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Reply to Sönmez et al.

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We thank Sönmez et al. for their comment on our paper providing a provisional decision tree for the genetic diagnosis of deficiency of adenosine deaminase 2 (DADA2). This autosomal recessive disorder was primarily described as inflammatory vasculitis [1, 2]. More recently, other phenotypes have been described, such as pure haematological presentation (aplastic anaemia, erythroblastopenia, etc), without vascular or inflammation features [3–6].

Gene sequencing can be performed by either Sanger or NGS (Next Generation Sequencing) technique. In our original article, Rama et al. proposed a decision tree to help physicians prioritise molecular screening among SAID patients with possible DADA2 and benefit from a fast diagnosis with Sanger analysis [7]. Patients who do not meet the prerequisites have less probability to have DADA2. However, lack of some of the prerequisites does

not exclude the diagnosis of DADA2, which can be made using NGS strategy.

Sönmez et al. have tested the proposed decision tree on ten genetically confirmed DADA2 patients and eight periarteritis nodosa (PAN) patients. All but one met the prerequisites: a true DADA2 patient with only haematological presentation who was not eligible for Sanger sequencing using the original tree. These authors pinpoint that atypical presentations such as aplastic anaemia are missed by our provisional decision tree. We concede that it might be relevant to implement the haematological features as an alternative prerequisite.

In the initial paper by Navon Elkan et al., *CECRI/ADA2* was discovered in a cohort of PAN patients sequenced by WES, supporting that PAN and DADA2 may be undistinguishable based on clinical features only prior to genetic analysis [1]. Therefore, it is not surprising that all of their PAN patients meet the prerequisites. True PAN patients are not disadvantaged by having Sanger sequencing. The authors had a high prevalence of DADA2 consanguineous patients (9/10 patients). Consanguinity is common in the Turkish population, but rare in the European population and in our confirmed DADA2 patients (2/11 families) [7]. Hence, we believe that in most populations, consanguinity is not relevant as a prerequisite for Sanger analysis.

In conclusion, Sönmez et al. have highlighted the importance of the pure haematological presentation. They

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propose to implement this feature in the diagnostic decision, and we agree with that. However, consanguinity should be considered in specific populations, but cannot be universally used in our opinion.

Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

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