R869C mutation in molecular motor KIF17 gene is involved in dementia with Lewy bodies

Orly Goldstein1 | Mali Gana-Weisz1 | Tamara Shiner2,3,4 | Reut Attar1 | Yael Mordechai1 | Yedael Y. Waldman5 | Anat Bar-Shira1 | Avner Thaler3,4,6 | Tanya Gurevich3,4 | Anat Mirelman3,4,6 | Nir Giladi3,4,6 | Avi Orr-Urtreger1,4

1 The Genomic Research Laboratory for Neurodegeneration, Neurological Institute, Tel Aviv Sourasky Medical Center, Tel Aviv, Israel
2 Cognitive Neurology Unit, Neurological Institute, Tel Aviv Sourasky Medical Center, Tel Aviv, Israel
3 Movement Disorders Unit, Neurological Institute, Tel Aviv Sourasky Medical Center, Tel Aviv, Israel
4 Sackler Faculty of Medicine, and Sagol School of Neuroscience, Tel Aviv University, Tel Aviv, Israel
5 NRGene Ltd., Ness-Ziona, Israel
6 Laboratory for Early Markers of Neurodegeneration, Neurological Institute, Tel Aviv Sourasky Medical Center, Tel Aviv, Israel

Abstract

Introduction: The GBA-N370S mutation is one of the most frequent risk factors for dementia with Lewy bodies (DLB) and Parkinson’s disease (PD). We looked for genetic variations that contribute to the outcome in N370S-carriers, whether PD or DLB.

Methods: Whole-genome sequencing of 95 Ashkenazi-N370S-carriers affected with either DLB (n = 19) or PD (n = 76) was performed, and 564 genes related to dementia and PD analyzed.

Results: We identified enrichment of linked alleles in PINK1 locus in DLB patients (false discovery rate $P = .0412$). Haplotype analysis delineated 1.8 Mb interval encompassing 29 genes and 87 unique variants, of them, KIF17-R869C received the highest functional prediction score (Combined Annotation Dependent Depletion = 34). Its frequency was significantly higher in 26 DLB-N370S-carriers compared to 140 PD-N370S-carriers (odds ratio [OR] = 33.4 $P = .001$, and OR = 70.2 when only heterozygotes were included).

Discussion: Because KIF17 was shown to be important for learning and memory in mice, our data further suggest, for the first time, its involvement in DLB, and possibly in human dementia.

KEYWORDS dementia with Lewy bodies, GBA, KIF17, Parkinson’s disease, risk allele

1 INTRODUCTION

Dementia with Lewy bodies (DLB) is the second most common form of neurodegenerative dementia after Alzheimer’s disease (AD), and shares clinical and pathological features, as well as genetic risk alleles, with both Parkinson’s disease (PD) and AD. The central feature of DLB is dementia, which often occurs with parkinsonism. When the parkinsonism occurs concurrently or within the first year of the onset of dementia, it is distinguished from PD dementia (PDD). In addition, patients may suffer from fluctuations in cognition and attention, visual hallucinations, and REM sleep behavior disorder.

In DLB patients, alpha-synuclein Lewy bodies (LBs), and amyloid beta and tau depositions are reported, while in PD, alpha-synuclein LBs are mostly observed. As opposed to PD, in which extended genetic knowledge has been accumulated in the past decade, our understanding of the genetic etiology of DLB is limited. Nevertheless, several
studies, using different approaches, identified common and rare risk alleles. In familial DLB, mutations in EIF4G, SNCA, PARK2, CHMP2B, PSEN2, SQSTM1, and others were reported (for reviews see Orme et al. and Vergouw et al.). The more common risk alleles were detected in a recent genome-wide association study (GWAS), an unbiased approach, in which apolipoprotein E (APOE), synuclein alpha (SNCA), and glucosylceramidase beta (GBA) were identified as significant loci in two independent cohorts, as well as a new probable locus, contactin 1 (CNTN1). The GBA-N370S mutation is the most common GBA risk allele for both DLB and PD worldwide, and more specifically in Ashkenazi Jews (AJ). There is not yet an explanation or presumption to why a GBA-N370S carrier will develop PD and not DLB, and vice versa. In this study we aimed to identify additional genetic variations carried by AJ individuals with the GBA-N370S mutation, which may contribute to the risk of an individual developing DLB rather than PD.

