

## Hereditary Isolated Renal Magnesium Loss Maps to Chromosome 11q23

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### Summary

Hypomagnesemia due to isolated renal magnesium loss has previously been demonstrated in two presumably unrelated Dutch families with autosomal dominant mode of inheritance. Patients with magnesium deficiency may suffer from tetany and convulsions, but the patients with hereditary renal magnesium wasting can also be clinically nonsymptomatic. In a genomewide linkage study, we first excluded a possible candidate region, on chromosome 9q, that encompasses the gene for intestinal hypomagnesemia with secondary hypocalcemia and, subsequently, found linkage to markers on chromosome 11q23. Detailed haplotype analyses identified a common haplotype segregating in both families, suggesting both their relationship through a common ancestor and the existence of a single, hypomagnesemia-causing mutation within them. The maximum two-point LOD score ( $Z_{\max}$ ) was found for marker *D11S4127* ( $Z_{\max} = 6.41$  at a recombination fraction of .00), whereas a multipoint analysis gave a  $Z_{\max}$  of 8.24 between markers *D11S4142* and *D11S4171*. Key recombination events define a 5.6-cM region between these two markers on chromosome 11q23. We conclude that this region encompasses a gene, involved in renal magnesium handling, that is mutated in our patients and is different from the gene involved in intestinal magnesium handling.

### Introduction

Hypomagnesemia due to isolated renal magnesium loss is a rare inherited disorder for which both autosomal

dominant and autosomal recessive modes of inheritance have been described. Patients suffering from magnesium deficiency can present with a number of symptoms, including tetany and convulsions, but, in patients with the familial form of magnesium wasting, nonsymptomatic hypomagnesemia has also been observed (Geven et al. 1987*b*). The autosomal dominant form (MIM 154020) appears to be associated with a lowered excretion of calcium in the urine, whereas in the autosomal recessive form (MIM 248250) the calcium urinary excretion is normal (Freeman and Pearson 1966; Milazzo et al. 1981; Rude et al. 1983; Geven et al. 1987*a*, 1987*b*). The renal reabsorption disorder has to be differentiated from the more commonly occurring hypomagnesemia caused by intestinal absorption failure (Stromme et al. 1969; Nordio et al. 1971; Haijamae and MacDowall 1972; Chery et al. 1994). The latter form of magnesium wasting is inherited as an autosomal recessive trait (MIM 602014) and is associated with secondary hypocalcemia (HSH) (Walder et al. 1997). In addition, urinary magnesium excretion is not increased in this form, since the excess of magnesium is presumed to be eliminated through the bowel. Recently, HSH has been linked to a 14-cM interval on chromosome 9q (Walder et al. 1997). For both the autosomal dominant and autosomal recessive forms of the renal disorder, as well as for the intestinal disorder, a genetic defect has not been identified yet.

Isolated renal magnesium wasting is different from other renal tubular disorders that have hypomagnesemia as a symptom. In Gitelman syndrome (MIM 263800), hypomagnesemia is considered one of the hallmarks of the disease, and, as in the case of the autosomal dominant form of isolated renal magnesium wasting, affected individuals are hypocalciuric and may lack symptoms during the first years of life. However, in Gitelman syndrome patients, hypokalemia and metabolic alkalosis occur, which is not the case in isolated renal magnesium loss. In classical Bartter syndrome (MIM 241200), approximately one-third of the patients have lowered serum magnesium levels. The presence of hypokalemia, metabolic alkalosis, and impaired urine-concentration ability makes differentiation from isolated renal mag-

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nesium loss usually not difficult (recently reviewed by Rodriguez-Soriano 1998). In another syndrome, familial hypomagnesemia is associated with hypercalciuria and nephrocalcinosis (MIM 248250) (Rodriguez-Soriano and Vallo 1994; Praga et al. 1995). In addition, ocular abnormalities such as myopia and horizontal nystagmus are often present.

