Interviews

EMJ is thrilled to introduce two key opinion leaders Philip Froguel, Imperial College London, UK, and Samuel Seidu, University of Leicester, UK, whose interviews discuss their careers so far, and their focuses for future research. The conversations cover topics including obesity genetics, continuous glucose monitoring, and how research in these areas has influenced clinical practice.

Featuring: Philippe Froguel and Samuel Seidu

Philippe Froguel

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Q1 Can you share the journey that led you from obtaining your medical degree from Saint-Antoine Medical School, Sorbonne University, Paris, France to becoming a leading figure in the field of diabetes and obesity genetics?

When I was a young resident, I met a famous French professor of diabetes Roger Assan who was doing clinical research, and thus I decided to follow a Master of Science course in human nutrition. Later I met with Jean Dausset, Nobel Prize winner for his work on human leukocyte antigen tissue markers, which allowed organ transplantation. He was creating the Human Polymorphism Study Center (CEPH), the first genome centre in the world, and was looking for someone to work on diabetes genetics, which was totally unknown. Therefore, I took a position of Assistant Professor in Saint-Louis Hospital in Paris, partly in the endocrinology department and partly at CEPH. I got my PhD there under another famous French geneticist, Daniel Cohen.

Q2 You were instrumental in identifying key genes responsible for monogenic Type 2 diabetes (T2D) and obesity, such as *GCK* and *HNF1*. Could you describe the challenges of these groundbreaking discoveries?

At that time, there was no cohort of families with diabetes, no map of the human genome, and very rudimentary tools to study the human DNA diversity. Using posters in the Paris Métro (underground) and the media, I collected very large families in 1990–1992. There were little clues, and I postulated that the enzyme glucokinase (*GCK*), given its putative role as a glucose sensor in insulin secreting cells, was a good candidate, and worked hard to have a probe of it. At that time, the mainstream idea was that diabetes was due to insulin resistance and not to defects in insulin secretion. I was correct, and thus we identified the first diabetes gene. Two years later, with the first probes of polymorphic markers covering the entire genome (although poorly), I

performed the first familial whole genome study and found a locus that, after 2 additional years of hard work with my colleague Graeme Bell in Chicago, Illinois, USA, led us to identify the second diabetes gene, the transcription factor *HNF1A*. Young researchers of today could not understand the extremely difficult but exciting challenges of that time: the genome had not been sequenced yet! I was thinking, immodestly, we were the Columbus of our time (or Indiana Jones in some respect). Incidentally, as our discoveries were against the odds and against the habits of the time of diabetes research, especially in France, I had little recognition in France, and in 2000 I left for the UK! The so called 'physiologists' hated me because genetics had proven more efficient than their studies to elucidate part of the origin of diabetes.

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Q3 Your 2007 Genome-Wide Association Study in T2D was the first of its kind and was described as the 'Breakthrough of the Year' by *Science*. What do you consider the most significant implications of this study for the field?

In the late 90s and the beginning of the 2000s, the most popular opinion was the fact that T2D had hidden 'major genes' similar to monogenic T2D. It was a dead-end approach, as our tools (family studies, candidate genes on small cohorts) were sterile. Statisticians in the field in the USA proposed a new concept of 'frequent DNA variants/ frequents diseases', which implies a polygenic basis of T2D and other common disorders. I decided to conduct a study with a big (for the time) cohort of T2D patients and tight controls (middle age people who were normal glycaemic after 9 years of follow-up). We got funding in Quebec, Canada for regular genetic research, but instead of doing what was intended we tested the experimental whole genome using arrays of single nucleotide polymorphisms by a new company called Illumina, and decided to do a genome wide association study. We were in non-friendly competition with the National Institutes of Health (NIH), the Wellcome Trust, and the Islandic/US Decode company who used other arrays. Our technology and our cohorts were better, and we completed and published our study months before the others. Originally, our colleagues were very sceptical about our data, but they independently replicated them. In order to publish, they decided to merge their data, and it was the first example of a genetic consortium. I am proud that our success had pushed them to develop this very efficient approach, that has since been followed in every medical field of genetics.