2 | METHODS

2.1 | Study cohorts

The DLB cohort included 99 unrelated patients of AJ origin (28% females), with average age at disease onset (AAO) of 69.92 (±7.08), who were consecutively recruited between 2013 and 2020. The PD cohort included a total of 1200 unrelated patients of AJ origin (39.7% females, AAO = 60.56 (±10.96), who were consecutively recruited between 2005 and 2016. Information about this cohort regarding recruitment, diagnosis, and sample collections, was previously described. All patients were examined at the Neurological Institute in the Tel Aviv Sourasky Medical Center, Israel, and the diagnosis of DLB or PD was confirmed by expert neurologists.

The control cohort included 334 elderly AJs (64.1% females, average age at enrollment 71.9±9.4) with no neurological symptoms confirmed by a neurologist (n = 111) or self-reported.

2.2 | Genotyping the founder AJ-PD mutations in GBA and LRRK2

All DLB, PD, and control individuals (n = 1633) were genotyped for the nine founder mutations in GBA and the LRRK2-G2019S mutation as previously described.

2.3 | Whole-genome sequencing and bioinformatics analysis

The complete genomes of 95 GBA-N370S carriers (19 DLB and 76 PD patients) were sequenced (WGS). This was carried out on DNBseq technology in a BGI Group facility in China, with an average 30X depth coverage. Paired-end reads (each of 100 bp length) were aligned to the human reference genome (GRCh38 build) using the BWA tool. We applied the Genome Analysis Toolkit (GATK4) on the alignment data of each sample for variant calling. This included marking duplicates (by Picard tools: http://broadinstitute.github.io/picard), base quality score recalibration (BQSR), local re-assembly of haplotypes and variant quality score recalibration (VQSR), as recommended by GATK’s best practices.

Variant extraction from a list of 564 genes annotated to dementia (n = 149), PD (n = 373), or both diseases (n = 42), including full transcripts and 1 Kb upstream and downstream to each gene (a total target of 36.86 Mb, Table S1 in supporting information), was done with SNP & Variation Suite v8.8.3 (Golden Helix, Inc.: www.goldenhelix.com), 

HIGHLIGHTS

1. Dementia with Lewy bodies (DLB) and Parkinson’s disease (PD) share a risk factor, GBA-N370S.
2. Do additional variants contribute to the risk of developing DLB rather than PD?
3. Whole-genome sequencing was performed for 19 DLB and 76 PD carriers of GBA-N370S.
4. The KIF17-R869C mutation is significantly enriched in DLB over PD (odds ratio 70.2).
5. KIF17 is involved in DLB and its potential role in dementia should be explored.

RESEARCH IN CONTEXT

1. Systematic review: The authors reviewed the literature using PubMed, Google Scholar, meetings, and presentations. The etiology of dementia with Lewy bodies (DLB) is largely unknown, although genetic risk factors were identified. Mutations in GBA are a known risk for both DLB and Parkinson’s disease (PD), most commonly N370S. The relevant citations are appropriately cited.
2. Interpretation: to understand why GBA-N370S carriers develop DLB and not PD we looked for additional risk alleles in genes associated with dementia and PD, and show that in GBA-N370S heterozygotes, carrying the KIF17-R869C mutation increases the risk for DLB over PD (odds ratio 70.2, P = .001, corrected for sex and age at disease onset).
3. Future directions: As PD and DLB are on the parkinsonism/dementia spectrum, with overlapping symptoms, we need to detect biomarkers that will help differentiate between these disorders. The role of KIF17 in DLB and dementia should further be studied in larger patient populations and in animal models.

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and evaluated for functional effect using the prediction tool CADD (Combined Annotation Dependent Depletion, version 1.5). Variants were filtered out if read depth was less than 10 and quality score genotype quality (GQ) less than 30.

2.4 | Genotyping the KIF17-R869C mutation

All DLB, PD, and control individuals (n = 1633) were genotyped for the KIF17-R869C mutation (rs141369367, TaqMan genotyping assay C_166301394_10; Applied Biosystems). Confirmation for the KIF17 mutation was done by polymerase chain reaction and Sanger Sequencing (Table S2 in supporting information).