In the current study, we present the results of a genome-wide linkage search for a locus involved in the autosomal dominant form of isolated renal hypomagnesemia. For this purpose, we have used those members with an autosomal dominant mode of inheritance of renal hypomagnesemia who are from the two families described elsewhere by Geven et al. (1987b) and have also included some additional family members. We decided to start our search on chromosome 9q, the region that encompasses the putative gene involved in hypomagnesemia caused by intestinal absorption failure (Walder et al. 1997), and, after exclusion of this region, we screened the entire genome.

## Patients, Materials, and Methods

### *Patients and Families*

Two Dutch families were recruited for this study (fig. 1). In family A, the proband presented with generalized convulsions at 7 years of age (individual III.9). Serum magnesium was measured for the first time when the individual was 15 years old and was found to be 0.39 mmol/liter (normal 0.75–1.25 mmol/liter). In family B, the disorder became apparent when a 13-year-old girl (individual III.18) was admitted because of generalized convulsions. On examination, serum magnesium was 0.40 mmol/liter. Laboratory data showed no other electrolyte abnormalities in either of the two patients. Urine examination showed a normal excretion of magnesium (7–9.5 mmol/24 h and 8.3 mmol/24 h) and a lowered calcium excretion (0.13–0.34 mmol/24 h and 0.57–0.88 mmol/24 h) in the probands in families A and B, respectively (normal calcium excretion 1.1–7.4 mg/kg/24 h) (data are from Geven et al. 1987b). Treatment consisted of oral administration of magnesium. After 35 additional members of family A and 12 additional members of family B were tested, the disorder was shown to be inherited in an autosomal dominant manner. Patients were identified on the basis of low serum magnesium (<0.65 mmol/liter) associated with a lowered renal excretion of calcium. Remarkably, none of the additional family members with hypomagnesemia showed any of the symptoms usually related to magnesium deficiency. Some adult patients in family A developed symptoms of pseudogout (for more detailed clinical data, see Geven et al. 1987b).

### *Marker Typing*

Samples of peripheral blood were taken from all available family members, and DNA was isolated by means of standard procedures (Miller et al. 1988). Individuals were genotyped in a genome-wide linkage analysis using 373 microsatellite markers with an average spacing of 11 cM. Semiautomated genotyping was performed as described elsewhere (Saar et al. 1997), by an ABI 377 DNA sequencer. Data were analyzed by Genescan 2.1 software and Genotyper 2.0 software (Perkin-Elmer).

### *Linkage Analysis*

Two-point LOD-score calculations were performed by the LINKAGE program package (Lathrop and Lalouel 1984) with the help of the newly developed LINKRUN computer program (T. F. Wienker, personal communication), using an autosomal dominant fully penetrant model. For computation of four-point LOD scores (disease locus and three marker loci), the program VITESSE (O'Connell and Weeks 1995) was used. Two-point and multipoint analyses assumed equal allele frequencies. Haplotyping was performed by CRI-MAP version 2.41 (see the Alphabetical List of Genetic Analysis Software Website), with the option CHROMPIC and by hand. For each chromosome, exclusion maps were displayed by LODVIEW EXCEL 5.0 (Hildebrandt et al. 1993).

The genetic maps and marker data were obtained from the 1996 Génethon map (Dib et al. 1996), and the detailed chromosomal localization of the ROMK gene was obtained from the Stanford Human Genome Center database. The ideogram in figure 2 was obtained from the Department of Pathology, University of Washington. Database searches were performed by use of the Genome Database.

