

## CORRESPONDENCE



## TREM2 and Neurodegenerative Disease

**TO THE EDITOR:** Guerreiro et al.<sup>1</sup> and Jonsson et al.<sup>2</sup> (Jan. 10 issue) report an association between the single-nucleotide polymorphism (SNP) rs75932628 in the gene encoding the triggering receptor expressed on myeloid cells 2 (*TREM2*) (predicting an R47H substitution) and Alzheimer's disease in persons of European ancestry.

We and other members of the Alzheimer's Disease Genetics Consortium assembled multiple data sets from a total of 5896 black patients (1968 cases and 3928 controls). First, the association of Alzheimer's disease with genotyped and imputed SNPs was individually assessed in each data set with the use of logistic regression for case-control data sets and generalized estimating equations for family-based data sets (with adjustment for age, sex, the presence or absence of the apolipoprotein E [*APOE*]  $\epsilon$ 4 allele, and population stratification). The results from the individual data sets were combined in a genomewide inverse-variance-weighted meta-analysis. Subsequently, a versatile gene-based association study (VEGAS)<sup>3</sup> was performed specifically to explore the association of the *TREM2* gene with Alzheimer's disease; the addition of 20 kb to each side yielded a list of SNPs (see the Supplementary Appendix, available with the full text of this letter at NEJM.org). With the use of

simulation based on the linkage-disequilibrium structure of a group of reference samples from HapMap, VEGAS allowed us to calculate the empirical P value for associations between disease status and variants in *TREM2* while taking into account gene size and linkage disequilibrium between the markers.<sup>3</sup>

The *TREM2* SNP described by Guerreiro et al. and Jonsson et al. (rs75932628) did not pass quality control because of a low minor allele frequency (0.0009). However, in the genomewide meta-analyses of the results from the individual data sets, five SNPs in the *TREM2* region were associated with Alzheimer's disease at a P value of less than 0.009; the G allele of rs7748513 was most strongly associated with affected status (odds ratio  $\pm$ SE, 1.16 $\pm$ 0.05; P=0.001). This SNP is located 1 kb downstream of and in linkage disequilibrium with rs75932628. In the VEGAS analyses in which linkage disequilibrium between the markers was taken into account, the *TREM2* gene was significantly associated with Alzheimer's disease (P<0.001). Also, in these analyses, the strongest single-marker association was observed for rs7748513 (P=0.001). Finally, in VEGAS analyses that were restricted to the largest individual data set (907 cases and 1675 controls), the *TREM* gene remained significantly associated with Alzheimer's disease (P=0.04). This genetic study of Alzheimer's disease in blacks provides support for a role of *TREM2* in Alzheimer's disease.

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No potential conflict of interest relevant to this letter was reported.

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**TO THE EDITOR:** Alzheimer's disease is a genetically heterogeneous disorder characterized by the coexistence of monogenic and genetically complex forms. Given the high heritability of the disease, the quest to identify genetic variants that confer risk has been pursued for more than three decades,<sup>1</sup> with the recent discovery, reported by Guerreiro et al. and Jonsson et al., of rare sequence variants in *TREM2*.

The authors of both studies point out that although the T allele at rs75932628 is rare (minor allele frequency, approximately 0.005), estimates of the effect size suggested an odds ratio ranging from 3 to 4, which is similar to that of the *APOE*  $\epsilon$ 4 allele. However, the risk of the development of Alzheimer's disease among homozygous carriers of *APOE*  $\epsilon$ 4 is approximately 15 times as high as that among noncarriers,<sup>2</sup> whereas homozygous carriers of the T allele of rs75932628 have been reported either to not exist (as in the study by Guerreiro et al.) or to be present in equal proportions among cases and controls (as in the study by Jonsson et al.).

