/10.3233/PNR-14091>
- Cetica, V., Hackmann, Y., Grieve, S., Sieni, E., Ciambotti, B., Coniglio, M. L., ... Aricó, M. (2015). Patients with Griscelli syndrome and normal pigmentation identify RAB27A mutations that selectively disrupt MUNC13-4 binding. *The Journal of Allergy and Clinical Immunology*, 135(5), 1310–1318.e1. <https://doi.org/10.1016/j.jaci.2014.08.039>
- Burns, D. T., Donkervoort, S., Müller, J. S., Knierim, E., Bharucha-Goebel, D., Faqeih, E. A., ... Bönnemann, C. G. (2018). Variants in EXOSC9 disrupt the RNA exosome and result in cerebellar atrophy with spinal motor neuronopathy. *The American Journal of Human Genetics*, 102(5), 858–873.
- GeneDx. (n.d.). *XomeDx: Clinical exome sequencing [test information sheet]*. Retrieved from [https://www.genedx.com/wp-content/uploads/2020/04/info\\_sheetXomeDx\\_4\\_10\\_20.pdf](https://www.genedx.com/wp-content/uploads/2020/04/info_sheetXomeDx_4_10_20.pdf)
- Griscelli, C., Durandy, A., Guy-Grand, D., Daguillard, F., Herzog, C., & Prunieras, M. (1978). A syndrome associating partial albinism and immunodeficiency. *The American Journal of Medicine*, 65(4), 691–702. [https://doi.org/10.1016/0002-9343\(78\)90858-6](https://doi.org/10.1016/0002-9343(78)90858-6)
- Haddad, E. K., Wu, X., Hammer, J. A., & Henkart, P. A. (2001). Defective granule exocytosis in Rab27a-deficient lymphocytes from ashken mice. *Journal of Cell Biology*, 152(4), 835–842. <https://doi.org/10.1083/jcb.152.4.835>
- Harfi, H. A., Brismar, J., Hainau, B., & Sabbah, R. (1992). Partial albinism, immunodeficiency, and progressive white matter disease: A new primary immunodeficiency. *Allergy Proceedings: The Official Journal of Regional and State Allergy Societies*, 13(6), 321–328. <https://doi.org/10.2500/108854192778816933>
- Henter, J.-I., Horne, A. A., Aricó, M., Egeler, R. M., Filipovich, A. H., Imashuku, S., ... Janka, G. (2007). HLH-2004: Diagnostic and therapeutic guidelines for hemophagocytic lymphohistiocytosis. *Pediatric Blood & Cancer*, 48(2), 124–131. <https://doi.org/10.1002/pbc.21039>
- Hume, A. N., Collinson, L. M., Rapak, A., Gomes, A. Q., Hopkins, C. R., & Seabra, M. C. (2001). Rab27a regulates the peripheral distribution of melanosomes in melanocytes. *Journal of Cell Biology*, 152(4), 795–808. <https://doi.org/10.1083/jcb.152.4.795>
- Jin, Z., Wang, Y., Wang, J., Zhang, J., Wu, L., Gao, Z., ... Wang, Z. (2018). Primary hemophagocytic lymphohistiocytosis in adults: The utility of family surveys in a single-center study from China. *Orphanet Journal of Rare Diseases*, 13(1), 17. <https://doi.org/10.1186/s13023-017-0753-7>
- Kogawa, K., Sato, H., Asano, T., Ohga, S., Kudo, K., Morimoto, A., ... Ishii, E. (2014). Prognostic factors of Epstein-Barr virus-associated hemophagocytic lymphohistiocytosis in children: Report of the Japan histiocytosis study group. *Pediatric Blood & Cancer*, 61(7), 1257–1262. <https://doi.org/10.1002/pbc.24980>
- Kuskonmaz, B., Ayvaz, D., Gokce, M., Ozgur, T. T., Okur, F. V., Cetin, M., ... Uckan Cetinkaya, D. (2017). Hematopoietic stem cell transplantation in children with Griscelli syndrome: A single-center experience. *Pediatric Transplantation*, 21(7), e13040. <https://doi.org/10.1111/petr.13040>