2.5 | Statistical analysis

Statistical analyses for basic allelic was done with SNP & Variation Suite v8.8.3, comparing variants observed in the 19 GBA-N370S-DLBs to the 76 GBA-N370S-PDs. For the full cohorts of DLB, PD, and controls, Fisher’s exact test or Chi-square test was used in categorical variables. To test for any deviation from Hardy-Weinberg equilibrium a goodness-of-fit test with 1 degree of freedom was applied. Odds ratio (ORs) and 95% confidence intervals (CI) were determined using an online calculator (https://www.medcalc.org). Logistic regression analysis for GBA-N370S-DLB and PD patients was done with SPSS software V25 (SPSS Inc.) for the model: disease ~ sex+AAO+KIF17, using sex, AAO, and rs141369367-carrier status as covariates. The information regarding years of education was available for 96.8% of the DLB patients with GBA-N370S or non-carriers (91/94), and for 351/927 (37.9%) of GBA-N370S-carrier or non-carrier PD patients. As the comparison between these two groups did not show significant difference (data not shown) we did not include years of education as a covariate in our logistic regression model.

For the logistic regression analysis of both GBA-N370S carriers and non-carriers together, the following model was used:

\[
\text{Disease} \sim \text{sex+AAO+N370S+KIF17+N370S*KIF17},
\]

where disease was zero for PD and one for DLB, and N370S*KIF17 was the interaction term, where zero was for individuals that do not carry both GBA-N370S and KIF17-R869C, and one for individuals that carry both mutations.

2.6 | In silico protein pathogenicity analysis

We evaluated the conservation of the KIF17-R869 region and its evolutionary constrains using Aminode and the effect of the mutation on the protein secondary structure using Phyre2. QP2E2 was entered as a query, and in the mutated protein amino acid arginine-869 was replaced with cysteine. We assessed protein stability using three different tools: I-Mutant, MUpro, and iStable. We used IntFOLD and VarSite for additional assessment of KIF17-R869C pathogenicity.

2.7 | Ethical approval and consent for publication

All participants provided informed consent before entering the study. All DNA samples were coded and tested in an anonymous manner. The Institutional and National Supreme Helsinki Committees for Genetics Studies approved the study protocols and informed consents.

3 | RESULTS

3.1 | A unique haplotype in PINK1 region is enriched in DLB-GBA-N370S-carrier patients

A total of 269,022 variants were identified within our 564 PD/dementia genes’ map. The frequencies of 23 variants were significantly enriched in DLB-GBA-N370S-carrier patients compared to PD-GBA-N370S-carriers (allelic association, false discovery rate [FDR], P-value = .0411). Of them, 19 were linked in 5 DLB patients, all in the PINK1 locus, suggesting the presence of a unique identical-by-descent haplotype shared by these patients. There was no hidden relatedness among these individuals (data not shown). Because all these variants received CADD Phred score lower than 10 (range 0.05 – 9.01, Table S3 in supporting information), and therefore are less likely to have a pathogenic effect, we expanded the analyses to a 3Mb interval flanking these hits. A shared haplotype was delineated by recombinants at position 20,116,198 at the proximal 5’-end, and at position 21,914,692 at the distal 3’-end (Figure 1A), encompassing 29 genes with 87 unique single nucleotide variants (SNVs) in a 1.8 Mb interval (Table S4 in supporting information; Figure 1B).

Four additional significant intronic variants were also found in FYN (n = 1) and CNTN1 (n = 3; Table S3). Haplotype analyses for these hits identified 827.4Kb and 318.6Kb blocks that included 14 and 3 unique SNVs, respectively, but none had a CADD Phred score higher than 12 (data not shown). Of note, when excluding patients with suspected PDD (n = 15), the re-analysis demonstrated the same results.

3.2 | KIF17-R869C is enriched in DLB-GBA-N370S-carriers but not in PD-N370S-carriers

The variant with the highest CADD Phred score in the 1.8 Mb interval was a missense mutation in KIF17 (NM_020816.3:c.2605C>T; NP_065867.2:p.R869C, rs141369367, CADD = 34 = top 0.1% of all CADD scores). We therefore expanded the analysis of KIF17-R869C and genotyped all AJ-DLB and PD patients who were either GBA-N370S heterozygotes, GBA-N370S homozygotes, or compound heterozygotes. Among the N370S heterozygote carriers, 25% of DLBs (5/20) and 1.6% of PDs (2/124) carried KIF17-R869C. Of note, the two PDs that carried the KIF17 mutation had an early AAO of 43 and 46 years. After correcting for sex and AAO, OR was 70.2 (95% CI: 6.3 – 778.9, P = .001, Table 1A). Of note, when excluding patients with...
In this analysis, the OR of KIF17-R869C mutation was 2.3 but not significant ($P = .218, 95\%\ CI: 0.608–8.851$), the OR of GBA-N370S was 2.272 ($P = .004, 95\%\ CI: 1.302–3.965$), and the OR of the interaction covariate GBA-N370S*KIF17-R869C was 13.953 ($P = .03, 95\%\ CI: 1.296–150.17$).

