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A Familial 4q12 Deletion Involving *KIT* Gene Causes Piebaldism

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ABSTRACT Piebaldism is a rare, autosomal dominant disorder characterized by the congenital absence of melanocytes in affected areas of the skin and hair. We report on a familial 4q12 deletion that involves the *KIT* gene and causes piebaldism in affected individuals. Whole-genome genotyping analysis of the proband using HumanCytoSNP-12v2.1 BeadChips (Illumina Inc., San Diego, CA, USA, revealed a 1.34-Mb microduplication of 1q21.1q21.2 and a 2.7-Mb microdeletion of 4q12. The analysis of the parents confirmed the paternal origin of the 4q12 microdeletion. The clinical and molecular findings in the proband and his affected relatives showed that the 2.7-Mb 4q12 microdeletion, the smallest microdeletion reported to date, causes isolated piebaldism due to the loss of the *KIT* gene.

KEY WORDS: piebaldism, proto-oncogene proteins c-kit, gene deletion

INTRODUCTION

Piebaldism (OMIM #172800) is a rare autosomal dominant disorder characterized by the absence of melanocytes in certain areas of the skin (leukoderma) and hair (poliosis) (1). The incidence of this pigmentary disorder is estimated to be less than 1:20000 (2). The most common features of piebaldism are a white forelock and persistent depigmented macules on the forehead, chin, anterior trunk, and extremities (3). These skin abnormalities are usually symmetrical and might have mild hyperpigmentation inside or around the macules. It is unlikely for the depigmented skin patches to be found on the dorsal trunk, hands, feet, and periorificial areas, which are common symptoms in similar diseases such as vitiligo and albinism (4). Almost all piebald traits are present at birth, and in most cases can change only slightly throughout an individual's life (3). A few studies have emphasized the possibility for patients with piebaldism to have *cafe-au-lait* spots, though these patients may be misdiagnosed as concurrently having neurofibromatosis type 1 and piebaldism (1). In the mild form of piebaldism, the leukoderma might be very small and a white forelock may not be seen, and in certain patients these features can be absent due to incomplete penetrance (5).

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Piebaldism was associated with interstitial deletion of the long arm of chromosome 4 in 1974 (6). We report on two patients, a father and son, with piebaldism and the smallest 4q12 microdeletion reported to date.

CASE REPORT

IV-3 (DECIPHER 339372). The proband, a man, was the first of twins born *per vias naturales* at 38 weeks of gestation. His birth weight was 2200 g (<3rd centile), birth length was 51 cm (25th-50th centile), and his Apgar score was 9 at 1 minute and 9 at 5 minutes. Respiratory tract infections were common: the patient contracted bronchiolitis at the age of 1.5 months, which was treated with antibiotics. He was hospitalized for acute bronchiolitis at the age of 4 months, and again a few months later for acute obstructive bronchitis and otitis media. Molecular genetic testing for cystic fibrosis was negative. The patient's psychomotor and language development was slightly delayed; he started to lift his head at the age of 5-6 months and he could walk independently at the age of 16 months. On admission to hospital at the age of 1 year and 1 month, his head circumference was 48.5 cm (50th-75th centile), his weight was 12 kg (75th-90th centile), and his height was 80 cm (50th-75th centile). The phenotype was remarkable for a white forelock, white skin patches on the trunk (Figure 1, A), and cryptorchidism on the right side.

IV-1. The 7-year-old sister of the proband was the first child in the family. She was born from the first pregnancy at full term. Her birth weight was 3250 g (25th-50th centile), birth length was 53 cm (75th-95th centile), and her Apgar scores at 1 and 5 minutes were 10 and 10, respectively. Congenital heart defect was suspected the second day after birth. Cardiac ultrasound examination revealed coarctation of the aorta, a ventricular septal defect, and mild aortic valve stenosis. Surgical repair of the coarctation of the aorta and ventricular septal defect was performed at the age of 2 months. She now receives antihypertensive therapy. She has no signs of piebaldism and her early psychomotor development was normal.

III-2 (DECIPHER 339373). The 31-year-old father of the proband was healthy and had normal intelligence. Upon physical examination, his height was 178 cm and his weight was 125 kg. He had poliosis, and there were hypopigmented macules visible on his forehead, mid trunk, and knees.

III-1 (DECIPHER 339374). The mother of the proband, 33 years of age, had congenital heart disease. Surgery for coarctation of the aorta was performed at the age of 3 years.

