

Griscelli Syndrome

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SUMMARY

We report a case of Griscelli Syndrome (GS). Our patient initially presented with a diagnosis of haemophagocytic lymphohistiocytosis (HLH). Subsequent microscopic analysis of the patient's hair follicle revealed abnormal distribution of melanosomes in the shaft, which is a hallmark for GS. Analysis of RAB27A gene in this patient revealed a homozygous mutation in exon 6, c.550C>T, p.R184X. This nonsense mutation causes premature truncation of the protein resulting in a dysfunctional RAB27A. Recognition of GS allows appropriate institution of therapy namely chemotherapy for HLH and curative haematopoietic stem cell transplantation.

KEY WORDS:

Griscelli syndrome, albinism, haemophagocytic lymphohistiocytosis

INTRODUCTION

Griscelli syndrome (GS, MIM 214450 and 607624) is a rare, autosomal recessive disorder which results in generalised hypopigmentation of the skin and the hair, the presence of clumps of pigment in the hair shafts and an accumulation of melanosomes in the melanocytes. It was first reported as an immunodeficiency syndrome associated with partial albinism¹. Two distinct genotype-phenotype classifications have been recognised namely those with mutations in RAB27A who develop dysfunctional T-lymphocytes and manifest with recurrent infections or haemophagocytic lymphohistiocytosis (HLH)², and those with mutations in MYO5A who present in infancy with severe neurological impairment without apparent immune abnormalities³. We report an instructive case of a Malaysian infant with Griscelli syndrome due to a RAB27A mutation.

CASE REPORT

The proband is a male infant of South Indian ethnicity who is the only child of a non-consanguineous couple. He presented at the age of six weeks with severe *Chryseobacterium* sepsis requiring invasive ventilatory and inotropic support. Clinically, he was noted to be fair-skinned with silvery hair and had hepatosplenomegaly on abdominal palpation. Serial blood investigations showed pancytopenia with no megagranular leucocytes in the peripheral blood film. Bone marrow aspiration demonstrated increased histiocytes

exhibiting haemophagocytosis. A diagnosis of HLH was made and therapy following the HLH-2004 protocol was commenced. This episode was subsequently complicated by necrotizing enterocolitis requiring bowel resection. Following recovery from his acute illness and completion of chemotherapy protocol, he successfully underwent haematopoietic stem cell transplantation from a matched unrelated donor. He is developmentally appropriate for his age of 14 months. There is a slight delay in his gross motor development where he can only stand with support. Since the patient presented with HLH and partial albinism, we performed microscopic examination of his hair follicle. This revealed small and large clumps of pigment irregularly distributed along the shaft (Figure 1). A clinical diagnosis of Griscelli syndrome was made based on these evidences.

Following informed consent, genetic studies of the proband and his parents were performed. Bidirectional sequencing of exons 2-6 of the coding region of RAB27A revealed a homozygous mutation in Exon 6, c.550C>T, p.(R184X) (Figure 2). The substitution of C to T is a nonsense mutation that leads to a termination codon and consequently, a non-functioning truncated protein. Genetic analysis of the parents revealed they are heterozygous carriers of this mutation.

DISCUSSION

RAB27A is expressed in melanocytes, peripheral leucocytes, platelets and certain tissues. It encodes one of the 60 known Rab GTPases which are critical regulators of vesicular transport particularly in two types of lysosome-related organelles namely melanosomes in melanocytes and lytic granules in cytotoxic T-lymphocytes. Loss-of-function mutations of RAB27A in patients with GS cause their T-cells to have low anti-CD3 induced cytotoxic activity and have defective release of granules containing perforin and granzyme, leading to a cascade of defective apoptosis, uncontrolled activation of histiocytes, hypercytokinemia and organ damage.

To date, there are more than 100 reports of 27 different RAB27A mutations in patients with GS type 2⁴. In addition to deletions, point mutations were found in the majority of these cases and these mutations are located in all coding exons. The point mutation we found in our patient in Exon 6, R184X, is not a novel mutation and has been reported in children from Europe, the Middle East and South America^{4,5}.

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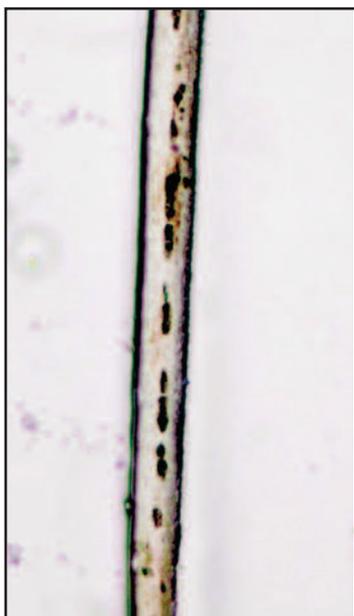


Fig. 1: Micrograph of hair follicle demonstrating characteristic abnormal clumping of melanin pigment along the shaft.

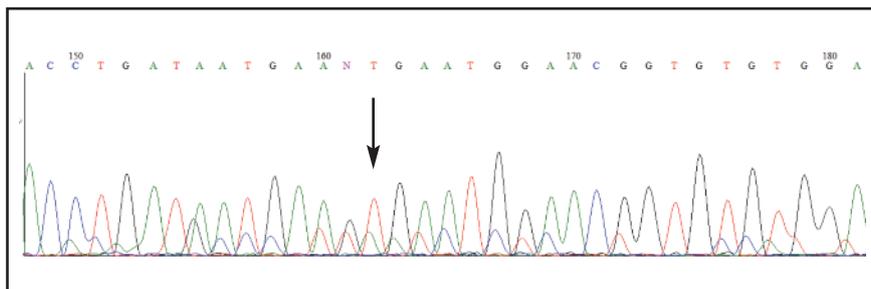


Fig. 2: Electropherogram for exon 6 of the RAB27A gene in the proband demonstrating single nucleotide substitution of C to T at position 550 (arrow) which results in a termination codon i.e. from CGA (arginine) to TGA (stop). The RAB27A sequence from the ENSEMBL database was used as reference.

The early recognition of GS is important because affected children are predisposed to recurrent, overwhelming infections and/or HLH, both of which may lead to a fatal outcome. Haematopoietic stem cell transplantation is the only curative option in this condition. Patients with GS who fail to be transplanted usually die within 5 years after diagnosis⁵.

In our patient, his fair skin and light hair were noted at birth. However, a lack of awareness on GS prevented him from being referred for further diagnostic workup where an early diagnosis of GS could be made. It should also be noted that children with GS can present with symptoms of macrophage activation syndrome or HLH, which overlap with those of sepsis. If treated solely for sepsis i.e. with antibiotics but without specific HLH-directed therapy which includes etoposide, steroids and cyclosporin, these children may still develop fatal multi-organ failure as the hypercytokinemia and uncontrolled histiocytic activity remain unaddressed.

The initial diagnosis of GS can be made without sophisticated tools but merely from microscopic examination of hair follicles for characteristic abnormal melanin clumps. However, subsequent referral to a tertiary centre to discover the underlying gene mutation is required to institute curative therapy and genetic counselling for future pregnancies.

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