

## Genetic Heterogeneity in Italian Families with IgA Nephropathy: Suggestive Linkage for Two Novel IgA Nephropathy Loci

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IgA nephropathy (IgAN) is the most common glomerulonephritis worldwide, but its etiologic mechanisms are still poorly understood. Different prevalences among ethnic groups and familial aggregation, together with an increased familial risk, suggest important genetic influences on its pathogenesis. A locus for familial IgAN, called "IGAN1," on chromosome 6q22-23 has been described, without the identification of any responsible gene. The partners of the European IgAN Consortium organized a second genomewide scan in 22 new informative Italian multiplex families. A total of 186 subjects (59 affected and 127 unaffected) were genotyped and were included in a two-stage genomewide linkage analysis. The regions 4q26-31 and 17q12-22 exhibited the strongest evidence of linkage by nonparametric analysis (best  $P = .0025$  and  $.0045$ , respectively). These localizations were also supported by multipoint parametric analysis, in which peak LOD scores of 1.83 ( $\alpha = 0.50$ ) and 2.56 ( $\alpha = 0.65$ ) were obtained using the affected-only dominant model, and by allowance for the presence of genetic heterogeneity. Our results provide further evidence for genetic heterogeneity among families with IgAN. Evidence of linkage to multiple chromosomal regions is consistent with both an oligo/polygenic and a multiple-susceptibility-gene model for familial IgAN, with small or moderate effects in determining the pathological phenotype. Although we identified new candidate regions, replication studies are required to confirm the genetic contribution to familial IgAN.

IgA nephropathy (IgAN [MIM 161950]) is the most common form of primary glomerulonephritis worldwide. The diagnosis is based on the occurrence of mesangial IgA deposits in the glomeruli in the presence of recurrent episodes of intrainfectious macroscopic hematuria or persistent microscopic hematuria and/or proteinuria. Abnormal deglycosylated IgA1 synthesis, selective mesangial IgA1 deposition with ensuing mesangial cell proliferation, and extracellular matrix expansion lead to renal fibrosis, with molecular mechanisms still poorly understood. Approximately 20%–50% of patients older than 30 years develop end-stage renal disease within 20 years after the onset of the disease.<sup>1</sup>

IgAN may occur in a sporadic or familial form. Familial IgAN was first described in two families with HLA-identical brothers.<sup>2,3</sup> After these reports were published, nuclear families with IgAN were reported worldwide.<sup>4-7</sup> The familial clustering and the striking ethnic variation in prevalence are suggestive of an important genetic component in the pathogenesis of the disease. IgAN does not exhibit basic Mendelian segregation patterns, although an increased risk of the disease was observed in close relatives of the probands.<sup>8</sup>

In an attempt to identify genes that underlie this disease, an initial genomewide scan was performed with 30 multiplex families with IgAN, of which 24 were from Italy. This study identified the *IGAN1* locus on 6q22-23, in linkage with IgAN. It yielded a significant LOD score of 5.6 in 60% of the linked families, with the assumption of an autosomal dominant mode of inheritance with incomplete penetrance.<sup>9</sup>

Since that first study, the partners of the European IgAN Consortium have recruited new informative families to better elucidate the genetic determination of the disease.<sup>10</sup> The current study is a second-generation genomewide scan to search for regions involved in IgAN susceptibility, performed in a completely independent subset of 22 Italian multiplex families with IgAN. Recruitment strategies and criteria for diagnosis have been reported elsewhere and are freely available on the European IgAN Consortium Web site.<sup>10</sup> Written informed consent was obtained from all participating patients and relatives before they entered the study. They were interviewed, and all personal and relevant clinical and laboratory data were recorded and stored in the IgAN Consortium database. At the time of the interview, a blood sample was collected for DNA ex-

