

## Blood platelet heterogeneity at a glance: new insights into the relationship between platelet distribution width and neuropsychiatric disorders

Benedetta Izzi, José J. Fuster

Centro Nacional de Investigaciones Cardiovasculares (CNIC), Madrid, Spain

Functional and morphological differences in blood platelet subpopulations, especially in relation to their volume variability, became a target of investigation about a

century later than the first discovery of blood platelets was made by Giulio Bizzozero in 1882.<sup>1</sup> Volume changes in blood platelets have been extensively associated with functional changes in numerous *in vitro* and *in vivo* studies, and platelet volume indices, such as mean platelet volume (MPV) and platelet distribution width (PDW), have often been described to be altered in several pathological human conditions.

PDW is an easily measured blood parameter that reflects platelet volume heterogeneity, and it is used in clinical practice to diagnose impaired megakaryocyte differentiation and thrombopoiesis.<sup>2</sup> PDW should be seen as an instant picture of how different circulating blood platelets are in a given individual with respect to their size. Even if platelet size/volume has been long recognized as an important proxy of platelet function in a plethora of *in vitro* and *ex/in vivo* studies,<sup>3</sup> the idea of PDW-dependent platelet heterogeneity as a driver of functional variability was raised only in the last years and still needs further clarifications.

In 2010, PDW was first reported as a marker of platelet anisocytosis, the process that goes side-by-side with platelet activation, during which pseudopods form, increasing platelet diameter and apparent volume.<sup>4</sup> In the Moli-family cohort we provided the first evidence of the association of PDW with several aspects of platelet function in a large general population: PDW specifically and significantly reflected *ex vivo* and *in vitro* P-selectin-dependent platelet activation, as well as platelet involvement in *in vitro* coagulation.<sup>5</sup> In the same population, PDW was also significantly associated with DNA methylation of *PEAR1*,<sup>6</sup> a gene known to modulate platelet activation and whose genetic variability has been associated with differential responses to anti-platelet treatment.

PDW was repeatedly reported as a predictor of prognosis of clinically defined inflammation-based conditions (including cardiovascular disease, cancer, metabolic syndrome, and diabetes). Interestingly, in a very recent study involving 200,453 participants of the UK Biobank study, PDW was also identified as the blood trait most significantly associated with somatic mutations linked to clonal hematopoiesis of indeterminate potential,<sup>7</sup> an emergent risk factor for cardiovascular disease.

In the last decade, a growing body of evidence originating from both epidemiological and genetic studies has

Correspondence: Benedetta Izzi, Spanish National Center for Cardiovascular Research Carlos III, C/Melchor Fernández Almagro 3, 28029 Madrid, Spain.

E-mail: benedetta.izzi@cnic.es

Citation: Izzi B, Fuster JJ. Blood platelet heterogeneity at a glance: new insights into the relationship between platelet distribution width and neuropsychiatric disorders. *Bleeding, Thrombosis, and Vascular Biology* 2023;2:65.

Key words: platelet distribution width; neuropsychiatric disorders; Mendelian randomization, Parkinson's disease.

Contributions: the authors contributed equally.

Conflict of interest: the authors declare no potential conflict of interest.

Acknowledgments/Funding: BI is supported by the program *Atracción de Talento* of the Comunidad de Madrid (GN:2022-T1/BMD-23767). JJF is supported by a Ramon y Cajal award (RYC-2016-20026) from the Spanish Ministry of Science and Innovation/Agencia Estatal de Investigación (AEI)/10.13039/501100011033 and Fondo Social Europeo *El FSE invierte en tu futuro*. Research work by BI and JJF is supported by grant PLEC2021-008194 from the Spanish Ministry of Science and Innovation (MCIN/AEI/10.13039/501100011033) and the European Union ("NextGenerationEU"/PRTR) and by grant LCF/PR/HR22/00732 from La Caixa Foundation. The CNIC is supported by the MICIN, the Instituto de Salud Carlos III, the Pro-CNIC Foundation, and is a Severo Ochoa Center of Excellence (grant number CEX2020-001041-S).

Received: 27 February 2023.

Accepted: 30 March 2023.

Publisher's note: all claims expressed in this article are solely those of the authors and do not necessarily represent those of their affiliated organizations, or those of the publisher, the editors and the reviewers. Any product that may be evaluated in this article or claim that may be made by its manufacturer is not guaranteed or endorsed by the publisher.

©Copyright: the Author(s), 2023

Licensee PAGEPress, Italy

*Bleeding, Thrombosis and Vascular Biology* 2023; 2:65

doi:10.4081/btvb.2023.65

This work is licensed under a Creative Commons Attribution-NonCommercial 4.0 International License (CC BY-NC 4.0).

consistently suggested PDW as a novel marker of neuropsychiatric disorders, including Parkinson's disease (PD).<sup>8</sup> On the contrary, less consistent data have been reported for the other platelet volume-dependent marker MPV in relation to the same clinical phenotypes.<sup>8</sup> The paper by Yang *et al.* recently published in Cell Genomics further support a possible causal role of PDW in neuropsychiatric disorders.<sup>9</sup> Therefore, the authors used large-scale genome-wide association study summary statistics in combination with blood-based (from eQTLGen) and platelet (from GeneSTAR) cis-expression quantitative trait loci (cis-eQTL). Through Mendelian randomization (MR) analysis, they reported, for the first time, a causal effect of increased PDW on PD, but not of MPV on any of the neuropsychiatric phenotypes studied. Even if blood platelets are known to play a role in thrombo-inflammation, this inferred causal relationship between increased PDW and PD risk was independent of C-reactive protein (CRP)-dependent inflammation, as using summary data from a large genome-wide association study of CRP as an adjustment left unchanged the magnitude of the effect. With this approach, the Authors identified 60 false discovery rate-significant functional genes associated with the PDW-PD trait pair, of which 40 showed a consistent direction of effect from multiple MR analyses. Worth of note, 11 out of those 40 genes are also known drug targets, opening up to drug re-purposing strategies to reduce PD risk.

