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Linkage of Infantile Bartter Syndrome with Sensorineural Deafness to Chromosome 1p

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Summary

Bartter syndrome (BS) is a family of disorders manifested by hypokalemic hypochloremic metabolic alkalosis with normotensive hyperreninemic hyperaldosteronism. We evaluated a unique, inbred Bedouin kindred in which sensorineural deafness (SND) cosegregates with an infantile variant of the BS phenotype. Using a DNA-pooling strategy, we screened the human genome and successfully demonstrated linkage of this unique syndrome to chromosome 1p31. The genes for two kidney-specific chloride channels and a sodium/hydrogen antiporter, located near this region, were excluded as candidate genes. Although the search for the disease-causing gene in this family continues, this linkage further demonstrates the genetic heterogeneity of BS. In addition, the cosegregation of these phenotypes allows us to postulate that a single genetic alteration may be responsible for the SND and the BS phenotype. The identification and characterization of this gene would lead to a better understanding of the normal physiology of the kidney and the inner ear.

Introduction

Bartter syndrome (BS; OMIM 241200 [http://www3.ncbi.nlm.nih.gov:80/htbin-post/Omim.dispmim?241200]) is an autosomal recessive disorder defined by hypokalemic metabolic alkalosis (Bartter et al. 1962; Rodrigues and van Wersch 1983; Clive 1995). Affected individuals also have elevated plasma renin activity and hyperaldosteronism, with normal blood pressure, altered prostaglandin metabolism (with increased levels of urinary prostaglandins), and increased urinary chloride excretion. Since the original report on BS, by Bartter et al. (1962), there has been much debate regarding the primary defect resulting in this syndrome (Clive 1995). To date, the consensus is that there are two major genetic entities of tubular hypokalemic metabolic alkalosis (Seyberth et al. 1996): BS with earlier clinical manifestations—including the infantile variant of BS (IBS), or hyperprostaglandin E syndrome (OMIM 241200 [http://www3.ncbi.nlm.nih.gov:80/htbin-post/Omim.dispmim?241200]), with severe perinatal manifestations—and the more common Gitelman syndrome (OMIM 263800 [http://www3.ncbi.nlm.nih.gov:80/htbin-post/Omim.dispmim?263800]), with later onset of symptoms and a relatively benign clinical course. In addition to the age at onset and the clinical severity, these disorders differ mainly in the occurrence of hypercalciuria and normal serum magnesium levels (in BS) versus the occurrence of hypocalciuria and hypomagnesemia (in Gitelman syndrome).

Several studies to identify the genetic basis of BS have been performed by use of a candidate-gene approach. The genes for atrial natriuretic factor (Graham et al. 1986), angiotensin II type I receptor (Yoshida et al. 1994), and renin (Higaki and Ogihara 1992) have been screened, and no polymorphism has been found to segregate with the phenotype. However, Gitelman syndrome recently has been found to be caused by mutations in the thiazide-sensitive Na^+-Cl^- cotransporter (TSC) gene on chromosome 16 (Simon et al. 1996*c*). Even more recently, mutations in the Na^+-K^+-$2Cl^-$ cotransporter gene on chromosome 15 have been identified in affected members of five families with IBS (Simon et al. 1996*a*). Functional studies have confirmed the apparent loss of function of the Na^+-K^+-$2Cl^-$ cotransporter in patients with classic BS. These patients showed insensitivity to furosemide infusion, compared with their unaffected siblings and with patients with Gitelman syndrome (Kockerling et al. 1996). In addition, mutations in the inwardly rectifying K^+-channel gene (ROMK) on chromosome 11 have been identified in BS patients

