Genetics of Neonatal Diabetes Mellitus

Sepideh Shahkarami1 and Nima Rezaei1,2

1 Research Center for Immunodeficiencies, Children’s Medical Center, Pediatrics Center of Excellence, Tehran University of Medical Sciences, Tehran, Iran
2 Department of Immunology, Molecular Immunology Research Center, School of Medicine, Tehran University of Medical Sciences, Tehran, Iran

Although exact etiology of diabetes mellitus is still unknown, it seems that it follows a polygenic trait, while genetic and environmental factors could influence its present in most cases. However, monogenic forms of disease have also been described, which usually presented either during neonate and early infancy period, named as neonatal diabetes mellitus (NDM), or during childhood and adolescence, named as maturity onset diabetes of the young (MODY). MODY seems to be more common than NDM (1-3).

According to different gene mutations, eleven different MODY types have already been described by now, while MODY type 2 due to mutation of the GCK gene seems to be the most common form. Mutations in the ABCC8 gene could cause permanent or transient NDM, while mutations of the KCNJ11 gene could lead to permanent NDM. Several other genes, including PLAG1, ZFP57, INS, EIF2AK3, FOXP3, PDX1, PTF1A, NEUROD1, NEUROG3, RXF6, IER3IP1, HNF1B, GLIS3, PAX6, WFS1, SLC19A2, and SLC2A2 have also been reported in association with NDM (2,4).

Fanconi-Bickel syndrome (FBS, OMIM#227810) is a rare monogenic disorder with autosomal recessive pattern of inheritance, due to homozygous or compound heterozygous mutations of the Soluble Carrier Family 2 (Facilitated Glucose Transporter), Member 2 (SLC2A2, OMIM*138160) gene, mapped on chromosome 3q26.1-26.3, which encodes glucose transporter protein 2 (GLUT2), expressing in pancreas, liver, intestine, and renal tubular cells (5,6).

Patients with FBS usually manifest hepatomegaly due to glycogen accumulation, proximal tubular dysfunction results in inappropriate urinary losses of mineral elements, repeated pneumonia, moon-shaped face, short stature, hypophosphatemic rickets, and glucose intolerance which may be due to a NDM and impaired galactose tolerance (6,7). It should be noted that a variety of manifestations, including neurodevelopmental disability, exocrine pancreatic insufficiency, thyroid dysfunction, kidney structural or functional defects, liver dysfunction, skeletal abnormalities, visual impairment, deafness, and megaloblastic anemia have been reported in association with different genetic mutations in NDM (4).

In a recently interesting published paper in the Acta Medica Iranica, entitled “Transient neonatal diabetes as a presentation of Fanconi-Bickel syndrome”, clinical features of a female case with diagnosis of FBS have been described. The patient had a short stature, hepatomegaly, and hypophosphatemic rickets, while history of diabetic ketoacidosis and transient NDM are well-noted. The diagnosis of FBS was made considering the clinical phenotype and homozygous mutation in the intronic region of the SLC2A2 gene (8). Molecular genetic studies over the past years have been resulted in identifying more than 30 different mutations (missense, nonsense, frame shift, and splice-sites), scattering through all of coding exons in the gene SLC2A2 among the patients with FBS (9). Interestingly, there are several reports of disease-causing mutations in the intronic regions of the SLC2A2 gene, such as c.963+1G>A in the mentioned article, which is predicted to be causative because of its aberrant effect on the splicing site (7,8). To strengthen the pathogenic role of such mutations, protein analysis or carrier frequencies detection of the mutations in non-related normal subjects is needed to see if they really disrupt protein sequence or not. However, clinical suspicious and known mutations could be useful for making definite diagnosis.

It is noteworthy that the most of reported mutations were novel, which makes the molecular diagnosis laborious (6,10-18). As a result, preparing genetic profile in the FBS patients could be helpful not only for
confirming the diagnosis as a diagnostic tool, but also for predicting the clinical phenotypes as a prognostic tool. It shows the value of mutation detection in the clinical settings. Therefore, besides the importance of clinical and laboratory findings, significance of genetic analysis should never be underestimated.

References


