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Original Article

Intragenic deletion mutation in the gene desmoglein 4 underlies autosomal recessive hypotrichosis in six consanguineous families

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ملخص

الأهداف: نقص الشعر الجسمي الموضعي المتنحي هو اضطراب فقدان الشعر البشري غير المتلازمة، التي تؤثر على فروة الرأس والحاجبين والرموش، وأجزاء أخرى من الجسم . ستة عوائل مصابين(بحيث كل عائلة فيما بينهم صلة قرابة) بهذا النوع من الاضطراب تساقط الشعر وقد تم التحقيق على المستويين السريرية والجزيئية.

الطريقة: تم اختبار الربط في ستة عوائل مع فرد مصاب واحد من كل عائلة بواسطة التنميط الجيني علامة الميكروستلايت مرتبطة بمواضع نقص الشعر الجسمية المتنحية بما في ذلك نقص الشعر الجسمي الموضعي المتنحي(LAH) ١،٢ و ٣. تم إجراء تحليل تسلسل مواقع الترميز واللصق كاملة من الجينDSG4 للبحث عن الطفرة المسببة للمرض.

النتيجة: ربط إنشاء التنميط الجيني في العوائل على الجين DSG4 في LAH1 الواقع على كروموسوم 18q21.1. الكشف عن تحليل تسلسل طفرة الحذف داخل الجين(EX5_8del)في الأفراد المصابين من كل العائلات الستة.

الخلاصة: تحديد الطفرات المتكررة في ست عائلات باكستانية إضافية يعزز من الأدلة على أن هذا هي طفرة الأجداد التي تنتشر على نطاق واسع بين مختلف الجماعات العرقية الباكستانية.

الكلمات المفتاحية: الجينات DSG4؛ داخل الجين طفرة الحذف؛ باكستان؛ طفرة المتكررة

Abstract

Objectives: Localized autosomal recessive hypotrichosis is a non-syndromic human hair loss disorder, affecting scalp, eyebrows and eyelashes, and other parts of the body. Six consanguineous families with this form of hair loss disorder were investigated at both the clinical and molecular levels.

Methods: Linkage in six families with twenty-one affected members was tested by genotyping microsatellite markers linked to autosomal recessive hypotrichosis loci including localized autosomal recessive hypotrichosis (LAH) 1, 2 and 3. Sequence analysis of the entire coding and splice sites of the gene *DSG4* was performed to search for the disease-causing mutation.

Results: Genotyping established linkage in families to the *DSG4* gene at LAH1 locus on chromosome 18q21.1. Sequence analysis detected an intragenic deletion mutation (Ex5_8 del) in affected members of all six families.

Conclusion: Identification of recurrent mutation in six additional Pakistani families strengthens the body of evidence that this is an ancestral mutation that is widespread among different Pakistani ethnic groups.

Keywords: *DSG4* gene; Intragenic deletion mutation; LAH; Pakistan; Recurrent mutation

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Introduction

Desmosomes are intracellular junctions that play important roles in cell-to-cell adhesion and signal development and differentiation in tissues that sustain mechanical stress, such as the heart, muscle and epidermis. These junctions contain three major protein groups: the desmosomal cadherins that comprise desmogleins (DSG1-4) and desmocollins (DSC1-3), the plakin family member desmoplakin (DSP), and arm (armadillo) proteins plakoglobin (PG) and plakophilins (PKP1-3).[1] Disruption of these junctions leads to a broad spectrum of inherited, infectious and auto-immune diseases. Pathogenic autosomal dominant and recessive mutations have been reported in ten different desmosomal genes, resulting in a spectrum of phenotypes that variably affect the skin, hair and heart. Out of these desmosomal proteins, the functional absence of desmoglein 4 (DSG4), usually expressed in the hair shaft cortex, leads to localized autosomal recessive hypotrichosis (LAH1) in humans and the lanceolate hair phenotype in rodents (lah).[1–3]

Localized autosomal recessive hypotrichosis is a non-syndromic human alopecia affecting scalp, eyebrows and eyelashes, trunk, arms and legs. In males, moustache and beard hair are either sparse or not affected. In addition, a few patients reported developing hyperkeratotic follicular papules, erythema, and pruritus in affected areas.[2,4] Three