This paper stems from recent studies investigating the genetic correlation of platelet traits and brain disorders and the tentative identification of a causal link through MR approaches. These studies were focused originally on major depressive disorders,<sup>8</sup> but expanded the spectrum of neuropsychiatric disorders by including other neurodegenerative phenotypes like PD or Alzheimer's disease (AD).<sup>10-12</sup>

Prior to the publication by Yang *et al.*,<sup>9</sup> the first evidence of significant genomic overlap between PDW and PD was observed by Tirozzi *et al.*,<sup>13</sup> through linkage disequilibrium score regression and polygenic risk score analyses. The same group, almost simultaneously to the paper by Yang *et al.*, additionally applied multi-trait association analysis to exploit genetic correlations and overlap of genetic features of platelet count test, MPV, and PDW with PD, AD, and major depressive disorders.<sup>14</sup> Also in this case, the authors identified 70 genome-wide significant multi-trait LD-independent associations ( $P < 5 \times 10^{-8}$ ) for PD, of which 34 were never reported before.

Overall, this evidence points to the characterization of PDW as a promising marker of PD risk in the general population, being in line with the already accepted idea that platelets can be considered a circulating mirror of neurons.<sup>15</sup> PD, like AD, is a neurodegenerative disorder occurring after the long-lasting accumulation of neurotoxic protein aggregates. Identifying easy-to-measure circulating biomarkers that can predict disease risk much earlier

than the clinical diagnosis is key. The paper by Yang *et al.* sets an important step forward in this quest.

Large longitudinal studies, with the possibility of identifying PD incident cases over time, will clarify and confirm whether PDW measurement is sufficient to predict PD risk much earlier than the onset of the disease, opening up new possibilities for population stratification-based prevention strategies and novel PD/anti-platelet therapeutic approaches.

---

## REFERENCES

1. Lesyk G, Jurasz P. Advances in platelet subpopulation research. *Front Cardiovasc Med* 2019;6:138.
2. Borkataky S, Jain R, Gupta R, et al. Role of platelet volume indices in the differential diagnosis of thrombocytopenia: a simple and inexpensive method. *Hematology* 2009;14:182-6.
3. Handtke S, Thiele T. Large and small platelets - (when) do they differ? *J Thromb Haemost* 2020;18:1256-67.
4. Vagdatli E, Gounari E, Lazaridou E, et al. Platelet distribution width: a simple, practical and specific marker of activation of coagulation. *Hippokratia* 2010;14:28-32.
5. Izzi B, Gialluisi A, Gianfagna F, et al. Platelet distribution width is associated with P-selectin dependent platelet function: results from the moli-family cohort study. *Cells* 2021;10:2737.
6. Izzi B, Gianfagna F, Yang WY, et al. Variation of PEAR1 DNA methylation influences platelet and leukocyte function. *Clin Epigenetics* 2019;11:151.
7. Kar SP, Quiros PM, Gu M, et al. Genome-wide analyses of 200,453 individuals yield new insights into the causes and consequences of clonal hematopoiesis. *Nat Genet* 2022;54:1155-66.
8. Izzi B, Tirozzi A, Cerletti C, et al. Beyond haemostasis and thrombosis: platelets in depression and its co-morbidities. *Int J Mol Sci* 2020;21:8817.
9. Yang Y, Zhou Y, Nyholt DR, et al. The shared genetic landscape of blood cell traits and risk of neurological and psychiatric disorders. *Cell Genom* 2023;3:100249.
10. Astle WJ, Elding H, Jiang T, et al. The allelic landscape of human blood cell trait variation and links to common complex disease. *Cell* 2016;167:1415-29.e19.
11. Nalls MA, Blauwendraat C, Vallerga CL, et al. Identification of novel risk loci, causal insights, and heritable risk for Parkinson's disease: a meta-analysis of genome-wide association studies. *Lancet Neurol* 2019;18:1091-102.
12. Gialluisi A, Izzi B, Di Castelnuovo A, et al. Revisiting the link between platelets and depression through genetic epidemiology: new insights from platelet distribution width. *Haematologica* 2020;105:e246-8.
13. Tirozzi A, Izzi B, Noro F, et al. Assessing genetic overlap between platelet parameters and neurodegenerative disorders. *Front Immunol* 2020;11:02127.
14. Tirozzi A, Quiccione MS, Cerletti C, et al. A multi-trait association analysis of brain disorders and platelet traits identifies novel susceptibility loci for major depression, Alzheimer's and Parkinson's disease. *Cells* 2023;12:245.