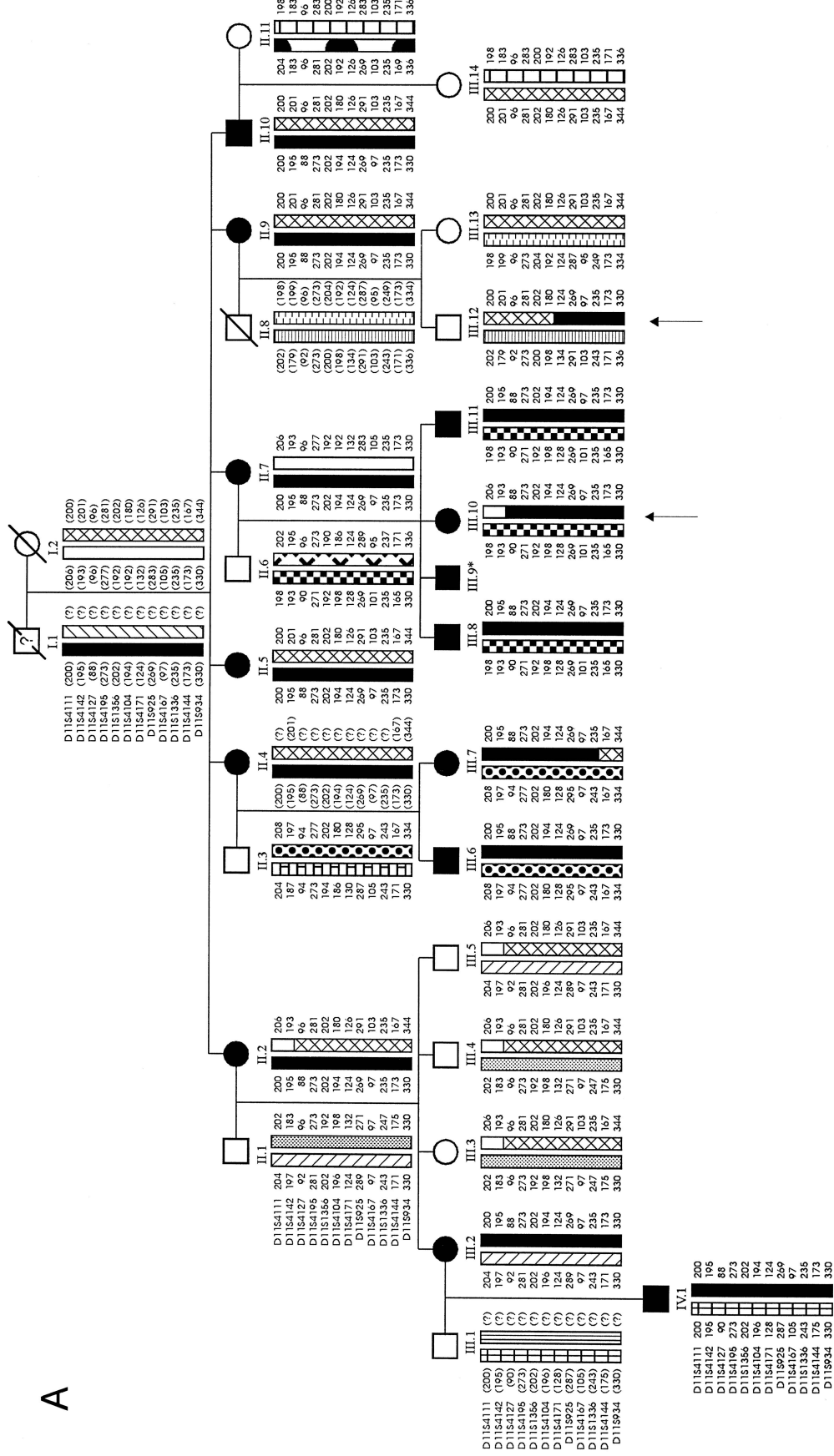
## Results

### *Exclusion of Chromosome 9q, and Genome-wide Screening*

The chromosome 9q region encompassing the putative gene involved in autosomal intestinal hypomagnesemia could be excluded by testing some of the markers reported by Walder et al. (1997) and by haplotyping (data not shown). Subsequently, a total genome scan was performed. Linkage was obtained for marker *D11S4127* (11q23) in both families, with a highest joint LOD score ( $Z_{\max}$ ) of 5.89 at a maximum recombination fraction ( $\theta_{\max}$ ) of .00 (table 1).

