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 2 gene depended on the body size at birth. Those individuals who had a small body size at birth and who 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. J. Nutr. 137: 1063–1065, 2007.

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 PPAR-γ 2 genotype in elderly people depended on their body size at birth (15). There was a significant interaction between birth size and genotype (P = 0.03).

A short birth length has repeatedly been associated with an increased risk of developing type 2 diabetes (5). However, the carriers of the Ala allele of the PPAR-γ 2 gene seemed to be protected against the negative influence of a small body size at birth in a similar way to that described above. Among 476 men and women with a mean age of 70 y, the prevalence of type 2 diabetes was 24.5% among those with a birth length <49 cm and who were carriers of the Pro12Pro genotype. The corresponding percentage was 14.3% among those with a birth length >49 cm (P = 0.02) (16). Even though the PPAR-γ 2 gene is closely linked to insulin sensitivity, this gene seems to have only weak effects on the occurrence of type 2 diabetes in the HBCS. This association became much stronger when the analyses were confined to individuals with a short birth length.

HDL-cholesterol concentration is closely associated with insulin sensitivity, and insulin-resistant subjects tend to have lower concentrations of HDL-cholesterol. A similar protective effect of the Ala allele among those born with a low birth weight was 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).

Previous studies have suggested that the I allele of the insertion/deletion polymorphism in the angiotensin-converting enzyme (ACE) gene is associated with a lower risk for complications among type 2 diabetic subjects (20). We have been able to show that the carriers of the I allele of the ACE gene had higher birth weights as well as lower glucose and greater insulin response to an oral glucose tolerance test. In other words, the I allele appeared to be associated with pancreatic β-cell function in an allele- and dose-specific way. The highest insulin values, at 30 min after the oral glucose challenge, were observed in homozygotes for the I allele, followed by the heterozygotes (ID) and homozygotes (DD) for the D allele. However, the effects of this polymorphism on insulin secretion were dependent on body size at birth (21).

The findings described above could be interpreted as manifestations of gene-early environmental interactions and as illustrative of the importance of gene-early environment interaction in relation to risk factors for CHD, hypertension, and type 2 diabetes. But what does all this mean? Can we take these findings further and draw some clinical implications?

We have been studying interactions between the PPAR-γ 2 gene and size at birth on blood pressure as well as on the use of antihypertensive medication (22). The objective of this examination was to assess whether the association between a small body size at birth and adult blood pressure was modified by the PPAR-γ 2 genotype. We also assessed whether the use of any

![Figure 1](https://example.com/Figure1.png)  
Figure 1  Mean fasting insulin concentration according to PPAR-γ 2 gene polymorphism and birth weight.

<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>

P-value 0.02 0.66
class of antihypertensive medication was related to birth size. Included in this study were 208 individuals with a mean age of ~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-γ 2 gene, a low birth weight was associated with the use of ACE/ARB. There were statistically significant interactions between birth size and the PPAR-γ 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 certain genotypes and birth size as determinants of adult health outcomes. These associations have largely been attributed to the phenomenon of developmental plasticity. Developmental plasticity can be defined as the phenomenon whereby 1 genotype can give rise to a range of different phenotypes depending on conditions during development.

**Literature Cited**


**TABLE 2** Percentage of subjects with hypertension who were taking ACE inhibitors and/or angiotensin receptor-blocking agents according to PPAR-γ genotype and birth size

<table>
<thead>
<tr>
<th>Birth weight, g</th>
<th>Pro12Pro</th>
<th>Pro12Ala/Ala12Ala</th>
</tr>
</thead>
<tbody>
<tr>
<td>≤3000</td>
<td>64</td>
<td>14</td>
</tr>
<tr>
<td>&gt;3000</td>
<td>26</td>
<td>28</td>
</tr>
<tr>
<td>All</td>
<td>33</td>
<td>25</td>
</tr>
</tbody>
</table>

*P*-value 0.003 0.32

*P*-value for interaction 0.01.