**KCNQ1, a susceptibility gene for type 2 diabetes**

In 2001, the Millennium Genome Project in Japan was established to identify susceptibility genes for five diseases, including type 2 diabetes mellitus, as a national undertaking. In 2002, the consortium, composed of 11 core facilities located in various regions of Japan, began a multistage genome-wide association study to identify disease-associated single-nucleotide polymorphisms (SNPs) for type 2 diabetes among a collection of 10,000 standard Japanese polymorphisms.

Three consecutive screenings resulted in the identification of 10 SNPs with a P value for association with type 2 diabetes of <0.05. Three of these 10 SNPs were located in intron 15 of **KCNQ1**, and one of these three, rs2237892, showed the most significant association. Further investigation of **KCNQ1** revealed the significant association of rs2237892 with type 2 diabetes not only in two additional Japanese subject panels but also in Chinese, Korean, and Swedish panels. The final data set with a total of 19,930 individuals (9569 cases and 10,361 controls) yielded a P value of 1.7 × 10⁻⁴⁷ and an odds ratio of 1.40 (95% confidence interval, 1.34–1.47) for rs2237892. Another Japanese group also independently identified **KCNQ1** as a susceptibility gene for type 2 diabetes. To date, **KCNQ1** has been confirmed as a susceptibility gene for type 2 diabetes not only in East Asians and Europeans but also in Mexican-Americans and South Asians, indicating that the disease susceptibility it confers is transethnic.

**KCNQ1** encodes the pore-forming subunit of a voltage-gated K⁺ channel that is essential for the repolarization phase of the action potential in cardiac muscle. Mutations of this gene are also associated with hereditary long QT syndrome and familial action potential in cardiac muscle. Mutations of this gene are expressed in tissues including the brain, adipose tissue, and pancreatic β-cells as well as in the insulin-secreting cell line INS-1. The risk allele of **KCNQ1** for type 2 diabetes is also associated with impaired insulin secretion1,3, suggesting that this impairment might underlie the diabetes susceptibility conferred by the allele. Attenuation of **KCNQ1** channel activity by the selective inhibitor chromanol 293B was found to enhance insulin secretion induced by tolbutamide in INS-1 cells. Furthermore, forced expression of **KCNQ1** in the MIN6 mouse β-cell line resulted in impairment of insulin secretion induced by glucose, pyruvate, or tolbutamide. These data are consistent with the idea that increased **KCNQ1** function impairs insulin secretion by inducing premature repolarization of the action membrane potential in pancreatic β cells. The risk allele of **KCNQ1** may therefore increase the expression of **KCNQ1** in pancreatic β cells and thereby promote the development of type 2 diabetes.

**KCNQ1** is also an imprinted gene. Genomic imprinting is a phenomenon whereby a subset of autosomal genes is mono-allelically expressed in a manner dependent on parental origin, with **KCNQ1** being expressed from only the maternally derived chromosome. Furthermore, **KCNQ1** contains KvDMR1, an imprinting control region within intron 10 of the gene. KvDMR1 is methylated on the maternal chromosome but not on the paternal one, and is transcribed from the latter to yield the noncoding antisense RNA KCNQ1OT1 (Figure 1). This RNA is thought to be responsible for the repression of **KCNQ1** and neighboring genes on the paternal chromosome (Figure 1). Although functional imprinting is known to be highly tissue and developmental stage specific, the rs2237892 risk allele of **KCNQ1** was found to be significantly associated with diabetes when maternally transmitted but not when paternally transmitted1, suggesting that **KCNQ1** and/or its neighboring genes are indeed imprinted in human pancreatic β-cells.

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**Figure 1** | Physical map of an imprinted gene cluster at human chromosome 1p15.5. The genes shown in green are expressed from the maternally derived chromosome, as indicated by the red arrows, but not from the paternally derived chromosome. The gene shown in blue is expressed from the paternal chromosome only. The genes shown in white are expressed from both chromosomes. KvDMR1 is a region within intron 10 of **KCNQ1** that is transcribed from the paternal chromosome to yield a noncoding antisense RNA (KCNQ1OT1); the corresponding region of the maternal allele is methylated (Me). Adapted by permission from Macmillan Publishers Ltd: Fitzpatrick et al10, copyright 2002.
More than 20 SNPs have been identified to date as susceptibility loci for type 2 diabetes by genome-wide association studies, although the mechanisms by which these gene variants contribute to disease pathogenesis remain unclear. Much work thus remains to be done in order to elucidate the mechanism by which the SNPs in intron 15 of KCNQ1 promote the development of diabetes. Generation of conditional knockout mice in which KCNQ1 is ablated specifically in pancreatic $\beta$ cells as well as of transgenic mice that overexpress KCNQ1 specifically in these cells should provide important tools for such studies. It will also be of great interest to analyze the expression of KCNQ1 in islets from patients with type 2 diabetes who harbor different SNPs of this gene. The identification of KCNQ1 as a susceptibility gene for type 2 diabetes thus affords opportunities to gain important insight into the pathogenesis of this disease, the prevalence of which is rapidly increasing worldwide.

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