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# Report

## A Gene for Hypotrichosis Simplex of the Scalp Maps to Chromosome 6p21.3

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**Hypotrichosis simplex of the scalp (HSS) is an autosomal dominant form of isolated alopecia causing almost complete loss of scalp hair, with onset in childhood. After exclusion of candidate regions previously associated with hair-loss disorders, we performed a genomewide linkage analysis in two Danish families and localized the gene to chromosome 6p21.3. This was confirmed in a Spanish family, with a total LOD score of 11.97 for marker D6S1701 in all families. The combined haplotype data identify a critical interval of 14.9 cM between markers D6S276 and D6S1607. Localization of the locus for HSS to 6p21.3 is a first step toward identification of the gene. The gene will give important insights into the molecular and cellular basis of hair growth on the scalp.**

Hypotrichosis simplex (MIM 146520) is a rare, autosomal dominant form of nonsyndromic alopecia. A generalized form affecting all body hair can be clinically distinguished from a scalp-limited form. Hypotrichosis simplex of the scalp (HSS) was first described by Toribio and Quiñones (1974), with several subsequent reports (Kohn and Metzker 1987; Hess and Uno 1991; Ibsen et al. 1991; Piraccini et al. 1993; Rodríguez Díaz et al. 1995). Usually, patients with the scalp-limited form present with normal hair at birth and in the first years of life. They experience a progressive, gradual loss of scalp hair, beginning at the middle of the 1st decade and leading to almost complete loss of scalp hair by the 3d decade. A few sparse, fine, short hairs can remain in some individuals. The body hair, beard, eyebrows, axillary hair, teeth, and nails are normally developed. Men and women are equally affected.

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Light and electron microscopy of hairs from early hypotrichosis has revealed no structural changes, whereas hairs from patients with advanced hypotrichosis have shown focal areas of defective cuticular structure (Toribio and Quiñones 1974; Kohn and Metzker 1987). The number of hair follicles may be either normal (Toribio and Quiñones 1974) or reduced (Hess and Uno 1991; Ibsen et al. 1991). Usually, no scarring or inflammatory changes are present. To date, no studies of the molecular basis of hypotrichosis simplex are available.

Here, we describe the localization of the first hypotrichosis simplex locus and provide evidence that HSS maps to the 6p21.3 region in two Danish families and one Spanish family.

After informed consent was obtained, we collected blood samples from 62 individuals, 27 of whom were affected. DNA was prepared according to standard methods. The pedigree structure of those individuals participating in this study is shown in figure 1. Detailed clinical data on the Danish five-generation family (family 1) have been presented elsewhere (Ibsen et al. 1991). Affected members of the smaller Danish family (family 2) showed similar clinical manifestations. The Spanish family (family 3) descends from a large eight-generation

