The Role of Genes in Growth and Later Health

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Abstract

Genetic factors are of importance for the development of the metabolic syndrome and type 2 diabetes, but despite extensive research the identification of the underlying genes has not been fruitful. This report focuses on the interactions between intrauterine growth and genes in relation to adult health outcomes based upon findings from the Helsinki Birth Cohort Study. Candidate genes for type 2 diabetes and the metabolic syndrome have been focused upon and we report on interactions between polymorphisms of the peroxisome proliferator-activated receptor (PPAR)γ-2, plasma cell glycoprotein (PC-1) and the glucocorticoid receptor (GR) genes and prenatal growth in relation to adult health outcomes. In elderly individuals the effects of the Pro12Pro/Pro12Ala polymorphisms of the PPARγ-2 gene depend on their body size at birth. Individuals, who had a small body size at birth and were carriers of the Ala allele, seem to be protected against insulin resistance and type 2 diabetes in later life. Similar gene environment interactions will be described in relation to the PC-1 and the GR genes. We propose that these findings reflect gene–early environment interactions and can be attributed to the phenomenon of developmental plasticity.

Epidemiological studies from various geographical regions have clearly established that there is a strong association between size at birth and later health. It has been repeatedly shown that, for instance, an increased coronary heart disease risk associated with a small body size at birth is a consequence of growth restriction during fetal life – not prematurity. These findings support the view that maternal and fetal undernutrition are important underlying risk factors for cardiovascular disease. In fact, not only fetal growth but also growth during infancy seem to be of major importance in the programming of adult health and disease [1–11].
According to the original fetal origins hypothesis put forward by Barker [12], fetal adaptations to an adverse intrauterine environment involve programming of different pathways and functions in the body, leading to lifelong metabolic changes. These changes predispose to metabolic and cardiovascular disease in adult life. Since the fetal adaptations include reduced intrauterine growth, a small body size at birth has been used as a proxy for the early intrauterine environment [12].

An alternative explanation for the association between a small birth size and adult health was put forward in 1999 [13]. The ‘fetal insulin hypothesis’ proposed that one genotype could be the common denominator altering intrauterine growth as well as influencing adult health outcomes. In other words it was proposed that a small body size at birth and, for example, impaired glucose regulation in adult life could be different phenotypes of the same underlying genotype. This hypothesis was originally based upon findings in monogenic forms of diabetes, for instance in diabetes caused by glucokinase gene mutations leading to maturity onset diabetes of the young (MODY). These MODY-linked mutations were known to cause diabetes, but the carriers of the mutations also had a lower birthweight. However, MODY is a rare form of diabetes and this specific gene defect is therefore not likely to explain the association between birth size and type 2 diabetes observed in epidemiological settings. More recently a study focusing on common variants of the glucokinase gene showed that the gene is associated with fasting glucose and fetal growth – although the impact on birthweight was small [14].

Several other genes associated with growth and glucose-insulin metabolism have been focused upon. For example, the insulin-like growth factor-1 and insulin genes have been suggested to be simultaneously related to both fetal growth and adult health outcomes. The ‘thrifty genotype hypothesis’, on the other hand, suggests that genotypes promoting survival during nutritional adversity would increase the risk of type 2 diabetes later in life [15].

One strong ‘thrifty gene’ candidate is the insulin gene and variation in the insulin gene variable number of tandem repeats (VNTR) polymorphism has been suggested to modify birth size and diabetes susceptibility. Insulin is a strong candidate gene as it is a major growth factor in fetal life and infancy, and is closely linked to glucose metabolism. The insulin VNTR polymorphism has mostly been studied in relation to its effects on early growth and diabetes – with inconsistent results [16–18].

Today, there is no strong evidence to suggest that any single common gene or gene variant would explain the common association between birth size and later health outcomes. In other words support for the original fetal insulin hypothesis is small [19]. However, the genetic field is making rapid progress and it is important to keep in mind that there might be important gene–environment interactions not easily identified in genetic studies with little or no information on early growth. The intrauterine environment might well interact with genes affecting health later in life by different mechanisms. Little is
known about the possible interactions between the intrauterine environment and genes associated with growth and adult health. This field can be studied using different measures of body size at birth as markers of the early environment. This report will focus on the interactions between intrauterine growth and genes in relation to adult health outcomes. The health outcomes focused upon will primarily be type 2 diabetes and its established risk factors and comorbidities.

**The Helsinki Birth Cohort Study**

The Helsinki Birth Cohort Study (HBCS) comprises two study cohorts consisting of 15,846 individuals born in Helsinki, Finland. The older cohort includes 7,086 individuals born 1924–1933, with information on birth characteristics as well as growth data between 7 and 15 years of age obtained from birth records and school healthcare records. Besides information on growth, these include information on health and socioeconomic factors. A younger cohort, born 1934–1944, consists of 8,760 individuals and includes growth information from birth to 11 years of age obtained from birth records, child welfare clinic and school healthcare records. Both cohorts have been followed up from 1971 by register linkage to national Finnish registers providing epidemiological information on both morbidity and mortality.

Clinical examinations of 500 individuals from the older cohort and 2,003 individuals from the younger cohort 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 upon findings from the 500 individuals born 1924–1933 and who participated in a clinical study at the age of ~70 years.

