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Localization of the Netherton Syndrome Gene to Chromosome 5q32, by Linkage Analysis and Homozygosity Mapping

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Netherton syndrome (NS [MIM 256500]) is a rare and severe autosomal recessive disorder characterized by congenital ichthyosis, a specific hair-shaft defect (trichorrhexis invaginata), and atopic manifestations. Infants with this syndrome often fail to thrive; life-threatening complications result in high postnatal mortality. We report the assignment of the NS gene to chromosome 5q32, by linkage analysis and homozygosity mapping in 20 families affected with NS. Significant evidence for linkage (maximum multipoint LOD score 10.11) between markers D5S2017 and D5S413 was obtained, with no evidence for locus heterogeneity. Analysis of critical recombinants mapped the NS locus between markers D5S463 and D5S2013, within an <3.5-cM genetic interval. The NS locus is telomeric to the cytokine gene cluster in 5q31. The five known genes encoding casein kinase Iα, the α subunit of retinal rod cGMP phosphodiesterase, the regulator of mitotic-spindle assembly, adrenergic receptor β2, and the diastrophic dysplasia sulfate–transporter gene, as well as the 38 expressed-sequence tags mapped within the critical region, are not obvious candidates. Our study is the first step toward the positional cloning of the NS gene. This finding promises a better understanding of the molecular mechanisms that control epidermal differentiation and immunity.

Introduction

Netherton syndrome (NS [MIM 256500]) is a rare autosomal recessive disease characterized by congenital ichthyosis, a specific hair-shaft defect (trichorrhexis invaginata), and atopic manifestations (Comèl 1949; Netherton 1958; Traupe 1989). At birth, infants exhibit generalized erythroderma and scaling, which may persist into childhood or may change to ichthyosis linearis circumflexa, consisting of migratory erythematous and scaling plaques with a double-edged scale (Comèl 1949; Altman and Stroud 1969; Hausser and Anton-Lamprecht 1996). Scalp hair is sparse and brittle, and examination by microscopy indicates that the hair has nodes (trichorrhexis invaginata, or "bamboo hair") resulting from the invagination of the distal part of the hair shaft to its proximal part. Expression of trichorrhexis invaginata is delayed and may be variable (Stevanovic 1969). As a result, diagnosis of NS in early childhood is difficult, and the first tentative diagnoses may mistake NS for other congenital ichthyosiform erythrodermas. Atopic manifestations are present in most instances of NS, including eczematous-like rashes, asthma, angioedema, hay fever, urticaria, high immunoglobulin E (IgE) levels in the serum, and hypereosinophilia, all nonspecific features (Judge et al. 1994; Smith et al. 1995; Rudikoff and Lebwohl 1998).

Failure to thrive in infancy is frequent; the prognosis is poor, because infants experience hypernatremic dehydration and recurrent infections. A number of associated findings have also been reported, including severe enteropathy with villous atrophy, renal failure, aminoaciduria, and growth retardation (Jones et al. 1986; Judge et al. 1994).

The primary cause of the disorder remains unknown. Thus far, no cytogenetic abnormalities have been described in patients with NS. Histological and ultrastructural studies of skin sections in patients with NS have indicated incomplete keratinization of the epidermis

