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Mapping of Gene Loci for Nephronophthisis Type 4 and Senior-Løken Syndrome, to Chromosome 1p36

Maria J. Schuermann,[1] Edgar Otto,[1] Achim Becker,[1] Katrin Saar,[2] Franz Rüschendorf,[2,3] Bettine C. Polak,[4] Sirpa Ala-Mello,[5] Julia Hoefele,[1] Alexander Wiedensohler,[1] Maria Haller,[1] Heymut Omran,[1] Peter Nürnberg,[2] and Friedhelm Hildebrandt [1]

[1]University Children's Hospital, Freiburg University, Freiburg, Germany; [2]Gene Mapping Center, Max-Delbrück Center for Molecular Medicine, Berlin-Buch, Germany; [3]Institute of Medical Biometry, Informatics and Epidemiology, University of Bonn, Bonn; [4]Vrieje Universiteit Academisch Ziekenhuis, Department of Ophthalmology, Amsterdam; and [5]The Family Federation of Finland, Helsinki

For nephronophthisis (NPHP), the primary genetic cause of chronic renal failure in young adults, three loci have been mapped. To identify a new locus for NPHP, we here report on total-genome linkage analysis in seven families with NPHP, in whom we had excluded linkage to all three known NPHP loci. LOD scores >1 were obtained at nine loci, which were then fine mapped at 1-cM intervals. Extensive total-genome haplotype analysis revealed homozygosity in one family, in the region of the *PCLN1* gene. Subsequent mutational analysis in this gene revealed *PCLN1* mutations, thereby allowing exclusion of this family as a phenocopy. Multipoint linkage analysis for the remaining six families with NPHP together yielded a maximum LOD score (Z_{max}) of 8.9 (at *D1S253*). We thus identified a new locus, *NPHP4*, for nephronophthisis. Markers D1S2660 and D1S2642 are flanking *NPHP4* at a 2.9-cM critical interval. In one family with NPHP4, extensive genealogical studies were conducted, revealing consanguinity during the 17th century. On the basis of haplotype sharing by descent, we obtained a multipoint Z_{max} of 5.8 for D1S253 in this kindred alone. In addition, we were able to localize to the *NPHP4* locus a new locus for Senior-Løken syndrome, an NPHP variant associated with retinitis pigmentosa.

Introduction

Nephronophthisis (NPHP) comprises a group of autosomal recessive cystic renal disorders that constitute the most common genetic cause of end-stage renal disease (ESRD) during the first 2 decades of life (Smith and Graham 1945; Fanconi et al. 1951; Hildebrandt 1999). Following the symptoms of polyuria, polydipsia, anemia, and growth retardation, ESRD inevitably develops during childhood or young adulthood, requiring renal-replacement therapy for survival. Three gene loci have been mapped: those for (i) juvenile nephronophthisis (NPHP1 [MIM 256100]), on chromosome 2q13 (Antignac et al. 1993; Hildebrandt et al. 1993*b*); (ii) infantile nephronophthisis (NPHP2 [MIM 602088]), on 9q22-q31 (Haider et al. 1998); and (iii) adolescent nephronophthisis, on 3q21-q22 (NPHP3 [MIM 604387]) (Omran et al. 2000). Although there is genetic-locus heterogeneity, disease variants are indistinguishable by renal histology, which exhibits a triad of interstitial-cell infiltrates, renal tubular-cell atrophy with cysts arising from the cortico-medullary junction of the kidneys, and renal interstitial fibrosis (Waldherr et al. 1982). Clinically, there is a statistically different age at onset at ESRD: terminal renal failure develops at median ages of 1 year, 13 years, and 19 years, in NPHP2, NPHP1, and NPHP3, respectively (Omran et al. 2000). We recently identified the causative gene, *NPHP1,* for juvenile nephronophthisis (Hildebrandt et al. 1997). The gene product nephrocystin contains an SH3 protein-protein–interaction domain (Otto et al. 2000). Since nephrocystin interacts with the focal-adhesion components p130CAS, tensin, and focal adhesion kinase 2 (Benzing et al. 2001), defects in focal-adhesion signaling are most likely involved in the pathogenesis of NPHP1 (Hildebrandt and Otto 2000). Associations of NPHP with autosomal recessive retinitis pigmentosa (RP) have been described as the so-called Senior-Løken syndrome (SLS [MIM 266900]) (Løken et al. 1961; Senior et al. 1961). A late-onset form of RP occurs in a small percentage of patients with *NPHP1* mutations without an apparent genotype/phenotype correlation (Caridi et al. 1998). Interestingly, another locus for early-onset SLS (i.e., Leber congenital amaurosis) colocalizes to the *NPHP3* locus (Omran et al. 2002). We here report chromosomal localization of a fourth gene locus, *NPHP4,* for NPHP. In addition, we localize to the new *NPHP4* locus a novel locus for SLS, termed "*SLSN4.*"

