Customer Case Study: The University of Cambridge

The effect of *IGF2* on developing gestational diabetes mellitus

The significance of gestational diabetes mellitus

Diabetes constitutes a major challenge to public health globally, with an estimated number of 285 million people living with the disease. One approach to prevent the rising burden of diabetes is to advance our understanding and monitoring of gestational diabetes mellitus (GDM), defined as any degree of glucose intolerance with onset or first recognition during pregnancy.[1]

Approximately 7% of all pregnancies are complicated by GDM, resulting in more than 200,000 cases annually.[2] In most cases, GDM develops in the third trimester (after 28 weeks) and usually disappears after the baby is born. However, women who develop GDM are more likely to develop type 2 diabetes later in life.

Babies born to mothers with GDM are typically at risk of being large for their gestational age, low blood sugar, and jaundice[3], with further risk factors including the development of obesity, glucose intolerance and type 2 diabetes in adulthood.

The effect of *IGF2* on developing GDM

It has been hypothesised that polymorphic variation in the fetal genome, in particular in the fetal growth genes, could lead to alterations in maternal metabolism during pregnancy.

Insulin-like growth factor 2 (*IGF2*) is one of three hormones that share structural similarity to insulin; and whose main role is to act as a growth-promoting hormone during gestation. In the human fetus and placenta, *IGF2* is imprinted such that only the paternally transmitted copy of the gene is expressed.

Dr Clive Petry, a researcher from the Department of Paediatrics, University of Cambridge, explains that;

> "Many well-characterised fetal growth genes are imprinted, meaning that they are expressed from either the paternally or the maternally transmitted copy, depending on the gene in question and the stage of development. In order to decipher the genetic architecture of such genes, appropriate genomic tools are required."

Technical challenge

In the report published by Dr Petry and his collaborators[4], the team used the principles of Haig's kinship, or conflict hypothesis, to lay the foundations for a study which investigated whether the polymorphic variation in the paternally transmitted fetal *IGF2* gene is associated with increased maternal glucose concentrations in the third trimester of pregnancy.

The theory suggests that paternally expressed fetal imprinted genes increase fetal growth, whereas maternally expressed genes will tend to restrain. This is thought to be achieved through modifying fetal and placental nutritional demand and supply, potentially including altering maternal glucose concentrations.

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Dr Petry explains, “We recently tested our hypothesis in phenotypically wild-type pregnant mice, that had a targeted 13kb genetic region disrupted, which included the imprinted *H19* gene and the *IGF2* control element[5]. Affected pups in this model are born 30% heavier than unaffected litter mates, principally as a result of bi-allelic *IGF2* expression resulting from the disruption of its control element. This was consistent with our hypothesis. We found that intraperitoneal glucose tolerance tests indicated that mice carrying knockout offspring had increased circulating glucose concentrations in late pregnancy in comparison with those of genetically matched controls.”

“In contemporary birth cohorts, we found that in first pregnancies, cord blood IGF-II concentrations were also associated with a polymorphic variant in *H19*, another imprinted gene in the 11p15.5 region in humans, and one that may regulate *IGF2* gene expression when transmitted from the mother to the fetus. This *H19* single nucleotide polymorphism (SNP) was also associated with maternal glucose concentrations, suggesting that our findings in mice may be relevant to humans.”

Thus researchers at the University of Cambridge identified that a study would be beneficial to investigate diabetes in the third trimester of pregnancy and specifically what affect the *IGF2* gene could have on developing GDM.

To do this they wanted to employ 17 haplotype tagged SNPs in the *IGF2* region to genotype over 1,000 mother / partner / offspring trios and combine this with data on maternal glucose concentrations and offspring birth weights.

In order to develop accurate results, Dr Petry and his team needed a reliable and efficient genotyping chemistry and service that generated good quality data so they could quickly and easily identify *IGF2* alleles.

SNPs are the most common type of genetic variation. They occur once in every 300 nucleotides on average, which means there are roughly 10 million SNPs in the human genome. They can act as biological markers, helping scientists locate genes that are associated with diseases, such as diabetes[6].