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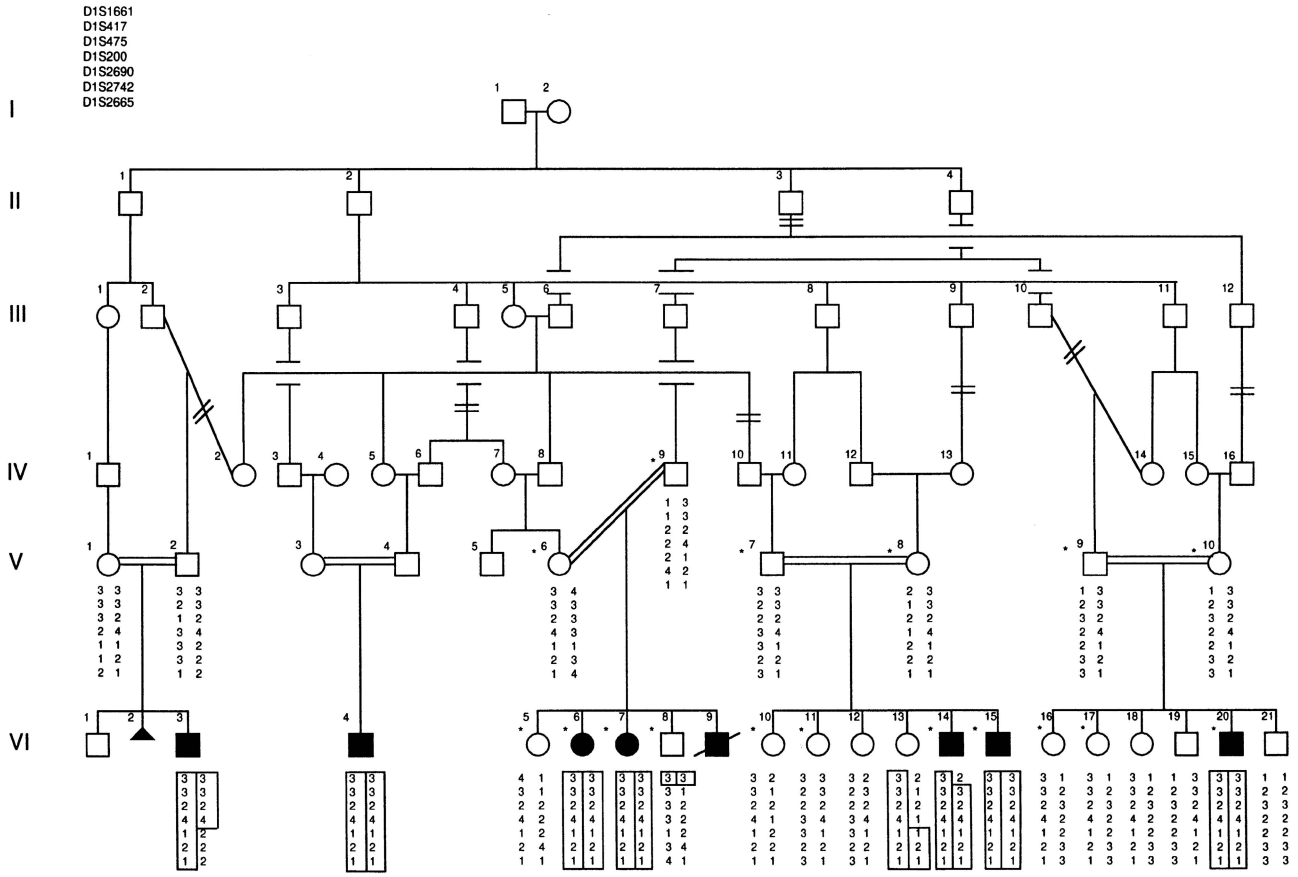

Figure 1 IBS with SND pedigree. Genotyping data are shown below the symbol for each individual. Males are represented by squares, and females are represented by circles. Blackened symbols indicate individuals with IBS and SND, and unblackened symbols indicate unaffected individuals. Boxed haplotypes denote affected chromosomes. Individuals used in the DNA-pooling strategy are marked with an asterisk (*). Individual VI-2 was spontaneously aborted; sex was not determined. Individual VI-9 died of this disorder. Double slashes indicate lines of inheritance that were broken, to simplify the pedigree for statistical analysis.

(Simon et al. 1996*b*). Finally, mutations in the chloride-channel gene (CLCNKB) on chromosome 1 have been identified in BS patients (Simon et al. 1997). The proteins ROMK and CLCNKB are believed to regulate the Na^+-K^+-$2Cl^-$ cotransporter, and, thus, loss of function of these proteins would produce a similar phenotype.

IBS has been reported in a previous study (Seyberth et al. 1985). Affected patients are born prematurely and present with prenatal maternal polyhydramnios and postnatal polyuria, potassium depletion, volume contraction, and failure to thrive. Some of the infants were reported to have severe hypercalciuria. Infants with IBS also may have a prominent forehead, triangular facies with drooping mouth, and large eyes and pinnae (Seyberth et al. 1985; Landau et al. 1995).

