From Base Change to Better Care: The Clinical Impact of Molecular Genetics

The long road from bench science understanding of the molecular genetics of diabetes to improved patient care has begun to be traveled, and more benefits will likely be on the way, according to Andrew Hattersley, FRCP, DM, Peninsula Medical School, Exeter, UK. But while the headlines in 2007 have publicized the finding of associations between diabetes risks and particular genetic features, the messages that have had the most impact on the public have been about connections between lifestyle, obesity, and diabetes. In searching for an answer to the *whys* of the increases in type 2 diabetes, such that there are now 200 million individuals affected, the fact that patients with diabetes tend to be more obese and engage in less physical activity looms large. While racial differences and familial differences have been apparent, the commonly held assumption has been that diabetes and obesity are increasing because of increased food consumption and reduced activity at the population level. The dogma that has emerged, Prof. Hattersley said, is that: Patients with diabetes are the most obese, eat the most, and do the least. Answers to diabetes/obesity are solely political/social and not scientific. Studying the genetics of type 2 diabetes/obesity is a waste of time.

This is simply not true.

The similarity of fat distribution among monozygotic twins has long pointed to the role of inherited traits, as does the fact that lifetime risk for diabetes is 10% when neither parent has diabetes, 30% with one affected parent, 70% with both parents affected, and 80-100% with an identical twin with diabetes.

"Can the role of molecular genetics be defined?" Prof. Hattersley asked. To find the answer to that question, large-scale collaborative sample collection for replication and phenotypic studies have been conducted. A British genomewide scan for type 2 diabetes revealed that several genes are associated with disease development. Analyzing 13 studies with approximately 38,500 participants of all ages, Prof. Hattersley and colleagues found that participants with a specific copy of the FTO gene tended to have an elevated body mass index (BMI). Further large-scale analyses showed FTO to be associated with 2-3 kg greater weight, higher BMI among children aged 7-11 years, and with fat mass increases of 15% (as shown on dual-energy x-ray absortiometry scanning) among children at age 9 years. "FTO predisposes to type 2 diabetes by increasing adiposity," Prof. Hattersley stated.

With studies now including 41,697 subjects, associations between FTO and reported exercise or reported food consumption have not been found. Putting FTO into the risk equation increased the risk of diabetes by 50% and obesity by 70% in the 16% of the population at highest risk compared to the 35% at lowest risk.

The discovery of this novel confirmed BMI gene is just the beginning, Prof. Hattersley said. It raises questions as to whether FTO alters metabolism at a given BMI and if understanding this biology can lead to new treatments.

Highlights from the
European Association for the Study of Diabetes Annual Meeting 2007

Next, Prof. Hattersley provided an example of how molecular genetics research can improve diabetes treatment. The child of a woman who had developed infancy-onset insulin-dependent diabetes at the age of 12 weeks had a child who developed diabetes at 4 weeks. The pediatrician realized that this was not type 1 diabetes. The key insight was the early development. Human leukocyte antigen (HLA) analysis has suggested that type 1 diabetes is very uncommon before the age of 6 months. "I would say to you that

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(eg, pregabalin and gabapentin) that can result in pain relief, pharmacologic pain treatment is still ineffective in too many patients and we urgently need more effective therapies."

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if anyone in your clinic is diagnosed before 6 months, he or she doesn't have type 1 diabetes, but rather what I would term neonatal diabetes."

Further research showed that mutations in the insulin gene that are responsible for permanent neonatal diabetes replace or introduce cysteine residues or alter cysteine's structure, substituting serine for glycine at B8 (Støy J et al. *Proc Nat Acad Sci USA* 2007). "We are beginning to understand the biology," Prof. Hattersley said. "So we can begin to think of exciting ways in which we can continue the normal allele and downregulate the mutant allele, which should result in the patients being able to keep their β-cells if we can do it early enough."

The aforementioned patient above had the Kir6.2 mutation, the most common cause of neonatal diabetes. With that mutation, ATP does not close the K_{ATP} channel and the membrane becomes hyperpolarized, with the result that there is no calcium influx and no insulin secretion. The Kir6.2 channel is also expressed in the muscles, nerves, and the brain. The most severe cases, about 5% of those with the Kir6.2 mutation, have the DEND (Developmental delay, Epilepsy and Neonatal Diabetes) syndrome that is characterized by severe developmental delay, epilepsy <12 months, and permanent neonatal diabetes; another 16% has what can be referred to as intermediate DEND in which there is mild developmental delay, no epilepsy, and permanent neonatal diabetes.

While mutational analysis helps predict onset and relapse of diabetes, Prof. Hattersley said, what is of preeminent interest to patients and the mother of the neonatal diabetes child is whether it can help with treatment. The ATP channel that does not close with the Kir6.2 mutation is acted upon by sulfonylureas, but by a different route — a non-ATP-dependent route. The question became, "Could sulfonylureas close the ATP channel and result in insulin secretion?"

A chance event helped answer this question. A man included in the first study, who had been diagnosed with diabetes 46 years earlier at the age of 3 months, had come from a rural family that, not being able to afford insulin, begged that he be allowed to take tablets. As a result, he had been treated with sulfonylureas all along and turned out to have the best glycemic control of all the patients in the series. Subsequent studies in Kir6.2 children showed better (Pearson ER et al. *New Engl J Med* 2006) and more stable (Zung A et al. *J Clin Endocrinol Metab* 2004) glycemic control with sulfonylureas (HbA1c 6.4%) than with insulin (HbA1c 8.1%). Clinical experience showed, unfortunately, that neurological features were not helped by sulfonylureas. However, a child with an insulin pump unable to pull himself up at nearly 2 years of age began walking 3 weeks after starting sulfonylurea treatment. Another child's school reported immediate changes in concentration and speech (he had been unable to speak at age 5). Every single case since has demonstrated improvement with sulfonylurea treatment in function and in diabetes, Prof. Hattersley said.

"We have shown that knowing the cause of people's diabetes can lead to very unexpected treatments. Also, the finding of new genes really gives the possibility that we may start to individualize treatment" Prof. Hattersley closed, urging that patients diagnosed with diabetes before 6 months should definitely be sequenced for Kir6.2 (and SUR1). "It's crucial because their lives can change."

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Improving Risk Calculations Through Genotyping

Traditional calculations of cardiovascular risk, such as the Framingham Risk Score, only accurately predict events only in a minority of subjects. Investigators from the United Kingdom evaluated whether a set of common variants in genes previously found related to coronary heart disease risk might enhance the utility of such algorithms. In a multivariate analysis, they found that several genes significantly ($p<0.001$) improved the predictive utility of such algorithms, including those related to uncoupling protein 2, apolipoprotein E, lipoprotein lipase, and apolipoprotein A4, as well as several genes showing interaction with smoking, interleukin-6 and platelet/endothelial cell adhesion molecule genotypes. In the future, risk estimates may include not only conventional risk factors but also a panel of selected genotypes concluded Philippa Talmud, PhD, University College London, United Kingdom.

Severe Mental Illness and Type 2 Diabetes

The prevalence of diabetes among patients with severe mental illness is 2-3 times higher than that for the general population. While this disproportionate risk has largely been attributed to treatment with atypical antipsychotic agents, Stephen Gough, MD, University of Birmingham, UK, said, "I think the link goes well beyond this."