Reply to RE: Steroid-resistant nephrotic syndrome: impact of genetic testing

We thank Dr. Muhammed Mubarak for his comments on our recent paper about the importance of genetic testing in children with steroid-resistant nephrotic syndrome (SRNS). He highlights the similarity between our results[1] and their published results.[2] We found that the frequency of identified disease-causing mutations in children older than 1 year with SRNS presented to KAUH was 11.4% (6.8% NPHS2 podocin gene and 4.5% NPHS1 [nephrin gene]), which was comparable to their report of 3.4% NPHS2 and 5.5% NPHS1. However, they find higher percentage of mutations (22%) in children with early onset disease, while we excluded children younger than 1 year of age in our study. The median (IQR—interquartile range age of our cohort at presentation was 3 (2.5) years with no difference between primary SRNS; 3 (2.5) years and secondary SRNS; 3 (3) years at presentation (P value .420). Regarding the timing of genetic testing, it was done after defining children as SRNS who did not respond to steroid for 4 weeks. However, the results usually arrive after a few months during which children are kept on immunsuppressions. Obtaining results takes long time as we do it as part of collaboration with Harvard medical school and previously Michigan medical school.[3] Concerning the effect of including children with membranoproliferative GN (MPGN) and IgA nephropathy (IgAN) in decreasing the frequency of genetic mutations, our inclusion criteria were children with SRNS regardless the underlying renal histology. IgA nephropathy is a known underlying cause of SRNS as well as MPGN.[4,5] We have reported mutations of only NPHS1, NPHS2, and WT1, and, therefore, some children with negative mutations initially were found to have other mutations such as TRPC6[6] or SMARCAL1.[7,8] Furthermore, we believe that we have other undiscovered mutations in our area as the underlying cause of childhood SRNS. We agree with Dr. Mubarak about the need for mult-center studies of larger scale and prospective nature, to develop international guidelines on the clinical utility of genetic testing in childhood SRNS.

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Re: Consanguinity and isolated atrial septal defect in the North East of Iran

To the Editor: I read with interest the study by Moghaddam et al[1] on the consanguinity and isolated atrial septal defect (ASD) in the North East of Iran. It is well known that congenital heart diseases (CHDs), particularly ASD, generally tend to follow multifactorial inheritance. However, autosomal dominant inheritance of ASD has been increasingly reported.[2,3] This genetic form of inheritance together with the fact that consanguinity increases the risk of couples to have offspring with CHDs could result in the familial aggregation of ASD. It is expected for the familial aggregation of ASD to be prevailed in Iran. This is based on the following 3 points. (1) Among various types of CHDs, ASD has been reported to be predominant in Iran.[4] (2) Consanguineous marriage is culturally preferable in Iran, and its trend has been noticed to be significantly on rise.[5] (3) A total of 44% of ASD patients in the study by Moghaddam et al[1] had parents with either the third-degree relationship or far relationship. Since associated cardiac, atrioventricular conduction, and skeletal anomalies are not uncommon in ASD, and in the view of potentially high occurrence of familial ASD in Iran based on the aforementioned 3 points, I presume

that large-scale multicenter studies are needed to verify the requirement to screen ASD parents and their first-degree and second-degree relatives for associated anomalies.

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