Next-generation Sequencing in the Identification of New Genes Causing Beta-cell Dysfunction

An Expert Interview with Elisa De Franco

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Elisa De Franco

Following graduation from the University of Turin, Italy, Dr De Franco joined the Monogenic diabetes group in Exeter in 2011 as a PhD student. The PhD was funded by the European Union as part of the Marie Curie Initial Training network BOLD (Biology of Liver and Pancreas Disease) project. During her PhD Dr De Franco investigated the role of transcription factors important for pancreatic development in pathogenesis of neonatal diabetes. Following completion of her PhD in 2014, Elisa has continued her research in neonatal diabetes and in 2015 and 2016 was a Naomi Berrie Research fellow in Diabetes Research. In 2018 Elisa received one of the Rising Star awards from the European Association for the Study of Diabetes (EASD) to continue her research identifying novel genetic causes of neonatal diabetes using whole genome sequencing.

Keywords

Next-generation sequencing, beta-cell dysfunction, neonatal diabetes

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Understanding the mechanisms that regulate beta cell development and function is crucial to identify therapeutic targets in type 1 and type 2 diabetes. One way to find the genes or factors needed for beta cells is to study the genetics of patients who develop diabetes in the first few months of life because of severe beta-cell dysfunction. This condition is called neonatal diabetes. Over the years many genes have been identified as causing this condition through impaired function or development of the beta cells.[1] Recently, next-generation sequencing (NGS) technologies have allowed researchers to perform a single test to identify mutations in any of the known genes, either for diagnostic test or as a preliminary screen in the search for novel disease genes.[2]

In an expert interview, Elisa De Franco discusses the challenges of NGS, as well as the impact of early testing of all known genetic causes of neonatal diabetes.

Q. What are the major challenges in using next-generation sequencing to identify genes responsible for beta-cell dysfunction?

NGS allows us to analyze as many genes as we want in a single test—a subset or all of them, just the regions that make proteins or all of the DNA. This has of course huge potential for finding the mutations that disrupt genes, which is important for pediatric diseases, such as neonatal diabetes which is caused by severe beta-cell dysfunction. However, NGS experiments produce a vast amount of data as every human differs by 3–4 million variants.[3] Most of these genetic variants don't have any visible effect, while some define characteristics such as eye color. The big challenge is finding the one genetic mutation that is responsible for beta cell-dysfunction in this sea of other variants—that's what we call "the needle in the haystack".

Q. Could you describe your "gene agnostic" approach?

Before the introduction of NGS, researchers had to test one gene at the time. Gene discovery studies were therefore based on analyzing genes that were thought to be important for beta-cell function based on studies in mice or other animal models. This approach had successfully identified genes in the past, but was of course limited by what was known at the time the gene discovery studies were performed, as only genes with known function would be analyzed.[4]

Now that we can test all the genes in our DNA quickly and inexpensively, we don't need to pre-select the genes in any way. We can let the genetics guide the discovery process and this means we can

identify genes that had never before been suspected to have a role in beta-cells as being essential for human beta-cell function.

Q. What have been your most interesting findings using this approach?

Using this approach I have recently discovered the genetic cause of a new syndrome that results in people being born without a pancreas and with a brain structural malformation called holoprosencephaly. This gene, that is called *CNOT1*, had never before been known to be important for pancreatic development. This gene is, however, known to be very important for stem cell function, suggesting that a defect affecting the very first stage of development can result in the pancreas not developing at all. These results will be published later this month in the *American Journal of Human Genetics*.[5]

Q. How has the proportion of identifiable mutations in patients with neonatal diabetes changed using this approach?

Before we started using NGS, we could identify a genetic cause in approximately 70% of patients diagnosed with diabetes before the age of 6 months. Using NGS we have discovered seven novel genetic causes of neonatal diabetes and we are now able to provide a genetic diagnosis for almost 89% of patients with neonatal diabetes.[5] The impact of NGS has been particularly important for patients with pancreatic agenesis (who have neonatal diabetes and exocrine pancreatic insufficiency). Before we started using NGS, a genetic cause was found in only 13% of patients, whilst today we find the genetic defect causing the disease in 97% of patients—an extraordinary result![4] Finding the correct genetic diagnosis is of paramount importance for the patients, as it allows targeted treatment and can guide the clinical management; for their families, as it allows us to estimate the risk of disease recurrence in the family; and for the clinicians who care for these patients with a rare genetic condition.

Q. What will be the next steps in this research?

We still have 11% of patients without a genetic diagnosis—I am going to work hard to find the genetic defect causing neonatal diabetes in all of them.[5] At the same time, gene discovery has now changed its role in science. Now that we are finding mutations in genes we know very little about, we need to do more studies to understand the mechanism. Finding these critically important genes and understanding how they work is allowing us to gain unique insights into how human beta cells develop and function, furthering our understanding of many types of diabetes. ❑

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