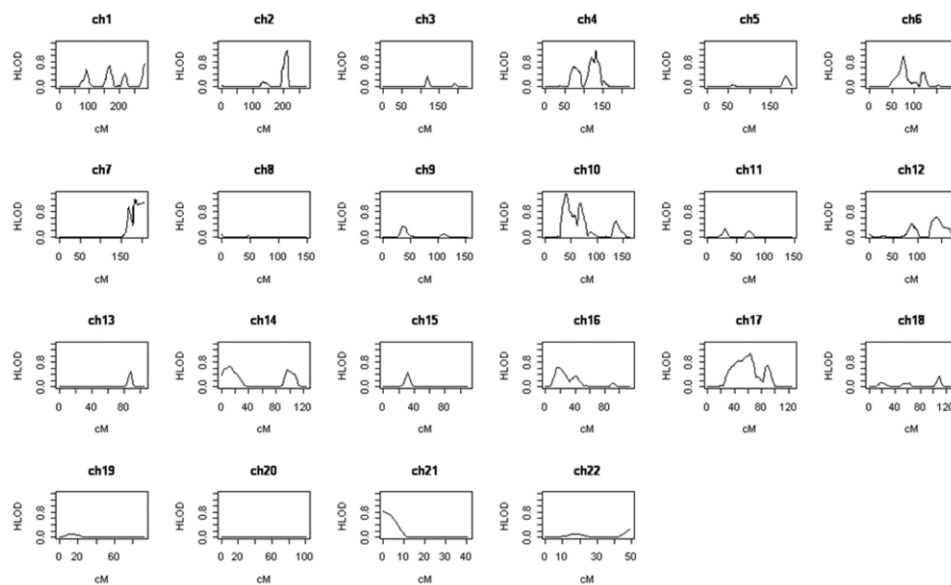
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**Figure 1.** Summary of the first-stage linkage results of multipoint linkage analysis of the data set of 16 multiplex Italian families with IgAN. ch = Chromosome.

traction, and a urinalysis was performed for all family members. Recurrent episodes of macroscopic hematuria were considered an indication for kidney biopsy. After urinalysis, relatives with microscopic hematuria and negative results of urine culture underwent Addis count with contrast phase microscopy and renal ultrasonography and were checked systematically once a year. Individuals with secondary forms of IgAN (systemic lupus erythematosus [MIM 152700], mixed cryoglobulinemia [MIM 123550], and chronic hepatitis) were excluded. Familial IgAN was diagnosed when at least two family members had biopsy-proven IgAN. The study plan was approved by the local ethics committees. This study included 59 affected (37 male and 22 female) and 127 unaffected (52 male and 75 female) subjects. The unaffected subjects were probands' first-, second-, and third-degree relatives aged >18 years. The number of patients affected with IgAN ranged from two to four subjects in each family. Macrohematuria, microhematuria, and renal insufficiency at onset were present in 18, 19, and 6 patients with IgAN, respectively. No documentation was available for the others. Mean ( $\pm$ SD) age at renal biopsy was  $29.6 \pm 13$  years, serum creatinine level was  $1.15 \pm 0.5$  mg/dl, daily proteinuria was  $1.1 \pm 1.2$  g, and creatinine clearance was  $93.3 \pm 30$  ml/min. These clinical characteristics were available for 48 patients with IgAN and were missing for 11. All renal biopsy specimens were classified, according to Lee's classification, as "mild" (grade 1–2,  $n = 14$ ), "moderate" (grade 3,  $n = 11$ ), or "severe" (grade 4–5,  $n = 7$ ) histologic lesions. These findings were missing for 16 patients because diagnosis of IgAN was made in other hospitals using a different histological classification, and the biopsy samples were no longer available for review. Hypertension was present in

15 (31%) of the patients. The mean duration of follow-up was  $12 \pm 8.5$  years, and 16 patients (33.3%) reached end-stage kidney disease.

DNA was extracted from whole-blood samples with the use of commercial kits (Genomix [Talent] and Blood and Cells Culture Midi DNA kit [Qiagen]). A two-stage genomewide scan was performed. In the first stage, 382 highly polymorphic markers along the 22 autosomal chromosomes, at  $\sim 10$  cM density, were typed in a subset of 16 informative families; interesting regions were subsequently investigated in the whole sample of 22 families. The pedigrees of the families analyzed can be visualized in the Registry–Clinical Finding Search Page of the European IgAN Consortium Web site. Microsatellite markers included in the ABI PRISM Linkage Mapping Set v2.5-MD10 were analyzed using the ABI Prism 3100 capillary electrophoresis apparatus (Applied Biosystems). GeneScan 3.7 and Genotyper 3.7 NT software were used for genotyping. Additional microsatellite markers, available in the Marshfield genetic map and the University of California–Santa Cruz (UCSC) draft of the human genome, were genotyped to increase the resolution of the genetic map in the fine mapping of the identified candidate regions. The inheritance of each marker in all pedigrees was tested by PedCheck for inconsistencies due to null alleles, mistyping, nonpaternity, or other errors, and repeat genotyping was performed as necessary.<sup>11</sup> All marker alleles were considered to have equal frequency.