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Address for correspondence and reprints: Dr. Friedhelm Hildebrandt, MD University Children's Hospital, Mathildenstrasse 1, D-79106 Freiburg, Germany. E-mail: hildebra@kikli.ukl.uni-freiburg.de

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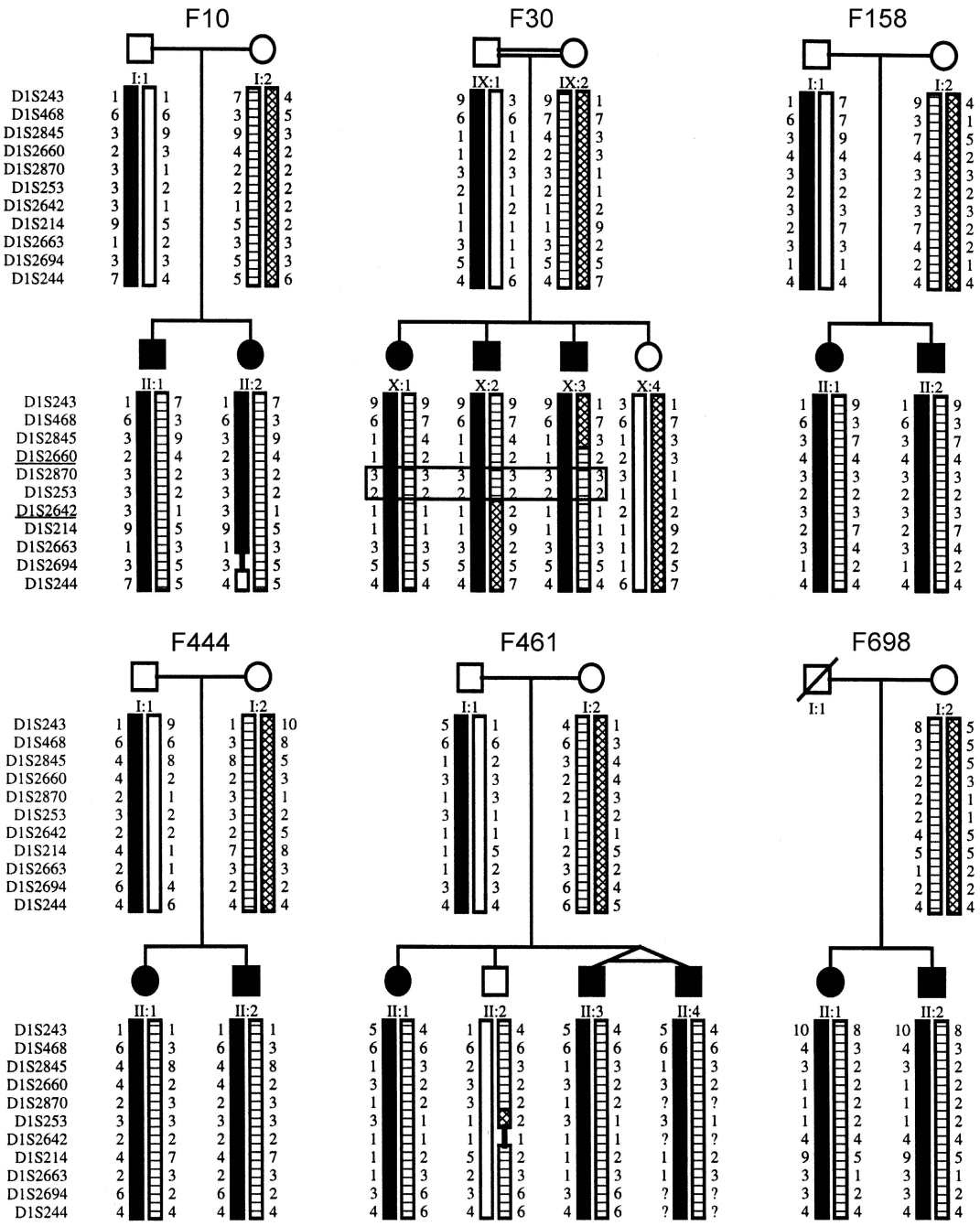