- Mamishi, S., Modarressi, M. H., Pourakbari, B., Tamizifar, B., Mahjoub, F., Fahimzad, A., ... Parvaneh, N. (2008). Analysis of RAB27A gene in Griscelli syndrome type 2: Novel mutations including a deletion hotspot. *Journal of Clinical Immunology*, 28(4), 384–389. <https://doi.org/10.1007/s10875-008-9192-5>
- Marsh, R. A. (2018). Epstein-Barr virus and hemophagocytic lymphohistiocytosis. *Frontiers in Immunology*, 8, 1902. <https://doi.org/10.3389/fimmu.2017.01902>
- Masri, A., Bakri, F. G., Al-Hussaini, M., Al-Hadidy, A., Hirzallah, R., de Saint Basile, G., & Hamamy, H. (2008). Griscelli syndrome type 2: A rare and lethal disorder. *Journal of Child Neurology*, 23(8), 964–967. <https://doi.org/10.1177/0883073808315409>
- Meeths, M., Bryceson, Y. T., Rudd, E., Zheng, C., Wood, S. M., Ramme, K., ... Henter, J.-I. (2010). Clinical presentation of Griscelli syndrome type 2 and spectrum of RAB27A mutations. *Pediatric Blood & Cancer*, 54(4), 563–572. <https://doi.org/10.1002/pbc.22357>
- Ménasché, G., Ho, C. H., Sanal, O., Feldmann, J., Teczan, I., Ersoy, F., ... de Saint Basile, G. (2003). Griscelli syndrome restricted to hypopigmentation results from a melanophilin defect (GS3) or a MYO5A F-exon deletion (GS1). *The Journal of Clinical Investigation*, 112(3), 450–456. <https://doi.org/10.1172/JCI18264>
- Mishra, K., Singla, S., Sharma, S., Saxena, R., & Batra, V. V. (2014). Griscelli syndrome type 2: A novel mutation in RAB27A gene with different clinical features in 2 siblings: A diagnostic conundrum. *Korean Journal of Pediatrics*, 57(2), 91–95. <https://doi.org/10.3345/kjp.2014.57.2.91>
- Netter, P., Chan, S. K., Banerjee, P. P., Monaco-Shawver, L., Noroski, L. M., Hanson, I. C., ... Orange, J. S. (2016). A novel Rab27a mutation binds melanophilin, but not Munc13-4, causing immunodeficiency without albinism. *The Journal of Allergy and Clinical Immunology*, 138(2), 599–601.e3. <https://doi.org/10.1016/j.jaci.2015.12.1337>
- Ohbayashi, N., Mamishi, S., Ishibashi, K., Maruta, Y., Pourakbari, B., Tamizifar, B., ... Parvaneh, N. (2010). Functional characterization of two RAB27A missense mutations found in Griscelli syndrome type 2: Functional characterization of two GS-2 missense mutations. *Pigment Cell & Melanoma Research*, 23(3), 365–374. <https://doi.org/10.1111/j.1755-148X.2010.00705.x>
- Panigrahi, I., Suthar, R., Rawat, A., & Behera, B. (2015). Seizure as the presenting manifestation in Griscelli syndrome type 2. *Pediatric Neurology*, 52(5), 535–538. <https://doi.org/10.1016/j.pediatrneurol.2015.01.010>
- Pastural, E., Barrat, F. J., Dufourcq-Lagelouse, R., Certain, S., Sanal, O., Jabado, N., ... de Saint Basile, G. (1997). Griscelli disease maps to chromosome 15q21 and is associated with mutations in the myosin-Va gene. *Nature Genetics*, 16(3), 289–292. <https://doi.org/10.1038/ng0797-289>
- Patiroglu, T., Akar, H. H., Unal, E., Chiang, S. C., Schlums, H., Tesi, B., ... Karakukcu, M. (2016). Partial oculocutaneous albinism and immunodeficiency syndromes: Ten years experience from a single center in Turkey. *Genetic Counseling (Geneva, Switzerland)*, 27(1), 67–76.
