Whole Exome Sequencing Could Help to Distinguish Between Pediatric Systemic Lupus Erythematosus and Primary Immunodeficiency Disease

Samaneh Zoghi1,2,3, Nima Rezaei4,5,6

1 Ludwig Boltzmann Institute for Rare and Undiagnosed Diseases, Vienna, Austria
2 CeMM Research Centre for Molecular Medicine of the Austrian Academy of Sciences, Vienna, Austria
3 Primary Immunodeficiency Diseases Network (PIDNet), Universal Scientific Education and Research Network (USERN), Vienna, Austria
4 Research Center for Immunodeficiencies, Pediatrics Center of Excellence, Children's Medical Center, Tehran University of Medical Sciences, Tehran, Iran
5 Department of Immunology, School of Medicine, Tehran University of Medical Sciences, Tehran, Iran
6 Network of Immunity in Infection, Malignancy and Autoimmunity (NIIMA), Universal Scientific Education and Research Network (USERN), Tehran, Iran

Systemic Lupus Erythematosus (SLE) is a multi-organ autoimmunity, which could be seen in young adults; while pediatric SLE (pSLE) refers to children below the age of 10 years is less frequent. Few pSLE cases experience very early-onset form of the disease in the first year(s) of life (1). Early onset presence of the disease raises the probability of genetic etiology, especially if patients show the phenotype in the first year of life. Monogenic form of SLE has already been reported. Among them, complement deficiencies, including C1q, C2, and C4 deficiencies are one of the most frequent monogenic cause of pSLE (2,3). Complement proteins such as C1q have important role in the clearance of apoptotic debris, while cell debris maintains in the absence of these proteins, which can initiate an autoimmune response (4).

Complement deficiencies are actually primary immunodeficiency diseases that have common manifestations with SLE. These type of monogenic SLE, sometimes have non-classical disease phenotype, which differs from manifestations of disease in the majority of pSLE cases. It has been reported previously, that children suffering from C1q deficiency, more often show skin lesions, glomerulonephritis, and central nervous system (CNS) involvement; however, elevated titers of Anti-ds DNA is rarely detectable in these patients (5). It should be stated that not only the genes encoding complement components, but also other genes that are involved in apoptosis and/or type I IFN pathways have been shown as causal gene defects in several studies.

New high throughput genetic approaches are very helpful in finding rare causal mutations in human genetic studies. Whole Exome Sequencing (WES) is one of the methods which is applied currently for gene hunting purposes in monogenic diseases. Meanwhile, direct sequencing of all coding regions in SLE associated complement genes, in addition to more than 30 other strongly associated gene defects for finding possible causal mutations in one patient is very hard. Also, the sequencing of all mentioned genes is time-consuming and not cost-effective. WES is more beneficial in these patients since it allows evaluation of genetic variants in all coding exons at the same time (6). This approach is very helpful not only for finding rare mutations in complement genes but also for finding other SLE causing mutations. Furthermore, WES is a powerful tool for finding novel rare variants, which was not reported before and can open a new window toward SLE genetic etiology.

Considering the high rate of consanguineous marriages in some parts of the world, including Middle-East, autosomal recessive genetic variants are seen more commonly; therefore, complement deficiencies as autosomal recessive monogenic cause of pSLE should be taken into account. WES could be an appropriate method to distinguish between pSLE and primary immunodeficiency disease such as complement deficiency.

Acknowledgments

This is supported by Tehran University of Medical Sciences, grant No. 95-01-30-31108.

References

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