Figure 1 Haplotypes on chromosome 1p36 in six families with NPHP4. Eleven microsatellites, from p-ter to cen (*top to bottom*), are shown to the left of the pedigrees. Circles denote females; squares denote males; filled symbols indicate affected status. Haplotypes are indicated by as differently shaded bars. In family F30, the double line indicates consanguinity, and genotypes homozygous by descent in affected individuals are boxed. Markers flanking the *NPHP4* locus, as defined by lack of homozygosity in family F30, are underlined.

Patients and Methods

Blood samples and clinical data for seven families with NPHP were obtained after informed consent was given by patients and their parents and siblings. Ethnic origins of these families were as follows: families F10, F30, and F158 are German; family F344 is Lebanese; family F444 is Finnish; family F461 is French; and family F698 is Belgian. The diagnosis of NPHP was made by a pediatric nephrologist who was the primary physician for these

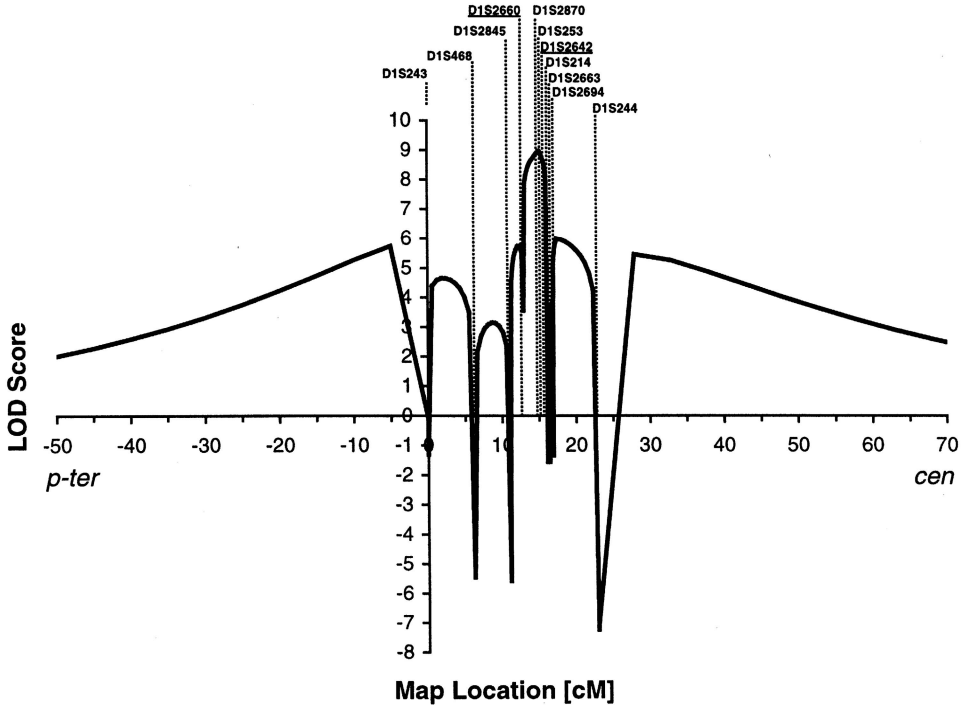

Figure 2 Multipoint LOD scores for the *NPHP4* locus, versus the 11 markers shown in figure 1, calculated in all six families with NPHP4. Positions (in cM) are according to the Généthon map relative to the position of D1S243 (Dib et al. 1996). The two markers—D1S2660 and D1S2642—that flank the *NPHP4* region (see fig. 1) are underlined. p-ter = p-terminal orientation; cen = centromeric orientation.

patients. Diagnostic criteria were (i) development of ESRD following a history of polyuria, polydipsia, and anemia; (ii) renal ultrasound compatible with NPHP; (iii) a kidney-biopsy result consistent with NPHP; and (iv) absence of extrarenal symptoms, such as RP, Cogan syndrome, liver fibrosis, and cone-shaped epiphyses. For family F461, kidney-biopsy results were not available. Since there was clearly no doubt regarding the diagnosis of NPHP in this family, an exception was made, a priori, to include this family, despite the lack of biopsy data. In these patients, ESRD commenced within a wide age range, 11–34 years.

