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Original article

Molecular characterization of piebaldism in a Tunisian family

Caractérisation moléculaire du piébaldisme chez une famille tunisienne

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ABSTRACT

Objective. – The present study is aimed at performing the molecular characterization of a Tunisian family with piebaldism.
Methods. – As the proband and her mother showed a severe phenotype, we first chose to screen exons 10, 11, 12, 13, 16, 17 and 18 of the *KIT* proto-oncogene by direct sequencing.
Results. – Direct sequencing analysis showed a C to T substitution at 1939 in exon 13 (c.1939C>T) in heterozygous state in the patient and his mother. The mutation was not found in their unaffected family members or normal controls.
Conclusion. – Our results provide additional support that mutations in the tyrosine kinase domain of the *KIT* gene are responsible for the severe form of piebaldism.

Mots clés :
Piébaldisme
Gène *KIT*
Domaine tyrosine kinase
Analyse mutationnelle

RÉSUMÉ

But de l'étude. – L'objectif de ce travail est de déterminer la (les) mutation(s) responsable(s) du piébaldisme chez une famille tunisienne.
Patients et méthodes. – La fille ainsi que sa mère montrent un phénotype sévère de piébaldime. Nous avons opté pour le séquençage direct des exons 10, 11, 12, 13, 16, 17 et 18 du gene *KIT*.
Résultats. – Le séquençage direct nous a permis d'identifier une substitution de C en T (c.1939 C>T) au niveau de l'exon 13 du gène *KIT* à l'état hétérozygote chez la patiente et sa mère. Cette mutation était absente chez les membres sains de la famille ainsi que chez les individus normaux.
Conclusion. – Nos résultats confirment que les mutations au niveau du domaine tyrosine kinase du gène *KIT* sont responsables de l'apparition du phénotype sévère du piébaldisme.

1. Introduction

Piebaldism (OMIM 172800) is a rare genetic disorder of melanocyte development. It is inherited in an autosomal dominant mode and is characterized by congenital leukoderma, principally affecting the frontal scalp, forehead, ventral trunk and extremities [1,2]. A white forelock of hair, often triangular in shape, may be the only manifestation in 80–90% of cases, or both the hair and the underlying forehead may be associated. The eyebrows and eyelashes may also be affected. Irregularly shaped white patches may be observed in the face, trunk and extremities mostly in a symmetrical distribution [3]. Some patients have *café-au-lait* spots or hyperpigmented spots in the depigmented skin area. The leukoderma is usually stable throughout life, although pigmented macules may develop at the margins and even within the white macules [2]. Three phenotypes are observed according to the depigmented patches: mild, moderate and severe. The mild type may only show white forelock or relatively smaller leukoderma on the ventral trunk and/or an extremity without a white forelock.

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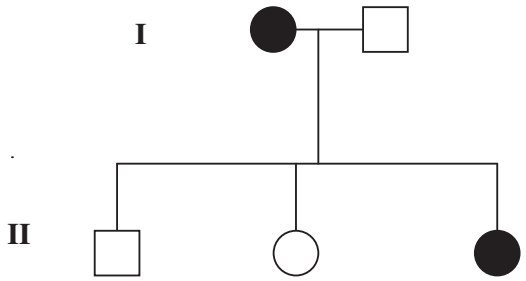

Fig. 1. Pedigree of family with piebaldism.

The severe form of piebaldism shows a typical white forelock on the frontal scalp and relatively large leukoderma on the chest, abdomen, arms and legs. The moderate phenotype is the intermediate type of these two forms [4,5].

Histologically, melanocytes are completely absent in the white spot area due to defective melanoblasts proliferation and/or migration from the neural crest during early embryonic development [5]. Because of its distinctive phenotype, the first descriptions of piebaldism date back to early Egyptian, Greek and Roman writings [3,5]. It was one of the first autosomal dominant genetic disorders recognized and was also one of the first genetic diseases for which a pedigree was presented. In fact, the disorder has been traced over hundreds of years in reported pedigrees [1,2].

Previous studies have reported that piebaldism is caused by mutations of the *KIT* proto-oncogene on chromosome 4q12 (also known as *c-kit* or *CD117* gene). The association of piebaldism with mutations in the *KIT* gene was first described by Giebel and Spritz in 1991 and many other studies have now provided further evidence of this association [1,2,6,7]. To date, more than 60 mutations of the *KIT* gene have been reported in human piebaldism including 32 missense mutations, 17 deletions, four insertions, seven nucleotide splice-site mutations, two nonsense mutations and one pericentric chromosomal inversion [4].

The *KIT* gene encodes a 145 kDa transmembrane receptor for the KIT ligand (KITL) also known as stem cell factor (SCF). The receptor KIT is a member of type III group of transmembrane receptor tyrosine kinase [2,8]. It is composed of an amino-terminal extracellular ligand-binding domain, a single transmembrane domain and a cytoplasmic region. Piebaldism clinical manifestations and phenotypic severity depend on the location of the causative mutations with those in the intracellular tyrosine kinase domain having a dominant-negative effect resulting in severe manifestations of the disease and those in the amino-terminal extracellular ligand-binding domain having a haplo-insufficiency effect and associated with the mildest forms of piebaldism [5,7].