3.3 | KIF17-R869C increases the risk of developing DLB but not PD

After genotyping our entire cohort of Ashkenazi DLB ($n = 99$) and the PD ($n = 1200$) patients, we compared the KIF17-R869C mutation frequency in DLBs and PDs to our 334 elderly AJ controls, and to gnomAD-AJ-non-neuro samples reported in the gnomAD database (version 2.1.1). Significant association of rs141369367 with DLB was observed compared to both our control cohort and the gnomAD-AJ-non-neuro samples, based on the allele frequencies of gnomAD-AJ-non-neuro samples, based on the allele frequencies.
### TABLE 1  
Associations and odds ratios of KIF17-R869C in dementia with Lewy bodies disease and Parkinson’s disease

| Disease status (PD = 0, DLB = 1) | Logistic regression analysis results (DLB compared to PD) |
|----------------------------------|----------------------------------------------------------|
|                                  | Beta | S.E. | P-value | OR (Exp(Beta)) | 95% CI of OR |
| DLB                              | 5    | 49   | –1.215  | 0.689         | 0.30         | 0.08-1.15  |
| PD                               | 4251 | 1228 | .001    | 70.21         | 6.34-778.90  |

#### A. Association of KIF17-R869 mutation in GBA-N370S/+ heterozygotes carriers

| Number | Sex, female (%) (M = 0, F = 1) | Average AAO (SD) | KIF17-R869C carriers (%) (non-carrier = 0, carrier = 1) |
|--------|--------------------------------|-----------------|------------------------------------------------------|
| 20     | 5 (25.0) 49 (39.5)             | 68.95 (8.5)     | 5 (25.0) 2 (1.6)                                      |
| 124    | –1.215 0.689                   | 0.133           | 4.251 1.228                                         |
|        | .078 0.30                       | <.001           | .001 70.21                                          |
|        | 0.08-1.15                       | 1.06-1.23       | 6.34-778.90  |

#### B. Association of KIF17-R869 mutation in GBA-N370S carriers (including homozygotes and compound heterozygotes)

| Number | Sex, female (%) (M = 0, F = 1) | Average AAO (SD) | KIF17-R869C carriers (%) (non-carrier = 0, carrier = 1) |
|--------|--------------------------------|-----------------|------------------------------------------------------|
| 26     | 7 (26.9) 57 (40.7)             | 67.69 (9.3)     | 5 (19.2) 2 (1.4)                                      |
| 140    | –0.842 0.546                   | 0.099           | 3.507 1.053                                         |
|        | .123 0.43                       | <.001           | .001 33.36                                          |
|        | 0.15-1.26                       | 1.05-1.17       | 4.24-262.63  |

#### C. Association of KIF17-R869 mutation in non-carriers

| Number | Sex, female (%) (M = 0, F = 1) | Average AAO (SD) | KIF17-R869C carriers (%) (non-carrier = 0, carrier = 1) |
|--------|--------------------------------|-----------------|------------------------------------------------------|
| 68     | 18 (26.5) 297 (37.1)           | 70.96 (5.9)     | 3 (4.4) 18 (2.3)                                      |
| 787    | –0.608 0.296                   | 0.099           | 0.834 0.683                                         |
|        | .04 0.54                       | <.001           | .222 2.30                                          |
|        | 0.31-0.98                       | 1.07-1.14       | 0.60-8.78  |

