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In reply

My coauthors and I thank Gutti and colleagues for their interest in our study on GBA mutations in PD. We fully agree with them that the 2.4% frequency of GBA mutations that we found in our Chinese population is likely to be an underestimate, and direct sequencing of the entire gene would have been the preferred screening method because additional mutations could be uncovered, as Gutti and colleagues have highlighted.

Differences in ethnicity, sample size, inclusion criteria of the patients, and mutational screening techniques may partly explain the contradictory results of the association between GBA mutations and PD reported in the literature. We have studied only L444P and N370S mutations because these 2 mutations are the most extensively examined by various investigators, thus allowing our findings to be appropriately compared with others.

While sequencing of the entire GBA gene would be recommended, we would advise caution in overinterpreting the findings because detection of a rare coding variant in a patient with PD does not always imply that the particular variant is a causative mutation. Segregation analysis supported by in vitro and in vivo functional data would still be needed. Nevertheless, genetic association studies certainly provide the basis and impetus for such further investigations.

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Type III Systemic Allergic Reaction to Natalizumab

With interest we read the article by Krumbholz et al¹ in the September 2007 issue of the *Archives*. Natalizumab (Biogen Idec, Cambridge, Massachusetts) is a humanized monoclonal antibody against α_4 integrins, recently approved by health authorities for treating relapsing forms of multiple sclerosis.² Infusion-related allergic reactions after the intravenous application of this drug include classical type I allergic anaphylactoid hypersensitivity reactions, typically occurring within 2 hours after infusion. The inci-

dence of these reactions in clinical trials has been reported to be 4%.³ Krumbholz et al¹ recently described a patient developing a type III hypersensitivity reaction after the second infusion of natalizumab. The clinical course of this allergic reaction appeared somewhat protracted, developing during several days; however, the overall clinical picture and the association with antinatalizumab antibodies supported the view of a delayed allergic reaction to the drug.

We describe a 35-year-old woman with relapsing-remitting multiple sclerosis that was diagnosed in 2005, clinically not responding to interferon beta-1b, and negative for neutralizing antibodies against interferon beta. She was treated with natalizumab. Ten days after the second infusion of natalizumab, she experienced a whole-body rash associated with itching. This was confirmed by her primary care physician and considered to be an allergic reaction. Treatment with dimethindene maleate for 5 days was initiated. However, neither the patient nor her primary care physician considered the reaction to be related to natalizumab; thus, this event was not reported to us. The third and fourth infusions of natalizumab were tolerated well; however, again after 10 days, our patient experienced a rash and itching that she treated as before. After the third allergic episode, she informed us about these clinical events. We discontinued the scheduled natalizumab applications and serum was analyzed for antinatalizumab antibodies, with positive results.

Our case supports the study by Krumbholz and colleagues and underlines that (1) delayed allergic reactions can occur after natalizumab treatment, even 10 days after the infusion, and (2) hypersensitivity reactions are associated with antibody formation and these antibodies can occur early in the treatment course with natalizumab. Treating physicians as well as patients should be aware that allergic reactions during treatment with natalizumab are not limited to the 2 hours after infusion but may also occur several days later. Given the increasing number of patients being treated with this humanized antibody, we anticipate that further cases with a type III systemic allergic reaction to natalizumab will be observed. Pretreatment strategies to lower the incidence of allergic reactions should be investigated systematically with this novel treatment modality.

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In reply

The case reported by Leussink and colleagues shows striking parallels with our previously described case of a delayed allergic reaction to natalizumab. We fully agree that we must anticipate additional cases of such delayed, type III systemic reactions to natalizumab in the future. The two

published cases should help to raise awareness of this type of complication.

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Correction

Incorrect Wording. In the article titled "Retromer Sorting: A Pathogenic Pathway in Late-Onset Alzheimer Disease," by Small, published in the March issue of the *Archives* (2008;65[3]:323-328), an incorrect word was used when discussing an observation by Small and Gandy. On page 327, left-hand column, "Overlapping Functions of Retromer and Presenilin Suggest Unifying Mechanisms of Disease Pathogenesis" section, second paragraph, second sentence, the sentence should have read as follows: "First, like the retromer, a growing number of studies have established that the presenilins play a general role in sorting type I transmembrane proteins, and that disease-causing mutations in presenilin cause protein missorting (as reviewed by Small and Gandy¹⁹)."