Piebaldism with multiple café-au-lait–like hyperpigmented macules and inguinal freckling caused by a novel *KIT* mutation

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INTRODUCTION

Piebaldism is a rare autosomal dominant disorder of pigmentation characterised by patches of leukoderma and white forelock. It is most often caused by mutations in the *KIT* proto-oncogene receptor tyrosine kinase (TK), which result in the defective migration and differentiation of melanoblasts and melanocytes.[1] Other mutations that have been described include a deletion and a double nucleotide variant in the gene encoding snail family zinc finger 2 (*SNAI2/SLUG*).[2,3]

The occasional coexistence of multiple café-au-lait macules (CALMs) in piebaldism and also piebaldism in association with CALMs and intertriginous freckling may lead to diagnostic confusion with neurofibromatosis type 1 (NF1). Another differential diagnosis is Legius syndrome, which is caused by loss-of-function mutations in the *SPRED1* gene. The syndrome is characterised by CALMs and intertriginous freckling with macrocephaly, lipomas, and learning disability. Unlike NF1, patients with Legius syndrome do not have cutaneous or plexiform neurofibromas, skeletal dysostosis, or optic pathway gliomas. The overlapping presentations of these related pigmentary disorders make it difficult to distinguish between them during the early stages and present a challenge for initial diagnosis.