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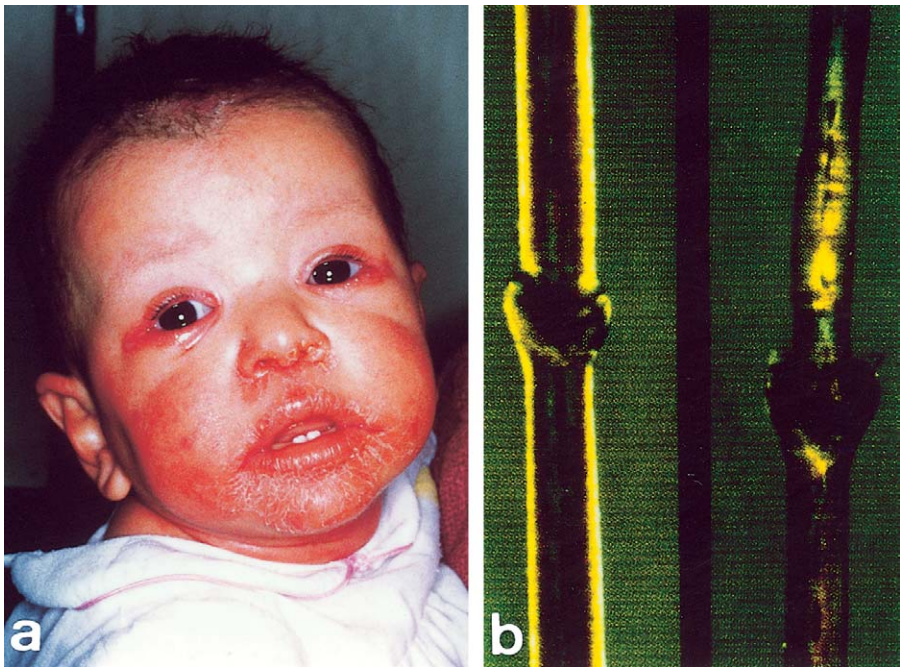

Figure 1 *A*, Child with NS, showing redness and peeling of skin, especially around the mouth and the eyes, and sparse and fragile hair. *B*, Light-microscopic aspect of scalp hair with trichorrhexis invaginata.

(Hausser and Anton-Lamprecht 1996) and have suggested as possible candidate loci the epidermal-differentiation complex on chromosome 1q21 (Mischke et al. 1996) and the transglutaminase 3 gene on chromosome 20p13 (Kim et al. 1994). Three chromosomal regions that have been associated with atopy, high IgE levels, or hypereosinophilia also have appeared as possible candidate regions: 5q31, which includes the cytokine-gene cluster (Marsh et al. 1994; Meyers et al. 1994; Mansur et al. 1998); 11q13, which comprises the gene encoding the β subunit of the high-affinity IgE receptor (Cox et al. 1998); and 16p12, which includes the gene for the interleukin-4 receptor (Hershey et al. 1997). Last, the lanceolate hair (*lah*) mutant mouse, which develops ichthyosiform dermatitis with hair-structural defects, has been proposed as an animal model of NS (Montagutelli et al. 1996). The *lah* mutation is recessive and maps to proximal chromosome 18, which is syntenic to human 18q12 and which thus has been suggested as a possible candidate region (Montagutelli et al. 1996).

Families and Methods

Families

Twenty families comprising 26 individuals affected with NS and 58 unaffected relatives were studied. Affected individuals ranged in age from newborn to 30 years at the time of the study. One family (family 1) had three affected siblings; four other kindreds had two affected children each. The other families had only one affected living offspring each. Parents were known to be first cousins in nine families (families 2, 4, 5, 8–12, and 19). In families 6 and 7, fathers were half-brothers and mothers were first cousins. Six families originated from western Europe, five from Pakistan, three from Turkey, three from Morocco, two from Japan, and one from Algeria. In all patients, trichorrhexis invaginata was assessed by microscopic examination of hair.

All patients exhibited typical features of NS (fig. 1), including scaly erythroderma at birth or soon after, sparse and short hair showing trichorrhexis invaginata, and allergic manifestations with elevated IgE serum concentrations. No other consistent immunological abnormality was found. In infancy, some patients developed ichthyosis linearis circumflexa. Failure to thrive was profound, and most patients with NS developed severe systemic infections during the neonatal period. In some patients, the clinical course was complicated by hypernatremic dehydration. One infant from family 19 died at age 2 mo, because of septic shock. The oldest child of family 6 died at age 10 mo, because of a severe chest infection and unexplained metabolic acidosis.