#### D. Genotypic (G) or allelic (A) association of KIF17-R869C with DLB or PD neurodegenerative diseases

| Number of alleles (number of individuals) | Sex, female (%) | KIF17-R869C alleles (%) | Comparison | P-value | Odds ratio | 95% CI of OR |
|------------------------------------------|----------------|-------------------------|------------|---------|------------|--------------|
| DLB                                      | 198 (99)       | 8 (4.0)                 | Compare to controls | .013    | 3.58 (G)   | 1.31-9.81    |
|                                          |                |                         | Compare to gnomAD  | .008    | 2.70 (A)   | 1.30-5.64    |
| PD                                       | 2400 (1200)    | 30 (1.3)                | Compare to controls | .907    | 1.05 (G)   | 0.48-2.31    |
|                                          |                |                         | Compare to gnomAD  | .323    | 0.81 (A)   | 0.54-1.23    |
| Controls                                 | 668 (334)      | 214 (64.1)              | 8b (1.2)    |         |            |              |
| gnomAD-AJ-non-neuro                      | 6456 (3228)    | 1572 (48.7)             | 99 (1.5)    |         |            |              |

**Abbreviations:** AAO, age at onset; AJ, Ashkenazi Jew; CI, confidence interval; DLB, dementia with Lewy bodies disease; OD, odds ratio; PD, Parkinson’s disease; SD, standard deviation.

*AAO was missing for 2 PD patients.

*All KIF17 mutation carriers were non-carriers of any of the GBA founder mutations or the LRRK2-G2019S mutation.

(GBA-N370S and KIF17-R869C), but not for PDs (OR = 1.08, 95% CI: 0.21–5.55, P = .9302).

#### 3.4 Is there additional evidence for pathogenicity of KIF17-R869C?

Along the KIF17 protein structure, arginine-869 is predicted to be part of an evolutionary constrained region (ECR), a region with relatively low substitution rates (Figure 2A red line in upper and lower panels; ECR, top orange band in lower panel), whereas this amino acid is specifically highly conserved (Figure 2A lower panel, red box). Moreover, modeling the secondary structure of KIF17 protein, with and without the mutation, shows that the alpha-helix secondary structure is modified by the presence of the mutant amino acid cysteine (Figure 2B).

Protein stability was predicted to be decreased or largely decreased by three different prediction tools (delta-delta-G of –1.03, –0.725, and –1.07 by I-Mutant, MUpro, and iStable, respectively). Another web
FIGURE 2  The evolutionary conservation of KIF17-R869-arginine (A), and the predicted effect the 869-cytosine mutation on the protein secondary structure (B), support its pathogenicity. A, Multiple sequence alignments and evolutionary constrained regions (ECRs) of KIF17 generated by Aminode. Upper panel presents the full KIF17 protein and the lower panel the mutated region, demonstrating that KIF17-R869 is highly conserved during evolution. The red line represents the relative rate of amino acid substitution calculated at each protein position. Local minima (highlighted by yellow bars above the graph) are ECRs with relatively low amino acid substitution rates. Peaks (local maxima) indicate regions with relatively high substitution rates. B, Phyre2 modeling for protein secondary structure of wild-type KIF17-R869 (upper panel) and mutant KIF17-C869 (lower panel). Arrow is depicting the difference in secondary protein structure, changing an alpha-helix (green in the wild-type protein) to coil (black line in the mutant protein).

4 | DISCUSSION

DLB and PD are heterogeneous diseases with many similarities in their clinical features, making diagnosis challenging. We studied the relatively genetically homogenous population, AJs, and clinically characterized cohorts of DLB and PD patients, to decipher the genetic differences between those who carry the common risk GBA-N370S and develop DLB compared to those who carry GBA-N370S and develop PD. We identified a significant enrichment of KIF17-R869C in the DLB cohort. This variant is extremely rare in world populations (allele frequencies of zero to 0.00219 by gnomAD database version 3.0) but is more frequent among AJs (allele frequency 0.015 in gnomAD database version 2.1 non-neuro individuals), making the AJ patient...
cohort suitable to study its effect. However, it is possible that other pathogenic variants in KIF17 may play a role in DLB in other world-wide populations.

The change of arginine to cysteine at position 869 in the C-terminus is suggested to be pathogenic by CADD. Moreover, this amino acid is located in an evolutionarily constrained region, which suggests that the change is likely deleterious under the reasoning that a site that has been intolerant to changes over long periods of evolutionary time is important for the protein function. In addition, protein structure models predict that R869 is part of an alpha-helix secondary structure that might change as a result of the substitution of arginine with cysteine, that the mutation might change the protein domains and domains’ boundaries, and that protein stability will be decreased in the mutant. As it has already been shown that the most mutated amino acid within secondary structural elements, among disease-causing mutations, is arginine, and the most mutant amino acid is cysteine, we further suggest that KIF17-R869C is a likely pathogenic mutation. Therefore, functional studies are needed to verify the potential effect of KIF17-R869C mutation, and its effect on genes and cellular pathways that are involved in dementia.

