Disputes & Debates: Editors' Choice

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Editors' Note: *D313Y* Variant in Fabry Disease: A Systematic Review and Meta-analysis

Fabry disease (FD) is an inherited neurologic disorder caused by deficiency of the enzyme alpha-galactosidase A. Dr. Palaiodimou et al. performed a systematic review and meta-analysis of 40 studies reporting *D313Y* as a single occurring variant in the galactosidase alpha (*GLA*) gene in different populations with or without clinical manifestations of FD. They concluded that *D313Y* variation seems to correlate with an atypical, mild late-onset phenotype with predominantly neurologic FD manifestations. They recommended monitoring for neurologic involvement to identify *D313Y*-positive patients with latent or early-FD pathology, who may qualify for enzyme-replacement therapy or chaperone treatment. In response, Dr. Lackova et al. cite their recent study which found *D313Y* variants in 4 of 127 consecutive patients with Parkinson disease, with an allele frequency 5 times that reported in the general population, and similar to that found in another study of 180 consecutively screened patients with multiple sclerosis, 6 of whom had the variant. They call for further epidemiologic, clinical, and basic research studies to better understand the role of this variant in patients with different neurologic disorders, especially because other authors have stated it has no pathogenic significance. Responding to these comments, the authors note that whereas parkinsonism is not considered a typical FD manifestation, misdiagnosis of multiple sclerosis in patients with an ultimate FD diagnosis has been previously reported. The authors also report that on updating their analysis with the findings shared by Dr. Lackova et al. the pooled proportion of *D313Y* variation among patients with neurologic disorders increased to 0.8% with significant subgroup differences compared with patient cohorts with cardiac or renal manifestations (whereas originally no significant differences were observed). Overall, this exchange highlights our evolving understanding of the potential association of the *D313Y* variation with central and peripheral neurologic manifestations.

Aravind Ganesh, MD, DPhil, FRCPC, and Steven Galetta, MD
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Reader Response: *D313Y* Variant in Fabry Disease: A Systematic Review and Meta-analysis

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We read with great interest the meta-analysis of Palaiodimou et al.[1] who evaluated prevalence and phenotypic characteristics of GLA *D313Y* variant carriers. Based on their results, the *D313Y* variant seems to correlate with an atypical, mild late-onset phenotype with predominantly neurologic manifestations of Fabry disease. We agree with their findings and would like to expand the spectrum of neurologic diagnoses associated with increased prevalence of the *D313Y* variant. As reported in our recent study,[2] 127 consecutive subjects with Parkinson disease (PD) were screened for the presence of *GLA* variants. The *D313Y* variant was identified in 4/127 subjects with allele frequency of 1.6% compared with 0.3% reported in the general population.[3] Similarly,

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in our cohort of consecutively screened subjects with multiple sclerosis using the same methodology,[2] the GLA *D313Y* variant was identified in 6/180 subjects (all female subjects), with an allele frequency of 1.7%, similar to that of PD subjects (previously unreported).

Although most prediction algorithms classify the *D313Y* variant as likely benign, based on the findings of higher prevalence of *D313Y* variant in various neurologic conditions, we believe that further epidemiologic, clinical, and basic research studies are needed to better understand the role of this variant in patients with neurologic disorders.

1. Palaiodimou L, Stefanou MI, Bakola E, et al. *D313Y* variant in Fabry disease: a systematic review and meta-analysis. *Neurology*. 2022; 99(19):e2188-e2200.
2. Lackova A, Beetz C, Oppermann S, et al. Prevalence of Fabry disease among patients with Parkinson's disease. *Parkinson's Dis*. 2022; 2022:1014950.
3. National Center for Biotechnology Information. *ClinVar; [VCV000010738.16]*. Available at: ncbi.nlm.nih.gov/clinvar/variation/VCV000010738.16. Accessed March 11, 2021.

Author Response: *D313Y* Variant in Fabry Disease: A Systematic Review and Meta-analysis

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We thank Lackova et al. for their comments on our systematic review and meta-analysis regarding *D313Y*-variation in Fabry disease (FD) and for presenting their interesting findings.[1,2] Although parkinsonism is not considered a typical FD manifestation,[3] the reported prevalence of *D313Y* variant in this single-center cohort of patients with Parkinson disease was higher compared with the general population.[2] Furthermore, misdiagnosis of multiple sclerosis (MS) in patients with an ultimate FD diagnosis has been previously reported, mandating the consideration of FD during differential diagnosis for MS, especially when atypical multisystemic findings or positive family history exists.[4]

In our systematic review and meta-analysis, among 11 cohorts of patients with neurologic disorders, *D313Y* variation prevalence was calculated at 0.6% (95% CI: 0.3%–1%), which was numerically higher (but not at a statistically significant level) compared with patient cohorts with cardiac or renal manifestations.[1]