The present study is aimed at performing the molecular characterization of a Tunisian family with piebaldism. This is the first molecular study of piebaldism in Tunisian families.

2. Subjects and methods

2.1. Case reports

A Tunisian family with piebaldism from the North of Tunisia was investigated for *KIT* mutation screening. The proband (II3; Fig. 1), a four-month-old girl, had a white forelock and leukoderma of the ventral trunk, arms, thighs, knees and legs. She had a multiple hyperpigmented spots (Fig. 2). Her mother was also affected with a white forelock and a large leukodermal patch on her abdomen, arms, thighs, knees and

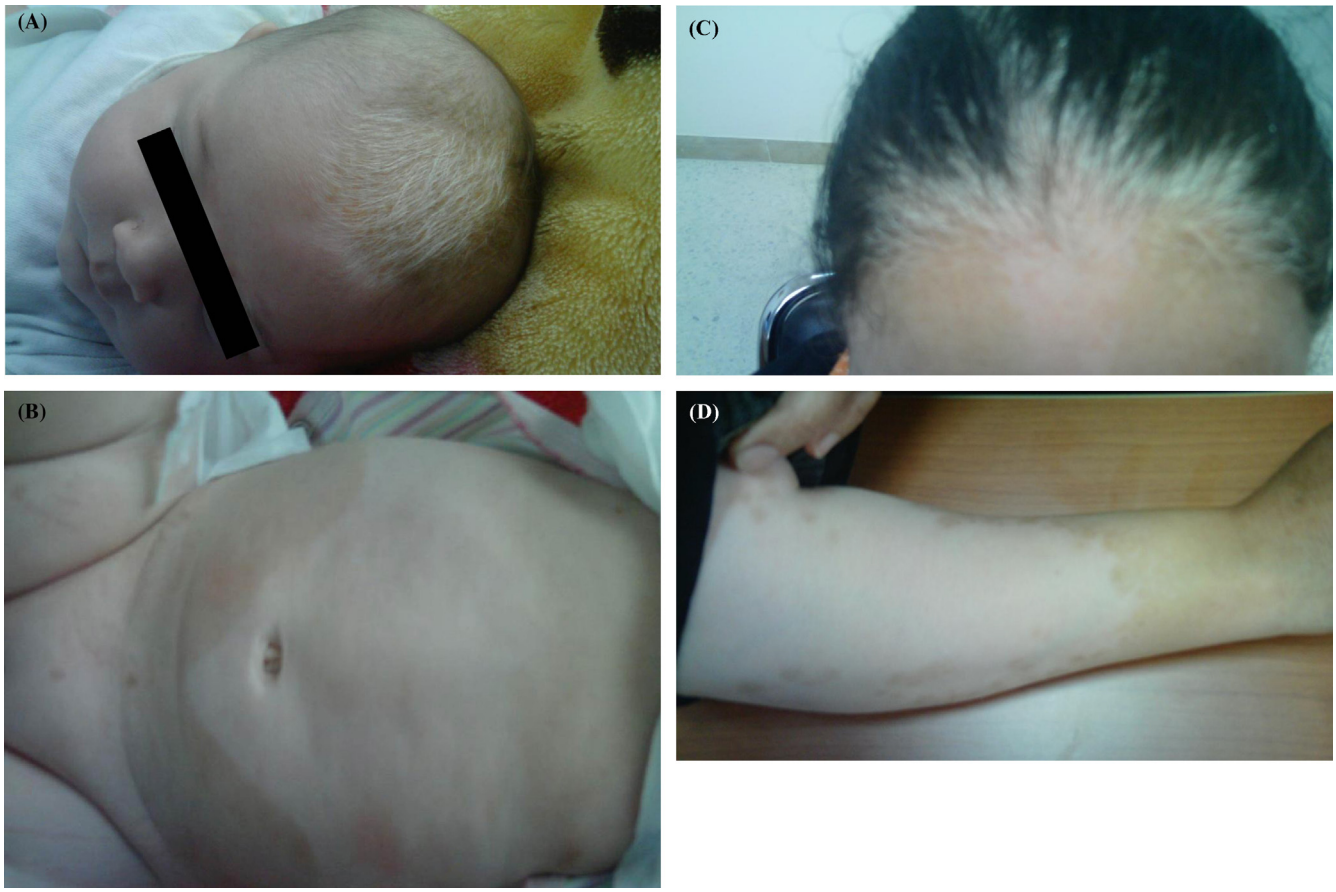

Fig. 2. Clinical features of patient (A, B) and of the mother (C, D) showing characteristic white forelock, poliosis and leucoderma with hyperpigmented areas in the depigmented patches.