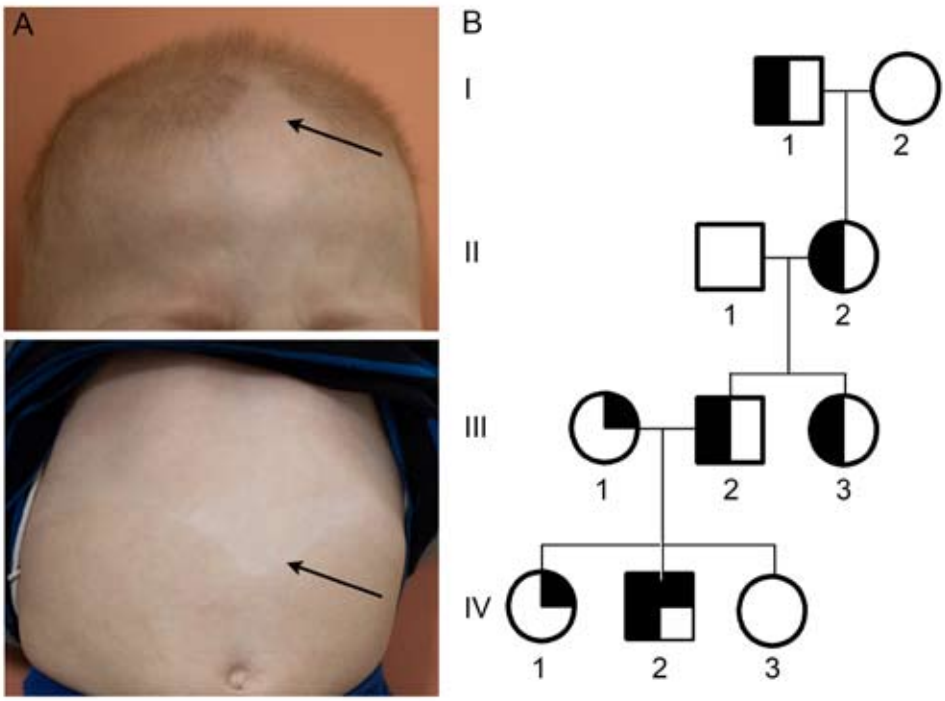

Figure 1. (A) The phenotype of the proband is remarkable due to a white forelock and white skin patches on the trunk (indicated by arrows). (B) The genealogy shows autosomal dominant inheritance of piebaldism (half black symbols). The black quarter denotes patients with congenital heart disease.

Genealogical analysis of the paternal lineage of the proband showed that the proband's aunt, grandmother, and great-grandfather also had the features of isolated piebaldism (Figure 1, B).

Whole-genome genotyping analysis of the proband using HumanCytoSNP-12v2.1 BeadChips (Illumina Inc., San Diego, CA, USA) revealed a 1.34-Mb microduplication of 1q21.1q21.2 and a 2.7-Mb microdeletion of 4q12 (arr[hg19] 1q21.1q21.2(146,476,526-147,820,342)×3,4q12(53,531,672-56,238,263)×1). Whole-genome genotyping analysis of the parents confirmed the paternal origin of the 4q12 microdeletion, while a 1q21.1q21.2 microduplication was detected in the mother (III:1) and sister (IV:1) of the proband (Figure 2). The study was approved by the Vilnius Regional Biomedical Research Ethics Committee. Informed consent for genetic investigations was obtained from the family.

DISCUSSION

Several reports of patients with piebaldism and deletions of the long arm of chromosome 4 suggest that the piebald trait locus may be located in band 4q12,(6-8), and a pathogenic variant in the *KIT* gene was reported as the cause of piebaldism in 1991 by Giebel and Spritz (9).

The *KIT* gene encodes the cell-surface receptor transmembrane tyrosine kinase c-Kit for the embryonic growth factor SCF (10). This protein is essential for the migration of melanoblasts from the neural crest in the embryonic stage of life and plays an overall important role in their proliferation and survival. It also contributes to processes such as pigmentation, reproduction, and hematopoiesis. The c-Kit receptor protein's main domains are five extracellular immunoglobulin-like domains and a tyrosine kinase domain, which is spilt into two halves, proximal and distal, by a kinase insert domain (11). The patient's phenotype strongly correlates with the site of the pathogenic variant within the *KIT* gene. The most significant variants are those that occur in the intracellular tyrosine kinase region. The variants located in the extracellular region and the complete deletion of the *KIT* gene from one chromatid are considered to be mild and are associated with a less serious form of piebaldism (1).