To further assess the effect size of the T allele at rs75932628, we genotyped 6421 samples. We used TaqMan to genotype samples obtained from family-based data sets from the National Institute of Mental Health (NIMH), the National Cell Repository for Alzheimer's Disease, and the National Institute on Aging Late Onset Alzheimer's Disease and National Cell Repository for Alzheimer's Disease Family Study (NIA-LOAD). We used IMPUTE software, version 2.2, and the 1000 Genomes Project phase 1 reference panels to genotype samples obtained from case-control data sets from the NIA-LOAD, Genetic Alzheimer's Disease Associations, Translational Genomics Research Institute series 2, and the Alzheimer's Disease Neuroimaging Initiative (ADNI).<sup>2</sup> We then tested for association with the risk of Alzheimer's disease using additive transmission models preparation.

A meta-analysis that combined sample-specific results revealed weak, but nominally sig-

nificant, support of an association between the T allele at rs75932628 and an increased risk of Alzheimer's disease ( $P \leq 0.05$ ). The effect size estimated in our analyses, however, suggests a substantially lower odds ratio of approximately 1.7, which is consistent with the lower 95% confidence interval boundaries in the articles by Guerreiro et al. and Jonsson et al. This discrepancy suggests that the original findings were inflated by the "winner's curse."<sup>3</sup> Even assuming an odds ratio of approximately 4, this would translate into a very small effect of the T allele at rs75932628 on the risk of Alzheimer's disease in the population as a whole, given the very low prevalence of the variant (approximately 0.5%). This effect can be estimated by calculating the population attributable fraction, which is 1.5% or less for rs75932628 ( $\leq 0.5\%$  when assuming the more realistic odds ratio of approximately 2); these fractions are hardly comparable to the 25% or more estimated for the *APOE*  $\epsilon$ 4 allele.<sup>2</sup> Thus, the tiny population effect and reduced penetrance of the T allele at rs75932628 in *TREM2* would limit its usefulness as being either a predictor or diagnostic for Alzheimer's disease.

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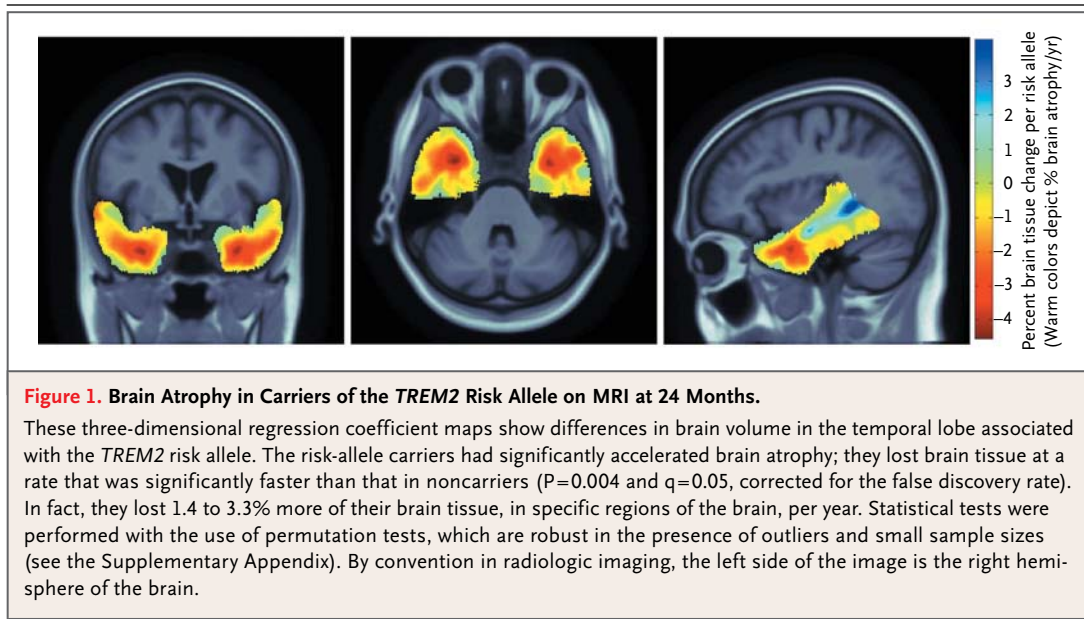
No potential conflict of interest relevant to this letter was reported.

