Association of Sequence Alterations in the Putative Promoter of RAB7L1 With a Reduced Parkinson Disease Risk

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Objective: To examine whether PARK16, which was recently identified as a protective locus for Parkinson disease (PD) in Asian, white, and South American populations, is also associated with PD in the genetically homogeneous Ashkenazi Jewish population.

Design: Case-control study.

Setting: A medical center affiliated with a university.

Subjects: Five single-nucleotide polymorphisms (SNPs) located between RAB7L1 and SLC41A1 were analyzed in 720 patients with PD and 642 controls, all of Ashkenazi Jewish origin.

Main Outcome Measures: Haplotypes were defined and risk estimates were determined for each SNP and haplotype. Bioinformatic analysis defined the putative promoter region of RAB7L1 and the transcription factor binding sites that are potentially affected by 2 of the tested SNPs.

Results: All tested SNPs were significantly associated with PD (odds ratios = 0.64–0.76; \( P = 0.0002–0.014 \)). Two of them, rs1572931 and rs823144, were localized to the putative promoter region of RAB7L1 and their sequence variations altered the predicted transcription factor binding sites of CdxA, p300, GATA-1, Sp1, and c-Ets-1. Only 0.4% of patients were homozygous for the protective rs1572931 genotype (T/T), compared with 3.0% among controls (\( P = 5 \times 10^{-5} \)). This SNP was included in a haplotype that reduced the risk for PD by 10- to 12-fold (\( P = 0.002–0.01 \)) in all patients with PD and in a subgroup of patients who do not carry the Ashkenazi founder mutations in the GBA or LRRK2 genes.

Conclusions: Our data demonstrate that specific SNP variations and haplotypes in the PARK16 locus are associated with reduced risk for PD in Ashkenazim. Although it is possible that alterations in the putative promoter of RAB7L1 are associated with this effect, the role of other genes in this locus cannot be ruled out.

Arch Neurol. 2012;69(1):105-110

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Parkinson disease (PD) (OMIM 168600) is a multifactorial, age-related disorder affecting about 2% of the elderly population. More than a decade of study of familial and sporadic PD has revealed PD as a disorder with complex genetic background involving multiple affected genes and genetic loci and also multiple environmental risk factors. Most of the genes studied were associated with increased risk for PD; however, 2 large-scale genome-wide association studies in Japanese and North American and European populations identified PARK16, a novel locus on chromosome 1q32 (OMIM 613164) that was associated with a reduced PD risk. This region encompasses 5 genes: SLC45A3 (OMIM 605097), NUCKS1 (OMIM 611912), RAB7L1 (OMIM 603949), SLC41A1 (OMIM 610801), and PM20D1 (OMIM 613164). Recently, the association between PARK16 and PD was also confirmed in ethnic Chinese, European, and Chilean populations but was not confirmed in other studies in Spanish, European, and North American populations.

The high prevalence of founder GBA and LRRK2 mutations in more than a third of the Ashkenazi Jewish patients with PD is an additional demonstration for the genetic homogeneity of this population. This phenomenon renders this population useful for detecting other common genetic variations that affect PD risk. Herein, we aimed to examine whether such alterations exist in the PARK16 locus in Ashkenazim.

Methods

The PD patient cohort included 720 consecutively recruited individuals (62.6% men) (Table 1), with a mean (SD) age at enrollment of 67.5 (10.4) years. The 642...
patients with PD. Mutations in the approved the study protocols and the informed consents. National Supreme Helsinki Committees for Genetic Studies sent before entering the study. The Institutional and estimated ABI 3100 Genetic Analyzer (Applied Biosystems). BigDye Terminator cycle sequencing chemistry in the automictive primers are detailed in eTable 2) and sequenced using the intron boundaries were amplified (Biometra GmbH) (the spe-
coding sequences of exons 2 through 6 and their exon-
RAB7L1 promoter region of
morphisms (SNPs) within the tem (Applied Biosystems). The 5 tested single-nucleotide poly-
say ID C_63498123_10 in the StepOnePlus Real-Time PCR Sys-
mation (rs34637584) was also detected using TaqMan as-
listically published.14,15 All participants signed informed con-
sent before entering the study. The Institutional and National Supreme Helsinki Committees for Genetic Studies approved the study protocols and the informed consents.

