Editorial
A LANDSCAPE OF GENETIC OF DIABETES IN ITS LAST PROVISIONAL MOVEMENT

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The new 3rd millennium could be considered as "the golden decade" for the genetic of diabetes mellitus. After 4 decades of intensive search of genes associate with various phenotypes of diabetes, related with Genome Wide Scan studies, permitted not only to discover new diabetogenic genes, but also to select from the previous studies based on "candidate gene approach" those really linked with both Type 1 and type 2 diabetes. Here is a short presentation of the new landscape of genetics of various phenotypes of diabetes.

Maturity Onset Diabetes of the Young (MODY) is a heterogeneous group of diabetic disorders. Clinically, MODY is characterised by nonketotic diabetes resulting from a primary defect of beta cell function, onset usually before the age of 25, frequently in childhood or adolescence, and presentation usually as mild asymptomatic hyperglycemia in non-obese subjects. The 6 classical MODY types are monogenic forms for which the gene defects affect beta cell proteins (Fajans 2001, McCarthy 2008). These are: Hepatocyte Nuclear Factor (HNF)-4α (MODY1); Glucokinase (MODY2); Hepatocyte Nuclear Factor (HNF)-1α (MODY3); Insulin Promoter Factor-1 (MODY4); Hepatocyte Nuclear Factor (HNF)-1β (MODY5) and NeuroD1/BETA2 (MODY6). Details regarding these 6 genes are given in Table 1. Genetically, MODY is characterised by a monogenic autosomal dominant pattern of transmission. Multigenerational involvement is common. In the recent years, MODY has been an invaluable model for genetic and physiologic studies of diabetes. Genetic studies of MODY have led to the identification of genes that play a key role in the development and function of beta cells. The lessons learned from the study of MODY also improved the understanding of the insulin secretory defect in type 2 diabetes. MODY phenotypes can explain ~2-5% of the total number of diabetes cases.

Recently, were described other monogenic forms (like MODY) induced by mutations of *INS* (insulin gene) and *CEL* (encoding the lipolytic enzyme carboxyl-ester lipase). Additional unknown MODY loci (MODY-X) may represent, depending on the population studied between 11% (McCarthy 2008) and 50% of the cases, being more prevalent in German and Spanish families (Vaxillaire 2008).

Diabetes diagnosed in the first few months (usually before 6 moths)) of life is defined clinically as *neonatal diabetes*. Neonatal diabetes mellitus is very rare, with incidence of ~1 case per 300,000-to-500,000 live births (Polak 2007). Neonatal diabetes can be stratified in *permanent* neonatal diabetes mellitus (PNDM) or *transient* neonatal

diabetes mellitus (TNDM), depending on whether the diabetes resolves in time. The available, combined data indicate that somewhat over half (~57%) of neonatal diabetes cases are transient, require insulin treatment initially and spontaneously resolve in less than 18 months, only to relapse in later years. Neonatal diabetes is part of the group of monogenic diabetes. While TNDM is usually associated with mutations at 6q ZAC locus (McCarthy 2008), PNDM is usually associated with monogenic defects of K_{ATP} channels, both Kir6.2 subunit encoded by *KCNJ11* (Gloyn et al. 2004) and SUR2 subunit encoded by *ABCC8* (Babenko et al. 2006), or proinsulin gene (Stoy 07). Rarely, PND is associated with homozygote mutations in *GCK* (glucokinase gene), HNF-1*β, IPF-1, PTF1A* (Pancreas Transcription Factor 1α) or other genes (McCarthy 08, Vaxillaire 08). All these forms have a variable clinical severity and interestingly, some of them (those induced by K_{ATP} channel defects, encoded both by *KCNJ11* or *ABCC8*) can be treated with sulphonylureas (Murphy & Hattersley 2008).