Ethical approval for the study was obtained from the respective ethics committees. After patients gave informed consent, peripheral-blood samples or mouth

swabs were collected so that DNA could be isolated. Genomic DNA from CEPH individual 1347-02 was used as a control for the genotyping.

Genotyping

We performed a genomewide search for linkage with the ABI PRISM Linkage Mapping Set of microsatellite markers, version 2 (PE Biosystems). To refine the region of linkage, additional markers were chosen from the Généthon map, from the physical map of the diastrophic dysplasia (DTD) gene locus (markers BT1 and CSFR1 [GenBank Overview]; Hästbacka et al. 1994), and from a report describing a dinucleotide repeat in the interleukin-9 gene (marker IL9 [Genome Database]; Polymeropoulos et al. 1991). All labels were either 6 FAM-, HEX-, TET-, or NED-5′-end labels.

All PCR reactions were carried out with 25 ng of genomic DNA as a template in a mixture of 1 × PE Biosystems PCR buffer, 2.5 mM $MgCl_2$, 200 nM of each dNTP, 5 pmol of each primer, and 0.1 μl of *Taq*Gold polymerase (PE Biosystems), in a final volume of 15 μl. The thermocycling conditions were 95°C for 16 min, followed by 30 cycles at 94°C for 5 s, 56°C for 40 s, and 72°C for 5 s, followed by a final extension step at 72°C for 5 min. PCR products were pooled with regard to their size range and labeling and were divided into fractions by denaturing electrophoresis on an ABI 373XL DNA sequencer (Applied Biosystems). All amplimers were scored with respect to the CEPH control genotype 1347-02, by means of GENOTYPER 2.1 software (Applied Biosystems).

Statistical Analysis

Data were simulated by the program SLINK (Weeks et al. 1990), to determine the power to detect linkage to a rare autosomal recessive locus, in the eight families used in the initial genome scan. Inbreeding loops were broken for the calculation of pairwise LOD scores. The power to obtain significant evidence for linkage (maximum LOD score [Z_{max}] >3) when the recombination value (θ) between the marker tested and the disease locus was assumed to be .05 or .00 was 72% and 100%, respectively. Z_{max} values were calculated by the ILINK routine of the FASTLINK program (Cottingham et al. 1993); we assumed an autosomal recessive mode of inheritance, with complete penetrance and a disease-allele frequency of .0001. Multipoint homozygosity mapping was carried out by the HOMOZ program (Kruglyak et al. 1995). Map order and genetic distances between markers were determined on the basis of the Généthon human linkage map (Dib et al. 1996) and the published physical map of the DTD locus (Hästbacka et al. 1994). Marker-allele frequencies were estimated on the basis of data on the noninbred founders.

Haplotype Analysis

Automated haplotype construction was carried out by the program SIMWALK (Sobel and Lange 1996). The most likely haplotype configuration for each pedigree was used for the recombinant-haplotype mapping.

Radiation-Hybrid Mapping

Markers D5S463, D5S2099, D5S2013, and BT1 were mapped by screening the Genebridge 4 radiation-hybrid panel (Research Genetics); we used the radiation-hybrid–mapper program of the Whitehead Institute for Biomedical Research/MIT Center for Genome Research. Data vectors were as follows: D5S463, 0000011100010000001010101110101001011000000101100110000012010101022000020001100021010110010101; D5S2099, 0000010100000010001010111110102001012000000201100010000010000000100000000000000000000001100010000; D5S2013, 0020012100211010001000001101102001011100010101100110000010010001002000000000101; and BT1, 000001110002101000100000110010100101110001010110011000001001000200000000000100000001110011001.

Results

Exclusion of Candidate Chromosomal Regions and Initial Assignment of the NS Gene to 5q32

We first tested linkage to six possible candidate chromosomal regions by using markers D1S252, D1S498 and D1S484 (1q21), D20S117 (20p13), D5S471 and D5S2115 (5q31), D11S987 and D11S1314 (11q13), D16S3046 (16p12), and D18S478 and D18S1102 (18q12). Pairwise linkage analysis showed no evidence for linkage with any of these markers, in an initial set of eight families (families 1–8).