Maximum-likelihood-based (LOD score) methods of linkage analysis were used, with the assumption of an autosomal dominant mode of inheritance, with disease-allele frequency of 0.001 and estimated penetrance of 75%. The phenocopy rate was set at 0.01. Multipoint NPL

**Table 1. First-Stage Genomewide Scan Results Obtained by Analyzing 16 Multiplex Families with IgAN: Most-Relevant Regions Identified by Parametric Linkage and NPL Analyses**

Marker	Distance from p-ter (cM)	Chromosome Location	Linkage Analysis Results		Candidate Interval	
			HLOD <sup>a</sup> ( $\alpha$ )	Nonparametric LOD ( $P$ )	Chromosomal	Marker (Distance)
<i>D4S402</i>	124	4q26	...	1.68 (.0445)	4q22.1-31.2	...
<i>D4S1575</i>	132	4q28	1.19 (.35)	...	...	<i>D4S2964-D4S424</i> (56 cM)
<i>D7S661</i>	155	7q34	...	1.73 (.0388)	7q33-36.3	...
<i>D7S798</i>	168	7q36.3	1.19 (.25)	...	...	<i>D7S640-D7S2465</i> (43 cM)
<i>D10S1653</i>	40	10p13	1.39 (.15)	...	10p13-15.3	...
<i>D10S189</i>	19	10p14	...	2.34 (.0093)	...	<i>D10S249-D10S1653</i> (38 cM)
<i>D17S798</i>	53	17q11.2	1.00 (.40)	...	17q11.2-23.3	...
<i>D17S1868</i>	64	17q21.32	...	2.63 (.0040)	...	<i>D17S1857-D17S944</i> (39 cM)
<i>D2S325</i>	204	2q33.3	1.13 (.20)	...	2q24.3-35	<i>D2S2330-D2S2382</i> (44 cM)
<i>D8S1784</i>	106	8q22.3	...	1.8 (.0319)	8q21.3-24.21	<i>D8S6270-D8S284</i> (37 cM)
<i>D10S1693</i>	137	10q26.11	1.08 (.44)	...	10q23.33-26.2	<i>D10S185-D10S217</i> (41 cM)
<i>D12S79</i>	125	12q24.21	...	1.97 (.0286)	12q23.3-24.33	<i>D12S78-D12S1723</i> (53 cM)
<i>D15S117</i>	51	15q21.3	...	1.71 (.0412)	15q13.2-22.3	<i>D15S165-D15S153</i> (42 cM)

<sup>a</sup> Data were obtained by assuming an autosomal dominant model of inheritance with incomplete penetrance (75%).

(NPL<sub>all</sub> statistic), parametric LOD score, and heterogeneity LOD score (HLOD) were calculated using Genehunter<sup>12</sup> in the first stage of the analysis and Simwalk<sup>2,13</sup> in the second, since some of the families included in the second stage were too large to be analyzed with the exact method implemented in Genehunter. The proportion of families linked ( $\alpha$ ) was allowed to vary until the HLOD was maximized. Recent studies demonstrate that, although the estimated value of  $\alpha$  is problematic when this method is used, the HLOD score remains a powerful method for detection of linkage in the presence of heterogeneity.<sup>14,15</sup> Parametric LOD scores were also evaluated using an affected-only strategy—that is, by assuming all unaffected individuals as phenotypically unknown, since they may not provide reliable information on the underlying disease-locus genotype for a complex disease.

First of all, we tested whether the families with IgAN were linked to the previous locus *IGAN1* on 6q22-23. We analyzed the markers *D6S287*, *D6S1702*, *D6S1690*, *D6S1705*, *D6S1040*, and *D6S262*, which span a 9.5-cM region overlapping the locus *IGAN1*. Multipoint parametric analysis yielded in the region maximum HLOD scores of 0.42 ( $\alpha = 0.20$ ) and 1.05 ( $\alpha = 0.45$ ) for the affected-only approach, whereas multipoint nonparametric analysis yielded  $P = .01$ .