The diagnosis of SLS was made according to the same criteria, with regard to renal symptoms, as were used for NPHP. In SLS, these renal symptoms are associated with RP. Clinical data for family F3 with SLS have been published previously (Polak et al. 1983): All three affected siblings had RP suggestive of Leber amaurosis congenita. Individual F3-II-1 had only central areas of vision and died in 1993, because of complications from chronic renal failure following renal transplantation. Individual F3-II-3 had received a cadaveric renal transplant before the age of 28 years. In patient F3-II-7, reexamination for this study revealed, at age 30 years, long-standing flat electroretinographic results and central tunnel vision of 10°, in both eyes. At age 35 years, visual acuity was reduced to only light perception by the right eye and hand-movement perception by the left eye. At the same time, there was ESRD, with a serum creatinine level raised to 751 μmol/liter.

Genomic DNA was isolated, by standard methods (Maniatis et al. 1987), either directly from blood samples or after Epstein-Barr–virus transformation of peripheral blood lymphocytes (Steel et al. 1977). Individuals were genotyped in a genomewide linkage analysis using 384 microsatellite markers with an average spacing of 11 cM. For haplotyping at fine resolution, novel microsatellite markers were generated by running the program BLAST with sequences of di-, tri-, and tetranucleotides as query against genomic sequence of the respective regions. Semiautomated genotyping was performed by a MegaBACE-1000 analysis system, as described elsewhere (Saar et al. 1997). Data were analyzed by Genetic Profiler Software, version 1.1. For two-point and multipoint analyses, genetic maps and allele numbers were taken from the Généthon data (Dib et al. 1996), with equal allele frequencies being assumed. For marker D1S253, which yielded the maximum LOD score (Z_{max}), allele frequency was 0.2. Two-point LOD-score calculations were performed by the