We therefore undertook a genomewide search for linkage in this set of families. We found preliminary evidence for linkage with marker D5S436 (Z_{max} = 3.50 at θ = .052) on 5q31-32 and with marker D20S195 (Z_{max} = 3.14 at θ = .068) on 20q11.2. No evidence for linkage (LOD score >2) with other markers could be detected.

Confirmation of Linkage by Homozygosity Mapping

Homozygosity mapping of the entirety of chromosomes 5 and 20 was carried out in these eight families to confirm linkage to D5S436, D20S195, or both. No significant evidence for linkage was obtained from neighboring markers of the chromosome 20 region, and haplotype analysis indicated that most of the support for linkage to this region was due to results for a single family (family 1).

Conversely, homozygosity mapping of the entirety of

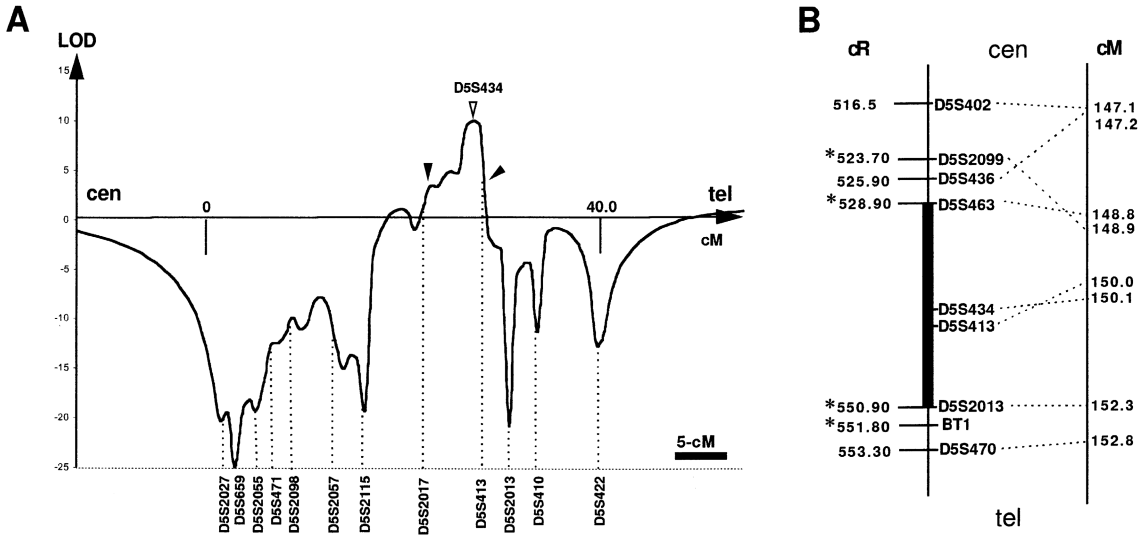

Figure 2 *A*, Multipoint linkage analysis of a 40-cM region encompassing the NS locus on 5q32. Markers D5S2017 and D5S413 (*blackened arrowheads*) delineate a 5.4-cM region of linkage in which multipoint LOD scores (LOD) are >3.0. The multipoint Z_{max}, 10.11, was obtained with marker D5S434 (*unblackened arrowhead*). *B*, Radiation-hybrid map of NS locus. The map is oriented centromeric (cen [*top*]) to telomeric (tel [*bottom*]). The physical distances (cR) between the NS locus and each marker are indicated on the left; we based them on either the radiation-hybrid map of chromosome 5 (Whitehead Institute for Biomedical Research/MIT Center for Genome Research) or our radiation-hybrid mapping results with the Genebridge 4 panel (*asterisks*). The genetic distances (cM) between the markers, according to the Généthon human linkage map, are shown on the right. Notably, the positions of markers D5S2099/D5S436 and D5S434/D5S413 are slightly discordant between the two maps. The NS critical interval is denoted by the thicker vertical line.

