Gene Polymorphisms, Size at Birth, and the Development of Hypertension and Type 2 Diabetes

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Abstract
Nonoptimal fetal growth, leading to a small-for-gestational-age body size at birth, is commonly followed by compensatory growth after birth. This pattern of growth is associated with an increased risk for type 2 diabetes, especially when the compensatory phase begins around 3 to 4 years of age. Genetic factors are of major importance for the development of type 2 diabetes, but despite extensive research, the identification of the underlying genes has not been particularly fruitful. This article focuses on interactions between intrauterine growth and genes in relation to adult health outcomes based on findings from the Helsinki Birth Cohort Study. We have shown that the effects of the Pro12Pro and Pro12Ala polymorphisms of the PPAR-γ gene depended on the body size at birth. Those individuals who had a small body size at birth and were carriers of the Ala allele seemed to be protected against insulin resistance and type 2 diabetes in later life. These findings reflect gene–early environment interactions and can be attributed to the phenomenon of developmental plasticity.

A large number of epidemiological studies have revealed that there is an inverse relation between early growth and the subsequent development of type 2 diabetes in later life; this was first shown in Hertfordshire, UK (1). Those men with the lowest birth weight had by far the highest odds ratio for impaired glucose tolerance and type 2 diabetes in adult life at age 64 y. Similar associations between body size at birth and adult health outcomes have been found in relation to coronary heart disease (CHD)² and hypertension (2–4). According to the original fetal origins hypothesis, fetal adaptation to an adverse intrauterine environment involves programming of pathways and functions leading to metabolic changes as well as metabolic and cardiovascular disease in adult life. The fetal adaptations, which include reduced intrauterine growth and therefore a small body size at birth, can be used as a proxy for the early intrauterine environment (5). Not only fetal growth but also postnatal growth is closely linked to several adult noncommunicable diseases such as type 2 diabetes and CHD (6–8). In other words, not only fetal growth but also growth during infancy and childhood is related to later disease risk.

Findings based on twin and family studies have largely contributed to our present knowledge of the importance of genetic factors in the development of noncommunicable disease such as type 2 diabetes and its risk factors. A large number of candidate genes for type 2 diabetes have been identified, but the search has not thus far been particularly fruitful, and the identified genes have been able to explain only a small part of the overall disease risk. In 1999 Hattersley put forward the “fetal insulin hypothesis,” offering an alternative explanation for the association between a low birth weight and adult health outcomes (9). He suggested that the same genetic influence alters both intrauterine growth and, e.g., adult glucose metabolism. In other words a small body size at birth and glucose intolerance in adult life would be phenotypes of the same insulin-resistant genotype. This hypothesis was primarily supported by findings in various monogenic forms of diabetes, e.g., in diabetes caused by glucokinase gene defects. In addition to the glucokinase gene, the IGF-I and insulin VNTR genes have also been suggested to be simultaneously related to both fetal growth and adult health outcomes (10,11).

However, today there is no strong evidence suggesting that there are common genes explaining the association between birth size and later health outcomes. Importantly, these alternatives are not mutually exclusive in explaining the pathogenesis of several noncommunicable diseases; the intrauterine environment might well interact with genes affecting health in later life.

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2 Abbreviations used: ACE, angiotensin-converting enzyme; CHD, coronary heart disease; HBCS, Helsinki Birth Cohort Study.
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This article focuses on interactions between intrauterine growth and genes in relation to adult health outcomes. The health outcomes focused on will primarily be type 2 diabetes and its established risk factors.

The Helsinki Birth Cohort Study (HBCS)

Two study cohorts consisting of 15,846 individuals born at Helsinki University Central Hospital and who grew up in the greater Helsinki area have been followed (12). Data from the older cohort, consisting of 7086 individuals born 1924–33, include birth characteristics as well as growth data between 7 and 15 y of age obtained from school health records. These records include information on health and growth as well as information on socioeconomic factors during childhood. The cohorts have been followed up from 1971 onward by register linkage to national Finnish registers providing information on both morbidity and mortality. Clinical examinations of 500 individuals have provided more detailed information on metabolic and genetic aspects and their associations with growth and adult health outcomes. The results presented here are based on findings from the 500 individuals born 1924–33 who participated in a clinical study around the age of ~70 y.

Genetic studies in HBCS

The PPAR genes play an important role in regulation of glucose, lipid, and energy metabolism (13,14). There is a common missense mutation in the functional domain of the human PPAR-γ gene resulting in a substitution of proline by alanine in codon 12. This has been found to modulate the transcriptional activity of the gene. The Pro12Ala variant of the gene has been found to be associated with improved insulin sensitivity and a lower risk for type 2 diabetes compared with the Pro12Pro genotype.

Fasting insulin concentration is commonly used as a proxy for insulin sensitivity, and higher fasting insulin levels indicate insulin resistance. We observed that elderly individuals within the HBCS who carried the Ala allele had lower fasting insulin and glucose concentrations i.e., they were more insulin sensitive than the carriers of the Pro12Pro genotype (15). There were no differences between the groups in body size at birth or childhood body size. Figure 1 shows the well-known association between a small body size at birth and insulin resistance. However, this association was observed only in individuals with the high-risk Pro12Pro genotype. In other words, the negative effect of a small body size at birth was abolished by the Ala allele; this means that the effect of the Ala allele among those born with a low birth weight is once again observed in relation to HDL-cholesterol concentration in adult life as shown in Table 1 (17).

The PC-1 gene is another candidate gene for type 2 diabetes being involved in the insulin signaling pathway (18). The 121Q variant of the PC-1 gene has a greater inhibitory action on the insulin receptor than the 121K variant and is consequently associated with insulin resistance. In the HBCS those subjects carrying the 121Q allele had a significantly higher prevalence of type 2 diabetes and hypertension combined, but only in the presence of a small body size at birth (19).

Table 1. Mean HDL-cholesterol concentrations (mmol/L) according to birth weight and PPAR-γ 2 gene polymorphism

<table>
<thead>
<tr>
<th>Birth weight, g</th>
<th>Pro12Pro</th>
<th>Pro12Ala</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;3000</td>
<td>1.37</td>
<td>1.48</td>
<td>0.16</td>
</tr>
<tr>
<td>3000–3500</td>
<td>1.42</td>
<td>1.44</td>
<td>0.68</td>
</tr>
<tr>
<td>&gt;3500</td>
<td>1.48</td>
<td>1.47</td>
<td>0.94</td>
</tr>
</tbody>
</table>

Figure 1. Mean fasting insulin concentration according to PPAR-γ 2 gene polymorphism and birth weight.
class of antihypertensive medication was related to birth size. Included in this study were 208 individuals with a mean age of \( \sim 70 \) y who were taking antihypertensive medication (22). A small body size at birth was related to the use of angiotensin receptor-blocking agents and/or ACE inhibitors but not to the use of other blood pressure medications. Interestingly, among those elderly subjects with the Pro12Pro variant of PPAR-\( \gamma \) 2 gene, a low birth weight was associated with the use of ACEI/ARB. There were statistically significant interactions between birth size and the PPAR-\( \gamma \) 2 gene polymorphism (Table 2).

Acknowledging the interactions between early growth and genotypes might help us to design individual therapies as well as to plan dietary and exercise interventions, taking into account individual variability not only in genetic setup but also in early growth phenotypes. This seems to be of utmost importance because our results suggest a significant interaction between birth size and the PPAR-\( \gamma \) 2 gene polymorphism (Table 2).

### Literature Cited