Table 1. Genetic defects associated to the various MODY phenotypes

MODY type	Gene	Chromosome	Gene function	Phenotype
MODY 1	HNF-4α	20q12-13.1	Transcription Factor/Nuclear Receptor	Neonatal hyperinsulinism Diabetes (early adulthood)
MODY 2	Glucokinase	7p13-15	Hexokinase IV	Mild hyperglycaemia (in early childhood)
MODY 3	HNF-1α (TCF1)	12q24.2	Transcription Factor /Homeodomain	Diabetes (early adulthood)
MODY 4	IPF-1	13q12-1	Transcription Factor /Homeodomain	Diabetes (pancreas agenesis in homozygote)
MODY 5	HNF-1β (TCF2)	17q21.3	Transcription Factor /Homeodomain	Diabetes, RCAD Pancreas hypoplasia
MODY 6	Neuro D1	13q	Transcription Factor	Diabetes (infancy and early adulthood)

Other monogenic forms of diabetes include rare genetic syndromes whose phenotype include in familial forms of diabetes associated with extra-pancreatic anomalies. In this group we could include: 1) *Diabetes and Pancreatic Exocrine Dysfunction* (DPED) associated with single-base deletions in the carboxyl ester lipase (CEL) gene (Vaxillaire 2008). 2) Diabetes associated with mitochondrial defects - *Maternally Inherited Diabetes and Deafness* (MIDD). This form was associated with a 10.4 kb deletion in the mitochondrial genome (Vaxillaire 08) or with an A to G transition at base-pair 3243 affecting tRNA (Leu) (Vaxillaire 08, McCarthy 08). Prevalence studies have suggested that 3243 A/G mutation accounts for ~1–2% of diabetes in Japanese and 0.2– 0.5% in European series (Murphy et al. 08). 3) Finally, diabetes associated with the *Wolfram Syndrome*, also known as *DIDMOAD*, which is a rare progressive neurodegenerative disorder, inherited in an autosomal recessive manner, associated with mutations of *WFS1* gene on chromosome 4p16.1 that encodes (as we discussed above) an 890-amino-acid polypeptide named wolframin.

The lifelong T1DM risk in the general population is 0.4% but increases to 6% in the first degree relatives of T1DM subjects [Risch 1987]. The 15 times higher risk in first degree relatives demonstrate the strong family aggregation of T1DM cases and sustains the importance of genetic/hereditary factors for this diabetes phenotype. Genetically speaking, T1DM is a complex, polygenic disease, with many predisposing/protective gene variants, interacting with each other in generating the global genetic disease risk [Todd et al. 1991].

Historically, the study of candidate genes in T1DM identified the major two susceptibility genes for T1DM: *IDDM1* encoded in the HLA region of the Major Histocompatibility Complex (MHC) on chromosome 6p21 [Singal and Blajchman 1973, Cudworth and Woodrow 1974, Nerup et al. 1974] and mapped to the *DRB1, DQB1* and *DQA1* loci [Todd et al. 1987, Cucca et al. 2001] and *IDDM2* encoded by the insulin gene region mapped to the *VNTR* region 5' of the insulin gene on chromosome 11p15 [Bennett et al. 1995, Barratt et al. 2004]. The same candidate gene approach also ravelled the association of other three loci, all with smaller contributions to T1DM susceptibility: *IDDM12* – the *CTLA4* (Cytotoxic T Lymphocite Associated Antigen 4) gene on chromosome 2q33 [Nistico et al. 1996, Ueda et al. 2003], the *PTPN22* (Lymphoid Tyrosine Phosphatase 22) gene on chromosome 1p13 [Bottini et al. 2004, Smyth et al. 2004] and the *IL2RA/CD25* gene region on chromosome 10p15 [Vella et al. 2005]. Using linkage analysis strategies by whole genome scaning (GW Linkage Studies), some other regions of the human genome were linked with T1DM [European Consortium for IDDM Genome Studies 2001, Concannon et al. 2005] but none of the putative diabetogenic genes from these regions has been identified yet. Finally, in the last two years, the Genome Wide Association (GWA) studies led to the identification of a sixth T1DM gene, *IFIH1* (Interferon Induced Helicase 1) on chromosome 2q24 [Smyth et al. 2006], as well as other four T1DM associated chromosome regions - 12q13, 12q24, 16p13 and 18p11 – for which the identification of the causal genes is still not elucidated [Hakonarson et al. 2007, WTCCC 2007, Todd et al. 2007].