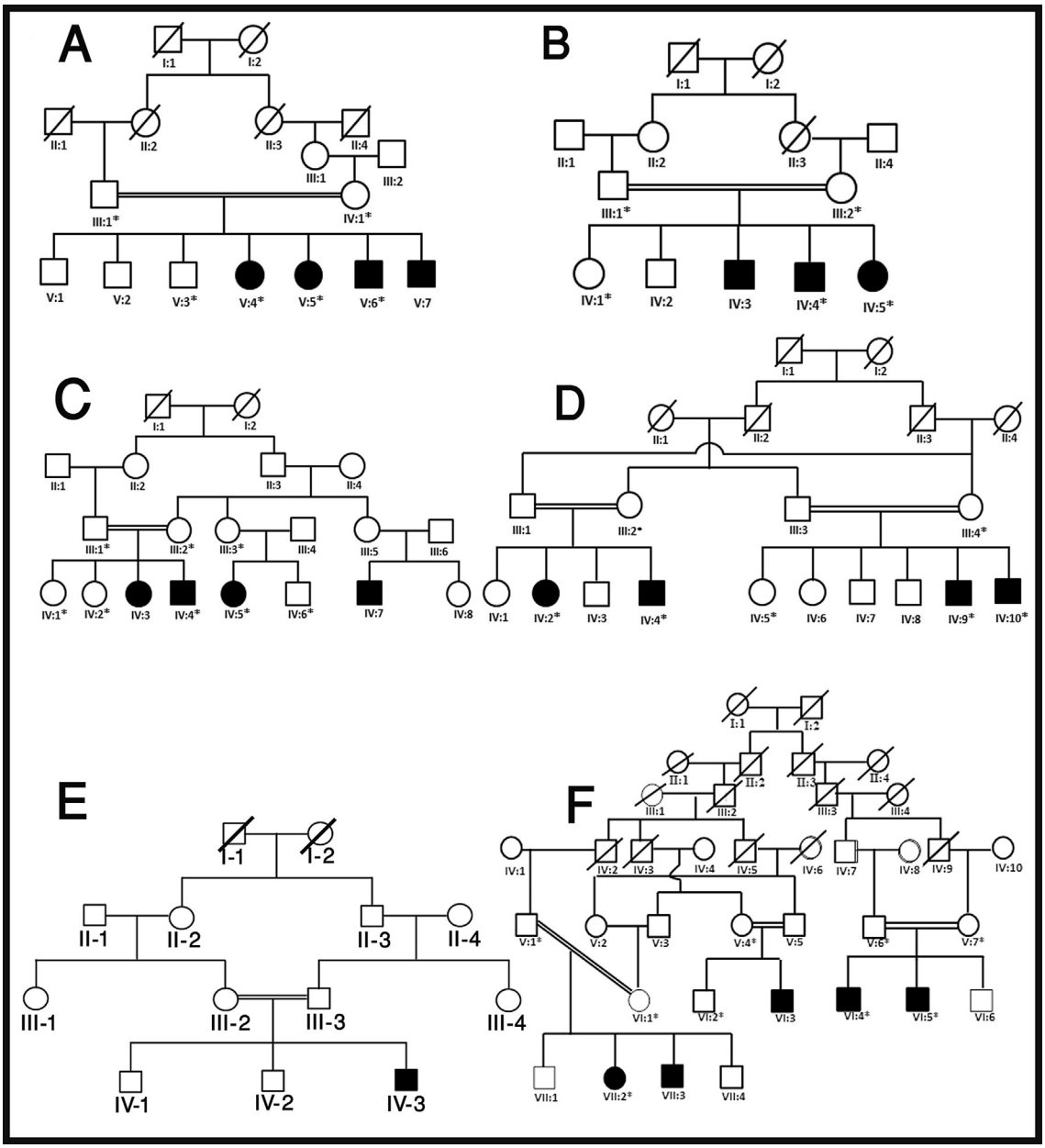

Figure 1: Pedigree drawing of the six families (A, B, C, D, E, F) segregating autosomal recessive localized hypotrichosis. Affected males and females are indicated by filled squares and circles, respectively. Crossed symbols indicate deceased individuals. Double lines between individuals represent consanguineous unions. The individual numbers labelled with asterisks indicate the samples available for this study.

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