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**TO THE EDITOR:** We were intrigued by reports of a discovery of a rare variant in *TREM2*<sup>1</sup> that roughly triples the lifetime risk of Alzheimer's disease. The frequency of this risk variant was reported as being 0.63% in the Icelandic population and somewhat variable across populations reported in the literature (see the Supplementary Appendix, available with the full text of this letter at NEJM.org).

We sought to understand how the gene variant affects the risk of Alzheimer's disease by



mapping its effects on the brain in 478 persons (mean age [ $\pm$ SD], 75.5 $\pm$ 6.5 years) from the ADNI who underwent brain magnetic resonance imaging (MRI) once a year for 2 years.<sup>2</sup> This study group involved 283 men and 195 women; 100 participants had Alzheimer's disease, 221 had mild cognitive impairment, and 157 were healthy controls. Using tensor-based morphometry, we computed the rates of brain-tissue loss per year over 24 months from the baseline MRI in a statistically defined region of interest within the temporal lobes; this region was based on voxels with significant rates of atrophy over time in Alzheimer's disease.<sup>2</sup> We then tested the hypothesis that annual rates of brain-volume loss over time in this region are associated with carrying the risk allele of rs9394721, a close proxy for the newly discovered risk variant rs75932628 in *TREM2* ( $r^2=0.492$ ) (see the Supplementary Appendix of our letter). The *TREM2* mutation carriers annually lost 1.4 to 3.3% more of their brain tissue than noncarriers in a pattern that mirrored the profile of Alzheimer's disease in the brain (Fig. 1). Mutation carriers lost brain tissue twice as fast as healthy elderly people (Table 2S in the Supplementary Appendix of our letter). Assessment at baseline MRI and after 24 months' follow-up (Table 1S in the Supplementary Appendix of our letter) showed that after adjustment for age and sex, the risk allele was also significantly associated with smaller hippocampal volumes and elevated levels of cerebrospinal fluid

biomarker p-tau181p, which are usually observed in Alzheimer's disease,<sup>3</sup> and poorer cognitive performance according to the standard Clinical Dementia Rating Scale and Alzheimer's Disease Assessment Scale.

The *TREM2* risk variant may affect signaling by *TREM2* receptors expressed on microglial cells in the brain, perhaps interfering with the antiinflammatory functions of these cells and their removal of apoptotic tissue. This may affect brain amyloid clearance, leading to Alzheimer's disease-like neurodegeneration and accelerated cognitive decline. We think that selection of carriers of this risk variant and probably other *TREM2* risk variants for enrollment in trials of interventions for Alzheimer's disease, in which MRI scans are used in obtaining outcomes, would increase the power of such trials.

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No potential conflict of interest relevant to this letter was reported.

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**TO THE EDITOR:** The finding that a rare nonsynonymous variant in *TREM2* (R47H, rs75932628-T) confers a risk of Alzheimer's disease (odds ratio, 2 to 5)<sup>1</sup> and the finding that rare variants in other Alzheimer's disease–related genes confer a risk of several other neurodegenerative diseases<sup>2</sup> prompted us to ask whether R47H confers a risk of Parkinson's disease.

Several other observations supported our hypothesis that *TREM2* variation may confer susceptibility to Parkinson's disease. *TREM2* is expressed mainly on microglia in the central nervous system and appears to mediate the phagocytosis of apoptotic neurons.<sup>3</sup> Microgliosis has been implicated in the pathogenesis of Parkinson's disease, a neurologic disorder characterized by degeneration of dopaminergic neurons in the substantia nigra pars compacta. Dopaminergic neurons express ligands that interact directly with *TREM2*,<sup>3</sup> and *TREM2* messenger RNA levels in the substantia nigra are the second highest among all brain regions. In addition, pathological findings in *TREM2* variant carriers have shown the presence of abundant Lewy bodies, a hallmark of Parkinson's disease.