The classical form of T2DM, with its various subtypes (normal weight vs. overweight for example), was associated with multiple gene defects. As for the common T1DM phenotype, in T2DM also susceptibility loci were identified by studying candidate genes or by scanning the whole genome using linkage (GW Linkage) or association (GWA) approaches. The candidate gene approach included traditional candidates, such as the K_{ATP} - *KCNJ11*, *AdipoQ* (adiponectin) or *PPARγ* loci, as well as candidates revealed by the study of the monogenic forms of diabetes (*KCNJ11, HNF1β, HNF4α, WFS1).* Currently ~17-18 loci (Table 2) were confirmed in various studies, including Candidate Gene Studies, Large Scale Association Studies or GWA's (Genome Wide Scan Association). This is only a provisory figure that explains <50% from the genetic basis of this polygenic disease.

Completion of the human genome project in 2003 and the Haplotype Mapping (HapMap) Project in 2005 opened the way for the GWA studies, applicable for many common diseases. The true explosion of

genetic studies in diabetes (Khoury et al. (2008) counted over 170 in 2007-2008), was recently reviewed and synthesized in several papers (McCharthy 08, Florez 08). According to the inventory mentioned by Khoury (2008) at 1st August 2008, 431 genes have been studied in relation with T2DM with > 1340 publications and 50 meta-analysis, as well as 15 published GWAS. We could expect that tens of other T2DM susceptibly genes will be identified in the future in various population.

Table 2. T2DM loci with proven contribution to disease susceptibility (McCarthy&Hatterslay 2008)

Gene	Chr	SNP	Risk allele freq	Effect size	Method	Hypothezised Function
PPARG	3	rs1801282	0.85	1.23	Candidate gene	Adipocyte differentiation and function
KCJN11	11	rs5219	0.40	1.15	Candidate gene	β-Cell K_{ATP} channel
TCF7L2	10	rs7901695	0.40	1.37	Large-scale association	Incretin signaling in the islet
WFS1	4	rs10010131	0.60	1.11	Large-scale association	Endoplasmic reticulum stress
TCF2/HNF1B	17	rs757210	0.43	1.08	Large-scale association	β-Cell development and function
HHEX	10	rs5015480	0.63	1.13	GWA	Pancreatic development
SLC30A8	8	rs13266634	0.72	1.12	GWA	Zn transport in β-cell insulin granules
FTO	16	rs8050136	0.45	1.23	GWA	Hypothalamic effect on weight regulation
CDKAL1	6	rs10946398	0.36	1.16	GWA	β -Cell function and mass
CDKN2A/B	9	rs10811661	0.86	1.19	GWA	Cell cycle regulation in the β-cell
IGF2BP2	3	rs4402960	0.35	1.11	GWA	mRNA processing in the β-cell
JAZF1	7	rs864745	0.50	1.10	GWA	Transcriptional repression in the islet
CDC123/ CAMK1D	10	rs12779790	0.18	1.09	GWA	Cell cycle regulation (*CDC123*)
TSPAN8	12	rs7961581	0.27	1.09	GWA	Cell surface glycoprotein
THADA	2	rs7578597	0.90	1.12	GWA	Apoptosis
ADAMTS9	3	rs4607103	0.76	1.06	GWA	Metalloprotease
NOTCH2	1	rs10923931	0.11	1.11	GWA	Pancreatic development

The combined analysis of various known genes associated with T2DM in the general population showed that the information offered by the currently established T2DM loci has a very weak predictable ability (van Hoek, Lango 08, Khoury 08). Thus, the 17 recently discovered T2DM genes (table 2) can explain less than 5% of the overall risk for

T2DM (Gaulton 08, Hoeke 08). Of course, the subjects carrying more risk alleles have higher T2DM risk (with the figure for ROC of 0.60). This indicator is lower then the ROC of the risk predicted by age, sex and BMI (of 0.78).

All these data show that, currently, the genetic polymorphisms only marginally improve the prediction of T2DM beyond clinical characteristics such as age, BMI and family history of diabetes (Gaulton 08, Hoeke 08). If more gene variants will be identified in the future, tests with better credibility and performance should become available for clinical practice (Lango 08).

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