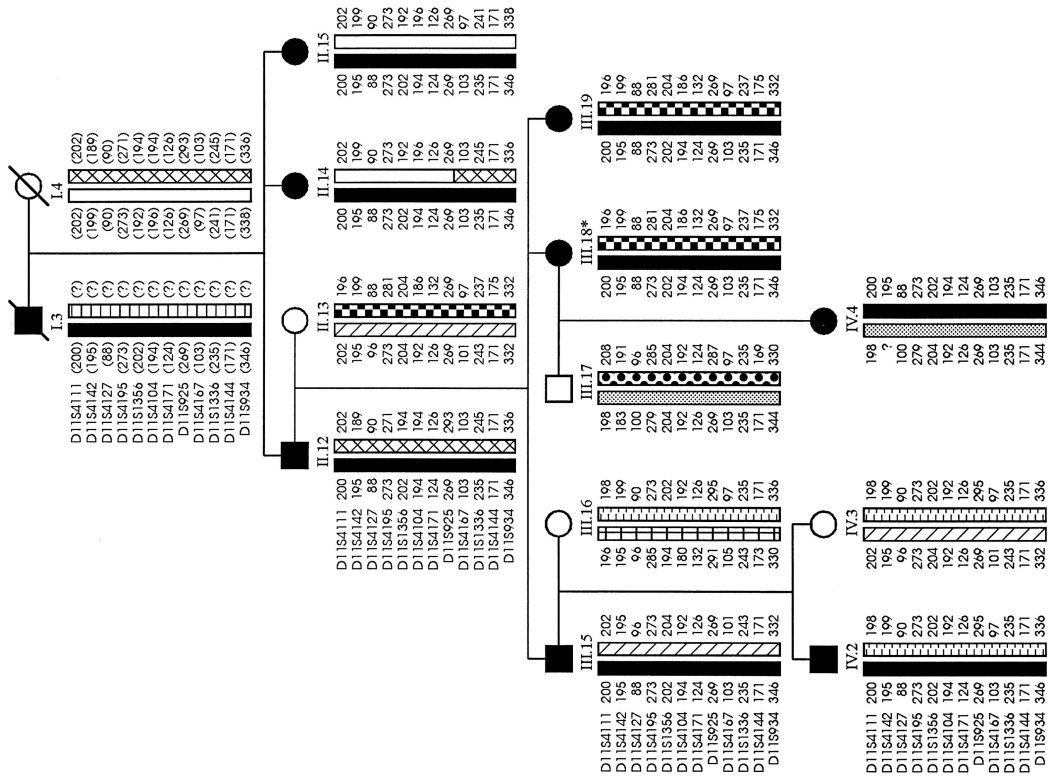
### *Interval Mapping and Haplotyping*

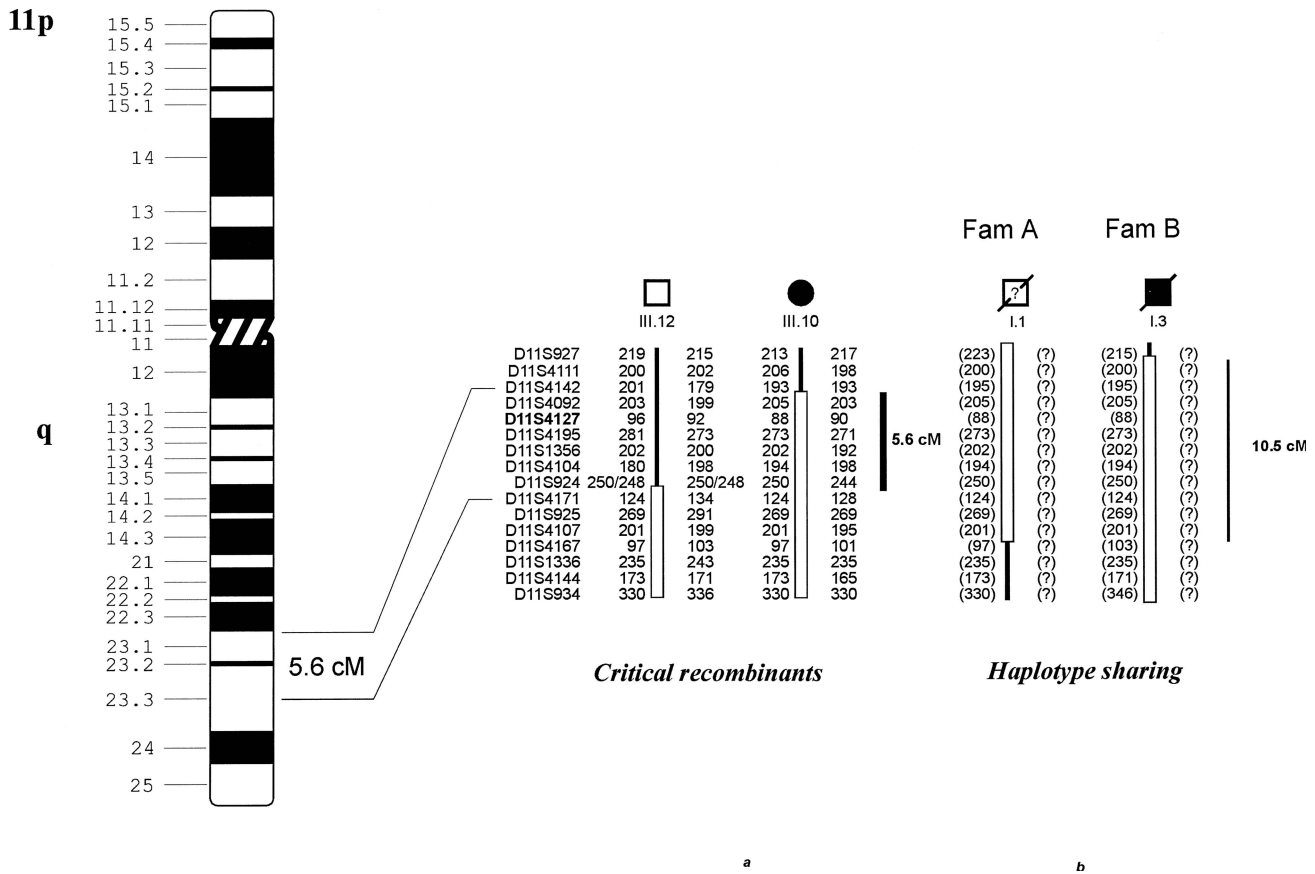
To determine the size of the linked region, the following markers in the vicinity of *D11S925* were characterized: *D11S927*, *D11S4111*, *D11S4142*, *D11S-*



**Figure 1** Pedigrees of families A and B, with autosomal dominant isolated renal hypomagnesemia. Blackened symbols denote affected family members. For haplotypes, linked genotypes are depicted as blackened bars; inferred phenotypes are within parentheses, and, if unknown, are denoted by a question mark (?); and critical recombinants (in individuals III.10 and III.12 in family A) are indicated by an upward-facing arrow (†). The proband in family A could not be haplotyped. In each family, the proband is indicated by an asterisk (\*).

B





**Figure 2** Left, Ideogram of chromosome 11. a, Closest recombinants (in individuals III.10 and III.12 in family A), limiting the linkage interval to a 5.6-cM region between *D11S4142* and *D11S4171*. Marker *D11S924* was not informative for individual III.12. b, Inferred haplotypes of the great-grandfathers (individuals I.1 and I.3 in families A and B, respectively). Recombinations defining the haplotype-shared region were divided arbitrarily between both individuals. Haplotype sharing is shown between *D11S4111* and *D11S4107*.

4092, *D11S4127*, *D11S4195*, *D11S1356*, *D11S4104*, *D11S924*, *D11S4171*, *D11S4107*, (*D11S925*), *D11S4167*, *D11S1336*, *D11S4144*, and *D11S934*. Figure 1 shows the haplotypes for families A and B, with additional markers around *D11S925* (markers *D11S927*, *D11S4092*, *D11S924*, and *D11S4107* are not shown). Key recombination events were observed with *D11S4171* telomeric (individual III.12 in family A) and with *D11S4142* centromeric (individual III.10 in family A), limiting the autosomal dominant renal hypomagnesemia locus to a 5.6-cM interval (fig. 2a; for LOD scores, see table 1).