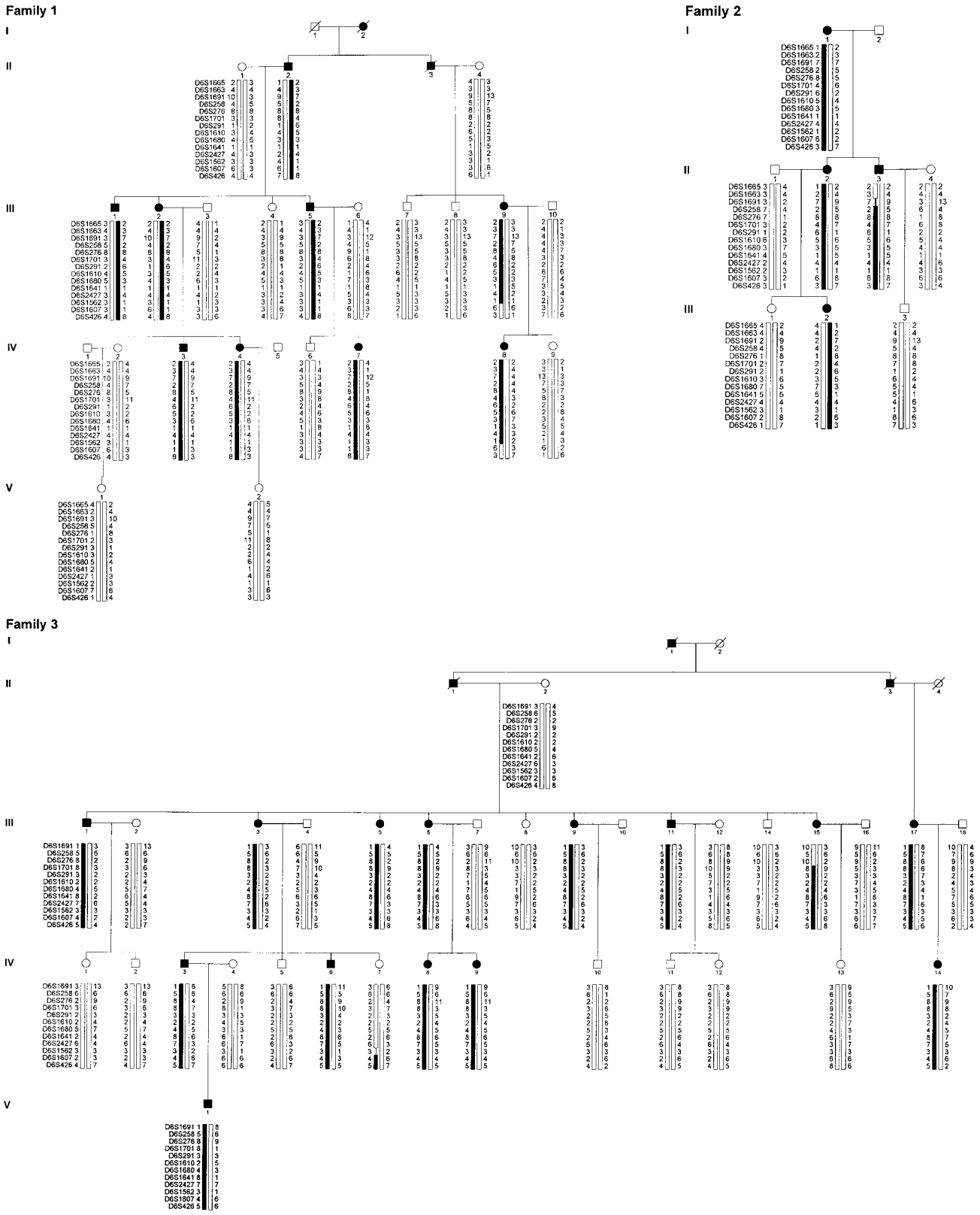


**Figure 1** Pedigrees of three families with HSS, showing segregating haplotypes for chromosome 6 markers and critical recombinations. Squares and circles denote males and females, respectively; blackened symbols denote affected individuals; and unblackened symbols denote unaffected individuals. Blackened bars denote segregating chromosomal segments and show regions of crossover, and vertical lines denote noninformative regions adjacent to critical recombination events.

