Gene panel sequencing in idiopathic erythrocytosis

With great interest we read the excellent article by Camps et al. on the usefulness of gene panel sequencing for the diagnosis of idiopathic erythrocytosis.[1] In the paper, the authors report that by using a next generation sequencing (NGS) panel of 21 relevant genes, 51 exonic variants were identified in 57 patients (45.6% of the total cohort), and validated by Sanger sequencing. These results highlight the very good « yield » of this NGS approach in a diagnosis algorithm, since its use increased the number of positive patients, i.e., with a relevant variant potentially implicated in the erythrocytosis, in comparison with Sanger sequencing. Indeed, so far, up to 20-30% of patients receive a correct diagnosis using the Sanger sequencing approach;[2] whilst, as the authors report in their study, an exonic variant is noted in nearly half of the patients. This is also our experience using a similar method in idiopathic erythrocytosis patients, despite minor differences in our gene panel.

In order to apply the NGS approach to diagnosis, it may be useful to consider the cost of such technology by performing, beforehand, a drastic selection of patients with erythrocytosis. Of note, in the paper by Camps et al., one patient had classical JAK2 exon 12 mutation-positive polycythemia vera, a diagnosis that needs to be rapidly ruled out due to the thrombotic complications associated with this variant.[3] Similarly, 4 patients had an HBB mutation, related to well-known high-affinity hemoglobin disorders that should have been suspected before the NGS due to the low P50. In our opinion, the measurement of venous P50 is a rapid, low-cost test that has to be performed systematically in initial screening for idiopathic erythrocytosis as it can orientate further screening towards HBB, HBA1 or HBA2 variants. Moreover, as mentioned by the authors, due to high sequence similarity, the detection of such variants using NGS techniques can be challenging. As a consequence, in patients with low P50, we recommend using an inexpensive sequencing technique for the HBB, HBA1 and HBA2 genes before NGS analysis.

Finally, the results of Camps et al. will probably modify the algorithms of investigations for erythrocytoses considerably: after excluding obvious causes of erythrocytosis by initially using quick blood screening tests that include the JAK2 mutations (both V617F and exon 12), and arterial and blood gases (to rule out pulmonary or cardiac disorders, and, more rarely, high-affinity hemoglobin), the use of NGS as a second-line step should lead to a positive diagnosis in a high proportion of patients.

As a consequence, the discovery of new variants with no (or as yet unknown) significance in these disorders makes the development of functional approaches urgent.

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