*Disease-Haplotype Sharing and Candidate Genes*

Haplotyping revealed that patients in both families share a common haplotype over a length of 10.5 cM (11 markers were tested) overlapping the critical region (fig. 2b). We also calculated LOD scores under the presumption that the two families are related through a common ancestor—that is, by considering them as one

large family. This resulted in a  $Z_{max}$  of 6.41 ( $\theta_{max} = .00$ ), for marker *D11S4127*. Figure 3 shows a four-point analysis between markers *D11S927*-*D11S4151*. The highest LOD score found was 8.24 between markers *D11S4142* and *D11S4171*.

Database searches yielded no candidate genes within the linked region. The nearest plausible candidate, the *ROMK* gene, lies ~16 cM telomeric from *D11S4171*. Therefore, the *ROMK* gene can be excluded as a candidate.

**Discussion**

In this study we have presented a linkage study in two Dutch families with autosomal dominant isolated renal magnesium loss. In biochemical studies, the affected status could clearly be distinguished. However, even though some of the affected family members have serum magnesium levels as low as 0.32 mmol/liter, none of

**Table 1**

**Joint Pairwise LOD Scores, for Families A and B (Calculated as if Unrelated), between the Locus for Hereditary Isolated Autosomal Dominant Renal Magnesium Loss and Markers on Chromosome 11**

MARKER <sup>a</sup>	LOD SCORE AT RECOMBINATION FRACTION OF							$Z_{\max}$	$\theta_{\max}$
	.0	.01	.05	.1	.2	.3	.4		
<i>D11S927</i>	-99.99	-6.97	-2.97	-1.29	-.03	.30	.25		
<i>D11S4111</i>	-99.99	2.90	3.22	3.02	2.30	1.44	.58	3.22	.05
<i>D11S4142</i>	-99.99	3.13	3.44	3.24	2.47	1.53	.59	3.44	.05
<i>D11S4092</i>	4.76	4.66	4.27	3.78	2.74	1.67	.66	4.76	.00
<u><i>D11S4127</i></u>	5.89	5.78	5.33	4.74	3.53	2.26	.97	5.89	.00
<u><i>D11S4195</i></u>	4.04	3.94	3.57	3.09	2.12	1.17	.38	4.04	.00
<i>D11S1356</i>	3.40	3.32	3.01	2.62	1.83	1.06	.41	3.40	.00
<i>D11S4104</i>	5.06	4.97	4.59	4.11	3.11	2.04	.91	5.06	.00
<i>D11S924</i>	4.86	4.78	4.44	3.99	2.99	1.91	.80	4.86	.00
<i>D11S4171</i>	-99.99	3.50	3.79	3.55	2.73	1.75	.73	3.79	.05
<i>D11S4107</i>	-99.99	3.30	3.61	3.42	2.68	1.76	.77	3.61	.05
<i>D11S925</i>	5.16	5.06	4.65	4.13	3.02	1.87	.75	5.16	.00
<i>D11S4167</i>	4.62	4.54	4.19	3.74	2.82	1.85	.82	4.62	.00
<i>D11S1336</i>	2.41	2.26	2.13	1.84	1.26	.71	.27	2.41	.00
<i>D11S4144</i>	-99.99	-.22	.90	1.16	1.05	.69	.29	1.16	.1
<i>D11S934</i>	-99.99	.85	1.89	2.04	1.69	1.07	.44	2.04	.1

<sup>a</sup> The marker (*D11S4127*) with the highest joint LOD score is underlined.

them, except the two index cases mentioned, showed clinical symptoms related to magnesium deficiency. In the larger family, family A, some affected adult family members developed symptoms of pseudogout that could possibly be related to the low serum magnesium values, but in the smaller family, family B, the lack of symptoms still requires explanation. The hereditary nature of the hypomagnesemia, however, enabled us to perform a linkage study in search of a gene involved in renal magnesium handling.