KIF17 belongs to the kinesin superfamily proteins (KIFs), which are molecular motors, using ATP energy to transport cargo along microtubules. These proteins mediate primarily fast anterograde transport, away from the cell body. KIF17 selectively transport glutamate ionotropic receptor NMDA type subunit 2B (GRIN2B; NR2B) in vesicles along microtubules from the cell body exclusively to dendrites of neurons. This interaction is done at the C-terminus tail by the mLin complex (KIF17 → mLin10 [APBA1] → mLin2 [CASK] → mLin7), and at destination, NR2B forms an integral subunit of the postsynaptic glutamatergic NMDA receptor. The interaction is regulated by CamkII, which phosphorylates KIF17’s tail region, at serine-1029 in mice.

Mice model experiments showed the importance of NR2B and KIF17 for learning and spatial memory. Knockdown experiments of KIF17 with antisense downregulated the expression of NR2B and mLin10, for learning and spatial memory. Knockdown experiments of neurons. This interaction is done at the C-terminus tail by the mLin complex (KIF17 → mLin10 [APBA1] → mLin2 [CASK] → mLin7), and at destination, NR2B forms an integral subunit of the postsynaptic glutamatergic NMDA receptor. The interaction is regulated by CamkII, which phosphorylates KIF17’s tail region, at serine-1029 in mice. Mice model experiments showed the importance of NR2B and KIF17 for learning and spatial memory. Knockdown experiments of KIF17 with antisense downregulated the expression of NR2B and mLin10, and reduced the basal whole cell NMDA receptor current in prefrontal cortical neurons. Because NR2B plays a role in long-term potentiation and learning and memory, and it is KIF17’s cargo, all studies mentioned above, together, link KIF17 to learning and memory, too. Indeed, experiments in mouse models strongly suggested that KIF17 plays an important role in learning and memory: over expression of KIF17 in transgenic mice enhanced spatial and working memory, and loss-of-function of KIF17−/− mice showed reduced NR2B, impaired long-term potentiation and performance in learning and memory.

As the calculated OR for DLB in AJ carriers of dual mutations (KIF17-R869C and GBA-N370S) is much higher (OR = 34.29) compared to the OR of carrying only one of these mutations separately (3.58 and 4.92 [data not shown], respectively), it is possible that there is some form of interaction between these two genes or their products, as suggested by our analysis of PD and DLB patients. Although past experiments in a rat model of PD showed that injection of AAV2-A53T-alpha-synuclein into the substantia nigra results in KIF17 protein level reduction 4 weeks after injection, no significant changes of KIF17 protein levels were detected in mice treated with inhibitor of GCase (the enzyme beta-glucocerebrosidase, which is encoded by the GBA gene). It is therefore yet to be determined if there is genetic and/or biological interaction between KIF17 and GBA.

In summary, we show for the first time the enrichment of KIF17-R869C in DLB patients and suggest that it is likely a pathogenic mutation. As the genetic basis of DLB is complex, most probably oligogenic/polygenic as in PD, KIF17-R869C significantly increases the risk of GBA-N370S carriers for DLB, but not for PD. Further studies are warranted on the molecular mechanisms in which KIF17-R869C acts. Follow-up studies are necessary to investigate the involvement of genetic variations in KIF17 in patients from different worldwide populations and ethnic origins; their potential interaction with GBA; and because KIF17 may be related to human dementia, its possible involvement in other forms of clinical dementia. Additional studies of molecular motor genes and proteins involved in cargo transport may also expand our understanding of dementia pathophysiology.

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CONFLICTS OF INTEREST

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AUTHOR CONTRIBUTIONS

Design and conceptualization: Orly Goldstein, Avi Orr-Urtreger. Data acquisition: Orly Goldstein, Mali Gana-Weisz, Tamara Shiner, Yedael Y. Waldman, Anat Bar-Shira, Avner Thaler, Anat Mirelman. Analysis of the
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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section at the end of the article.

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