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Association of Piebaldism, Multiple Café-au-lait Macules, and Intertriginous Freckling: Clinical Evidence for a Common Pathway between KIT and SPRED1

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Abstract

Piebaldism is a rare genodermatosis caused by *KIT* mutations. We report the case of a 5-year-old boy who had the white forelock and leukoderma of piebaldism, yet the diagnosis was complicated by the presence of many café-au-lait macules and axillary and inguinal freckling. Patients with similar cutaneous findings have been previously reported, and their disorder has been attributed to an overlap of piebaldism and neurofibromatosis type 1. Legius syndrome is a recently described syndrome caused by *SPRED1* mutations that also has multiple café-au-lait macules and intertriginous freckling. Based on current understanding of KIT and SPRED1 protein interactions, we propose that café-au-lait macules and freckling may be seen in some patients with piebaldism and does not necessarily represent co-existence of neurofibromatosis type 1.

Keywords

piebaldism; KIT; café-au-lait macules; axillary freckling; inguinal freckling; Legius syndrome; SPRED1

Introduction

Piebaldism (OMIM #172800) is a rare autosomal dominant disorder characterized by depigmented patches of skin and hair due to an absence of melanocytes. Most cases are caused by loss-of-function mutations in the *KIT* gene encoding a protein tyrosine kinase receptor (1). While hyperpigmentation may be present at the periphery and within depigmented patches, café-au-lait macules (CALM) and axillary and inguinal freckling are not usual features. We describe a multigenerational family with dominantly inherited cutaneous manifestations of piebaldism associated with multiple CALM, and intertriginous freckling. The presence of a *KIT* mutation in the proband confirms the diagnosis of piebaldism, and current understanding of KIT tyrosine kinase function may explain the unusual phenotype.

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Case Report

The proband is a 5 year old male with a white forelock since birth and multiple CALM developing over time. He is the product of a nonconsanguineous union between parents of Colombian, Irish, German and Native American (Cherokee) descent. His past medical history is mostly unremarkable without developmental delay. He had previously been evaluated by multiple physicians with concern for neurofibromatosis type 1 (NF1), tuberous sclerosis, and Waardenburg syndrome. He was found to have normal hearing by audiology evaluation, a normal ophthalmologist eye exam, and normal brain magnetic resonance imaging.

The boy is non-dysmorphic with appropriate growth parameters and an overall fair complexion including blond hair and blue eyes. A midline diamond-shaped, depigmented patch was noted on his forehead with adjacent white forelock and poliosis of the medial eyebrows (Fig. 1a). On the midline chest and bilateral calves were barely perceptible, geographic, depigmented patches. Numerous CALM, twelve of which were >1 cm in size, were dispersed over his entire body (Fig. 1b). Freckles were present bilaterally in the axillae and inguinal folds. There were no neurofibromas. Eye examination was normal; no iris heterochromia, dystopia canthorum, nor Lisch nodules were present.

A similar phenotype of white forelock and multiple CALM in the patient's father was confirmed in clinic. By report, there is similar phenotypic expression of depigmented patches and CALM in several paternal relatives (Fig. 2). There are no reported findings in the family history of hearing loss, iris heterochromia, mental retardation, skin lesions suggestive of neurofibromas, cancers, or melanoma.

KIT gene testing was performed with complete gene sequencing of all DNA-coding regions. A novel heterozygous mutation p.E640D:c.1920A>T was identified, resulting in an amino acid substitution in the intracellular tyrosine kinase domain. The PolyPhen-2 tool (<http://genetics.bwh.harvard.edu/pph2/>, accessed 9/17/11) was used to predict the effect of this mutation on protein structure and function, and this mutation was predicted to be probably damaging with a score of 1.000 (maximum score of 1.000) (2).

Discussion

In this case report, we describe a family with autosomal dominant inheritance of a piebaldism phenotype in association with multiple CALM and intertriginous freckling. Piebaldism is a disorder of melanocyte development resulting in leukoderma (white skin) and poliosis (white hair) (3). The distinctive white forelock present at birth is the most common manifestation, and affected patients may also have depigmented patches on the midline anterior trunk and midline arms and legs. The white patches may be surrounded by a rim of hyperpigmentation or have freckling within. Mutations in two genes, the *KIT* proto-oncogene or *SLUG* (*SNAIL2*) zinc finger transcription factor, have been described to cause piebaldism which is inherited as an autosomal dominant trait (1, 4).

Patients with the coexistence of piebaldism and multiple CALM and intertriginous freckling have been reported (3, 5-8). In these prior reports, the children had congenital depigmentation consistent with piebaldism and met diagnostic criteria for NF1. No neurofibromas were seen in any of the cases; however, Lisch nodules and scoliosis were present in one girl (8). Genetic testing was performed in two cases, and *KIT* mutations were present in both (3, 7). Most of the prior published reports attribute the cutaneous findings to the coexistence of piebaldism with NF1. Angelo et al. postulate that haploinsufficiency of neurofibromin rescues the pigmentary defect through restoration of the KIT signaling

pathway (5). Duarte and colleagues hypothesize that the lack of KIT prevents neurofibroma formation when piebaldism and NF1 coexist (7). We have a different theory for the overlap seen in these patients based on current understanding of KIT interaction with SPRED1, a protein that is defective in patients with a NF1-like syndrome.