GENETIC VARIATIONS ANALYSIS

Genomic DNA was isolated from peripheral blood using standard protocols or from saliva according to the manufacturer’s instructions (Oragene; DNA Genotek). Table 1 details some demographic and clinical characteristics and the frequencies of the GBA and LRRK2 G2019S mutations in our cohort of 720 patients with PD. Mutations in the LRRK2 and GBA genes were identified as previously described.14,15 and the LRRK2 G2019S mutation (rs34637584) was also detected using TaqMan assay ID C_63498123_10 in the StepOnePlus Real-Time PCR System (Applied Biosystems). The 5 tested single-nucleotide polymorphisms (SNPs) within the PARK16 locus (eTable 1, http://www.archneurol.com) were analyzed using TaqMan assays.

A 1588–base pair (bp) fragment that contains the putative promoter region of RAB7L1, exon 1 and part of exon 2, and the coding sequences of exons 2 through 6 and their exon-intron boundaries were amplified (Biometra GMBH) (the specific primers are detailed in eTable 2) and sequenced using the BigDye Terminator cycle sequencing chemistry in the automated ABI 3100 Genetic Analyzer (Applied Biosystems).

BIOINFORMATIC ANALYSIS OF THE RAB7L1 PUTATIVE PROMOTER REGION

The following tracks, implemented in the University of California, Santa Cruz, Genome Browser, were used to predict the putative promoter region of RAB7L1: CpG Islands, ENCODE Transcription Factor ChIP-seq, and ENCODE Promoter-Associated Histone Mark (University of California, Santa Cruz). To analyze the possible effects of the rs823144 and rs1572931 SNPs located within this promoter on the putative transcription factor binding sites, 15-bp sequences from each side of the SNP were analyzed using TFSEARCH (http://www.cbrc.jp/research/db/TFSEARCH.html). The parameters used for this comparison were vertebrate matrices only, with a threshold score of 75.0 points (of a maximum 100.0), as was previously described.17,18

STATISTICAL ANALYSIS

Differences in continuous variables were tested using analysis of variance or a t test. A χ² or Fisher exact test was used for comparison of categorical variables. Bonferroni correction for multiple comparisons was applied and a cutoff P value of .01 was set for the analysis of the 5 SNPs (Table 2). Since the allele and genotype frequencies of all tested SNPs did not differ between the young and elderly controls (Table 2) or between men and women (data not shown), these variables were not included as covariates in the analysis. To test for any deviation from Hardy-Weinberg equilibrium among patients with PD and controls, a goodness of fit test with 1 df was applied. Calculations of odds ratios (ORs) for minor allele carriers were done using the online Hutchinson calculator.19 For haplotype analysis, HPlus software version 3.2 was used.20 Analysis of the Affymetrix SNP 6.0 array results was done using the Golden Helix SNP & Variation Suite software (Golden Helix, Inc). To calculate linkage equilibrium (D’ and r²), we used the CubeX online calculator.21 SPSS software version 17 (IBM SPSS Inc) was used for all other data analyses.

RESULTS

IDENTIFICATION OF SNPS THAT ARE ASSOCIATED WITH MODIFIED PD RISK

The PARK16 locus was defined by Satake et al4 on chromosome 1q32 between 203 910 000 and 204 070 000 (genome assembly GCRh37). To select candidate SNPs for this study, we used unpublished results from a genome-wide analysis of 426 DNA samples done in our laboratory (A.O., unpublished data, June 2009). The samples were from 128 elderly controls and 298 patients with PD, all of Ashkenazi origin. Since the patients samples were greatly enriched for LRRK2 G2019S carriers (25.2%) and for GBA mutations carriers (31.2%), they did not represent the true carrier rate in the Ashkenazi PD population. These 426 samples were processed on the Human
SNP array 6.0, according to the manufacturer’s protocols (Affymetrix Inc). In this array, 40 SNPs are included in the PARK16 region. Two of them, rs1772153 and rs1775151, with uncorrected \( P \) values \( <.007 \) (red circles in the eFigure) were chosen for the initial analysis of the entire unselected consecutively recruited cohort of 720 patients with PD.

