TYPE 3 GRISCELLI'S SYNDROME IN TWO SIBLINGS

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Abbreviation **GS** = Griscelli's syndrome.

Case report. Two siblings, aged 9 (patient 1) and 8 (patient 2), born to consanguineous parents, presented with gray hair and body hair since birth and facial hyperpigmentation that had developed over the past 4 years. Psychomotor developmental milestones were within normal limits, and both children were up to date on their immunizations.

Medical history was negative for recurrent fever, respiratory tract infections, and visual or hearing deficits. Academic performance was age-appropriate.

Dermatological examination revealed gray hair and body hair overall (including the scalp, eyebrows, eyelashes, forearms, and legs) along with bronze-tan hyperpigmentation on the face and neck (Fig. 1, 2). Teeth, nails, and systemic physical examination were all unremarkable.

Trichoscopy of the hair shaft demonstrated uneven, large aggregates of melanosomes within the medulla, displaying the classic "road dividing line" pattern (Fig. 3). A peripheral blood smear showed a normocytic normochromic red blood cell profile.

Genetic testing via targeted gene sequencing identified a homozygous nonsense variant in exon 2 of the *MLPH* gene (chr2:g.237493496C>T; Depth: 131x) that results in a stop codon and premature truncation of the protein at codon 24 (p.Arg24Ter; ENST00000264605.8). The final diagnosis was Type 3 Griscelli's syndrome.

Discussion. "Silvery hair syndrome" is an umbrella term used to describe a group of rare genetic disorders characterized by premature graying or silvering of the hair in association with systemic features. It encompasses Chédiak-Higashi syndrome (CHS), Griscelli syndrome (GS), and Elejalde syndrome (ES).

These rare autosomal recessive disorders are present at birth. While all three conditions share similar cutaneous and hair shaft abnormalities, they differ markedly in their neurological and immunological manifestations. The disorders with neurologic or immunological involvement are typically fatal in childhood, with only a small minority of patients surviving into adulthood.

CHS and Type 2 GS are characterized by immune dysfunction that, if untreated, can progress to hemophagocytic lymphohistiocytosis. Patients with CHS, Type 1 GS, and ES who survive into adulthood display severe neurological impairment. In contrast, patients with Type 3 GS exhibit isolated skin and hair changes without neurological or immunological involvement, making this specific type frequently underdiagnosed.

Griscelli's syndrome, also known as "partial albinism with immunodeficiency," is extremely rare, with the majority of reported cases originating from Turkish and Mediterranean populations. It is an autosomal recessive disorder causing pigmentary dilution of the skin and hair, accompanied by large pigment clumps along the hair shafts due to the accumulation of melanosomes within melanocytes (1). The three distinct subtypes of Griscelli's syndrome are caused by mutations in different genes (2):

