Disputes & Debates: Editors' Choice

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. In 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, Dr. Palaiodimou et al. 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 might qualify for enzyme replacement therapy or chaperone treatment. In response, Dr. Bauer et al. express concerns about the article's data ascertainment and statistical evaluations, arguing that a calculation was erroneous; 2 observational studies contributed most of the positive cases in the article; several studies had methodological flaws that increased the risk of false positives; the frequency of p.D313Y in the genome aggregation database was over 10 times higher than that reported in the meta-analysis; and the largest control cohort in the review risked false negatives because the screening method did not include healthy carriers with normal enzyme activity. They argue that the GLA variant p.D313Y should be classified as benign. Responding to these comments, the authors clarify their calculation; report similar findings on removing the highlighted studies and on performing leave-one-out meta-analysis; acknowledge quality concerns with the included studies; clarify their protocol-based exclusion of the genome aggregation database; and discuss methodological nuances in how subjects with different levels of enzymatic activity were screened in the included studies. The authors conclude that while well-designed epidemiologic studies are still warranted, their results suggest the need to monitor *D313Y* carriers for manifestations of FD. This exchange highlights the ongoing debate regarding the clinical significance of *D313Y* variants.

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

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The publication by Palaiodimou et al.[1] seems to have significant flaws in its data ascertainment and statistical evaluation:

1. The estimate of p.D313Y frequency in the subgroup of patients is incorrectly calculated as 0.049 (0.02 is correct given the numbers provided in Figure 2).
2. Two observational studies (ref. 37-1+39) contribute >60% of the positive cases. No matched controls were assessed and predominantly no other genetic causes evaluated.

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3. Several publications evaluated for this review show substantial methodological flaws that create a high risk of false positives among the included cases.
4. The frequency of p.D313Y in the genome Aggregation database (version V2.1.1 and V3.1.2) is 0.003, which is >10× higher than the reported 0.00027 in this meta-analysis.
5. The largest control cohort (ref. 41) misses p.D313Y carriers (especially female individuals) because the screening method used did not include healthy p.D313Y carriers with normal GLA enzyme activity. This enhances the risk of false negatives, as recently documented.[2]

From a genetics perspective, the GLA variant p.D313Y should be classified as "benign" according to American College of Medical Genetics and Genomics/Association for Molecular Pathology criteria, as most genetic laboratories worldwide have already done for many years.[3] We strongly suggest a critical reevaluation of the presented data and correction of the inaccurate analysis and result interpretation.

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. doi:10.1212/WNL.0000000000201102
2. Effraimidis G, Rasmussen ÅK, Bundgaard H, et al. Is the alpha-galactosidase A variant p.Asp313Tyr (p.D313Y) pathogenic for Fabry disease? A systematic review. *J Inherit Metab Dis*. 2020;43(5):922-933. doi:10.1002/jimd.12240
3. *ClinVar*. ncbi.nlm.nih.gov/clinvar/variation/10738/.

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

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We would like to thank Bauer et al.[1] for their interest and constructive criticism on our work.

1. Regarding the p.D313Y frequency, we repeated the analysis using the R software version 3.5.0 (package: meta),[2] and identical results were documented. Let us again remind the readers that meta-analysis of proportions was performed after the implementation of the variance-stabilizing double-arcsine transformation, using the random-effects model.[3]
2. We further performed a sensitivity analysis, removing the studies indicated by Bauer et al.; however, subgroup differences between patients with Fabry disease (FD) suspicion vs the general population remained significant ($p < 0.01$). In addition, leave-one-out meta-analysis to investigate for potential exaggerated effect sizes did not reveal any significantly influential study.
3. We have performed a thorough quality assessment of the included studies, and the results are provided in a supplementary file together with the main manuscript. Indeed, the included studies are of moderate quality, mostly suffering by the lack of control group. Therefore, further epidemiologic, basic research studies and well-designed registries of *D313Y* variation carriers are warranted, as we discuss in our manuscript.
4. According to the prespecified protocol for our systematic review, online databases presenting GLA mutations in the general population were excluded, thus failing to include the frequency reported in the genome aggregation database. Yet, even if this reported frequency is included, the overall results and the subgroup differences do not differ compared with our primary analysis.
5. In the subgroup of general population, Colon et al. screened patients with reduced α-galactosidase activity presenting a theoretical risk of false negatives[4]; however, in the study of Koulousios et al. healthy patients were evaluated irrespective of α-galactosidase activity.[5] As mentioned earlier, the leave-one-out meta-analysis did not disclose any significantly influential study. After further comparison between the frequencies among patients with suspected FD vs the frequency reported in the genome aggregation database, we detected again significant subgroup differences ($p < 0.01$).

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In conclusion, following the results of this meta-analysis, which can only provide prevalence estimates and cannot be compared with results of well-designed epidemiologic studies that are warranted, we propose not to a priory exonerate the presence of *D313Y* variation but rather thoroughly monitor the D313Y carriers for FD manifestations.

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. doi:10.1212/WNL.0000000000201102
2. Balduzzi S, Rücker G, Schwarzer G. How to perform a meta-analysis with R: a practical tutorial. *Evid Based Ment Health*. 2019;22(4): 153-160.
3. DerSimonian R, Laird N. Meta-analysis in clinical trials revisited. *Contemp Clin Trials*. 2015;45(pt A):139-145.
4. Koulousios K, Stylianou K, Pateinakis P, et al. Fabry disease due to D313y and novel Gla mutations. *BMJ Open*. 2017;7(10):e017098.
5. Colon C, Ortolano S, Melcon-Crespo C, et al. Newborn screening for Fabry disease in the North-West of Spain. *Eur J Pediatr*. 2017; 176(8):1075-1081.

CORRECTION & REPLACEMENTS

Endoluminal Biopsy for Molecular Profiling of Human Brain Vascular Malformations

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In the Research Article entitled "Endoluminal Biopsy for Molecular Profiling of Human Brain Vascular Malformations" by Winkler et al.,[1] the fifth label on the y-axis of the graph shown in Figure 1C should read "Thrombin signaling." The figure has been replaced by a corrected version. The original version with the change highlighted is available from a link in the corrected article. The editorial staff regrets the error.

Reference

1. Winkler E, Wu D, Gil E, et al. Endoluminal biopsy for molecular profiling of human brain vascular malformations. *Neurology*. 2022; 98(16):e1637-e1647.

Data-Driven Phenotyping of Central Disorders of Hypersomnolence With Unsupervised Clustering

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In the Research Article entitled "Data-Driven Phenotyping of Central Disorders of Hypersomnolence With Unsupervised Clustering" by Gool et al.,[1] the top-to-bottom order of the values of the color bar in Figure 2 should be as follows: 6σ (dark red), 3σ, 0, -3σ, and -6σ (dark blue). Figure 2 has been replaced by a corrected version. The original version with the change highlighted is available from a link in the corrected figure. The publisher regrets the error.

Reference

1. Gool JK, Zhang Z, Oei MSSL, et al. Data-driven phenotyping of central disorders of hypersomnolence with unsupervised clustering. *Neurology* 2022;98(23):e2387-e2400.

Author disclosures are available upon request (journal@neurology.org).