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Netherton Syndrome is Not Linked to 18q12, a Region Homologous to the Murine Lanceolate Hair (*lah*) Locus

To the Editor:

Netherton syndrome (NTS), an autosomal recessive congenital ichthyosis, is defined by a triad of clinical symptoms: (i) generalized erythrodermic ichthyosis or ichthyosis linearis circumflexa; (ii) hair shaft abnormalities, including trichorrhexis invaginata; and (iii) immunologic abnormalities such as atopic diathesis, markedly elevated IgE levels and recurrent infections (Comèl, 1949; Netherton, 1958). The disorder may be associated with severe electrolyte imbalance, inability to regulate body temperature, immunodeficiency, and failure to thrive, which can be life-threatening in the neonatal period (De Wolf *et al*, 1996); however, the disease usually stabilizes over time. Ichthyosis linearis circumpscripta and hair abnormalities may develop at any time during childhood (Smith *et al*, 1995), making the diagnosis of NTS sometimes challenging.

The pathogenesis of this intriguing disorder remains elusive. Ultrastructural studies revealed distinctive findings in skin biopsies from Netherton patients, including premature secretion of lamellar body contents and impaired maturation of lamellar membrane structures (Fartasch *et al*, 1999). Trichorrhexis invaginata has been suggested to result from focal softening of the hair shafts due to reduced cysteine to cystine conversion and hence diminished cross-linking of hair keratins during hair shaft formation (Ito *et al*, 1984).

Recently, a novel mouse mutant termed Lanceolate Hair (*lah*) has been described (Montagutelli *et al*, 1996). The *lah* mutant is characterized by thin skin covered with fine scales, and sparse, irregular, and short hair, which resemble lance heads on microscopic examination. The abnormally formed hair shafts are considered to result from the accumulation of abnormal keratin filaments. Histologic examination of the mouse skin revealed epidermal and follicular hyperplasia around anagen follicles and a mild mononuclear infiltrate in the dermis. Based on the coexistence of ichthyosis and hair shaft abnormalities in both NTS and *lah* mice, the lanceolate mouse was proposed to represent an animal model for NTS (Montagutelli *et al*, 1996). The *lah* mutation was found to map to the centromeric end of murine 18q, a region with homology and conserved synteny to human 18q12 (Montagutelli *et al*, 1996). As this region is known to include the genes encoding several proteins involved in the formation of the desmosomal plaques, Fartasch *et al* (1999) speculated that aberrant interactions between desmosomal proteins and keratins may underlie the pathogenesis of NTS.

To test this hypothesis, we analysed five families with 11 affected individuals for linkage of NTS to the candidate region at 18q12. Three families had multiple affected siblings whereas two families had one affected individual and several unaffected siblings (**Fig 1**). All families were seemingly unrelated to each other and there was no evidence of consanguinity in any family. The diagnosis of NTS was based on results of clinical examination, microscopic analysis of

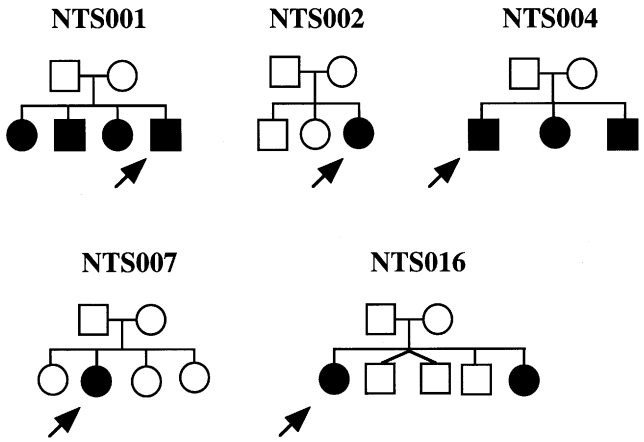

Figure 1. Pedigrees of the families included in this study.

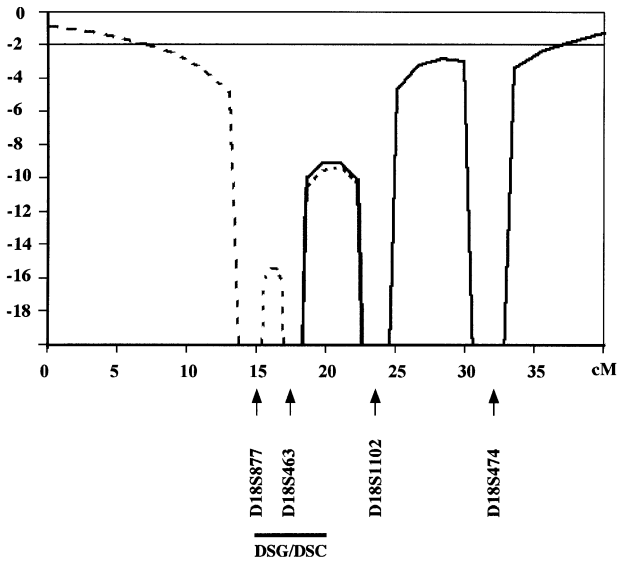

Figure 2. No linkage of Netherton syndrome to chromosome 18q12 harboring the human homolog of murine *lah*. Two overlapping multipoint linkage maps (map 1, gray; map 2, black) show lod scores less than –2 across an 30-cM region excluding NTS from the entire area. DSG, genes encoding desmoglein-1, –2, and –3; DSC, genes encoding desmocollin-2, –3.

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skin biopsies and hairs, and serum IgE levels. We performed automated genotyping of all individuals to analyse 6 di- and tetranucleotide repeats (D18S478, D18S877, D18S463, D18S56, D18S1102, and D18S474) distributed over a region of approximately 20 cM on 18q12. The microsatellite markers were polymerase chain reaction-amplified from buccal cell samples (Richards *et al*, 1993) using fluorescently labeled and tailed primers, and AmpliTaq Gold (PE Biosystems, Foster City, CA) according to the manufacturer's instructions. The polymerase chain reaction products were analysed on an ABI Prism 377 sequencer using the GeneScan 3.1 and GenoTyper 2.0 software. Pairwise and multipoint linkage analyses between markers and the disease locus were performed using the LINKAGE package (Lathrop *et al*, 1984). NTS was modeled as a recessive disorder with a disease allele frequency of 0.0001. Allele frequencies of the tested marker loci were either derived from the Genome Database or established from a series of unaffected Caucasian controls. Multipoint lod scores were computed in two overlapping subsets of three markers at a time based on the marker map D18S877–2.4 cM-D18S463–6.2 cM-D18S1102–8 cM-D18S474 (Marshfield Chromosome 18 sex-averaged linkage map).

We observed obligate recombinations between the NTS locus and each of the six marker loci tested. Our two-point linkage analysis yielded strongly negative lod scores between –2.83 and –6.99 at 0.01 recombination distance for each marker, giving odds greater than 100:1 to almost 10,000,000:1 against linkage. Multipoint lod scores less than –2 across the entire region between D18S877 and D18S474, completely excluded NTS from about 30 cM in 18q12 harboring the desmosomal gene cluster and presumably the homolog of murine *lah* (**Fig 2**).

In addition to the lack of immunologic aberrations in the *lah* mutant and the poor resemblance between lanceolate hairs and trichorrhexis invaginata, our results strongly suggest that the *lah* mutant does not represent a model for Netherton syndrome. A genome-wide marker screen will likely be the most suitable approach to identify the chromosomal location and nature of the NTS gene.

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