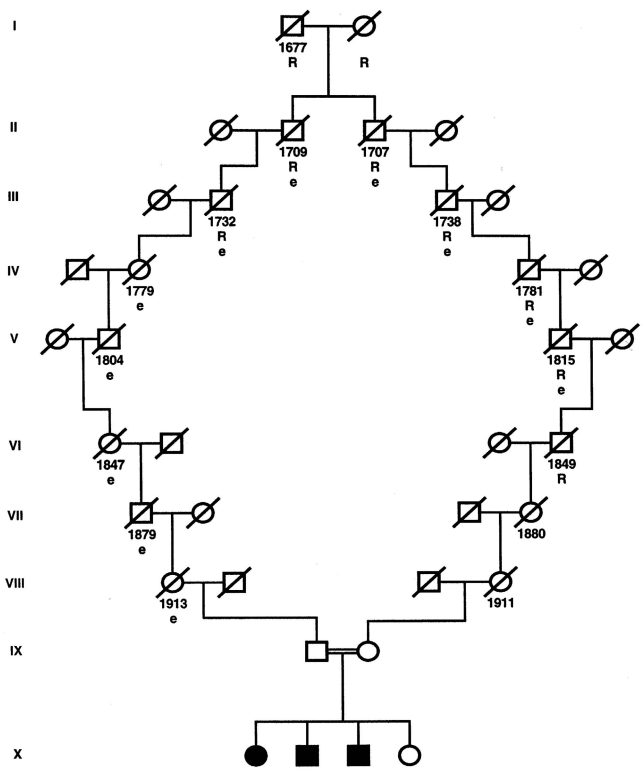

Figure 3 Discovery of consanguinity in family F30. Year of birth is indicated below the symbol for each individual (but, in the last two generations, is omitted, to ensure anonymity). Note that consanguinity in the 17th century was detected; tracing of the consanguinity loop was facilitated by the occurrence of a rare name ("R") and residence in a small township ("e"). Symbols are as in figure 1. A slash through a symbol indicates that the individual is deceased.

LINKAGE program package (Lathrop and Lalouel 1984), with the help of the newly developed LINKRUN computer program (Saar et al. 1997), using an autosomal recessive model with 100% penetrance, a gene frequency of NPHP, and SLS frequency set at 0.00001 (Potter et al. 1980). For computation of multipoint LOD scores, the programs VITESSE (O'Connell and Weeks 1995) and SIMWALK (Barnes et al. 2001) were used. Haplotyping was performed by GENEHUNTER (Kruglyak et al. 1996) and, in a total-genome synopsis of all examined families in tabular form, by Excel 5.0 (Microsoft). The "LODmax − 1 support interval" was defined as the genetic-map positions intersecting the LOD-score curve at $Z_{max} - 1$ (Conneally et al. 1985). For display of genomewide two-point LOD-score data, the programs MAKESCAN and LODVIEW (Hildebrandt et al. 1993*a*) were used. Graphic display of pedigree structure was accomplished by CYRILLIC 2.1 (Cherwell Scientific) and, for multipoint LOD scores, by Excel 5.0 (Microsoft).

Results

During the past 10 years we ascertained, worldwide, 61 multiplex families with NPHP. In 26 of them, we excluded NPHP1, on the basis of either absence of mutations in *NPHP1* or lack of linkage to this locus (Hildebrandt et al. 2001). After exclusion both of families with extrarenal symptoms and of families compatible with linkage to either *NPHP2* or *NPHP3,* seven multiplex families remained, indicating the presence of an additional, unknown locus for NPHP, with exclusive renal involvement. A total-genome search for linkage was performed in these seven families. Suggestive LOD scores >2 were obtained on chromosomes 1q and 6q, and LOD scores >1 were obtained on chromosomes 1p, 3p, 9q, 12p, 16, 17p, and 22q. To extract maximum information from the total-genome search, total-genome haplotypes generated by the GENEHUNTER program were evaluated in tabular form, on the basis of physical-map order, for regions of compatibility with linkage in at least four of the seven families with NPHP4. In these regions, additional markers were haplotyped at fine resolution of ~1 cM, partially on the basis of newly generated microsatellite markers. This led to the identification, in family F344, of a 62-cM region of homozygosity on 3q29, in the region of the *paracellin-1* (*PCLN1*) gene (Simon et al. 1999). Further scrutiny revealed that recessive loss-of-function mutations were present in this gene, thereby identifying this family, on a molecular genetic basis, as a phenocopy actually representing primary hypomagnesemia with hypercalciuria and nephrocalcinosis (FHHN [MIM 603959]). Thus, we were able, a posteriori, to exclude family F344 from the study.