Q4 In your recently published opinion, entitled 'Towards the recognition of oligogenic forms of type 2 diabetes'. You suggested that the blurred demarcation of polygenic and monogenic T2D may be linked by oligogenic T2D. How might this new view shape diagnosis and treatment of genetic T2D?

The traditional view is T2D is either a monofactorial disorder due to a unique rare mutation in a gene controlling insulin secretion, or a multifactorial disease due to the interaction of age, the environment, and of hundreds or thousands or frequent variations in the human genome increasing the risk of diabetes by many means. Actually, the sequencing of the human genome in large populations discovered that a proportion of patients with diabetes (around 10–20% in the so-called atypical forms of T2D: before 40 years old and without obesity) also carry rare mutations in important genes for glucose

control. In this case, this rare mutation increases the risk of T2D by two- to five-fold, and the polygenic background, plus exposure to the environment (bad nutrition, sedentary lifestyle, etc), contribute to the development of the disease (as well as age of onset and severity). We believe that the presence of some other rare mutations in other genes may also favour the development of serious complications of diabetes, in the kidney, or in the heart and vessels. That is also why we sequence the entire genome of patients with diabetes.

Q5 How have your research findings in diabetes and obesity genetics translated into clinical practice?

I am very proud that what I have contributed to monogenic diabetes is in the textbooks for clinical doctors, as these cases should be recognised and diagnosed as soon as possible. This is because there are specific diabetes care protocols and drugs that are very helpful to control patient glycaemia and improve quality of life, in addition to significantly decreasing costs for society. It is a win–win strategy. Regarding genome-wide association studies, the situation is still unclear, and it remains to be demonstrated that calculating diverse polygenic risk scores is useful for better management of patients. My feeling is yes, but the evidence is still modest. For diabetes complications, more research is necessary, but whole genome sequencing will help.

Q6 You currently have more than 820 peer-reviewed publication to your name for your research in diabetes and obesity. What do you believe to be the current gaps in literature and what topics merit greater attention?

The world community of clinicians and researchers in metabolic diseases is large, and I don't see many domains that are not covered. However, some are weaker than others, especially nutrition, as this literature is often going in every direction without consistency. A recent paper suggested that two-thirds of new diabetes cases are attributable to bad nutrition, but in a very different way among nations (such as too much meat in the USA or Eastern Europe, versus too much white rice in Asia).

> **Two-thirds of new diabetes cases are attributable to bad nutrition, but in a very different way among nations**

This study also suggested that, in 1990, human nutrition around the age of 55–60 years was critical for the development of diabetes, but today, the priority populations to target to prevent diabetes should be young adults who have inadequate diets. This information should guide public health action to prevent diabetes. More research is however necessary to improve our knowledge and to define new policies in nutrition (especially for the food industry), adapted to each country.

Q7 Looking back on your career, what are you most proud of?

I am proud that I went against the mainstream thinking of the time, and proposed and evidenced that diabetes and obesity can be mostly genetic.

> **I am proud that I went against the mainstream thinking of the time**

I also contributed to evidence that T2D is primarily driven by pancreatic insulin secretion failure, instead of by tissue insulin insensitivity, and that obesity is driven by food intake behaviour, not by fat storage. By the way, the newest efficient drugs against diabetes, GLP1 receptor agonists, target both insulin-secreting cells, and also the brain, and that is why patients decrease their weight. The importance of the brain and appetite in obesity is also a field I have contributed to for 30 years by identifying many genes that control food intake. This opened the way to new generations of treatments such as GLP1 receptor and other incretin (hormones secreted by the gut) agonists that decrease appetite and favour insulin secretion, but also protect the heart, kidney, and the brain against diabetes complications. Later, in 2007, I contributed to inventing a simple and robust methodology to study complex traits genetics, named genome-wide association studies, that is still used now. Beyond that, to be in pupils' books at school and in textbooks for medical students is also a great reward.