After an exploratory analysis by including the findings that Lackova et al. shared, the pooled proportion of *D313Y* variation among patients with neurologic disorders increased to 0.8% (95% CI: 0.4%–1.4%). Eventually, this showed significant subgroup differences ($p = 0.028$) when compared with cardiological or renal cohorts and supporting the notion that *D313Y* variation may be associated with predominantly neurologic manifestations, involving both the central and the peripheral nervous system.[1,5]

1. Palaiodimou L, Stefanou MI, Bakola E, et al. *D313Y* variant in Fabry disease: a systematic review and meta-analysis. *Neurology*. 2022; 99(19):e2188-e2200.
2. Lackova A, Beetz C, Oppermann S, et al. Prevalence of Fabry disease among patients with Parkinson's disease. *Parkinson's Dis*. 2022; 2022:1014950.
3. Palaiodimou L, Kokotis P, Zompola C, et al. Fabry disease: current and novel therapeutic strategies. A narrative review. *Curr Neuropharmacol*. 2023;21(3):440-456.
4. Colomba P, Zizzo C, Alessandro R, et al. Fabry disease and multiple sclerosis misdiagnosis: the role of family history and neurological signs. *Oncotarget*. 2018;9(8):7758-7762.
5. Zompola C, Palaiodimou L, Kokotis P, et al. The mutation *D313Y* may be associated with nervous system manifestations in Fabry disease. *J Neurol Sci*. 2020;412:116757.

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CORRECTION

Incidence of Amyloid-Related Imaging Abnormalities in Patients With Alzheimer Disease Treated With Anti–β-Amyloid Immunotherapy

A Meta-analysis

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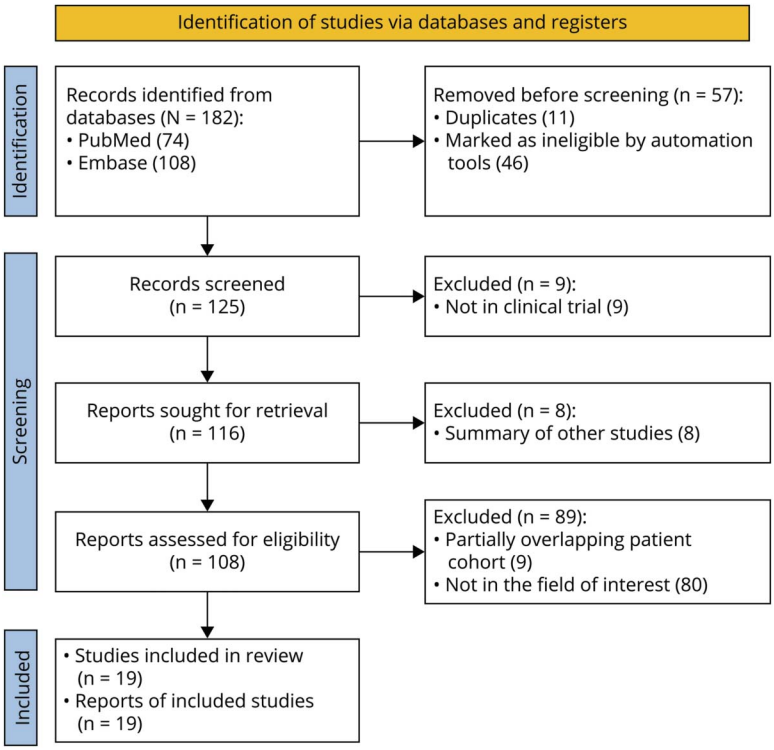
In the Research Article entitled "Incidence of Amyloid-Related Imaging Abnormalities in Patients With Alzheimer Disease Treated With Anti–β-Amyloid Immunotherapy: A Meta-analysis" by Jeong et al.,[1] there were errors in Figure 1. The number of partially overlapping patient cohorts should be "9," and the number of studies included in review and the number of reports of included studies should both be "19." The corrected Figure 1 is below. The authors regret the errors.

Figure 1 Flow Diagram Showing the Study Selection Process



Reference

1. Jeong SY, Suh CH, Shim WH, Lim JS, Lee JH, Kim SJ. Incidence of amyloid-related imaging abnormalities in patients with Alzheimer disease treated with anti–β-amyloid immunotherapy: a meta-analysis. *Neurology*. 2022;99(19):e2092-e2101.

Incidence of Amyloid-Related Imaging Abnormalities in Patients With Alzheimer Disease Treated With Anti–β-Amyloid Immunotherapy: A Meta-analysis

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