- Rajadhyax, M., Neti, G., Crow, Y., & Tyagi, A. (2007). Neurological presentation of Griscelli syndrome: Obstructive hydrocephalus without haematological abnormalities or organomegaly. *Brain and Development*, 29(4), 247–250. <https://doi.org/10.1016/j.braindev.2006.09.007>
- Rajyalakshmi, R., & Chakrapani, R. N. B. (2016). Griscelli syndrome type 2: A rare and fatal syndrome in a South Indian boy. *Indian Journal of Pathology & Microbiology*, 59(1), 113–116. <https://doi.org/10.4103/0377-4929.178230>
- Retterer, K., Juusola, J., Cho, M. T., Vitazka, P., Millan, F., Gibellini, F., ... Bale, S. (2016). Clinical application of whole-exome sequencing across clinical indications. *Genetics in Medicine*, 18(7), 696–704. <https://doi.org/10.1038/gim.2015.148>
- Sarper, N., Akansel, G., Aydoğan, M., Gedikbaşı, D., Babaoglu, K., & Gökalp, A. (2002). Neuroimaging abnormalities in Griscelli's disease. *Pediatric Radiology*, 32(12), 875–878. <https://doi.org/10.1007/s00247-002-0752-1>
- Shamsian, B. S., Norbakhsh, K., Rezaei, N., Safari, A., Gharib, A., Pourpak, Z., ... Arzanian, M. T. (2010). A novel RAB27A mutation in a patient with Griscelli syndrome type 2. *Journal of Investigational Allergology & Clinical Immunology*, 20(7), 612–615.
- Shen, Y.-T., Gu, Y., Su, W.-F., Zhong, J.-F., Jin, Z.-H., Gu, X.-S., & Chen, G. (2016). Rab27b is involved in Lysosomal exocytosis and proteolipid protein trafficking in oligodendrocytes. *Neuroscience Bulletin*, 32(4), 331–340. <https://doi.org/10.1007/s12264-016-0045-6>

- Stinchcombe, J. C., Barral, D. C., Mules, E. H., Booth, S., Hume, A. N., Machesky, L. M., ... Griffiths, G. M. (2001). Rab27a is required for regulated secretion in cytotoxic T lymphocytes. *Journal of Cell Biology*, 152(4), 825–834. <https://doi.org/10.1083/jcb.152.4.825>
- Tesi, B., Rascon, J., Chiang, S. C. C., Burnyte, B., Löfstedt, A., Fasth, A., ... Bryceson, Y. T. (2018). A RAB27A 5' untranslated region structural variant associated with late-onset hemophagocytic lymphohistiocytosis and normal pigmentation. *The Journal of Allergy and Clinical Immunology*, 142(1), 317–321.e8. <https://doi.org/10.1016/j.jaci.2018.02.031>
- Wilson, S. M., Yip, R., Swing, D. A., O'Sullivan, T. N., Zhang, Y., Novak, E. K., ... Jenkins, N. A. (2000). A mutation in Rab27a causes the vesicle transport defects observed in ashen mice. *Proceedings of the National Academy of Sciences*, 97(14), 7933–7938. <https://doi.org/10.1073/pnas.140212797>
- Wu, X., Rao, K., Bowers, M. B., Copeland, N. G., Jenkins, N. A., & Hammer, J. A. (2001). Rab27a enables myosin Va-dependent melanosome capture by recruiting the myosin to the organelle. *Journal of Cell Science*, 114(Pt 6), 1091–1100.
- Zhang, M., Bracaglia, C., Prencipe, G., Bemrich-Stolz, C. J., Beukelman, T., Dimmitt, R. A., ... Cron, R. Q. (2016). A heterozygous RAB27A

mutation associated with delayed cytolytic granule polarization and hemophagocytic lymphohistiocytosis. *Journal of Immunology* (Baltimore, Md.: 1950), 196(6), 2492–2503. <https://doi.org/10.4049/jimmunol.1501284>

## SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section at the end of this article.

**How to cite this article:** Al-Sulaiman R, Othman A, El-Akouri K, et al. A founder RAB27A variant causes Griscelli syndrome type 2 with phenotypic heterogeneity in Qatari families. *Am J Med Genet Part A*. 2020;182A:2570–2580. <https://doi.org/10.1002/ajmg.a.61829>