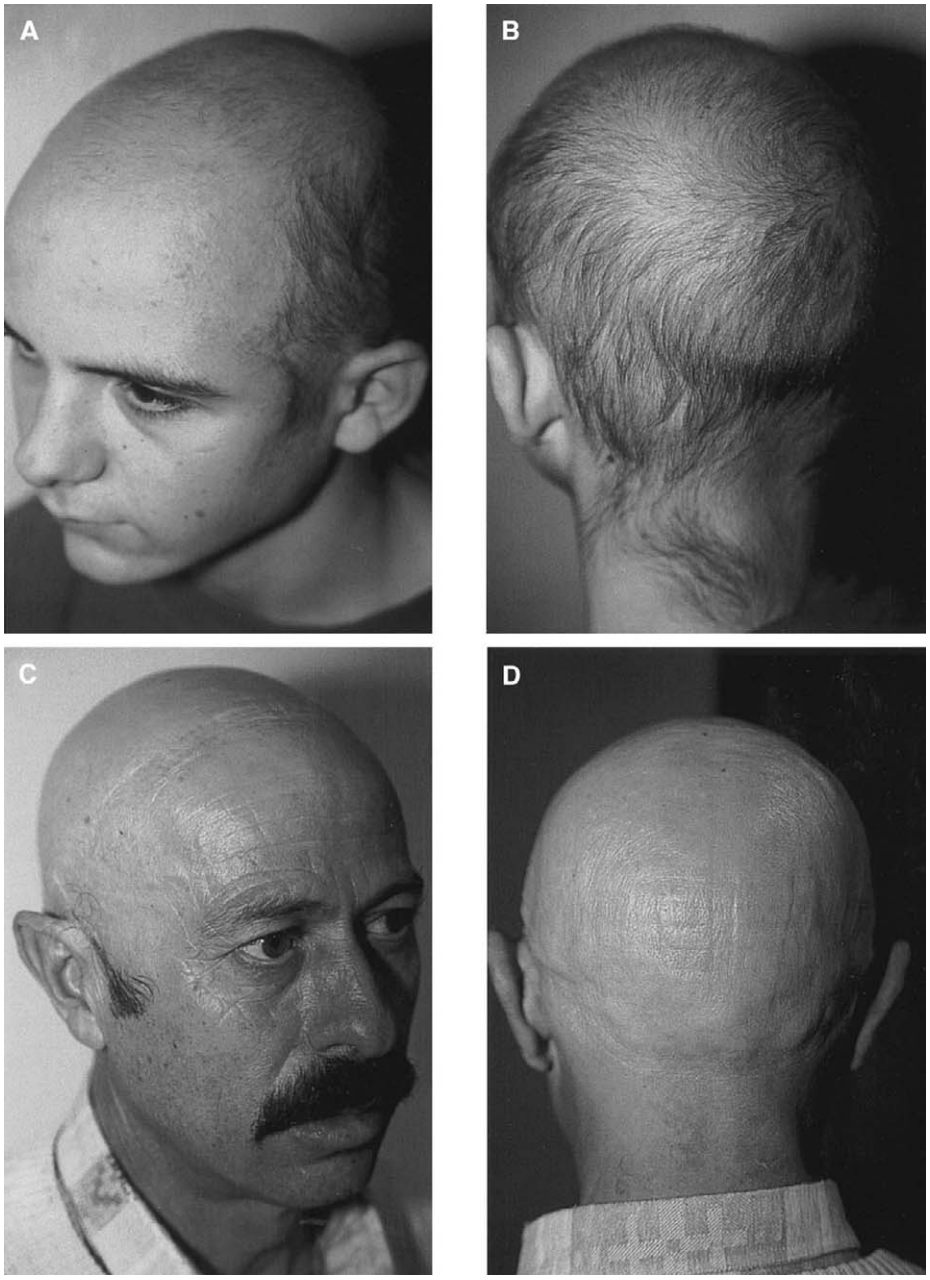


**Figure 2** Clinical appearance of HSS in affected individuals V-1 (*A* and *B*), age 17 years, and III-11 (*C* and *D*), age 48 years. Both individuals are from family 3 and show the characteristic pattern of hair loss. Note the unaffected beard, eyebrows, and eyelashes.

family originally reported by Toribio and Quiñones (1974), who gave detailed clinical information. All affected persons from the three families had normal hair at birth. At age 5–17 years, a retardation of hair growth of the scalp, combined with a diffuse hair loss, was observed, progressing to almost complete alopecia by the 3d decade, as illustrated in figure 2. There were no other abnormalities, and men and women were equally affected. All pedigrees clearly demonstrate an autosomal dominant mode of inheritance with full penetrance.

Families 1 and 2 were used for the initial exclusion of candidate loci and the subsequent genomewide linkage analysis. Candidate loci included the *hairless* gene on 8p21-p22 (Ahmad et al. 1998; Cichon et al. 1998), the *winged-helix-nude* gene on 17q11.2 (Frank et al. 1999), and the *keratin* gene clusters on 17q12-q21 and

**Table 1**

**Two-Point LOD Scores, between the Disease Locus and 14 Chromosome 6 Microsatellite Markers**

| Marker | Genetic-Map Location[a] (cM) | LOD Score at $\theta$ = .00 | .01 | .05 | .10 | .20 | Maximum $\theta$ | $Z_{max}$ |
|---|---|---|---|---|---|---|---|---|
| D6S1665 | 36.4 | −1.88 | 1.37 | 1.83 | 1.85 | 1.57 | .077 | 1.87 |
| D6S1663 | 40.1 | 0 | 3.22 | 3.59 | 3.46 | 2.84 | .051 | 3.59 |
| D6S1691 | 42.3 | −∞ | 9.20 | 9.19 | 8.56 | 6.84 | .025 | 9.34 |
| D6S276 | 44.4 | −∞ | 6.22 | 6.37 | 5.96 | 4.73 | .031 | 6.43 |
| D6S258 | 44.4 | 8.93 | 8.76 | 8.05 | 7.14 | 5.21 | 0 | 8.93 |
| D6S1701 | 47.7 | 11.97 | 11.78 | 11.00 | 9.98 | 7.78 | 0 | 11.97 |
| D6S291 | 49.5 | 8.61 | 8.47 | 7.91 | 7.18 | 5.61 | 0 | 8.61 |
| D6S1610 | 53.8 | 8.02 | 7.89 | 7.34 | 6.63 | 5.10 | 0 | 8.02 |
| D6S1680 | 53.8 | 8.91 | 8.76 | 8.14 | 7.33 | 5.62 | 0 | 8.91 |
| D6S1641 | 53.8 | 7.99 | 7.87 | 7.36 | 6.69 | 5.27 | 0 | 8.00 |
| D6S2427 | 53.8 | 6.79 | 6.68 | 6.25 | 5.68 | 4.45 | 0 | 6.79 |
| D6S1562 | 58.0 | 3.73 | 3.67 | 3.39 | 3.04 | 2.29 | 0 | 3.73 |
| D6S1607 | 59.3 | −∞ | 6.57 | 7.25 | 6.92 | 5.58 | .048 | 7.25 |
| D6S426 | 60.4 | −∞ | 5.13 | 5.94 | 5.79 | 4.75 | .059 | 5.95 |

[a] Measured from 6pter and taken from the Center for Medical Genetics, Marshfield Medical Research Foundation sex-averaged linkage map (Broman et al. 1998).