“Researchers expect that SNPs may help predict an individual’s response to certain drugs, susceptibility to environmental factors such as toxins, and risk of developing particular diseases; in addition to being used to track the inheritance of disease genes within families.” - **Dr Petry**

The solution

“We required a solution that offered rapid sample turnaround and full sample traceability, with full application and technical support. When we outsource the service to LGC it is far more efficient, the throughput is much greater, and it’s also much more cost effective than the University of Cambridge setting up the assay for one particular polymorphism.” **- Dr Petry**

Dr Petry goes on to say, “KASP overcame previous technological limitations, from analysing the relatively modest size of the cohorts used, by providing the flexibility of handling any combination of ‘sample X’ markers”.

“As a department, we were confident that LGC could meet the demands of our project, delivering excellent service for our study.” **- Dr Petry**

Results

“Our results show that polymorphic variation in the fetal *IGF2* gene, specifically in the copy of the gene transmitted from the father, is associated with increased maternal glucose concentrations in the third trimester of pregnancy. No associations were found between the maternal *IGF2* genotype and blood glucose concentrations, unlike the findings in one previous study assessing maternal *IGF2* restriction fragment–length polymorphisms in 96 women with GDM.”

Dr Petry goes on to say that, “In our mouse model, we showed that pregnant mice carrying pups with a doubling in *IGF2* expression levels have worse glucose tolerance than controls in the final week of their 3-week pregnancies. Unlike recent findings for a maternal progesterone receptor gene polymorphism and peroxisome proliferator–activated receptor-g, in our study there was no significant interactive effect of fetal sex on the associations with maternal glucose concentrations, suggesting that these associations are mediated by different mechanisms.”

Although the association found between paternally transmitted fetal *IGF2* alleles and increased maternal glucose concentrations in the study are partially consistent with the kinship hypothesis, Dr Petry notes that “There were no associations between any of the *IGF2* fetal or maternal variants and offspring birth weight, probably because the effect sizes on maternal glucose concentrations were too small to make a detectable difference in birth weight in our sample. Indeed, from using data from the Hyperglycemia and Adverse Pregnancy Outcome Study, our largest effect size would have given an odds ratio of only 1.11 for a birth weight above the 90th percentile.

Conclusion / future

The University of Cambridge has reported for the first time an association between polymorphic variation in a paternally transmitted fetal gene, namely, *IGF2*, and maternal glucose concentrations in pregnancy. These findings are consistent with recent findings from animal models and support the hypothesis that variations in fetal imprinted genes regulate the maternal availability of nutrients.

Due to an increasing number of people developing GDM there is now an urgent need to reduce the adverse effects of GDM in pregnancy. The University of Cambridge has laid the foundations for further studies into the effect of inheriting *IGF2* gene variants and other diabetes-associated gene variants on the chances of developing GDM.

References

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University of Cambridge

The Department of Paediatrics is part of the School of Clinical Medicine, at the University of Cambridge, located on the Addenbrooke’s Hospital site. The staff of 68 comprises: clinicians, scientists, research nurses, postgraduate students and visiting fellows.

The department is an internationally recognised centre for research in physiological, genetic and metabolic studies of child development; with the last UK Government Research Assessment Exercise awarding the University a 5* rating for the research over the previous 5-year period.

As part of the Juvenile Diabetes Research Foundation / Wellcome Trust Diabetes and Inflammation Laboratory (DIL), researchers at the university are currently collecting over 10,000 DNA samples from children with diabetes throughout the UK. This will include a study of early markers and genetics of diabetic complications combining the “Oxford Regional Prospective Study” and a new nephropathy family study cohort. An area of specific interest is the field of genetic and hormonal determinants of fetal and childhood growth; analysing the genetic and hormonal determinants of size at birth and early growth. The work centres on the Avon Longitudinal Study of Parents and Children and the Cambridge Baby Growth Study which is focusing on genetic and environmental influences on fetal and early childhood growth. Collaborations with other cohorts study the genetic determinants of abnormal puberty and polycystic ovary syndrome in adolescent girls.

The university additionally studies the genetic and hormonal causes of DSD (Disorders of sexual development), as well as maintaining the Cambridge DSD database. The database has been kept for over 20 years and contains clinical and biochemical information about patients the university have helped to diagnose and the results of their DNA and protein analysis.

Recent initiatives in the UK and Europe have been launched to share information with other doctors working in the field of DSD. This will improve planning of services across the UK and the EU and help our understanding of these rare conditions.

Prof. David Dunger (Department of Paediatrics, University of Cambridge) who’s work contributed to the study

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