The third SNP for analysis was rs947211, the most significantly PARK16-associated SNP in Satake et al. Table 2 details the genotypes and minor allele frequencies in all patients and controls. Since the minor allele frequencies were similar in both subgroups of controls, young and elderly, the 2 groups were analyzed together (total controls in Table 2). In addition, although most young controls were women, there were no differences in the allele and genotype frequencies between men and women (data not shown), allowing us to analyze both sexes together. Table 2 (top 3 SNPs) demonstrates that all the minor alleles of these 3 SNPs were significantly associated with a reduced risk for PD.

Since rs1772153 and rs1775151 are closely located to RAB7L1, 1698 and 1600 bp from its translation start site (Figure), we searched for additional variations in this gene. First, the RAB7L1 putative promoter region was defined based on data available from the University of California, Santa Cruz, Genome Browser (Figure). Second, a 1588-bp region that includes the putative promoter was sequenced in 8 individuals: 4 homozygous for both rs1772153 and rs1775151 (C/C and T/T, respectively) and 4 heterozygous (C/T and T/C). All 4 heterozygous individuals carried 2 additional alterations within the putative RAB7L1 promoter, 461 and 133 bp from its translation start site, an A/C alteration in position 205744546 (rs823144) and a C/T alteration in position 205744218 (rs1572931). Linkage disequilibrium (LD) analysis was performed to determine the linkage between these 5 SNPs. Linkage disequilibrium was demonstrated between all these SNPs as detailed in eTable 3 (\( D' = 0.89-1.0; r^2 = 0.37-1.0 \)). The LD statistics were similar in patients with PD and controls.

IN SILICO ANALYSIS SUGGESTED THAT rs823144 AND rs1572931 MAY AFFECT TRANSCRIPTION FACTOR BINDING SITES

The online software TFSEARCH was used to predict whether rs823144 and rs1572931 may modify the bind-

### Table 2. Genotypes and MAFs of SNPs Within the PARK16 Locus Among Ashkenazi Patients With PD and Controls

<table>
<thead>
<tr>
<th>SNP and Genotypes</th>
<th>Patients With PD (n = 720)</th>
<th>Controls (n = 642)</th>
<th>OR (95% CI)(^a)</th>
<th>( P ) Value(^a)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>rs1772153 (C&gt;T)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>C/C</td>
<td>452 (62.8)</td>
<td>147 (55.1)</td>
<td>203 (54.1)</td>
<td>350 (54.5)</td>
</tr>
<tr>
<td>C/T</td>
<td>240 (33.3)</td>
<td>100 (37.4)</td>
<td>143 (38.1)</td>
<td>243 (37.9)</td>
</tr>
<tr>
<td>T/T</td>
<td>28 (3.9)</td>
<td>20 (7.5)</td>
<td>29 (7.8)</td>
<td>49 (7.6)</td>
</tr>
<tr>
<td>MAF (T)</td>
<td>0.206</td>
<td>0.262</td>
<td>0.266</td>
<td>0.71 (0.57-0.88)</td>
</tr>
<tr>
<td><strong>rs1775151 (T&gt;C)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>T/T</td>
<td>441 (61.3)</td>
<td>144 (53.9)</td>
<td>197 (52.5)</td>
<td>341 (53.1)</td>
</tr>
<tr>
<td>T/C</td>
<td>246 (34.1)</td>
<td>100 (37.5)</td>
<td>146 (38.9)</td>
<td>246 (38.3)</td>
</tr>
<tr>
<td>C/C</td>
<td>33 (4.6)</td>
<td>23 (8.6)</td>
<td>32 (8.6)</td>
<td>55 (8.6)</td>
</tr>
<tr>
<td>MAF (C)</td>
<td>0.217</td>
<td>0.273</td>
<td>0.280</td>
<td>0.72 (0.58-0.89)</td>
</tr>
<tr>
<td><strong>rs947211 (G&gt;A)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>G/G</td>
<td>443 (61.5)</td>
<td>149 (55.8)</td>
<td>204 (54.4)</td>
<td>353 (55.9)</td>
</tr>
<tr>
<td>G/A</td>
<td>244 (33.9)</td>
<td>98 (36.7)</td>
<td>141 (37.8)</td>
<td>239 (37.2)</td>
</tr>
<tr>
<td>A/A</td>
<td>33 (4.6)</td>
<td>20 (7.5)</td>
<td>30 (8.0)</td>
<td>50 (7.8)</td>
</tr>
<tr>
<td>MAF (A)</td>
<td>0.215</td>
<td>0.258</td>
<td>0.268</td>
<td>0.76 (0.62-0.95)</td>
</tr>
<tr>
<td><strong>rs823144 (A&gt;C)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>A/A</td>
<td>441 (61.3)</td>
<td>144 (53.9)</td>
<td>197 (52.5)</td>
<td>341 (53.1)</td>
</tr>
<tr>
<td>A/C</td>
<td>246 (34.1)</td>
<td>100 (37.5)</td>
<td>146 (38.9)</td>
<td>246 (38.3)</td>
</tr>
<tr>
<td>C/C</td>
<td>33 (4.6)</td>
<td>23 (8.6)</td>
<td>32 (8.6)</td>
<td>55 (8.6)</td>
</tr>
<tr>
<td>MAF (C)</td>
<td>0.217</td>
<td>0.273</td>
<td>0.280</td>
<td>0.72 (0.58-0.89)</td>
</tr>
<tr>
<td><strong>rs1572931 (C&gt;T)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>C/C</td>
<td>584 (81.1)</td>
<td>201 (75.3)</td>
<td>276 (73.6)</td>
<td>477 (74.3)</td>
</tr>
<tr>
<td>C/T</td>
<td>133 (18.5)</td>
<td>60 (22.5)</td>
<td>86 (22.9)</td>
<td>146 (22.7)</td>
</tr>
<tr>
<td>T/T</td>
<td>3 (0.4)</td>
<td>6 (2.2)</td>
<td>13 (3.5)</td>
<td>19 (3.0)</td>
</tr>
<tr>
<td>MAF (T)</td>
<td>0.097</td>
<td>0.135</td>
<td>0.149</td>
<td>0.64 (0.51-0.81)</td>
</tr>
</tbody>
</table>