Abbreviations used:

CALM:	café-au-lait macules
NF1:	neurofibromatosis type 1
TK:	tyrosine kinase

CASE REPORT

This 7-year-old girl was conceived via in vitro fertilization by a nonconsanguineous couple of German and Chinese descents. She was born in Germany prematurely at 33 weeks of gestation via emergency lower-segment cesarean section for in vitro fertilization dichorionic, diamniotic twins in labor. Perinatal history was uncomplicated, and she had good Apgar scores of 9 at both 1 and 5 minutes of life. At birth, she was noted to have a white forelock with patches of depigmentation and CALM-like hyperpigmented lesions. Results from head ultrasound scan and audiology test for hearing evaluation were both normal. Genetic testing for *NF1* gene mutation returned negative results.

She first presented to our clinic when she was 4 years and 5 months old after relocation to Singapore from Germany. On examination, she was noted to have whitish blonde forelock with well-demarcated, hypopigmented patch over the central forehead continuing to the glabella, rhinion,

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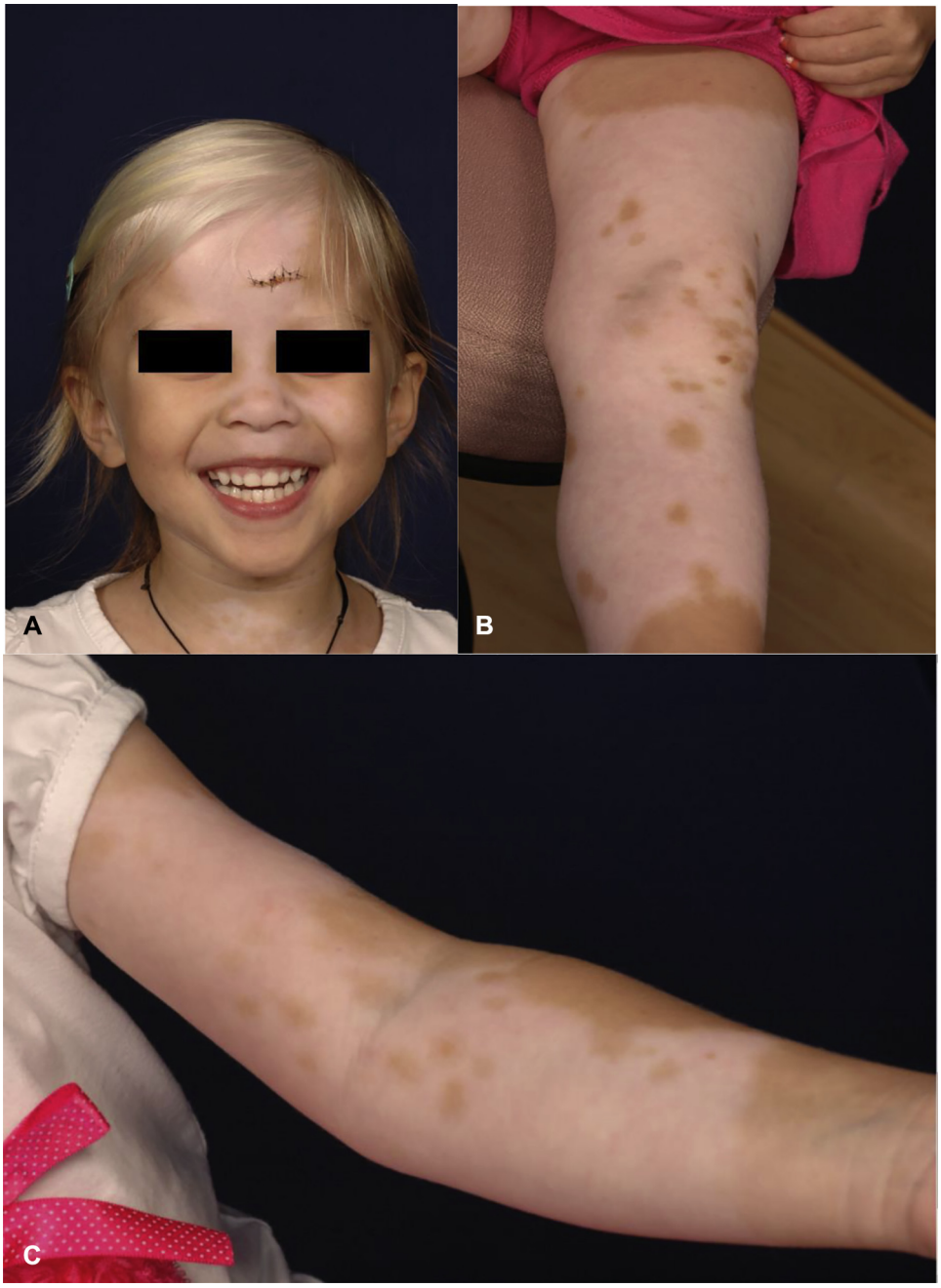