Familial multiple café-au-lait spots, also called Legius syndrome, is a recently described disorder with features similar to NF1 (OMIM #611431) (9). Affected patients have multiple CALM and axillary or inguinal freckling developing in childhood (10). In fact, many of the patients with Legius syndrome may meet National Institutes of Health diagnostic criteria for and be misdiagnosed as NF1 (11). Other features include macrocephaly, lipomas, Noonan syndrome-like facies, and neurocognitive disorders such as learning disability or developmental delay (10). Despite the similarities to NF1, Legius syndrome can be distinguished by the lack of tumor formation, and reports to date indicate that affected individuals do not develop neurofibromas, Lisch nodules, or central nervous system tumors (10). Legius syndrome is caused by autosomal dominant loss-of-function mutations in *SPRED1*, which inhibits the same pathway as neurofibromin, the defective protein in NF1 (12, 13).

The KIT protein product is a receptor tyrosine kinase composed of an extracellular ligand-binding domain, a transmembrane domain, and an intracellular tyrosine kinase domain (Fig. 3A) (14). Once activated by its ligand stem cell factor, KIT phosphorylates proteins in several signal transduction pathways (14). KIT has been shown to phosphorylate and activate SPRED1 at its KIT-binding domain (Fig. 3B) (13, 15). SPRED1 normally functions to suppress the Ras/MAPK pathway, and phosphorylation of the KIT-binding domain of SPRED1 by kinases such as KIT is required for activation and efficient suppression of the Ras/MAPK pathway (13, 15). Conversely, loss of SPRED1 activity as in Legius syndrome induces the Ras/MAPK pathway (13). Hyperactivity of the Ras/MAPK pathway has been implicated in the pathogenesis of CALM (16). Inadequate phosphorylation of SPRED1 by a defective KIT tyrosine kinase would result in loss of inhibition of the Ras/MAPK pathway with a clinical phenotype similar to Legius syndrome.

We assert that multiple CALM and intertriginous freckling can be seen within the piebaldism spectrum of disease and that loss of function of SPRED1 due to inadequate phosphorylation of the KIT-binding domain by KIT is the cause for the hyperpigmented lesions seen in some piebaldism patients. Of the three reported cases of piebaldism with multiple CALM and intertriginous freckling where KIT genetic testing was performed, including ours, all three mutations were in the tyrosine kinase domain (3, 7). None of the prior reports included genetic testing results of *NF1* or *SPRED1*, so true co-occurrence of both disorders cannot be ruled out. Previous papers have reported the variability of the piebald phenotype depending on the specific KIT mutation (17, 18), and this case may be considered a novel phenotype of piebaldism when the mutation is in the intracellular tyrosine kinase domain.

We considered the coincidental presence of both *KIT* and *SPRED1* mutations in our patient, yet that would be exceedingly unusual as each are rare diseases, and similarly, the chances of having both *KIT* and *NF1* mutations would be highly unlikely. The genes would not co-segregate as each is on different chromosomes; the *KIT* gene is on chromosome 4q, the *SPRED1* gene is on chromosome 15q, and the *NF1* gene is on chromosome 17q. Waardenburg syndrome was considered as a diagnostic possibility as patients may have white forelock, leukoderma, and CALM, but the patient and his family lacked other characteristic features such as hearing loss, dystopia canthorum, and heterochromia irides. Gain-of-function mutations in the KIT ligand (*KITLG*) have been reported to cause familial progressive hyperpigmentation and hypopigmentation (19), a condition characterized by

CALM and multiple lentigines; however, these patients typically have smaller hypopigmented macules rather than the depigmented patches of piebaldism. Based on the genetic testing results with a *KIT* mutation that was predicted to be highly damaging, we believe that this family has piebaldism with an unusual phenotype due to loss of the KIT tyrosine kinase function and subsequent effect on SPRED1 and the Ras/MAPK pathway.

Conclusion

Piebaldism is an uncommon pigmentary disease with a range of phenotypic presentations. There are rare reports of piebaldism patients with associated features of CALMs and axillary and/or inguinal freckling. Prior authors have concluded that these patients had the coexistence of piebaldism and NF1. We contend that CALMs and intertriginous freckling are variants in the piebaldism spectrum as a result of inadequate SPRED1 activity due to loss of phosphorylation by KIT. Future patients with these features should be tested for KIT mutations. To date, *SPRED1* mutations and Legius syndrome have not been associated with neurofibromas and other tumors, suggesting that piebaldism patients with multiple CALM and axillary and/or inguinal freckling may not need the rigorous monitoring that NF1 patients require.

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Figure 1. Pigmentary findings. (A) White forelock and poliosis of eyebrows. (B) Examples of café-au-lait macules on the legs.

Figure 2.
Family pedigree.

Figure 3.

(**A**) KIT protein schematic. The location of the mutations from reference 16 (G610D), reference # (R791G), and this report (E640D) are indicated. LBD = ligand binding. TK1 = tyrosine kinase domain 1. TK2 = tyrosine kinase domain 2. (**B**) SPRED1 protein schematic, showing the KIT-binding domain. EVH-1 = Ena/Vasodilator-stimulated phosphoprotein homology-1 domain. KBD = KIT-binding domain. SPR = Sprouty domain.