We have identified and evaluated an inbred Bedouin kindred (fig. 1) with IBS with sensorineural deafness (SND) (Landau et al. 1995). The Bedouin kindred in this study is the first reported with the IBS variant with SND (Landau et al. 1995). We report the use of a DNA-pooling strategy to screen the human genome rapidly and efficiently, to identify the locus causing this unique variant of BS. We have mapped the disease-causing locus to chromosome 1p31 and have excluded three candidate genes on chromosome 1p. The identification of this locus further demonstrates the genetic heterogeneity of BS.

Material and Methods

DNA Isolation and Genotyping

DNA was isolated and purified from peripheral blood by use of standard protocols (Miller et al. 1988). DNA concentrations were determined by spectrophotometric readings at OD_{260} (optical density). On the basis of initial spectrophotometric readings, samples were diluted to 100 ng/μl, and a second OD_{260} reading was taken to confirm the concentration. The diluted samples then

were PCR amplified to test the quality of the DNA and to assure equal amplification. Equal amounts of diluted DNA samples were pooled and diluted to a final concentration of 20 ng/μl. The affected pool comprised DNA from five individuals with IBS with SND (fig. 1). An unaffected-sibling pool comprised DNA from six individuals. The DNA from six parents of the affected individuals also was pooled.

Cooperative Human Linkage Center short-tandem-repeat polymorphism (STRP) screening set version 6 (Research Genetics) was used to screen the pooled DNA. Amplification of STRP markers was performed by use of 40 ng of pooled DNA in an 8.4-μl reaction mixture containing 1.25 μl of 10 × PCR buffer (100 mM Tris HCL, pH 8.8, 15 mM $MgCl_2$, and 0.01% w/v gelatin); 300 mM each of dATP, dCTP, dGTP, and dTTP; 2.5 pmol each of forward and reverse primers; and 0.25 U of *Taq* DNA polymerase. Samples were subjected to 35 cycles of 94°C for 30 s, 55°C for 30 s, and 72°C for 30 s. PCR products were analyzed on 6% denaturing polyacrylamide gels (7.7 M urea). Gels were silver stained by use of the protocol used by Bassam et al. (1991). Genotyping of individual family members was performed as described above, by use of 40 ng of individual DNA as template. Gels were scored independently by two investigators.

Evaluation of Candidate Genes

In order to evaluate the candidate genes, primers were selected from published sequences (Sardet et al. 1989; Takeuchi et al. 1995) and were synthesized by use of standard phosphoramidite chemistry. DNA was amplified by use of the PCR protocol described above. The PCR fragments were evaluated by SSCP analysis as described elsewhere (Sheffield et al. 1993). The primer sequences for the polymorphic fragment of the gene for the kidney-specific chloride channel hClC-Kb are as follows: forward, 5′-GGC AAC ACC CTC TTC CTC-3′, and reverse, 5′-CCT CAG ATG GCT TTT GTC AC-3′. This primer pair amplifies a 207-bp product with a two-allele polymorphism. The primer sequences for the amiloride-sensitive Na^+-H^+ antiporter are as follows: forward, 5′-CCC AGG ATT GTG CAA TAG TC-3′, and reverse, 5′-TCT GTA CAG GCA GCA GAG TG-3′.

Radiation hybrid mapping was performed with the GeneBridge 4 Radiation Hybrid Panel (Research Genetics), by use of the PCR protocol described above. PCR products were electrophoresed on 1.5% agarose gels and were visualized with ethidium bromide. Products were scored as positive according to correct size and equal intensity, compared with that of the positive control; lanes with a product of correct size but of lesser intensity were scored as ambiguous. The reactions were performed in duplicate and were submitted separately to the Whitehead Institute/MIT Center for Genome Research web site (http://www.genome.wi.mit.edu/).

Statistical Analysis of Linkage Data

LOD-score analysis was performed by use of the MENDEL program. Given the complexity of the pedigree, which has extensive consanguinity, the MENDEL program could not be run on the original pedigree. The pedigree was simplified by the breaking of inbreeding loops in generations II–IV. These broken inbreeding loops are indicated in figure 1 by a double slash through the line of inheritance. The LOD scores determined by use of the simplified pedigree were thought to be conservative, because of the loss of information resulting from the breaking of these inbreeding loops.