chromosome 5 revealed significant support for linkage between markers D5S2115 and D5S436 (data not shown). The full data set of 20 families was then typed for additional markers across a 40-cM region spanning D5S2115 and D5S436. Initially, an additional 13 markers (D5S2027, D5S659, D5S2055, D5S471, D5S2098, D5S2057, D5S2115, D5S2010, D5S436, D5S2090, D5S2014, D5S422, and D5S410, centromeric to telomeric) from the Généthon human linkage map were tested, to achieve an average of 3 cM of spacing across the region. Haplotype analysis indicated that three of these loci (D5S436, D5S2090, and D5S2014, centromeric to telomeric), spanning an 8.8-cM region, showed complete segregation with the disease, under the recessive model (data not shown).

We next typed 13 additional microsatellite markers within the 8.8-cM region, including 10 markers (D5S2033, D5S463, D5S2099, D5S413, D5S434, D5S2013, D5S636, D5S640, D5S470, and D5S2015, centromeric to telomeric) from the Généthon map, two markers (BT1 and CSF1R [GenBank Overview]; Hästbacka et al. 1994) located between D5S413 and D5S434, and one marker (IL9 [Polymeropoulos et al. 1991]) within the interleukin-9 gene, between D5S2115 and D5S2017. Homozygosity mapping of the full set of 26 markers showed multipoint LOD scores >3.0 for eight markers spanning ~5.4 cM, with the markers D5S2017 and D5S413 defining the centromeric and telomeric boundaries, respectively (fig. 2*A*). The greatest support for linkage on the multipoint curve was observed above marker D5S434 (multipoint Z_{max} = 10.11). Haplotype analysis revealed that the disease locus was linked to chromosome 5q in all the families, suggesting genetic homogeneity.

Radiation-Hybrid Mapping of Markers Showing Critical Recombinants

To check the position of the markers showing critical recombinants at the NS locus, we mapped D5S2099, BT1, D5S463, and D5S2013 by means of the Genebridge 4 radiation-hybrid panel. Markers D5S2099, D5S463, D5S2013, and BT1 were placed 7.1 centirays (cR), 19.5 cR, 41.5 cR, and 43.4 cR, respectively, telomeric to marker D5S402 in the Genebridge 4–panel framework (fig. 2*B*).

Haplotype Analysis and Refinement of the Critical Region

Careful examination of the haplotypes confirmed that disease-associated alleles cosegregated with the phenotype of NS in all families (fig. 3*A*). Critical meiotic recombinants could be identified (fig. 3*B*). A recombination event in individual 12.10 placed the disease locus

