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 jaundice3, 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 collaborators4, 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.
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. 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.

“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
About LGC

LGC is an international science-based company and market leader in the laboratory services, measurement standards, genomics, reference materials and proficiency testing marketplaces. LGC operates in a variety of markets – including, but not confined to, Food & Agriculture, Government, Pharmaceuticals and Biopharmaceuticals and Sports – which underpin the safety, health and security of the public and the regulation of industry, for both private and public sector clients.

With headquarters in Teddington, South West London, LGC employs over 2,000 staff, operating out of 22 countries worldwide. Its operations are extensively accredited to international quality standards such as ISO/IEC 17025.

Set up in 1842 as the Laboratory of the Government Chemist, for more than 100 years LGC has held the unique function of the Government Chemist in the UK. LGC was privatised in 1996 and is now majority-owned by funds managed by Bridgepoint.

For further information:

Our genomic solutions provide high quality services and products for DNA and genetic analysis, and sample preparation including:

- Genotyping services, assays and reagents
- Sanger and next-generation sequencing services
- DNA and RNA extraction products and services
- Instruments, reagents and consumables.

Follow our genomic solutions on:

Twitter: twitter.com/LGCGenomics
Facebook: www.facebook.com/LGC.Genomics
LinkedIn: www.linkedin.com/company/lgc-genomics

Follow LGC on:

Twitter: twitter.com/LGCGroup
LGC’s Science blog: www.blog.lgcgroup.com
Web: www.lgcgroup.com

www.lgcgroup.com/genomics • genomics@lgcgroup.com

Science for a safer world