The overall results obtained from the first-stage genomewide scan are represented in figure 1 and table 1. Four loci yielding multipoint HLOD  $\geq 1$  and NPL  $P \leq .05$  were identified. The region 4q22.1-31.2 yielded maximum HLOD 1.19 ( $\alpha = 0.35$ ) and nonparametric LOD 1.68 ( $P = .0445$ ). The multipoint curves identified a 56-cM interval bounded by markers *D4S2964* and *D4S424*. The region 7q33-36.3, spanning 43 cM between *D7S640* and *D7S2465*, yielded maximum HLOD 1.19 ( $\alpha = 0.25$ ) and nonparametric LOD 1.73 ( $P = .0388$ ). The 38-cM region 10p13-15.3, bounded by *D10S249* and *D10S1653*, yielded maximum HLOD 1.39 ( $\alpha = 0.15$ ) and nonparametric LOD 2.34 ( $P = .0093$ ). The region 17q11.2-23.3

yielded maximum HLOD 1.00 ( $\alpha = 0.40$ ) and nonparametric LOD 2.63 ( $P = .0040$ ). The multipoint curves identified a 39-cM interval bounded by *D17S1857* and *D17S944*. Other loci showing only multipoint HLOD  $\geq 1$  or NPL  $P \leq .05$  were not further investigated. In particular, the 44-cM region 2q24.3-35, between *D2S2330* and *D2S2382*, yielded HLOD 1.13 ( $\alpha = 0.20$ ); the 37-cM region 8q21.3-24.21, between *D8S270* and *D8S284*, yielded NPL 1.8 ( $P = .0319$ ); the 41-cM region 10q23.33-26.2, between *D10S185* and *D10S217*, yielded HLOD 1.08 ( $\alpha = 0.44$ ); the 53-cM region 12q23.3-24.33, between *D12S78* and *D12S1723*, yielded nonparametric LOD 1.97 ( $P = .0286$ ); and the 42-cM region 15q13.2-22.3, between *D15S165* and *D15S153*, yielded nonparametric LOD 1.71 ( $P = .0412$ ). The analysis of the four regions identified in stage I was then extended to six other new collected families with IgAN. In the final sample of 22 families, only chromosomes 4 and 17 provided HLOD scores  $>1$  and  $P$  values  $<.05$  for the multipoint NPL<sub>all</sub> statistic of Simwalk2 (table 2). In particular, the NPL  $P$  value of .0059 and the HLOD of 3.80 were obtained at *D17S1868* when an affected-only approach was used. The highest evidence in the chromosome 4 region was reached at *D4S402*, with an NPL  $P$  value of .0454 and an HLOD of 1.05 ( $\alpha = 0.45$ ). These chromosomal regions were considered a high priority for fine-mapping analysis.

Fifteen additional markers were genotyped between *D4S1572* and *D4S424* (~36 cM), with a final average spacing of ~2 cM between markers; five additional markers were genotyped between *D17S798* and *D17S944* (~30 cM), with a final average spacing of ~3.7 cM. The strongest evidence, shown in table 3, was observed on 17q12-22, where HLOD 2.56 ( $\alpha = 0.65$ ) was obtained at *D17S944* with use of the affected-only model, and the peak NPL  $P$  value of .0045 was observed at *D17S943*, located ~12 cM from *D17S944*. NPL  $P$  values  $<.05$  were observed in the whole 30-cM region. The analysis of the region 4q26-31 yielded the maximum HLOD

**Table 2. Results from Parametric Linkage and NPL Analyses Performed in 22 Families with IgAN in the Regions Identified in Stage I**

Chromosome	Marker Interval	Region Span (cM)	Peak Marker	HLOD <sup>a</sup> ( $\alpha$ )	NPL <i>P</i>
4	<i>D4S2964–D4S424</i>	91.3–147.4	<i>D4S402</i>	1.05 (.45)	.0454
7	<i>D7S640–D7S2465</i>	146.9–191.1	<i>D7S798</i>	1.02 (.40)	NS <sup>b</sup>
10	<i>D10S249–D10S1653</i>	.0–40.1	...	<1	NS <sup>b</sup>
17	<i>D17S798–D17S944</i>	45.0–90.0	<i>D17S1868</i>	3.80 (1.0)	.0059

<sup>a</sup> HLOD scores were calculated by assuming the dominant model, described in the text, and by using an affected-only approach.

<sup>b</sup> NS = not significant.

1.83 ( $\alpha = 0.50$ ) and NPL *P* = .0025 at *D4S2965*; NPL *P* values <.05 were obtained in an ~32-cM region spanning from *D4S1513* to *D4S424* (table 3). The pedigrees of the larger families with genotypes and reconstructed haplotypes are represented in figure 2.

Our data show that, besides *IGAN1*, the existence of at least two other loci candidates contain causative and/or susceptibility genes for familial IgAN. Although the families in our data set were similar from a clinical and demographic point of view, these results and those obtained for locus *IGAN1* strongly pointed to genetic heterogeneity in familial IgAN. The evidence of IgAN linked to multiple chromosomal regions is consistent with both an oligo/polygenic and a multiple-susceptibility-gene model for familial IgAN, all having a small or moderate effect in determining the pathological phenotype, as observed in complex diseases.