By further high-resolution haplotyping, we detected a chromosome 1p36.31 interval compatible with linkage for all other six NPHP families (fig. 1). Multipoint linkage analysis of 11 markers at the *NPHP4* locus, which were calculated together for all six remaining families with NPHP4, yielded a Z_{max} of 8.9, for marker D1S253 at relative position 15.1 (fig. 2). The 95% CI at $Z_{max} - 1$ (Conneally et al. 1985) extends over a 2.9-cM interval between markers D1S2660 and D1S2642 (which are at relative positions 13.1 and 16.0, respectively) (fig. 2).

In family F30, there were two markers found to be homozygous in affected individuals (fig. 1). We therefore inverted the paradigm of homozygosity mapping (Lander and Botstein 1987), by postulating homozygosity *by descent* for these individuals (Omran et al. 2002). On both the paternal and the maternal sides of family F30, we identified an ancestor with a rare surname that occurs only 96 times among 40 million entries in the German online telephone registry. The fact that both the paternal and the maternal ancestors came

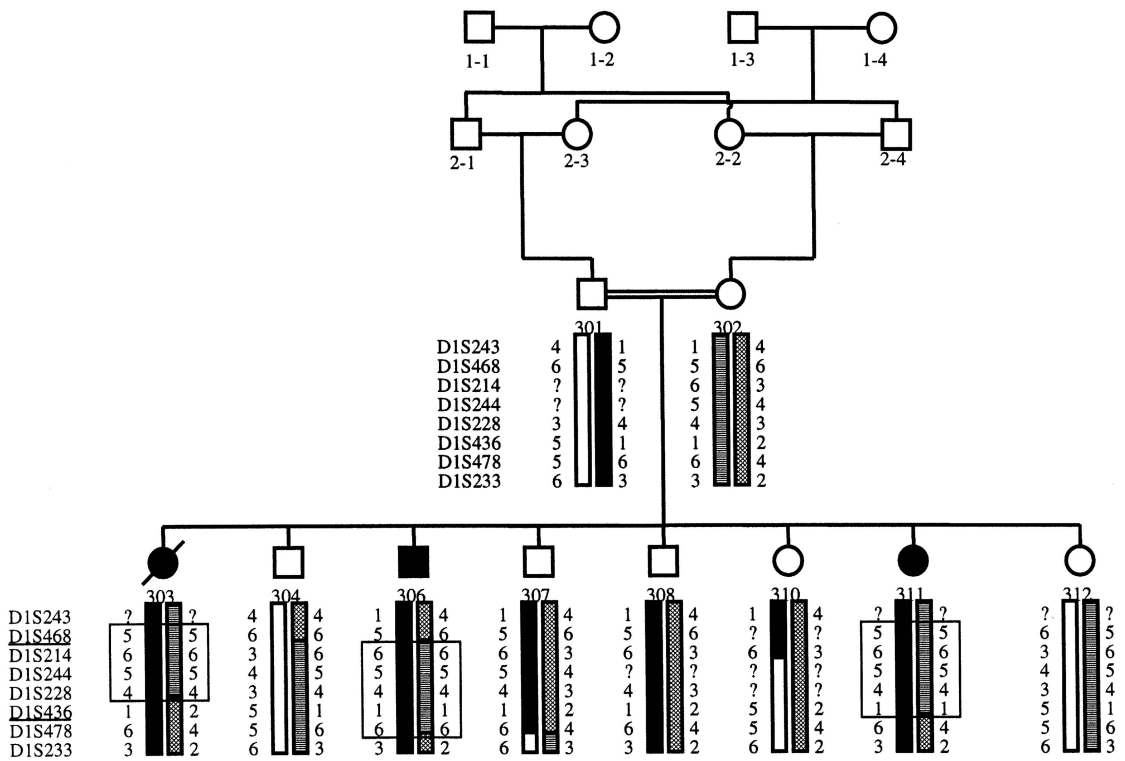

Figure 4 Haplotypes on chromosome 1p36.31 of family F3 with SLS. Eight microsatellite markers, from p-ter to cen (*top to bottom*), are shown to the left of the pedigrees. Symbols are as in figure 1. In each of the affected individuals, the genotypes homozygous by descent are boxed. The two markers—D1S468 and D1S436—that flank the *SLSN4* region are underlined.