We directly genotyped rs75932628, which encodes the R47H variant, in 478 patients with Parkinson's disease and 837 healthy persons from the Movement Disorders Center at Washington University in St. Louis<sup>4</sup> as well as in 654 patients with Parkinson's disease and 550 con-

**Table 1. Association between the rs75932628-T Variant and Parkinson's Disease in Samples Obtained from Two Groups with Different Genetic Backgrounds.\***

| Study Group           | Cases    |                        | Controls        |                        | P Value |
|-----------------------|----------|------------------------|-----------------|------------------------|---------|
|                       | Patients | Minor Allele Frequency | Healthy Persons | Minor Allele Frequency |         |
|                       | no.      | %                      | no.             | %                      |         |
| Washington University | 478      | 0.30                   | 837             | 0                      | 0.02    |
| University of Navarra | 654      | 0.45                   | 550             | 0                      | 0.02    |
| Both groups           | 1132     |                        | 1387            |                        | 0.005   |

\* Comparisons were assessed with the use of the Cochran–Mantel–Haenszel chi-square test, with 1 degree of freedom for each series and 4 degrees of freedom for the combined analysis.

trols from the Memory Disorders Unit at the University Clinic of Navarra of the University of Navarra School of Medicine in Pamplona, Spain.<sup>1</sup> A diagnosis of Parkinson's disease was established according to the United Kingdom Brain Bank criteria. We found three R47H heterozygous carriers among the U.S. patients with Parkinson's disease and six among the Spanish patients with Parkinson's disease, but we did not find any R47H heterozygous carriers among the screened controls (Table 1). The R47H variant was associated with Parkinson's disease in both the U.S. sample (P=0.02) and the Spanish sample (P=0.02). The combined analysis confirmed the association of the R47H variant with Parkinson's disease (P=4.7×10<sup>-3</sup>). These results suggest that the R47H variant not only increases the risk of Alzheimer's disease, but also increases the risk of Parkinson's disease.

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No potential conflict of interest relevant to this letter was reported.



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**TO THE EDITOR:** Jonsson et al. and Guerreiro et al. both report an association of a heterozygous DNA variant in *TREM2* with late-onset Alzheimer's disease. Homozygous mutations in *TREM2* were previously shown to be associated with a rare autosomal recessive disease called polycystic lipomembranous osteodysplasia with sclerosing leukoencephalopathy and presenile dementia (Nasu-Hakola disease). In their editorial, Neumann and Daly<sup>1</sup> state that "amyloid plaques have not been reported in patients with Nasu-Hakola disease." This association has been reported, although it has been buried in the older literature. In a 1983 article,<sup>2</sup> my colleagues and I described a family with Nasu-Hakola disease, and in 2002, Paloneva et al.<sup>3</sup> found a homozygous mutation (D134G) in *TREM2* in this family. In 1983, we noted that brain tissue from one 48-year-old family member had an abundance of senile plaques and neurofibrillary tangles. Because of that person's young age, this was not likely to be a coincidence, and we suggested a possible relationship between Nasu-Hakola disease and Alzheimer's disease. Little did we know this relationship would be confirmed almost 30 years later.

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No potential conflict of interest relevant to this letter was reported.

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**DRS. JONSSON AND STEFANSSON REPLY:** Reitz and Mayeux report that the allelic frequency of rs75932628 was very low (0.0009) in the black cohort in their study. This frequency is similar to that reported for samples obtained from black persons in the University of Seattle Human Exome Variant database.<sup>1</sup> The reported weak association with a common correlated variant in blacks, which we note is rare in whites, is not inconsistent with the presence of another rare high-risk variant in *TREM2* in blacks. Sequence analysis of *TREM2* in samples obtained from black persons should reveal such a variant, if present.

Bertram et al. report an odds ratio of about 1.7 for the T allele of rs75932628, which is lower than the lower limit of the 95% confidence interval in both our study and that of Guerreiro et al. A potential contributory factor to this apparent discrepancy may be the choice of controls, which we found to have a substantial effect on observed odds ratio values. Another factor may be statistical fluctuations; the total sample size in the two original studies was substantially larger than that of Bertram et al. We also note that because of the low frequency of the T allele of rs75932628, our study lacks statistical power to reliably determine the risk among homozygous carriers. The fact remains that the odds ratio for heterozygous carriers of the T allele of rs75932628 is similar to that of the *APOE*  $\epsilon$ 4 allele.