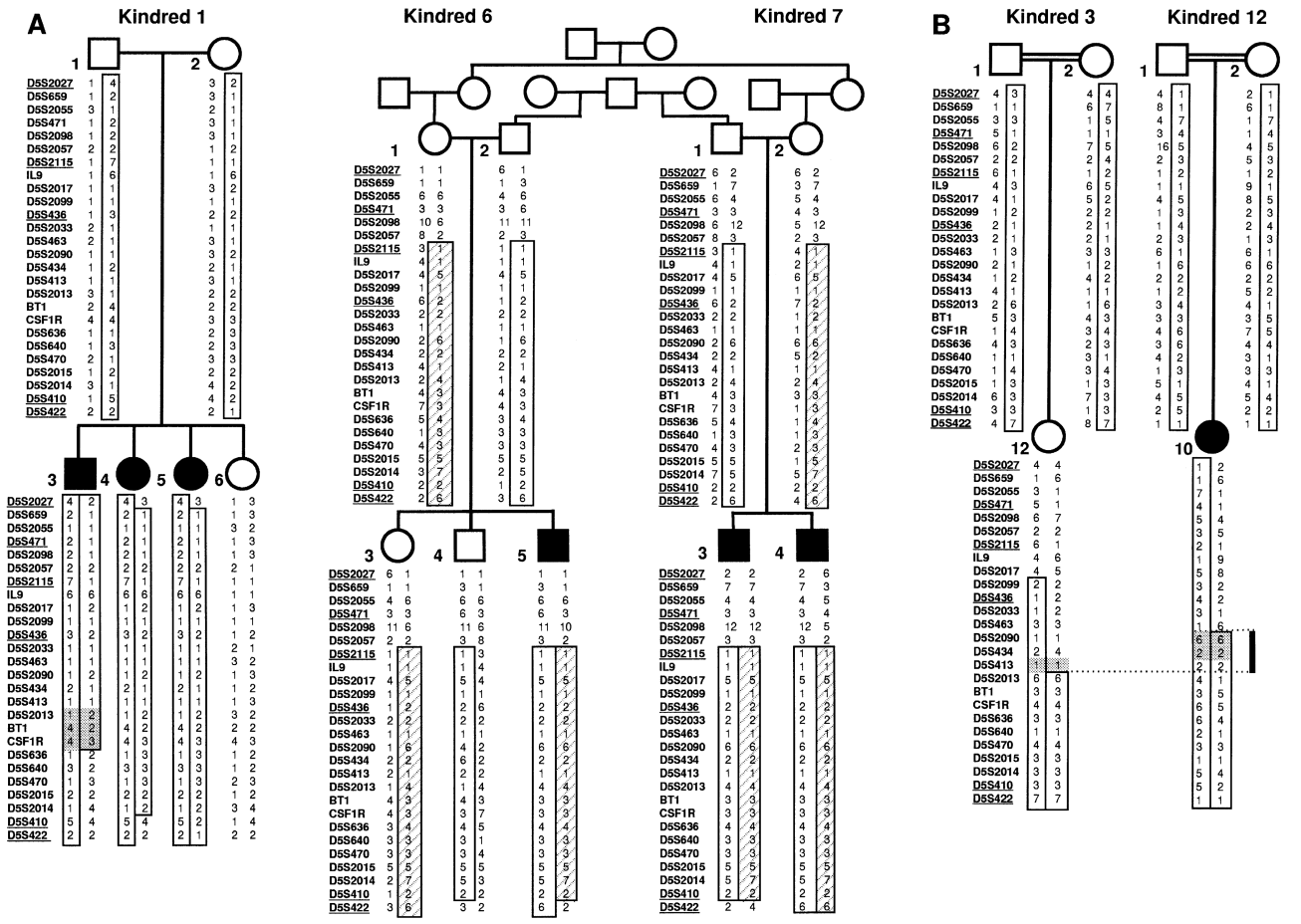

Figure 3 Pedigree structure and haplotype analysis of representative families with NS (*A*) and critical recombination events (*B*). Haplotypes for 26 polymorphic markers on 5q are shown. Markers are ordered centromeric (*top*) to telomeric (*bottom*), according to the Généthon human linkage map, except markers D5S2099 to D5S470, which have been ordered on the basis of our radiation-hybrid mapping results and the radiation-hybrid map of chromosome 5 (Whitehead Institute for Biomedical Research/MIT Center for Genome Research). Markers used for the initial genomewide scan are underlined. Disease-linked haplotypes are boxed. Noninformative markers are gray shaded. *A,* Families 1, 6, and 7, which were included in the initial genomewide search for linkage. In each family, affected offspring share the same genotype at the NS locus. In affected individual 1.3, a maternal recombination event places the NS locus centromeric to D5S636. Markers D5S2013, BT1, and CSF1R are not informative for recombination localization in this individual. In families 6 and 7, the fathers (6.2 and 7.1) are half-brothers, and the mothers (6.1 and 7.2) are first cousins. The haplotype shared by descent is boxed, in the case of the fathers, and cross-hatched, in the case of the mothers. Interestingly, the affected offspring (6.5, 7.3, and 7.4) are homozygous for the same disease-associated haplotype, from D5S2115 to D5S2015, suggesting identity by descent, possibly due to a founder ancestor. *B,* Critical recombination events occurring in families 3 and 12. Only key individuals are shown. Haplotype analysis in unaffected individual 3.12 locates the NS locus proximal to marker D5S2013, although marker D5S413 is not fully informative. Haplotype analysis of affected individual 12.10 places the NS locus distal to marker D5S463, although markers D5S2090 and D5S434 are not fully informative. The NS critical region is indicated by the thickest vertical line.