Results

Phenotypic Data

We have identified an extended consanguineous Bedouin kindred with IBS with SND (Landau et al. 1995). The pedigree is shown in figure 1. The biochemical and clinical data for this kindred have been described elsewhere in detail (Landau et al. 1995). In brief, polyhydramnios and subsequent premature birth had occurred for all cases. Soon after birth, all patients developed severe polyuria, resulting in salt wasting and a loss of $\leqslant$25% of birth weight, with subsequent transient azotemia and hyponatremia. Hypokalemic metabolic alkalosis developed. Serum aldosterone and plasma renin activities were elevated. Urinary excretion of prostaglandin E2 was markedly elevated. None of the patients had hypomagnesemia, but all of them had hypercalciuria. In some cases, medullary nephrocalcinosis was noted, by renal sonography. Hearing tests, performed as part of the investigation of developmental delay or because of the family history, disclosed complete SND, with the diagnosis made in one case at 3 wk of age, by brain-stem auditory-evoked response, or BAER, examination. None of the described patients was treated with an aminoglycoside or furosemide. None of the unaffected family members showed any facial resemblance to the patients, and no individuals with only either IBS or deafness were found.

Linkage Data

In order to rapidly and efficiently identify the locus causing IBS with SND, we utilized a DNA-pooling strategy (Sheffield et al. 1994; Carmi et al. 1995). This approach assumes that affected individuals share a chromosomal region inherited from a common ancestral founder. Rapid screening for the IBS with SND locus was accomplished by use of the affected and control pooled DNA as template for 161 STRP markers. Link-

Table 1

Two-Point Linkage Data between the Locus for IBS with SND and Chromosome 1 Markers

	LOD Score at θ =						
Marker	.00	.05	.10	.20	.40	θ_{max}	Z_{max}
D1S1661	$-\infty$	3.53	3.37	2.49	.67	.06	3.54
D1S417	$-\infty$	3.06	2.91	2.10	.47	.05	3.06
D1S475	4.62	3.99	3.37	2.21	.46	.00	4.62
D1S200	7.51	6.57	5.63	3.83	.86	.00	7.51
D1S2690	$-\infty$	3.22	3.06	2.21	.49	.05	3.22

age was suggested by a significant reduction in the number of alleles with a single prominent allele in the affected pool, compared with that in the controls (Sheffield et al. 1994; Carmi et al. 1995). Ten STRP markers, on seven chromosomes, were viewed as candidate loci, on the basis of the above criteria. These loci were evaluated further by the screening of adjacent markers, again by use of the pooling strategy. A locus was excluded if adjacent markers did not display a pattern consistent with linkage (i.e., there was no single prominent allele in the affected DNA pool). Marker D1S2134, on chromosome 1, was a candidate locus, after the initial screening was performed. In the subsequent screening, adjacent markers D1S2130 and D1S1669 displayed patterns consistent with linkage. All other candidate loci from the first screening were excluded in the second screening. The chromosome 1 candidate region was evaluated further by the genotyping of all available individuals in the pedigree, by use of marker D1S2134 and its adjacent markers. D1S2134 and its adjacent STRPs gave significantly positive LOD scores. Marker D1S200, located ~2.6 cM centromeric to D1S2134, was found to be completely informative and completely linked (see the Center for Medical Genetics web site [http://www.mfldclin.edu/genetics/]). The maximum LOD score (Z_{max}) for this marker was 7.5 (recombination fraction of $\theta = .00$). The genotyping data for this marker and its adjacent markers are shown in figure 1. The IBS with SND locus lies within a 3.4-cM region flanked by D1S1661 and D1S2690. Additional fine mapping of this region is currently limited by the paucity of informative polymorphic markers in this region. Table 1 summarizes the two-point maximum likelihood data between the linked markers in this region and the disease phenotype. Cytogenetically, the disease locus maps to 1p31, as shown in figure 2 (see the Human Transcript Map web site [http://www.ncbi.nlm.nih.gov/SCIENCE96/]).

