Determination of individual DNA variants allows for more effective polycythaemia vera treatment

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Polycythaemia vera is a chronic malignant disease of the haematopoietic system and is treated with interferon-alpha-based drugs, in most cases with long-lasting success. However, in some cases this therapy is unsuccessful for reasons that are not yet understood. A research group led by Robert Kralovics from MedUni Vienna's Department of Laboratory Medicine and from CeMM has now conducted genetic

association studies, which show that patients with certain DNA variants commonly found in the population do not respond sufficiently to the treatment. Hence, personalized determination of genetic factors may lead to improved forms of treatment. The study has been published in the journal *Blood*.

Polycythaemia vera (PV) is one of a group of diseases called myeloproliferative neoplasms (MPN), which are rare chronic malignant blood diseases. A feature of MPN is the over-production of various blood cells. Sustained therapeutic success can be achieved by the administration of drugs based on interferon alpha (IFNa), which can eliminate the mutated cell clone and are able to permanently restrict malignant cell growth. However, the treatment is not equally successful in all patients.

Up until now, there was no explanation as to why patients respond differently to the treatment, although we know from other diseases that genetic factors can play a crucial role. The research group led by molecular biologist Robert Kralovics from MedUni Vienna's Department of Laboratory Medicine and from the CeMM Research Center for Molecular Medicine of the Austrian Academy of Sciences has now investigated a possible effect of hereditary DNA variants in PV patients given the novel drug ropeginterferon alfa-2b in the context of clinical trials. Genome-wide association studies (GWAS) were conducted first of all but these did not indicate any marked influence of genetic markers on therapeutic success. This suggests that all PV-patients are suitable for treatment with IFNa, regardless of their genetic makeup.

A feature of GWAS is that they only identify strong genetic associations but struggle to highlight weaker causal correlations. Therefore, the research team carried out targeted association analyses in the chromosomal region of the IFNL4 gene, which had previously been

described in association with IFNa-based treatment of a completely different disease (hepatitis C). These analyses showed a strong effect due to a specific combination of two hereditary DNA variants in the IFNL4 gene (IFNL4 diplotype), which is widespread in the population. Patients with a specific IFNL4 diplotype status show significant resistance of the mutated malignant cell clone during the course of treatment. This affects around one third of patients.

The study suggested that genetic determination of IFNL4 diplotype status could enable customized, more effective treatment, since a significant reduction of the malignant cell clone is crucial to the therapeutic success. The IFNL4 diplotype status has the potential to serve as a pharmacogenetic marker for the development of personalized forms of treatment for PV and other myeloproliferative neoplasms.

More information: Roland Jäger et al. Germline Genetic Factors Influence Outcome of Interferon Alpha Therapy in Polycythemia Vera, *Blood* (2020). DOI: 10.1182/blood.2020005792

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