**Abbreviations:** CI, confidence interval; MAF, minor allele frequency; OR, odds ratio; PD, Parkinson disease; SNP, single-nucleotide polymorphism.

\(^a\)Comparing the MAFs in patients and all controls.

\(^b\)Comparing patients and all controls: \( \chi^2 = 14.30; P = .001 \).

\(^c\)Comparing patients and all controls: \( \chi^2 = 13.87; P = .001 \).

\(^d\)Comparing patients and all controls: \( \chi^2 = 9.27; P = .01 \).

\(^e\)Comparing patients and all controls: \( \chi^2 = 18.63; P = 9 \times 10^{-5} \).
ing capacity of known transcription factors. The change at rs1572931 adds a putative binding site for the CdxA transcription factor (TFSEARCH score, 75.0) (Figure, B), and the substitution at rs823144 potentially eliminates the binding site for c-Ets-1 (c-Ets-1; TFSEARCH score, 78.4) while adding binding sites for 3 others (p300, GATA-1, and Sp1; TFSEARCH scores: 76.2, 75.5, and 75.3, respectively) (Figure, B).

**ONE OF THE POSSIBLE HAPLOTYPES GREATLY REDUCES PD RISK**

Table 2 (bottom 2 SNPs) details the genotypes and minor allele frequencies of rs823144 and rs1572931 in all patients with PD and controls. Of the 5 tested SNPs, individuals with the rs1572931 C>T alteration had the lowest risk for PD (OR=0.64; P = .0002). Among patients with PD, only 0.4% were homozygous for rs1572931 T/T, compared with 3.0% in controls (P = 5×10^{-8}, Fisher exact test).

Since rs823144 sequence changes were fully linked to those in rs1772153 (eTable 3), and since all SNPs tested herein demonstrated a reduced PD risk, we hypothesized that a specific protective haplotype may exist in Ashkenazim. Five haplotypes with a frequency of more than 0.001 were defined for the tested SNPs (HPlus version 3.2). These haplotypes, designated as A to E in Table 3, were tagged by 3 SNPs (rs947211, rs1772153, and rs1572931). As expected, carriers of haplotypes B and D who harbor the rs1572931 C>T change had a significantly reduced risk for PD. Notably, haplotype D demonstrated a particularly high protective effect, a 10-fold lower risk (P = .002) (Table 3).