Evaluation of Candidate Genes

Recently, the gene for two kidney-specific chloride channels, hClC-Ka and hClC-Kb, have been identified and characterized (Kieferle et al. 1994; Takeuchi et al. 1995). The hClC-Ka and hClC-Kb genes have been localized on chromosome 1p36, by FISH (Brandt and Jentsch 1995). Primers were synthesized for the hClC-Ka and hClC-Kb genes, and a two-allele polymorphism in hClC-Kb was identified by SSCP analysis. For this kindred, genotyping of individuals with this polymorphic marker excluded this gene, with a LOD score of -2 ($\theta = .23$). We were unable to identify a polymorphism in hClC-Ka; the coding sequences of these genes were >90% homologous (Kieferle et al. 1994; Takeuchi et al. 1995). However, the hClC-Ka gene has been shown, by radiation hybrid mapping, to map near the hClC-Kb gene and outside the disease interval (B. C. Schutte and F. Lamb, unpublished data), thus excluding this gene as a candidate.

Another candidate gene known to be near this cytogenetic region is the amiloride-sensitive Na^+-H^+ antiporter (Mattei et al. 1988). Using primers that amplify a fragment in the 3′ UTR (Sardet et al. 1989), we used radiation hybrid mapping (Cox et al. 1990) to exclude this gene, by defining its map location to be outside the disease-causing region. Using the GeneBridge 4 Radiation Hybrid Panel (Research Genetics), we linked this

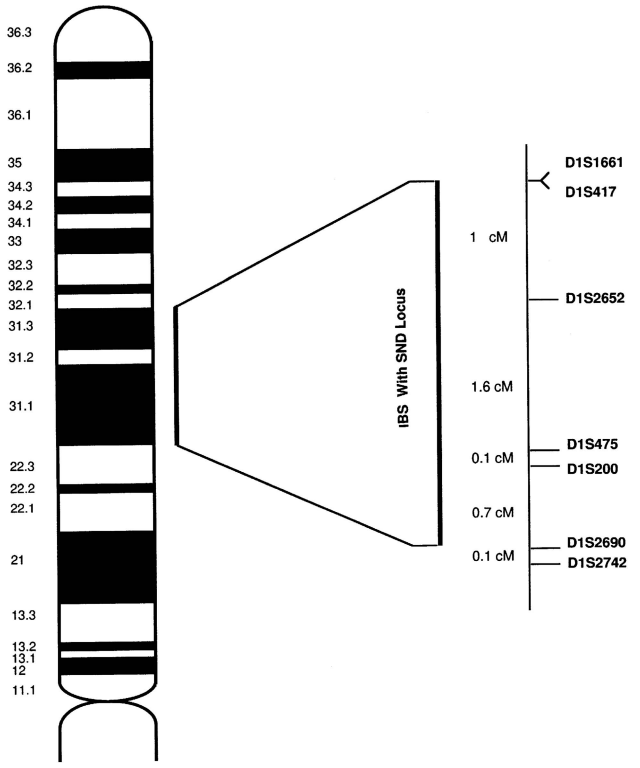

Figure 2 Schematic diagram of chromosome 1p, indicating linked region for IBS with SND. Distance between markers is shown in centimorgans and is based on published maps (see the Center for Medical Genetics web site [http://www.mfldclin.edu/genetics/]; Dib et al. 1996). Cytogenetic location was obtained from the Human Transcript Map web site (http://www.ncbi.nlm.nih.gov/SCIENCE96/).

gene to WI-9232 and mapped it to the interval between WI-9232 and WI-611 (LOD score >3.00), which is >60 cR telomeric to D1S417.

Discussion

Using a DNA-pooling strategy, we screened the human genome and identified a locus causing IBS with SND in this inbred Bedouin kindred. Linkage to this locus is supported by a significantly positive LOD score of 7.5 and by homozygosity in all affected individuals. The disease interval lies within a 3.4-cM region flanked by D1S1661 and D1S2690 (fig. 1). Each flank is defined by a recombination event in both an affected individual and an unaffected individual.