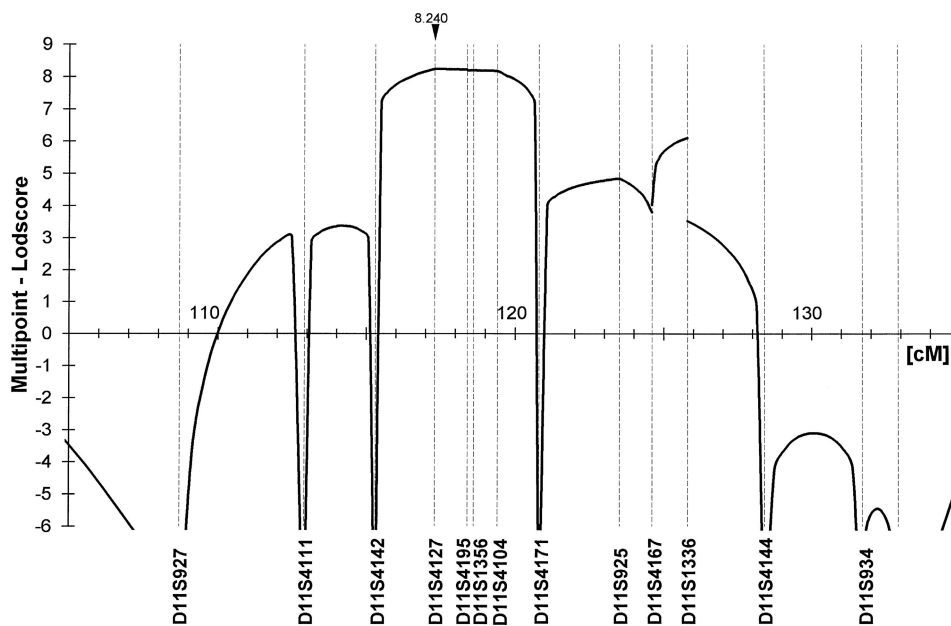
In the whole-genome screen, we found linkage—and mapped a locus involved in autosomal dominant isolated renal hypomagnesemia—to a 5.6-cM region on chromosome 11q23. After additional markers were genotyped, it became evident that the two examined families share the affected haplotype over a region of 10.5 cM, which overlapped the critical region. The shared haplotype is most likely the result of a founder effect, and it suggests the existence of a single hypomagnesemia-causing mutation in both families.

The number of generations back to the common ancestor can be very roughly estimated as 6–10. The expected genomic sharing between two distantly related (i.e., identical by descent) individuals is  $200/n$ , where  $n$  is the number of meioses that have taken place between them (i.e., up to the common ancestor and down to the other individual) (Fisher 1965). The best estimate for  $n$  is therefore  $200/10.5 \approx 19$ , which accounts for 9–10 generations in each family; the largest possible shared region is 15.9 cM (the distance between the markers flanking the shared region), which makes the best estimate 6–7 generations in each family. Because the dis-

tribution of the shared region is approximately exponential, the variance is very high, resulting in an SD of 6–10 generations (Te Meerman et al. 1995). Possibly, if a founder can be identified, more families can be recruited, to further narrow the candidate region. Genealogy studies should prove to be a helpful tool for this goal.

Database searches did not result in possible candidate genes within our linked region. We found that a gene involved in glycogen-storage disease type 1b (Annabi et al. 1998) is located within the same region as our putative gene; but the disease phenotypes are completely unrelated. Also, the *ROMK* gene was found to be located immediately distal to this region. Mutations in this gene have been shown to cause the antenatal variant of Bartter syndrome (International Collaborative Study Group for Bartter-like Syndromes 1997). However, the *ROMK* gene was mapped first on chromosome 11q, by FISH (Krishnan et al. 1995), and later between markers *D11S1351* and *D11S4131*, by radiation hybrid mapping (Stanford Human Genome Center map; resolution 500 kb). Therefore, the *ROMK* gene must lie  $\geq 16$  cM telomeric to the critical region and can be effectively excluded as a candidate for autosomal dominant isolated renal magnesium wasting.