distal to D5S463, since this affected individual inherited only one of the disease-linked alleles of D5S463 in family 12. A recombination event in individual 3.12 placed the disease locus proximal to D5S2013, since this unaffected individual inherited the two disease-linked alleles of D5S2013 in family 3. We concluded that the maximal interval of linkage with the NS phenotype is bordered by D5S463 (centromeric) and D5S2013 (telomeric), in a region estimated to be ~3.5 cM.

Search for Candidate Genes or Transcripts

Examination of the GeneMap'99 consensus map identified eight genes and 38 expressed-sequence tags (ESTs) within the D5S463–D5S2013 interval. Of these genes, PDGFRB, SPARC, and CDX1, which encode platelet-derived growth factor–receptor β, osteonectin, and caudal-type homeobox transcription factor 1, respectively, have been mapped distal to BT1, on the published phys-

ical maps for the DTD and the Treacher Collins syndrome regions (Hästbacka et al. 1994; The Treacher Collins Syndrome Collaborative Group 1996), and thus they could be excluded from the NS region. The five other genes localized within the interval were CSNK1A1, PDE6A, ADRB2, RMSA1, and DTDST, coding for casein kinase Iα, the α subunit of retinal rod cGMP phosphodiesterase, adrenergic receptor β2, the regulator of mitotic-spindle assembly, and the DTD sulfate transporter, respectively. Together with the 38 ESTs in the CNS critical region, they did not appear to be obvious candidates.

Discussion

In this study, we have mapped the NS gene to chromosome 5q32 in a panel of 20 affected families. Significant evidence of linkage to this chromosomal region was found, with multipoint $Z_{max} = 10.11$, between markers D5S2017 and D5S413. Haplotype analysis located the NS locus in a <3.5-cM genetic interval between D5S463 and D5S2013. This region spans a 22-cR physical distance that is estimated to be ~6 Mb, if it is assumed that 3.7 cR is equivalent to ~1 Mb in the Genebridge 4 panel. Notably, markers D5S2090 and D5S434, which are immediately distal to D5S463, were not fully informative in individual 12.10; and neither was marker D5S413, which is proximal to D5S2013, in individual 3.12 (fig. 3*B*). These results suggest that further reduction of this interval could be possible through the identification of new polymorphic markers between D5S463 and D5S2013 and through haplotype analysis in these families.

Our results exclude the cytokine-gene cluster (Frazer et al. 1997), which spans a 1-Mb region proximal to marker D5S2099 and which has been reported to be associated with asthma and atopy (Postma et al. 1995; Mansur et al. 1998), asthma and high IgE levels (Bleecker et al. 1995), high circulating IgE levels (Marsh et al. 1994; Meyers et al. 1994), and hypereosinophilia (Broide et al. 1999), all of which are common features in patients with NS. The chromosomal proximity of the NS locus to the cytokine-gene cluster suggests a possible functional clustering of genes involved in immune response and atopy. Mapping of the NS gene to a region proximal to D5S2013 excludes several genes that map telomeric to the critical region: TCOF1, which is mutated in Treacher Collins syndrome (The Treacher Collins Syndrome Collaborative Group 1996), and CSF1R, ANX6, CD74, and IL12-B, which encode colony-stimulating factor 1 receptor, annexin VI, CD74 antigen, and interleukin-12B, respectively.