Fig 1. Depigmented patches observed (**A**) on the central forehead continuing to the glabella, rhinion, and bilateral cheeks; (**B**) on the lower limb with islands of normally pigmented skin; and (**C**) on the upper limb with islands of normally pigmented skin.

and bilateral cheeks, sparing the columella and chin (Fig 1, *A*). She also had multiple patches of hypopigmented/depigmented skin with islands of normally pigmented skin distributed across the anterior neck, ventral aspect of bilateral upper limbs (from proximal upper arms to distal forearms), and ventral aspect of bilateral lower limbs (from proximal thighs to distal lower legs) (Fig 1, *B* to *C*). Furthermore, multiple hyperpigmented lesions (some >1 cm) were also noted predominantly in the lower limbs and back. Freckling was seen in the inguinal folds, but no neurofibromas were seen. Ophthalmologic examination did not find heterochromia, Lisch nodules, or optic nerve glioma. She was otherwise developmentally appropriate for her age. There is no family history of pigmentary disorders.

Venous blood was collected with written informed consent from her mother. Sequencing was performed using the TruSight One (Illumina,

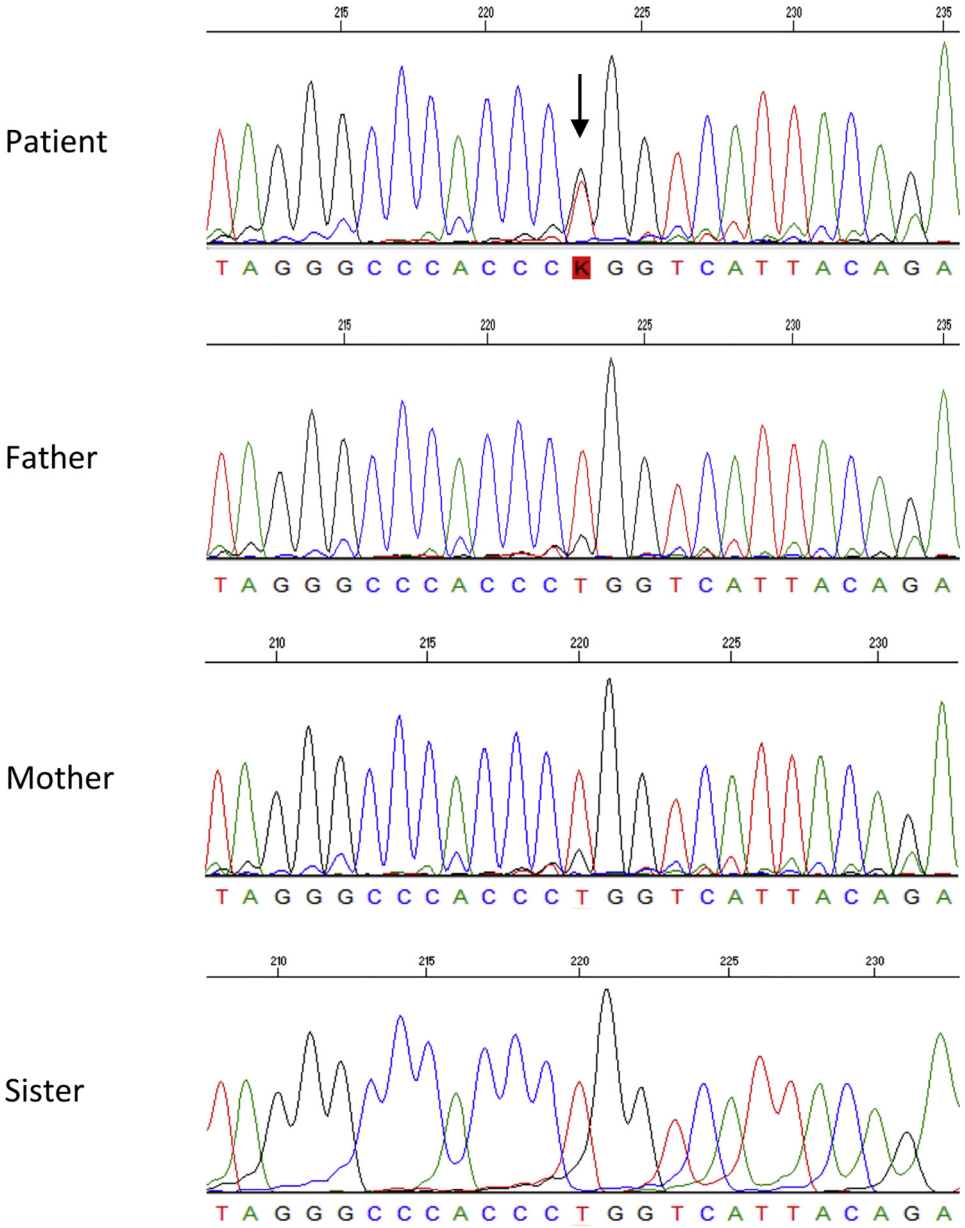

Fig 2. Sanger sequencing results show the mutation in *KIT1* in the patient (top-most panel) and the wild-type allele in her family members.

San Diego, California) next-generation sequencing panel on the MiSeq System. Sequence data were processed using MiSeq Reporter and annotated using wANNOVAR.[4]

No pathogenic variant was identified for *NF1* or *SPRED1*. A heterozygous variant was found in *KIT* (NM_000222.2: c.2000T>G) and confirmed by Sanger sequencing. The variant was not present in the saliva sample of her unaffected twin sister or the blood samples of her parents (Fig 2). It has not been reported previously and is not found in ClinVar (https://www.ncbi.nlm.nih.gov/clinvar/) or the Human Gene Mutation Database (http://www.hgmd.cf.ac.uk/ac/index.php).

The variant is expected to result in the substitution of leucine with arginine at codon 667 in the intracellular tyrosine kinase domain (TK1). The substitution is predicted to be pathogenic by

SIFT (http://sift.jcvi.org) and Polyphen2 (http://genetics.bwh.harvard.edu/pph2/), although protein modeling using a Swiss model and rendered with PyMOL (www.pymol.org) showed no change in the 3-dimensional structure.