Interstitial deletions involving the *KIT* gene of chromosome 4q are rare. Only two of a reported 14 deletions within the 4q11-q31 region, both more than 20 Mb in size, have been detected by chromosomal microarray analysis (12,13). All others were visible cytogenetically and were therefore too large in size to allow precise genotype-phenotype correlations. The DECIPHER database also revealed one patient (278024) with an overlapping 4.24 Mb deletion involving the *KIT* gene, but the phenotype of this patient was not provided. The deletions reported were associated with short stature, minor facial anomalies, hypotonia, seizures, intellectual disability, and piebaldism (13). Interestingly, the patient reported by Hemati *et al*. (12) had no features of piebaldism, suggesting that not only the dosage effect of *KIT* plays the main role in the pathogenesis of piebaldism. The 2.7-Mb familial 4q12 deletion detected in our proband was the cause of piebaldism in the family. Although the proband has mild developmental delay, the intellect of his relatives with piebaldism was normal, and therefore we consider piebaldism an isolated feature associated with this chromosomal alteration in chromosome 4.

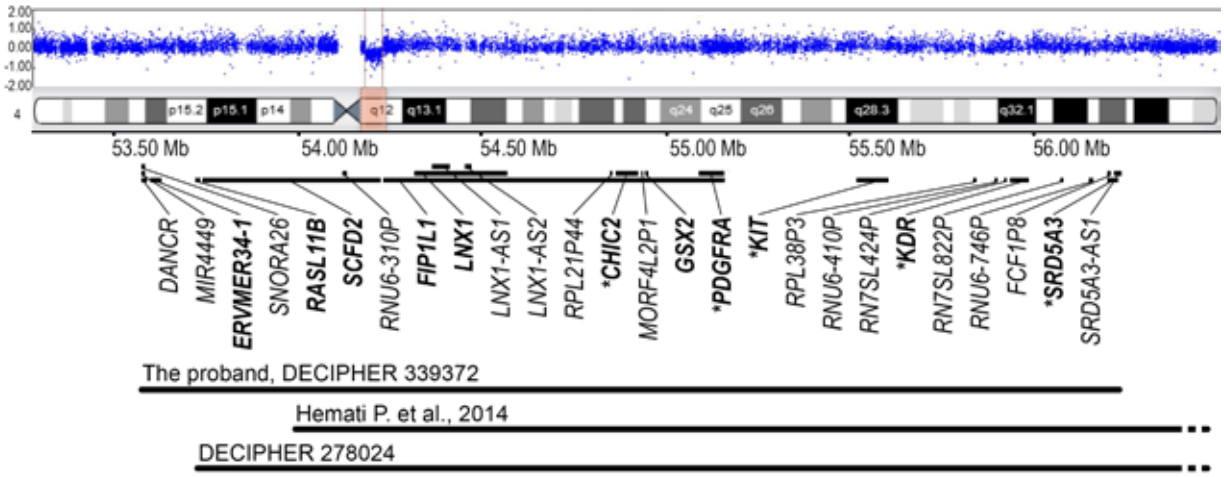

Figure 2. 2.7-Mb microdeletion 4q12(53,531,672-56,238,263)×1 detected by whole genome SNP-array analysis and schematic view of the genes involved in the deletion are presented in the top portion. Protein-coding genes are highlighted in bold, and asterisks indicate morbid genes. Horizontal lines in the lower part of the picture represent previously reported overlapping deletions.

The 4q12 deletion detected in our proband and his father encompasses 26 genes; 11 of them are protein coding genes: *CHIC2, ERVMER34-1, FIP1L1, GSX2, KDR, KIT, LNX1, PDGFRA, RASL11B, SCFD2,* and *SRD5A3*. Five of those (*CHIC2, KDR, KIT, PDGFRA,* and *SRD5A3*) are considered morbid. The low ranks of the *SRD5A3* gene haploinsufficiency score (HI 63.72%) indicate that the haploinsufficiency effect of this gene is not likely. While the HI score of the *CHIC2, KDR,* and *PDGFRA* genes were lower than 11%, affected individuals in the family did not show any clinical features associated with those genes.

Our proband also had a 1.34-Mb 1q21.2 duplication inherited from his mother. The same duplication was detected in the proband's sister, who along with their mother suffered from heart problems. Contrarily to them, the proband did not present any cardiac features considered to be associated with this duplication. It is possible that additional genetic or environmental factors are involved in the development of cardiac symptoms, because some individuals having 1q21.2 duplication do not show any apparent features of the condition (14).

CONCLUSION

The clinical and molecular findings in the proband and his affected relatives showed that the 2.7-Mb 4q12 microdeletion causes isolated piebaldism due to the loss of the *KIT* gene. This report provided additional evidence that the haploinsufficiency of the *KIT* gene is associated with piebaldism. Further studies are required for the elucidation of the dosage imbalance effect of other genes implicated in the rearrangement.

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