We have identified, by a database search, five genes and 38 nonredundant ESTs mapping between D5S463 and D5S2013, none of which appear as obvious candidates. Of the five genes, two are involved in human diseases sharing no common features with NS: the PDE6A gene, which encodes the α subunit of retinal rod cGMP phosphodiesterase, is mutated in autosomal recessive retinis pigmentosa (Huang et al. 1995); and the DTDST gene, coding for a transmembrane sulfate transporter is defective in DTD and achondrogenesis type Iβ (Hästbacka et al. 1994; Superti-Furga et al. 1996). The other three genes encode casein kinase Iα (CSNK1A1), adrenergic receptor β2 (ADRB2), and the regulator of mitotic-spindle assembly (RMSA1). Casein kinase Iα is a ubiquitously expressed serine-threonine protein kinase involved in the regulation of G-protein–coupled receptors (Tobin et al. 1997), the cell cycle (Gross et al. 1997), and DNA and RNA synthesis (Ceglieska and Virshup 1993). Polymorphisms in ADRB2 have been associated with susceptibility to nocturnal asthma and obesity (Turki et al. 1995; Large et al. 1997), and targeted disruption of the ADRB2 gene in the mouse leads to abnormal vascular tone and impaired energy metabolism during exercise (Chruscinski et al. 1999). Last, the RMSA1-gene product is required for mitotic spindle assembly and chromosomal segregation (Yeo et al. 1994). To assess the expression of the CSNK1A1, ADRB2, and RMSA1 genes in the skin, we performed northern blot analyses of total RNA extracted from cultured normal human epidermal keratinocytes. No specific signal could be detected, although reverse transcriptase (RT)-PCR analysis showed that these genes were transcribed in keratinocytes. Computer-assisted EST walking was performed for all of the 38 nonredundant ESTs mapping within the NS interval, by means of the EST-BLAST program of the UK Human Genome Mapping Project Resource Center. We found ESTs with homologies to the serine-protease inhibitor precursor VAKTI, the P1 chain of alcohol dehydrogenase class II, the chemokine RANTES, the leukosialin precursor, and rat arylsulfatase B (GenBank accession numbers stSG28807, WI-22716, stSG53883, H14645, and stSG15286, respectively). These ESTs were detectable, by RT-PCR analysis, in cultured keratinocytes and are currently being further investigated. Physical mapping of the region is also underway, to identify new polymorphic markers and to search for novel transcribed sequences.

In conclusion, we report here, for the first time, the localization of the gene for NS. Our findings provide the basis for DNA-based genetic counseling and prenatal diagnosis in families at risk. This result is the first step toward positional cloning of the NS gene, whose identification is anticipated to provide new insights into epidermal differentiation and its links with atopy.

Acknowledgments

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Electronic-Database Information

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

GenBank Overview, http://www.ncbi.nlm.nih.gov/Genbank/GenbankOverview.html (for human markers BT1 and CSFR1 [accession number X14720])
Généthon, http://genethon.fr (for polymorphic markers from chromosome 5q)
GeneMap'99, http://www.ncbi.nlm.nih.gov/genemap99 (for genes and ESTs within the NS interval)
Genome Database, The, http://www.gdb.org (for polymorphic marker IL9 [accession number 155233])
Online Mendelian Inheritance in Man (OMIM), http://www.ncbi.nlm.nih.gov/Omim (for NS [MIM 256500])
UK Human Genome Mapping Project Resource Center, http://www.hgmp.mrc.ac.uk (for the EST BLAST search)
Whitehead Institute for Biomedical Research/MIT Center for Genome Research, http://www-genome.wi.mit.edu (for radiation-hybrid map of chromosome 5)

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