12q13 (Winter et al. 1997). Negative LOD scores were obtained for all these loci (data not shown).

Subsequently, a genomewide linkage scan using highly polymorphic microsatellite markers was performed on DNA from families 1 and 2. Two-point LOD scores were calculated between each marker locus and hypotrichosis, under the assumption of autosomal dominant inheritance with complete penetrance, a frequency of $10^{-5}$ for the disease allele, and equal allele frequencies for each marker, using the LINKAGE version 5.21 software (Lathrop et al. 1984). After performing linkage analysis for 54 markers, we found evidence for linkage to the marker D6S291, with a LOD score of 5.61 at recombination fraction ($\theta$) 0. We tested 13 additional markers, located around D6S291, for fine mapping and could confirm linkage to this region. The highest two-point LOD score obtained was 5.65 at $\theta = 0$ from D6S1701. A common haplotype spanning a 19.2-cM region between markers D6S1663 and D6S1607 segregated in all affected members (fig. 1). The telomeric boundary of this interval was defined by a recombination between markers D6S1663 and D6S258 in patient II-3 from family 2. This limit could not be defined more precisely, since the affected mother (individual I-1) was homozygous for marker D6S1691. The centromeric boundary of this interval corresponded to an inferred recombination between markers D6S1562 and D6S1607, which was observed in individual III-9 from family 1 and which probably occurred in her paternal grandmother. Interestingly, both families showed a common disease-associated haplotype, suggesting the existence of a common ancestor. This is supported by the fact that both families originate from the same geographic region of Denmark (Island of Fuen).

Once linkage to the short arm of chromosome 6 was established in the Danish families, individuals in the Spanish family (family 3) were typed for the same markers. The highest two-point LOD score, 6.32 ($\theta = 0$), was observed with markers D6S1641 and D6S1701. Combined LOD scores for all three families are given in table 1. One additional recombination event, in patient III-15, allowed us to narrow the region to a 14.9-cM interval between markers D6S276 and D6S1607. The results of the present study have identified the first locus for HSS, on chromosome 6p21.3. All three families showed linkage to this region; so, on the basis of this small series, there is no evidence for genetic heterogeneity.

A search for candidate genes in this region identified a large number of expressed-sequence tags, most with unknown function, and numerous cloned genes (GeneMap'99). However, on the basis of available functional information for these genes, there is no clear candidate gene for HSS. A gene encoding a tumor-necrosis factor (TNF), located between markers D6S276 and D6S1701, could be envisaged as a candidate gene for the disease. It recently has been shown that a novel member of the TNF-receptor family is involved in inductive specification of hair-follicle fate (Headon and Overbeek 1999). It is notable, however, that other members of the TNF receptor family are primarily involved in maintenance of homeostasis and immune regulation (Gruss and Dower 1995), rather than cell-fate specification during development. Part of the recently sequenced human

MHC (MHC Sequencing Consortium 1999) is localized in the mapped region. Interestingly, the MHC is involved in the development of alopecia areata, a multifactorial hair-loss disorder with a strong autoimmune component (Colombe et al. 1999; de Andrade et al. 1999). However, there is no evidence from clinical or histological studies that the gene for HSS is involved in processes regulated by the autoimmune system. Therefore, it seems rather unlikely that the same gene contributes to these distinct disorders.

Relatively little is known about the processes at the molecular level that control hair growth. Investigation of genetic conditions in individuals with isolated alopecia offers the unique possibility to identify factors that are not only necessary but also specific for hair growth. HSS, with no involvement of body hair, eyebrows, and eyelashes, may be particularly important for our understanding of the genetic, molecular, and cellular pathways that regulate growth of scalp hair. Interestingly, the histological picture of scalp biopsies from patients with HSS has many features of androgenetic alopecia, such as miniaturized follicles of the vellus type and absence of scarring (Ibsen et al. 1991). Ultimately, the identification of the mutated gene could illuminate our understanding of common androgenetic alopecia.

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## Electronic-Database Information

Accession number and URLs for data in this article are as follows:

Center for Medical Genetics, Marshfield Medical Research Foundation, http://www.marshmed.org/genetics/

GeneMap'99, http://www.ncbi.nlm.nih.gov/genemap99/

Online Mendelian Inheritance in Man (OMIM), http://www.ncbi.nlm.nih.gov/Omim/ (for hypotrichosis simplex [MIM 146520])

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