Despite the success of linkage studies in defining regions of the genome containing important disease loci, the process is slow, and it is difficult to convert this information into genes and responsible DNA variants. The gene(s) associated with onset and/or progression of IgAN lying in the *IGAN1* locus has not yet been identified. A genome-wide scan in a novel murine model identified a susceptibility locus on chromosome 10 in a region syntenic to human *IGAN1*.<sup>16</sup> However, this animal model does not fully resemble human IgAN, since hematuria is completely absent, and there are fundamental differences between the human and murine IgA system. The association of *IGAN1* with mesangioproliferative glomerular injury with IgA deposition emerges from this study. Our overall linkage analysis also suggests to search for the critical genes among the 199 and 347 genes mapped in the regions 4q26-31 and 17q12-22, respectively. We carefully analyzed these

genes and identified the following potential candidate genes of major interest located in 4q26-31: *transient receptor potential channel 3* (*TRPC3* [MIM 602345]), *interleukin-2* (*IL-2* [MIM 147680]), and *interleukin-21* (*IL-21* [MIM 605384]), which could be largely involved in the unbalanced T-helper 1/T-helper 2 immune response observed in patients with IgAN.<sup>17–19</sup> These genes should be investigated, to assess their role in the pathogenesis of IgAN. Moreover, a recently published paper has evidenced an altered gene-expression pattern in leukocytes of patients with IgAN, through an Affimetrix GeneChip microarray experiment.<sup>20</sup> Among the genes with increased expression, we identified some candidate genes mapped in 17q12-22 and 6q22-23. The *histone deacetylase 5* (*HD5* [MIM 605315]) and *granulin* (*GRN* [MIM 138945]) genes on 17q12-22 could be involved in immune-response deregulation. The *serine/threonine protein kinase* (*SGK* [MIM 602958]) gene, localized on chromosome 6q23, could induce extracellular matrix expansion, which leads to renal fibrosis. The *vanin 3* (*VNN3* [MIM 606592]) gene, localized on 6q23, could be implicated in abnormal deglycosylated IgA1 synthesis, which represents another important pathogenic factor for IgAN.<sup>21</sup>

Our data suggest that newly found loci trigger or participate in familial IgAN and that gene-gene and gene-environment interactions may play an important role in the development of this disease. Although we identified new candidate regions, replication studies are required to confirm the genetic contribution in familial IgAN.

It is common to describe IgAN as a single disease, but the present limited understanding of the etiology and pathogenesis of IgAN does not yet provide evidence for such a view. Mesangial IgA deposition and subsequent injury may eventually turn out to represent a final common pathway of the glomerular response to a wide range of causative and pathogenic processes. The major task in dissecting this complex disorder is not only to shed light on its pathogenesis but also to provide potential targets for treatment, screening, and prevention and to increase the understanding of why some patients do not respond to currently available treatments whereas others do.

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**Table 3. Results from the Fine-Mapping Analysis of the Regions 4q26-31 and 17q12-22, with Parametric Linkage and NPL Analyses**

Peak Marker	Region	Region Span (cM)	HLOD <sup>a</sup> ( $\alpha$ )	NPL <i>P</i>
<i>D4S2965</i>	4q26-31	117.0–147.0	1.83 (.50)	.0025
<i>D17S943</i>	17q12-22	57.0–90.0	...	.0045
<i>D17S944</i>	17q12-22	57.0–90.0	2.56 (.65)	...

<sup>a</sup> HLOD scores were calculated by assuming the dominant model, described in the text, and by using an affected-only approach.



The figure is available in its entirety in the online edition of *The American Journal of Human Genetics*.

**Figure 2.** Pedigrees of the families 1-4, 1-15, 2-18, 1-344, and 1-385, with genotypes and reconstructed haplotypes.

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## Web Resources

Accession numbers and URLs for data presented herein are as follows:

European IgAN Consortium Web site, <http://www.igan.net/>  
Marshfield genetic map, <http://www.marshfieldclinic.org/research/genetics/default.html>

Online Mendelian Inheritance in Man (OMIM), <http://www.ncbi.nlm.nih.gov/Omim/> (for IgAN, systemic lupus erythematosus, mixed cryoglobulinemia, *TRPC3*, *IL-2*, *IL-21*, *HD5*, *GRN*, *SGK*, and *VNN3*)

UCSC Genome Browser, <http://www.genome.ucsc.edu/>

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