Rajagopalan et al. indicate that rs9394721, a proxy for rs75932628, correlates with several biologic and pathologic measures of Alzheimer's disease in an elderly population (mean age, 75.5 $\pm$ 6.5 years). This finding is consistent with our observation that each copy of the T allele of rs75932628 lowers the age at the onset of Alzheimer's disease by about 3 years. It is not surprising that this effect is manifested in measurable biologic changes in a cohort that is of the age when the risk of Alzheimer's disease increases exponentially.

Finally, although the study by Benitez and Cruchaga is intriguing, we tested and did not find evidence of the involvement of rs75932628 in Parkinson's disease in Iceland. On the basis of the study involving 2730 cases and 73,710 controls, we found an odds ratio for the T allele of rs75932628 of 1.24, which is nonsignificant ( $P=0.31$ ).

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Since publication of their article, the authors report no further potential conflict of interest.

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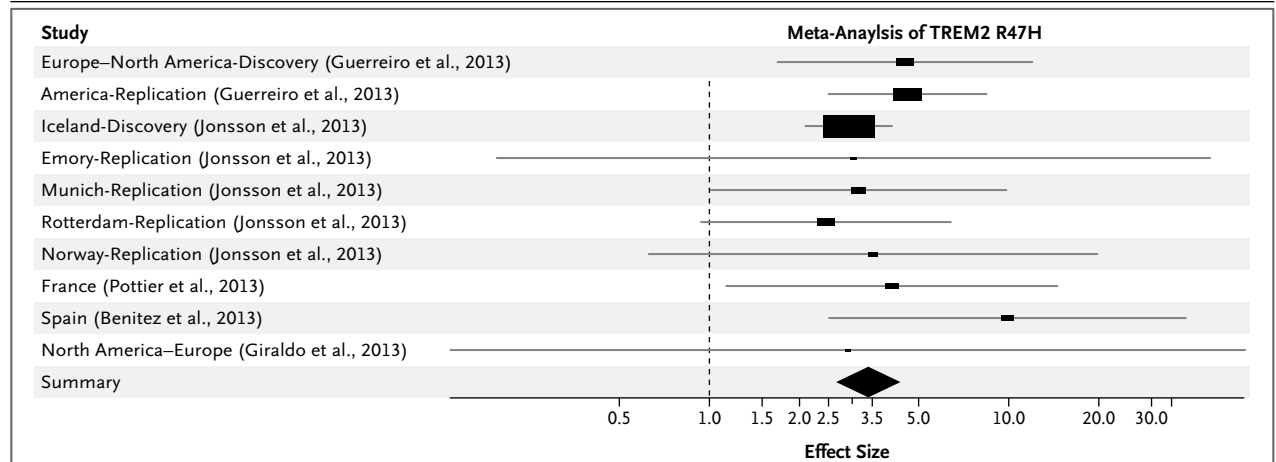
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**DRS. GUERREIRO AND HARDY REPLY:** In addition to our study and that reported by Jonsson et al., three other studies<sup>1-3</sup> have replicated the association between the heterozygous R47H protein variant in *TREM2* and Alzheimer's disease. A global meta-analysis of all these studies now shows a highly significant association (odds ratio, 3.4; 95% confidence interval, 2.65 to 4.35;  $P < 0.001$ ) (Fig. 1).

The prevalence of the minor allele (the "minor allele frequency") varies widely across populations (see the table in the Supplementary Appendix, available with the full text of this letter at [NEJM.org](http://www.nejm.org)), with a reported minor allele frequency from the Exome Variant Server of 0.02% among 2203 African Americans and of 0.26% among

4300 European Americans. Clearly, for this and other rare variants, association tests should be performed only on sufficiently large and well-matched case and control groups.

