Genome, Exome, and Targeted Next-Generation Sequencing in Neonatal Diabetes

Elisa De Franco, PhD, Sian Ellard, PhD, FRCPath*

KEYWORDS

• Next-generation sequencing • Gene discovery • Genetic testing • Neonatal diabetes

KEY POINTS

- Next-generation sequencing has revolutionized the approach to genetic testing and research.
- The 3 main applications of next-generation sequencing technology are targeted gene panels and exome and genome sequencing.
- Neonatal diabetes is a genetically and clinically heterogeneous disease, which means that genetic testing and research of new causes of the disease are challenging.
- A targeted gene panel has been developed to test all the known causes of neonatal diabetes in a single test. Early comprehensive testing has changed the way patients with neonatal diabetes are managed.
- Exome sequencing is a powerful tool to identify novel disease genes. In neonatal diabetes, it has led to the identification of 2 novel causes: mutations in *GATA6* and *STAT3*.
- Genome sequencing is the most comprehensive test available, and it was used to identify mutations in a novel enhancer that cause pancreatic agenesis.

INTRODUCTION TO NEONATAL DIABETES

Neonatal diabetes diagnosed before 6 months is a rare disease (approximate incidence of 1:100,000 live births[1]) that reflects severe β-cell dysfunction (**Fig. 1**). Two separate studies[2,3] have shown that diabetes diagnosed before 6 months of age is most likely to have a monogenic cause rather than being caused by autoimmunity.

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Institute of Biomedical and Clinical Science, University of Exeter Medical School, Barrack Road, Exeter EX2 5DW, UK
* Corresponding author. University of Exeter Medical School, RILD level 3, Royal Devon & Exeter Hospital, Barrack Road, Exeter EX2 5DW, UK.
E-mail address: sian.ellard@nhs.net

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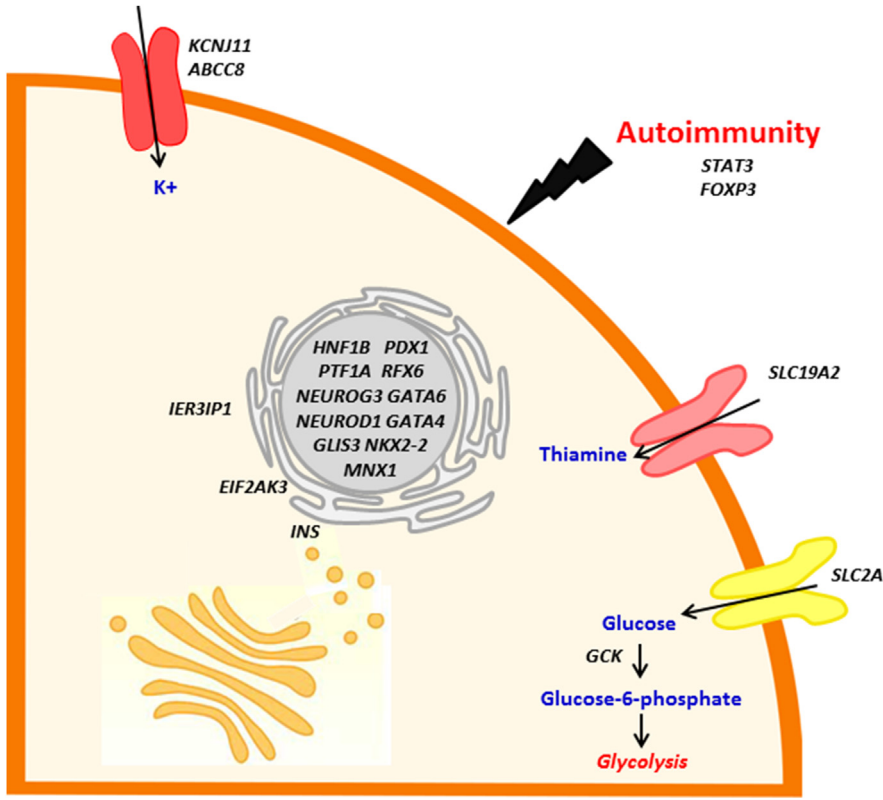

Fig. 1. The β cell and genes causing neonatal diabetes. Gene names are reported in black font. KCNJ11, ABCC8, SLC19A2, and SLC2A2 are transmembrane channels. FOXP3 and STAT3 are involved in the immune response. HNF1B, PDX1, PTF1A, RFX6, NEUROG3, GATA6, NEUROD1, GATA4, GLIS3, NKX2-2, and MNX1 are transcription factors that regulate genes in the nucleus. EIF2AK3 and IER3IP1 regulate protein trafficking in the endoplasmic reticulum. Mutations in the *INS* gene cause neonatal diabetes either by resulting in absence of insulin or by producing a defective insulin protein that accumulates in the endoplasmic reticulum and is not secreted in the blood stream. For genes encoding proteins acting within the β cell, the position of the gene name indicates the intracellular location of the protein. Substrates and transported molecules are indicated in blue. Biological processes are indicated in red.

Neonatal diabetes is a clinically and genetically heterogeneous disease. To date there are 23 different genetic causes of neonatal diabetes that identify different clinical subtypes of the disease (De Franco and colleagues, *submitted for publication* and[4]) (see **Fig. 1**, **Table 1**).

The most common causes of neonatal diabetes are mutations in the genes encoding the subunits of the voltage-dependent potassium channel *ABCC8* and *KCNJ11*.[8,9,27] Correct function of the potassium channel is necessary for secretion of insulin in response to glucose levels. Approximately 40% of patients with neonatal diabetes have a potassium channel gene mutation.[27,50] Patients with mutations in these two genes are sensitive to sulfonylurea treatment, and their glycemic control can be greatly improved switching from insulin to sulfonylurea therapy.[51,52] This