The physiology of renal magnesium handling has been studied mainly in the rat. Most reabsorption of magnesium appears to be passive and located in the cortical thick ascending limb of Henle's loop (cTAL). It has recently been recognized that, in the rat, the distal convoluted tubule (DCT) plays an important role in active magnesium reabsorption. Although the DCT reabsorbs



**Figure 3** Four-point analysis (disease locus and three marker loci), calculated by VITESSE (O'Connell and Weeks 1995), for the region from marker *D11S927* to marker *D11S934*. The highest LOD score (8.24) is indicated by a downward-pointing arrowhead (▼).

only ~10% of the total filtered load of magnesium, this is 70%–80% of the magnesium delivered to the DCT (recently reviewed by Quamme 1997), suggesting that an active magnesium-transporting system is expressed there. If this model applies to the human kidney as well, this could be the system that is disrupted in our patients. In that case we would expect the expression of the gene, mutated in our affected family members, to be located within the DCT.

In recent years, several genes encoding proteins involved in renal tubular transport have been identified. Their physiological role became apparent when mutations in these genes were found in renal tubular disorders. Thus, in Bartter syndrome, mutations were found in the *NKCC2* gene (Bartter syndrome type I) (Simon et al. 1996a; Vargas-Poussou et al. 1998), the *ROMK* gene (Bartter syndrome type II) (Simon et al. 1996b; International Collaborative Study Group for Bartter-like Syndromes 1997), and the *CLCNKB* gene (Bartter syndrome type III) (Simon et al. 1997). We now know that the recycling of potassium across the luminal membrane of the TAL by ROMK is essential for the normal functioning of the Na-K-Cl cotransporter (*NKCC2*), which reabsorbs ~30% of filtered sodium. The *CLCNKB* gene encodes a chloride channel and is expressed basolaterally in the medullary thick ascending limb of Henle (mTAL). Mutations in this gene, leading to either loss of function or dysfunction of the channel, impair transepithelial chlorine transport in the mTAL (reviewed by Rodriguez-Soriano 1998). Mutations in another chloride-channel

gene, *CN5*, are associated with Dent disease (MIM 300009) (Lloyd et al. 1996). In patients suffering from Gitelman syndrome, mutations were found in the *SLC12A3* gene, which encodes the thiazide-sensitive Na-Cl cotransporter (Simon et al. 1996c). Mutations in another gene involved in renal electrolyte handling, the calcium-sensing-receptor gene, can cause hypercalciuria (MIM 601199) (Baron et al. 1996) or, depending on the type of mutation, hypocalciuria (MIM 601198) (Janjic et al. 1995). Until now, for magnesium, only bacterial transporters have been reported (Smith and Maguire 1993; Townsend et al. 1995). Also, the recently isolated yeast aluminum-resistance genes *ALR1* and *ALR2* have been suggested to be involved in magnesium transport (MacDiarmid and Gardner 1998). Still, even though magnesium is the fourth most abundant cation in the body and is the second most abundant intracellular cation (Kelepouris and Agus 1998), a gene involved in renal magnesium handling has not yet been found. The establishment of a locus for autosomal dominant isolated renal magnesium loss might enable the isolation of such a gene. Familial isolated renal magnesium loss has been found in both the autosomal dominant and autosomal recessive forms. It is unclear whether these two modes of inheritance are caused by different mutations in the same gene or whether more than one gene is involved. Our research is a first step toward identification of one or more genes involved in renal magnesium handling and will lead to a better understanding of renal magnesium reabsorption.

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## Electronic-Database Information

URLs for data in this article are as follows:

Genetic Analysis Software, <http://linkage.rockefeller.edu/soft/list.html> (for CRI-MAP version 2.41 documentation)  
 Department of Pathology, University of Washington, <http://www.pathology.washington.edu/>  
 Genome Database, <http://gdbwww.gdb.org/>  
 Online Mendelian Inheritance in Man (OMIM), <http://www.ncbi.nlm.nih.gov/Omim> (for autosomal dominant and autosomal recessive renal hypomagnesemia [MIM 154020 and MIM 248250, respectively], Bartter syndrome [MIM 241200], Gitelman syndrome [MIM 263800], Dent disease [MIM 300009], hypocalciuria [601198], hypercalciuria [MIM 601199], and autosomal recessive intestinal hypomagnesemia [MIM 602014])  
 Stanford Human Genome Center, <http://shgc-www.stanford.edu/>

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