BS has long been thought to be a heterogeneous group of disorders. Stein (1985) divided BS patients into three physiological subtypes: (1) patients with a primary potassium-transport defect; (2) patients with primary Na^+-Cl^-–transport defects in multiple nephron segments; and (3) patients with a localized defect in Na^+-Cl^- transport in the thick ascending limb of the loop of Henle (TALH). The identification of mutations in the ROMK gene in patients with classic BS (Simon et al. 1996*b*), the Na^+-Cl^- TSC in patients with Gitelman syndrome, and the Na^+-K^+-$2Cl^-$ cotransporter (Simon et al. 1996*a*) and the chloride channel CLCNKB in patients with classic BS demonstrates subsets 1, 2, and 3, respectively. The IBS patients from the kindred investigated in this study have biochemical abnormalities similar to those found in the classic BS patients described by Simon et al. (1996*a,* 1996*b,* 1997). We have genetically excluded the Na^+-K^+-$2Cl^-$ cotransporter and CLCNKB (hClC-Kb) in our kindred. By radiation hybrid mapping of the gene for hClC-Ka, which is known to be located on chromosome 1p, we also have excluded it as the disease-causing gene in this kindred. Another candidate gene is that for the amiloride-sensitive Na^+-H^+ antiporter, a ubiquitous membrane-bound enzyme involved in pH regulation, via the mediation of the exchange of intracellular H^+ and extracellular Na^+ ions. This enzyme plays a major role in the maintenance of intracellular pH and volume (Seifter and Aronson 1986). The gene has been shown to map to chromosome lp (Mattei et al. 1988). We have confirmed the mapping of this gene to outside the disease interval, by using radiation hybrid mapping.

The unique cosegregation of SND with this variant of BS is quite intriguing. At least three mechanisms for the cosegregation of these two phenotypes could be postulated. First, given that all affected individuals have both disorders (no individual in this kindred has isolated IBS or SND), it would seem likely that a single pleotropic gene is responsible for both the biochemical abnormalities and the SND. Given that these patients are metabolically indistinguishable from patients who abuse loop diuretics and that it has been well documented that furosemide administration can result in hearing loss (Vargish et al. 1970; Lloyd-MostYn and Lord 1971), a common pathway responsible for these two phenotypes could be postulated. The renal tubular cells of the TALH actively maintain Na^+, K^+, and Cl^- homeostasis, through the actions of the Na^+-K^+-$2Cl^-$ cotransporter in the tubular membrane and the Na^+-K^+ ATPase in the basolateral membrane of the renal tubular cells. The administration of furosemide inhibits the Na^+-K^+-$2Cl^-$ cotransporter, resulting in loss of Na^+, K^+, and Cl^- in the urine. This leads to volume depletion resulting in activation of the renin-angiotensin system and hypokalemia. The mechanism for furosemide-induced ototoxicity is not understood clearly, but furosemide may act on the stria vascularis. The stria vascularis is important in generating the normally high resting endocochlear potential necessary for normal hearing (Steel and Brown 1994), and animal studies have shown reduced endocochlear potential after furosemide dosing (Chodynicki and Kostrzewska 1974). It has been proposed that the Na^+-K^+-$2Cl^-$ cotransporter exists in the marginal cells of the stria vascularis and that, in conjunction with an Na^+-K^+ ATPase, it maintains the K^+ and Cl^- ion gradients in these cells (Ikeda and Morizono 1989). Therefore, if furosemide can alter ion regulation in the kidney and in the inner ear, leading to hypokalemic metabolic alkalosis and sensorineural hearing loss, respectively, a genetic defect in a gene encoding a single protein regulating ion transport both within the renal tubular cells of the TALH and within the marginal cells of the stria vascularis could lead to both of these phenotypic abnormalities. This protein might directly regulate the Na^+-K^+-$2Cl^-$ cotransporter, the ion current within the renal tubular cells of the thick ascending limb of the loop of Henle (ROMK, hClC-Kb, etc.), or the second messenger signaling within these cells. The identification of the gene responsible for the BS phenotype in this kindred will lead to a new understanding of the physiology of salt and water regulation by the kidney, as well as of the function of the inner ear in normal hearing.

Second, we have not excluded the possibility that two tightly linked genes are responsible for the cosegregation of these phenotypes. Further refinement of the interval and/or identification of the causative mutation(s) will aid in the determination of the etiology of this cosegregation. Finally, we cannot exclude completely the possibility that the SND is secondary to the metabolic abnormalities of IBS. However, this would appear to be unlikely, since patients with hypokalemic metabolic alkalosis (secondary to a variant of BS, surreptitious vomiting, or diuretic abuse) do not acquire SND. In IBS, the severity and early onset of these metabolic abnormalities may increase the risk of secondary physiologic alterations, but SND has

not been seen in patients with similar manifestations (Seyberth et al. 1985; Simon et al. 1996*a*, 1996*b*, 1997). Moreover, testing of brain-stem auditory-evoked responses, performed on two affected individuals from this family soon after birth, unequivocally showed severe hearing loss. Ultimately, the mechanism will be elucidated by the identification of the causative mutation(s) in the disease gene(s).

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