Bird describes a finding of which we had not been aware: in 1983, he reported plaques and neurofibrillary tangles in the brain tissue of the index case from a family presenting with Nasu-Hakola disease. His study dates from before the syndrome was named or the *TREM2* locus was cloned. This study is of particular importance because this co-occurrence of Alzheimer's disease with Nasu-Hakola disease provides strong support for the notion that loss of *TREM2* function is the most likely mechanism for the development of Alzheimer's disease. Our examination of five brains with heterozygous *TREM2* variants revealed typical features of Alzheimer's disease and cerebral amyloid angiopathy. Some brains also showed very mild Lewy-body disease and TAR DNA-binding protein 43 disease, as well as small white-matter abnormalities. It is important, however, to note that most persons with Nasu-Hakola disease have not been reported to have pathological findings of Alzheimer's disease, although few autopsies have been carried out.



**Figure 1.** Forest Plot Based on a Meta-Analysis of Published Studies of the Association of the *TREM2* R47H Protein Variant and Alzheimer's Disease.

The results shown are derived from a fixed-effects meta-analysis of R47H based on odds ratios and confidence intervals reported in five studies of *TREM2* R47H in Alzheimer's disease. These studies were published before May 2013. A zero-cell correction was performed in the study by Benitez et al.<sup>2</sup> because the variant was not detected in any control studied. In the study by Jonsson et al., the odds ratio corresponding to the association between Alzheimer's disease and a control population older than 85 years of age was used. The study by Giraldo and colleagues<sup>3</sup> was based on imputed genotypes. Evidence of heterogeneity was tested with the use of Cochran's Q test ( $P = 0.84$ ). The size of each rectangle is proportional to the weight of the cohort in the meta-analysis. The diamond represents the overall estimate from the meta-analysis, with the lateral points indicating the limits of the 95% confidence interval. The vertical line indicates no effect.

The facts that *TREM2* homozygous loss-of-function mutations cause Nasu–Hakola disease and heterozygous variants increase the risk of Alzheimer's disease suggest that *TREM2* is part of a functional network that is involved in various neurodegenerative dementias. Recent analyses of *TREM2* expression have confirmed earlier studies of cell biology suggesting that *TREM2* is a key component of a microglial activation network.<sup>4</sup> It will be of interest to determine whether genetic variability in other members of this network are also associated with neurologic disease.

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## Device Surgery without Interruption of Anticoagulation

**TO THE EDITOR:** Birnie et al. (May 30 issue)<sup>1</sup> report on the Bridge or Continue Coumadin for Device Surgery Randomized Controlled Trial, which showed a 16.0% rate of device-pocket hematomas in the heparin-bridging group. This rate was significantly higher than that in the continued-warfarin group (3.5%). Arguably, the rate of bleeding in the continued-warfarin group was also unacceptably high. The early resumption of therapeutic heparin 24 hours postoperatively may explain, in part, the difference in rates of bleeding. Restarting low-molecular-weight heparin bridging 12 to 24 hours after a procedure confers a 20% rate of bleeding after major surgery.<sup>2</sup> Resuming low-molecular-weight heparin 48 to 72 hours after surgery or using a low-dose low-molecular-weight heparin regimen is associated with a more acceptable rate of major bleeding (<3%).<sup>2-5</sup> Can we simply withhold warfarin perioperatively? As of this writing, there is no direct evidence that bridging anticoagulation, as compared with withholding warfarin alone, reduces the risk of thromboembolism, whereas it appears to increase bleeding.<sup>4</sup> If bleeding develops in patients, warfarin may be withheld for an extended duration, placing them at an increased risk for thromboembolism.<sup>3,5</sup> Two randomized, placebo-controlled trials (A Safety and Effectiveness Study of LMWH Bridging Therapy Versus

Placebo Bridging Therapy for Patients on Long Term Warfarin and Require Temporary Interruption of Their Warfarin [PERIOP-2]; ClinicalTrials.gov number, NCT00432796; and Effectiveness of Bridging Anticoagulation for Surgery [The BRIDGE Study]; NCT00786474) are under way to determine whether postprocedural heparin is necessary for the perioperative treatment of patients with atrial fibrillation or mechanical heart valves.

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No potential conflict of interest relevant to this letter was reported.

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