DISCUSSION

The association between a *KIT* mutation and piebaldism was first reported in a large family of Ashkenazi Jews.[1] Since then, other *KIT* mutations were identified in patients with piebaldism. The novel missense mutation in our patient is in the TK1 domain and is predicted to lead to defective TK activation and impaired melanoblast differentiation, melanocyte migration, and melanogenesis. Known mutations in this domain include Gly610Asp,[5] Glu640Asp,[6] Arg791Gly,[7] [Cys674Tyr;Tyr675Ser],[8] Phe811Val,[9] and Arg812Val,[7] with all carriers presenting with CALMs or CALMs with freckling in addition to the piebaldism phenotype. However, it is not known whether there was CALMs or freckling in the family with the Gly664Arg mutation.[1] Two Korean patients with different mutations in this domain (Phe584Leu and Glu583Asp) were reported to have only mild piebaldism phenotype with the authors suggesting incomplete penetrance as a possible reason.[10]

Duarte et al[5] proposed that the existence of CALMs in patients with piebaldism could involve the activation of the Ras-MAPK pathway because of inactivating mutations in *NF1*. Chiu et al[6] proposed that multiple CALMs is part of the piebaldism spectrum of disease, as mutations affecting the TK1 domain result in the failure of phosphorylation and activation of SPRED1 at the KIT-binding domain, leading to subsequent insufficient suppression of the Ras/MAPK pathway. The genetic findings in our patient support the view that the presence of CALMs or hyperpigmented lesions is part of the piebaldism spectrum, as she has no *NF1* mutation.

Our patient has mixed ancestry. In a large pedigree comprising 7 individuals with piebaldism who all carried the same 2 *KIT* mutations, only the 2 half brothers who were of African-white parentage met the diagnostic criteria for NF1 but not their mother and 3 other white relatives.[8] The authors speculated that the finding might be because of the different distribution and size of melanosomes in people of different skin colors.

We report a child of mixed race who is only the third person of mixed race with piebaldism and CALM-like hyperpigmented lesions and freckling (after 2 half brothers). The finding of a de novo *KIT* mutation clarified her diagnosis and ruled out NF1 and Legius syndrome. It also illustrates the importance of molecular confirmation to prevent diagnostic confusion. A molecular diagnosis is also important for tumor surveillance, as various types of cancers have been reported in some patients, such as brain stem gliomas for *NF1* and stromal tumors for *KIT* mutations.

REFERENCES

1. Giebel LB, Spritz RA. Mutation of the KIT (mast/stem cell growth factor receptor) protooncogene in human piebaldism. *Proc Natl Acad Sci U S A*. 1991;88(19):8696-8699.
2. Sanchez-Martin M, Perez-Losada J, Rodriguez-Garcia A, et al. Deletion of the SLUG (SNAI2) gene results in human piebaldism. *Am J Med Genet A*. 2003;122A(2):125-132.
3. Yang YJ, Zhao R, He XY, et al. SNAI2 mutation causes human piebaldism. *Am J Med Genet A*. 2014;164A(3):855-857.
4. Chang X, Wang K. wANNOVAR: annotating genetic variants for personal genomes via the web. *J Med Genet*. 2012;49(7):433-436.
5. Duarte AF, Mota A, Baudrier T, et al. Piebaldism and neurofibromatosis type 1: family report. *Dermatol Online J*. 2010;16(1):11.
6. Chiu YE, Dugan S, Basel D, Siegel DH. Association of Piebaldism, multiple cafe-au-lait macules, and intertriginous freckling: clinical evidence of a common pathway between KIT and sprouty-related, ena/vasodilator-stimulated phosphoprotein homology-1 domain containing protein 1 (SPRED1). *Pediatr Dermatol*. 2013;30(3):379-382.
7. Spritz RA, Holmes SA, Itin P, Kuster W. Novel mutations of the KIT (mast/stem cell growth factor receptor) proto-oncogene in human piebaldism. *J Invest Dermatol*. 1993;101(1):22-25.
8. Stevens CA, Chiang PW, Messiaen LM. Cafe-au-lait macules and intertriginous freckling in piebaldism: clinical overlap with neurofibromatosis type 1 and Legius syndrome. *Am J Med Genet A*. 2012;158A(5):1195-1199.
9. Jia WX, Xiao XM, Wu JB, et al. A novel missense KIT mutation causing piebaldism in one Chinese family associated with cafe-au-lait macules and intertriginous freckling. *Ther Clin Risk Manag*. 2015;11:635-638.
10. Lee H, Oh SH, Koo KY, Suzuki T, Lee JS. Novel mutations of KIT gene in two Korean patients: variegated shades of phenotypes in tyrosine kinase 1 domain. *J Dermatol Sci*. 2014;76(1):74-76.