Genetics of Neonatal Diabetes Mellitus

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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 *PLAGL1, ZFP57, INS, EIF2AK3, FOXP3, PDX1, PTF1A, NEUROD1, NEUROG3, RFX6, IER3IP1, HNF1B, GLIS3, PAX6, WFS1, SLC19A2,* and *SLC2A2* have also been reported in association with NDM (2,4). Since mutations of these genes would initiate particular clinical phenotypes and complications and therefore might require a specific therapeutic protocol, identification of the NDM-causing genes seems essential for efficient and specific treatment.

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

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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.

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