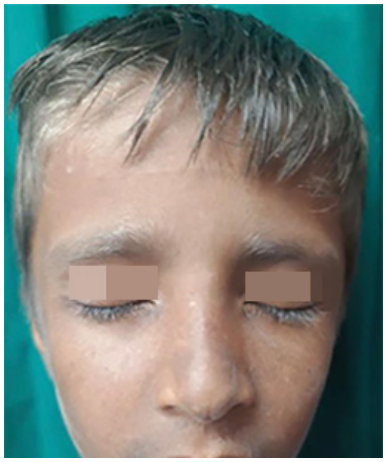

Fig. 1

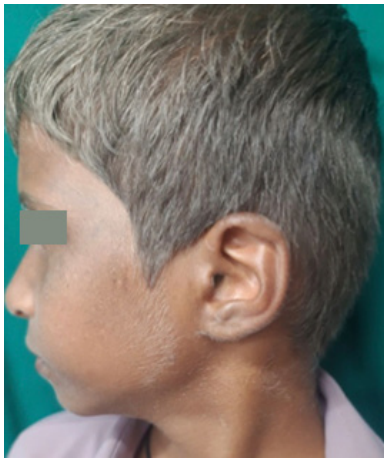

Fig. 2

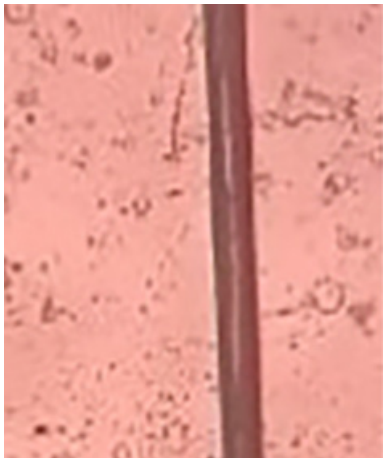

Fig. 3

Fig. 1, 2, 3: Griscelli's syndrome in two siblings: silvery-gray hair, eyebrows, and eyelashes, and bronze-tan hyperpigmentation of the face (Fig. 1, 2). Trichoscopy showing the characteristic " road dividing line" sign of the hair shafts (Fig. 3).

Type 1 results from mutations in *MYO5A*, Type 2 is caused by mutations in *RAB27A*, and Type 3 stems from mutations in *MLPH*.

Melanosome transport is a bidirectional process dependent on motor proteins such as dyneins, kinesins, and Myosin Va (Myo5a). Myo5a interacts with Rab27a and Mlph to form a tripartite protein complex essential for intracellular melanosome transport. Disruption of any of these proteins impairs melanosome trafficking, leading to hypopigmentation—most prominently affecting the hair and skin.

Beyond their role in melanosome transport, MYO5A and RAB27A are involved in other tissues. Specifically, the protein encoded by *MYO5A* transports intracellular material within neurons, which is critical for neural function. The protein encoded by *RAB27A* is expressed in immune cells, where it mediates the exocytosis of lytic granules that destroy external pathogens like viruses and bacteria. Pathogenic mutations in these genes disrupt these critical cellular processes, giving rise to the neurological deficits and immunological abnormalities observed in Type 1 and Type 2 GS, respectively (3).

All three types exhibit pigmentary dilution characterized by silvery-gray hair, fair skin that tans persistently upon sun exposure, and ocular abnormalities secondary to reduced pigmentation. Despite these phenotypic similarities, prognosis varies significantly depending on the presence of neurological or hematological manifestations.

Type 1 GS is characterized by primary, severe neurological impairment, including early-onset developmental delay, muscle hypotonia, and intellectual disability. This condition is linked to mutations in *MYO5A*, which encodes the organelle motor protein Myosin 5A (MyoVa), essential for neuronal function (4).

Type 2 GS results from mutations in the gene encoding the Rab27a GTPase (4). Rab27a deficiency impairs the exocytosis of cytotoxic granules by T lymphocytes and natural killer cells—leading to impaired cell-mediated cytotoxicity—as well as melanosome exocytosis. Clinical features of Type 2 GS include a history of severe infections, absent delayed-type hypersensitivity, and hypogammaglobulinemia. Hemophagocytic lymphohistiocytosis, a life-threatening hyperinflammatory complication, involves the uncontrolled activation of T cells and macrophages, presenting with fever, splenomegaly, cytopenias, hypofibrinogenemia, hypertriglyceridemia, and hyperferritinemia. Without prompt therapeutic intervention, it is fatal. Although chemotherapy can induce disease remission, allogeneic hematopoietic stem cell transplantation remains the only curative therapy for Type 2 GS (5).

In Type 3 GS, defects in the melanophilin gene (*MLPH*) lead to isolated cutaneous and hair hypopigmentation without systemic organ involvement. Consequently, patients with Type 3 GS have a favorable prognosis and require no specific treatment (6).

The clinical hallmark of GS is hair hypopigmentation, characterized by a silvery-gray sheen and irregular, large melanin clumps along the hair shaft on microscopic evaluation. Given that treatment, prognosis, and genetic counseling differ drastically among subtypes, achieving an accurate early genetic diagnosis is of paramount clinical importance.

Conclusion. This case of Type 3 Griscelli's syndrome is reported due to its rarity and to emphasize the importance of distinguishing this benign, isolated cutaneous phenotype from the far more severe subtypes presenting with life-threatening neurological or immunological complications.

Conflicts of interest

The authors declare that they have no conflicts of interest.

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