from a small township facilitated the tracing of the postulated consanguinity loop (fig. 3). With the help of church records, we were able to demonstrate consanguinity in family F30, through a common ancestor born in 1677 (fig. 3). On the basis of consanguinity by descent, the LOD score for family F30 alone was Z_{max} = 5.8 (recombination fraction 0) for marker D1S253. The existence of shorter loops of consanguinity, however, cannot be excluded in this kindred. Closer chains of kinship, as well as the use of higher allele frequencies for markers, would lower the Z_{max} attainable, as has been discussed elsewhere (Omran et al. 2002).

We thus identified a new gene locus, *NPHP4,* for a new disease entity of nephronophthisis, NPHP4. Since markers D1S2660 and D1S2642 are lacking homozygosity by descent in family F30 (fig. 1), they delimit, as flanking markers, the *NPHP4* critical region, to within a 2.9-cM critical interval of genetic distance. On the Project Ensembl physical map, this interval measures ~2.0 Mb (relative marker positions are 4,950,934 and 6,876,371, respectively).

A gene locus for SLS—that is, the association of NPHP with RP—has been described in patients with homozygous deletions in the *NPHP1* gene (Caridi et al. 1998). In addition, an SLS locus has been colocalized to *NPHP3* (Omran et al. 2002), raising the question of whether pleiotropic genes at both loci are responsible for NPHP as well as for SLS phenotypes. We therefore tested the hypothesis that a gene locus for SLS might colocalize to the newly identified, *NPHP4* locus. In family F3, a consanguineous family with SLS (fig. 4) and with three individuals affected with late-onset RP, pedigree structure was sufficient to yield a LOD score >2. This is sufficient proof of linkage if only a few candidate regions are examined, thus avoiding the problem of multiple testing, a problem that is inherent in a total-genome search for linkage (Ott 1991). In family F3, haplotype analysis of eight markers at the *NPHP4* locus was compatible with homozygosity by descent in all three affected children (fig. 4). Multipoint linkage analysis for these markers yielded a Z_{max} of 2.7, for marker D1S214 (data not shown). This marker is positioned, on a physical map, only 0.3 Mb from marker D1S2642, which flanks the *NPHP4* region on the centromeric side (fig. 2). We thus identified a new locus, *SLSN4,* for SLS. Lack of homozygosity defined markers D1S468 and D1S436 as flanking markers delimiting a 36.8-cM interval that overlaps with the critical *NPHP4* interval

delimited by markers D1S2660 and D1S2642. The critical regions for *NPHP4* and *SLSN4* thus overlap each other.

The question of whether the phenotypes of NPHP4 with isolated kidney involvement and of SLS4 arise (i) from the pleiotropic action of one and the same gene or (ii) from a large homozygous deletion of two neighboring genes can only be answered once the responsible gene has been identified. In projects of total-genome analysis for linkage of recessive traits, for which a large number of pedigrees is difficult to ascertain, the approach described here might be useful. It includes extraction of complete linkage information by total-genome haplotyping in tabular form, with consecutive fine mapping of all regions, in which linkage is not excluded for at least half of the pedigrees. If fine mapping reveals homozygosity in affected individuals, then consanguinity, even if remote, should be actively sought.

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Electronic-Database Information

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

Généthon, http://www.genethon.fr/ (for map positions)
Online Mendelian Inheritance in Man (OMIM), http://www.ncbi.nlm.nih.gov/Omim/ (for NPHP1 [MIM 256100], NPHP2 [MIM 602088], NPHP3 [MIM 604387], SLS [MIM 266900], and FHHN [MIM 603959])
Project Ensembl, http://www.ensembl.org

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