Because of high frequencies of mutations in the GBA and LRRK2 genes that increase PD risk among Ashkenazim\textsuperscript{14,15} (Table 1), it was possible that the carriage of these mutations affected the risk estimates in Table 2. We therefore reanalyzed the haplotypes after excluding all 241 carrier patients (Table 3). In noncarrier patients, only haplotype D showed a significant protective effect (OR=0.077; P = .01) (Table 3), suggesting that this allele reduces the risk for PD independently of the existence of founder mutations in the GBA and LRRK2 genes. Since the status of GBA and LRRK2 mutations in most controls was not known, and the expected number of con-
Haplotype Frequency

GBA list of genes (eg, the importance of genetically homogeneous Ashkenazi population strengthen cohort). No additional sequence variations were found. was not even 1 homozygous carrier of haplotype D in our type B, and 3 heterozygous carriers of haplotype D (there carriers of haplotype A, 3 homozygous carriers of haplotype B, and 3 heterozygous carriers of haplotype D (there was not even 1 homozygous carrier of haplotype D in our cohort). No additional sequence variations were found.

ANALYSIS OF RAB7L1 CODING SEQUENCE AND EXON-INTRON BOUNDARIES

To examine the possibility that the significant SNPs and haplotypes detected herein are merely markers for functional sequence changes in RAB7L1, we completed the analysis of its coding exons and exon-intron boundaries. Nine individuals were sequenced: 3 homozygous carriers of haplotype A, 3 homozygous carriers of haplotype B, and 3 heterozygous carriers of haplotype D (there was not even 1 homozygous carrier of haplotype D in our cohort). No additional sequence variations were found.

COMMENT

To our knowledge, our study demonstrates for the first time the association between the PARK16 locus and PD risk in the Ashkenazi Jewish population. The significance of this locus for PD was recently demonstrated in multiple population-based studies, suggesting that it may be involved in PD pathogenesis worldwide. However, other genome-wide association studies in Europeans and North Americans, including a large meta-analysis, and a study of a Spanish population could not confirm this association. Our results from the genetically homogeneous Ashkenazi population strengthen the importance of PARK16 in PD and add it to the short list of genes (eg, SNCA [PARK1/4], LRRK2 [PARK8], and GBA) that were already shown to affect PD risk in multiple populations.

We identified new genetic elements related to the reduced risk for PD. A highly protective haplotype associated with a 10-fold risk reduction (designated herein as haplotype D) was defined between the SLC41A1 and RAB7L1 genes. This haplotype includes 2 SNPs in the putative promoter region of RAB7L1 that alter predicted transcription factor binding sites. No coding or splice site alterations in RAB7L1 sequence were found that could explain the protective effect, suggesting that other, yet unknown, molecular mechanisms are involved. Although our analysis focused on the minor alleles and haplotypes that are associated with reduced PD risk, it is clear that in this locus there are genetic elements that are associated with increased risk for PD, such as haplotype A (Table 3). Our results do not rule out the possibility that other genes or genetic variations within the PARK16 region are responsible for its effect on PD.

The small LD block detected in our analysis of the PARK16 locus is approximately 10 kilobases long. This is smaller than the sizes of the PARK16 haplotypes expected in the Ashkenazi population. To better define the actual size, sequencing of the entire region is necessary. While the LD block described herein (eFigure) involves the RAB7L1 and SLC21A1 genes, previously published results suggested that the LD blocks in the Japanese and North American and European populations encompass a much larger region of about 160 kilobases, which includes 3 additional genes (SLC45A3, NUCKS1, and PM20D1). Differences in LD block sizes could have resulted from the different genotyping platforms used; the differences between populations tested, ie, their sizes and/or genetic homogeneity; or from a combination of any of these.

The function of the protein encoded by RAB7L1 (RAB7, member RAS oncogene familylike 1) is not known. The RAB7L1 gene homology to human RAB7 (OMIM 602298) suggests that it is a member of the Rab (Ras-related in brain) family of proteins. More than 60 Rab genes are spread across the human genome, and they function as regulators in different membrane traffic pathways. Mutations in RAB7 cause Charcot-Marie-Tooth type 2B neuropathy and knockdown of the Caenorhabditis elegans Rab7 gene caused severe growth and motor abnormalities selectively in α-synuclein transgenic worms. Other Rab proteins were also suggested to be involved in neurodegeneration and PD, including Rab1, Rab3a and Rab8a, and Rab11a.

