The insulin gene paper that led to an avalanche 26 years later

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Bell GI, Pictet R, Rutter WJ (1980) Analysis of the regions flanking the human insulin gene and sequence of an Alu family member. *Nucleic Acids Research* **8**: 4091–109

Bell GI, Karam JH, Rutter WJ (1981) Polymorphic DNA region adjacent to the 5' end of the human insulin gene. *Proceedings of the National Academy of Sciences of the United States of America* **78**: 5759–63

Bell GI, Horita S, Karam JH (1984) A polymorphic locus near the human insulin gene is associated with insulin-dependent diabetes mellitus. *Diabetes* **33**: 176–83

Frayling TM, Timpson NJ, Weedon MN et al (2007) A common variant in the FTO gene is associated with body mass index and predisposes to childhood and adult obesity. *Science* **316**: 889–94

Hattersley AT, Pearson ER (2006) Minireview: pharmacogenetics and beyond: the interaction of therapeutic response, beta-cell physiology, and genetics in diabetes. *Endocrinology* **147**: 2657–63

Hitman GA, Jowett NI, Williams LG et al (1984) Polymorphisms in the 5'-flanking region of the insulin gene and non-insulin-dependent diabetes. *Clinical science (London)* **66**: 383–8

Hitman GA, Tarn AC, Winter RM et al (1985) Type 1 (insulin-dependent) diabetes and a highly variable locus close to the insulin gene on chromosome 11. *Diabetologia* **28**: 218–22

Sladek R, Rocheleau G, Rung J et al (2007) A genome-wide association study identifies novel risk loci for type 2 diabetes. *Nature* **445**: 881–5

Tager HS (1984) Lilly lecture 1983. Abnormal products of the human insulin gene. *Diabetes* **33**: 693–9

Ullrich A, Dull TJ, Gray A et al (1980) Genetic variation in the human insulin gene. *Science* **209**: 612–5

Zeggini E, Weedon MN, Lindgren CM et al (2007) Replication of Genome-Wide Association Signals in U.K. Samples Reveals Risk Loci for Type 2 Diabetes. *Science* e-print PMID: 17463249

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In 1981, Graeme Bell published the first diabetes genetic association study (Bell et al, 1981) that captured the imagination of myself and Professor David Galton and led to me being awarded a Diabetes UK RD Lawrence Research Fellowship and a lifetime passion into the genetics of diabetes. A year before, Graeme Bell and Alex Ullrich set the scene with a pair of papers describing the cloning and characterisation of the insulin gene (Bell et al, 1980; Ullrich et al, 1980); the first gene of relevance to diabetes to be identified. In Bell's 1981 paper, of which the principle importance was the description of the polymorphic region, 52 people (12 with type 2 diabetes, 12 with type 1 diabetes, 24 controls and 4 presumably untyped) were studied for variation of a single marker in the promoter region of the gene. It was concluded that no association existed between this marker and either type 1 or type 2 diabetes.

In 1984 and 1985, I published two papers describing possible associations between the so-called class III allele of the insulin gene in type 2 diabetes and the class I allele with type 1 diabetes (studying fewer than 100 people with type 1 diabetes and 100 controls; Hitman et al, 1984; Hitman et al, 1985). The association with type 1 diabetes confirmed a previous report by Graeme Bell et al (1984) and has subsequently stood the test of time despite the small numbers studied. At the same time as these early association studies others were identifying the first genetic causes of monogenic diabetes/hyperinsulinaemia due to mutations in the insulin gene (Tager, 1984). These early studies set the scene for the next 25 years that culminated in the elucidation of the majority of the causes of maturity-onset diabetes of the young (MODY) and the recent publications using genome-wide scans to identify genes in type 1 and type 2 diabetes.

The power of the genetic approach in diabetes has been proven in MODY, where discoveries are now being used for clinical benefit (Hattersley and Pearson, 2006). The most common causes of MODY are mutations of the glucokinase and hepatic nuclear factor 1α (HNF1α) genes. Those with glucokinase mutations can be told that they are unlikely to get diabetic complications and generally have diabetes that can be frequently treated by lifestyle alone. The clinical phenotype of people with HNF1α mutations are similar to many people who are not overweight and who have diabetes. Individuals with an HNF1α mutation are sensitive to sulphonylureas and many are incorrectly treated with insulin. This highlights the importance of making a genetic diagnosis: in some people currently treated with insulin, it is possible to stop insulin and maintain good glycaemic control using oral agents.

Until recently progress in type 2 diabetes was painfully slow and waited for a collaboration of all major gene hunters in the UK initially stimulated by Moira Murphy and Simon Howell at Diabetes UK. The realisation of the importance of studying very large numbers of people in association studies, which included replication sets, information from the human genome mapping project and the revolution in technology using gene chips, allowed grand experiments that were not even dreamed about 26 years ago. The culmination of this approach was our contribution to the Wellcome Trust Case Control Consortium (WTCCC) study that studied half a million markers in 3000 controls and 2000 cases in each of seven multifactorial diseases, including type 2 diabetes. These results will be published soon.

Meanwhile, 2007 has already seen us publish two papers in the journal *Science* detailing the replication studies from the type 2 diabetes component of the WTCCC (Frayling et al, 2007; Zeggini et al, 2007); the type 2 diabetes contribution was led by Mark McCarthy and Andrew Hattersley working with all the key players in the UK. In type 2 diabetes, we confirmed the importance of three previously identified candidate genes (PPARγ, KCNJ11 and TCF7L2) and verified two identified by a genome-wide association published a month previously (HHEX/IDE and SLC30A8; Sladek et al, 2007). Furthermore, we identified four new genes (FTO, CDKAL1, CDKN2A/CDKN2B and IGF2BP2; Zeggini et al, 2007). In our second *Science* paper we identified the FTO gene as an important contributor to weight gain (Frayling et al, 2007). If a single allelic variant of this gene is present in an individual, it leads to an average weight gain of 1.2 kg and when two copies are present (the individual is homozygous) this can lead to an average of 3 kg extra weight. With the homozygous weight predisposing variant present in 16% of the population, this discovery is of major importance.

In 'the paper that changed my life', 52 subjects in 1981 were studied using a single marker. In 2007, the importance of the FTO gene was discovered by studying 41 697 subjects and initially 500 000 markers – how times have changed!