To conclude, our data confirmed the association between the PARK16 locus and reduced PD risk and dem-

### Table 3. Frequencies of RAB7L1 Haplotypes in Ashkenazi Patients With PD and Controls

<table>
<thead>
<tr>
<th>Population</th>
<th>Designation</th>
<th>Variations</th>
<th>Patients (n = 1440)</th>
<th>Controls (n = 1284)</th>
<th>OR (95% CI)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Entire cohort</td>
<td>A</td>
<td>GCC</td>
<td>0.783</td>
<td>0.723</td>
<td>1.950 (1.250-3.044)</td>
<td>.003</td>
</tr>
<tr>
<td></td>
<td>B</td>
<td>AT</td>
<td>0.109</td>
<td>0.122</td>
<td>0.901 (0.697-1.164)</td>
<td>.424</td>
</tr>
<tr>
<td></td>
<td>C</td>
<td>AC</td>
<td>0.11</td>
<td>0.012</td>
<td>0.951 (0.466-1.939)</td>
<td>.889</td>
</tr>
<tr>
<td></td>
<td>D</td>
<td>GTT</td>
<td>0.011</td>
<td>0.012</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>E</td>
<td>ACC</td>
<td>0.015</td>
<td>0.012</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Patients without founder LRRK2 or GBA mutations</td>
<td>A</td>
<td>GCC</td>
<td>0.767</td>
<td>0.723</td>
<td>1.857 (1.125-3.066)</td>
<td>.016</td>
</tr>
<tr>
<td></td>
<td>B</td>
<td>AT</td>
<td>0.097</td>
<td>0.130</td>
<td>0.786 (0.571-1.027)</td>
<td>.074</td>
</tr>
<tr>
<td></td>
<td>C</td>
<td>AC</td>
<td>0.120</td>
<td>0.122</td>
<td>1.031 (0.779-1.363)</td>
<td>.833</td>
</tr>
<tr>
<td></td>
<td>D</td>
<td>GTT</td>
<td>0.001</td>
<td>0.013</td>
<td>0.877 (0.010-0.576)</td>
<td>.012</td>
</tr>
<tr>
<td></td>
<td>E</td>
<td>ACC</td>
<td>0.15</td>
<td>0.122</td>
<td>1.259 (0.602-2.635)</td>
<td>.540</td>
</tr>
</tbody>
</table>

Abbreviations: CI, confidence interval; OR, odds ratio; n, number of alleles; PD, Parkinson disease.

a The nucleotides represent rs947211, rs1772153, and rs1572931, respectively.
onstrated that alterations within the RAB7L1 putative promoter are associated with this effect. However, further studies are necessary to determine whether it is RAB7L1 or other genes or genetic elements in the PARK16 locus that are involved in modifying the risk for PD.

Accepted for Publication: May 4, 2011.

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Author Contributions: Dr Orr-Urtreger takes full responsibility for the integrity of the data and the accuracy of the data analysis. Study concept and design: Gan-Or, Giladi, and Orr-Urtreger. Acquisition of data: Gan-Or, Bar-Shira, Mirelman, Kedmi, Gurevich, Giladi, and Orr-Urtreger. Analysis and interpretation of data: Gan-Or, Dahary, and Orr-Urtreger. Drafting of the manuscript: Gan-Or and Orr-Urtreger. Critical revision of the manuscript for important intellectual content: Bar-Shira, Dahary, Mirelman, Kedmi, Gurevich, Giladi, and Orr-Urtreger. Statistical analysis: Gan-Or, Dahary, Kedmi, and Orr-Urtreger. Obtained funding: Giladi and Orr-Urtreger. Administrative, technical, and material support: Mirelman, Gurevich, Giladi, and Orr-Urtreger. Study supervision: Bar-Shira, Giladi, and Orr-Urtreger.

Financial Disclosure: None reported.

Funding/Support: This work was supported by a Tel-Aviv Sourasky Medical Center Grant of Excellence, the Kahn Foundation, Chief Scientist of the Ministry of Health grant 3-4893, and Legacy Heritage Biomedical Science Partnership Program of the Israel Science Foundation grant 1922/08

Online-Only Material: The eTables and eFigure are available at http://www.archneurol.com.

Additional Contributions: We thank Mali Gana-Weisz, PhD, Idan Amshalom, BMedSci, and Liron Rozenkrantz, BA, for their assistance. This work was performed in partial fulfillment of the requirements for a PhD degree of Mr Gan-Or, Sackler Faculty of Medicine, Tel Aviv University, Tel Aviv, Israel.

REFERENCES