**Genetic Studies in HBCS**

A number of candidate genes mostly related to insulin and glucose metabolism have been focused upon in the HBCS. This overview will focus upon the peroxisome proliferator-activated receptor-γ-2 (PPARγ-2), the plasma cell glycoprotein (PC-1) and glucocorticoid receptor (GR) genes in relation to early growth and adult health outcomes.

**Peroxisome Proliferator-Activated Receptor Genes**

The PPARs play an major role in the regulation of glucose, lipid and energy metabolism. A common missense mutation in the functional domain of the human PPARγ-2 gene resulting in a substitution of proline by alanine in
Eriksson

**Table 1.** Mean fasting insulin concentrations (pmol/l) according to PPARγ-2 gene polymorphism and birthweight

<table>
<thead>
<tr>
<th>Birthweight, g</th>
<th>&lt;3,000</th>
<th>3,000–3,500</th>
<th>&gt;3,500</th>
<th>p value*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pro12Pro</td>
<td>84</td>
<td>71</td>
<td>65</td>
<td>0.003</td>
</tr>
<tr>
<td>Pro12Ala/Ala12Ala</td>
<td>60</td>
<td>60</td>
<td>65</td>
<td>0.31</td>
</tr>
<tr>
<td>p value#</td>
<td>0.008</td>
<td>0.02</td>
<td>0.99</td>
<td></td>
</tr>
</tbody>
</table>

*p = 0.03 for interaction between birthweight and genotype.
*#p value for the difference among birthweight groups.
#p value for the difference between the Pro12Pro and Pro12Ala/Ala12Ala genotypes.

codon 12 has been found to modulate the transcriptional activity of the gene [20]. In meta-analysis the Pro12Ala variant of the gene has been found to be associated with improved insulin sensitivity and a lower risk of type 2 diabetes compared with the carriers of Pro12Pro genotype [21, 22]. However, in general the published findings in relation to the PPARγ-2 genotype have been inconsistent in relation to glucose and insulin metabolism.

We have reported associations between the PPARγ-2 gene and birth size in relation to metabolic characteristics associated with the metabolic syndrome. In the HBCS we observed that elderly carriers of the Ala allele had lower fasting insulin and glucose concentrations, i.e., they were more insulin-sensitive compared to the carriers of the Pro12Pro genotype [23]. There were no differences between the groups in body size at birth or childhood body size. Interestingly the association between a small body size at birth and insulin resistance was observed only in individuals with the high risk Pro12Pro genotype (table 1). In other words the Ala allele was protective against the negative effect of a small body size at birth. There was a strong interaction between birth size and PPARγ-2 genotype (p = 0.03).

We have also examined the combined effects of the same PPARγ-2 gene polymorphisms and birth length on the occurrence of type 2 diabetes. The Pro12Pro genotype was associated with a higher cumulative incidence of type 2 diabetes (p = 0.08). This association was confined to people who were ≤49 cm in length at birth, among whom the cumulative incidence of type 2 diabetes was 24.5%, compared with those >49 cm in length at birth, in whom the cumulative incidence was 14.3% (p = 0.02) [24].

A small body size at birth is associated with insulin resistance as well as other features of the metabolic syndrome. Consequently low HDL-cholesterol concentrations have been reported in association with a small body size at birth. A protective effect among the carriers of the Ala allele of the PPARγ-2 gene – even in the presence of a low birthweight – was observed in relation to HDL-cholesterol concentrations as shown in table 2 [25].
**Plasma Cell Glycoprotein Gene**

Being an important regulator of the insulin-signaling pathway, the PC-1 gene is another candidate gene for type 2 diabetes. PC-1 inhibits autophosphorylation of the insulin receptor and impairs insulin signaling downstream of the insulin receptor. 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 [26]. We have investigated whether the K121Q polymorphism of the PC-1 gene association with insulin sensitivity, type 2 diabetes and hypertension in adult life depends on body size at birth. In the HBCS, those individuals 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 [27]. Figure 1 shows the prevalence of type 2 diabetes in relation to birth size and the K121Q polymorphism of the PC-1 gene. Only the carriers of the high risk 121Q variant had a higher diabetes prevalence in association with a small body size at birth.

**Table 2.** Mean fasting HDL-cholesterol concentrations (mmol/l) in elderly individuals from the HBCS according to birthweight groups and PPARγ-2 gene polymorphism

<table>
<thead>
<tr>
<th>Birthweight, g</th>
<th>Pro12Pro</th>
<th>Pro12Ala</th>
<th>p value*</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;3,000</td>
<td>1.37</td>
<td>1.48</td>
<td>0.16</td>
</tr>
<tr>
<td>3,000–3,500</td>
<td>1.42</td>
<td>1.44</td>
<td>0.68</td>
</tr>
<tr>
<td>&gt;3,500</td>
<td>1.48</td>
<td>1.47</td>
<td>0.94</td>
</tr>
<tr>
<td>p value*</td>
<td>0.02</td>
<td>0.66</td>
<td></td>
</tr>
</tbody>
</table>

p = 0.01 value for interaction between birthweight and genotype.
*p value for the difference among birthweight groups.
#p value for the difference between the Pro12Pro and Pro12Ala/Ala12Ala genotypes.

![Fig. 1. Prevalence of type 2 diabetes according to length at birth and the PC-1 gene polymorphism. *p = 0.005; p < 0.05 for interaction between genotype and birth length.](image-url)
Glucocorticoid Receptor Gene

Glucocorticoids are important regulators of fetal growth and development as well as regulators of glucose metabolism. The glucocorticoids mediate their cellular action by complexing with the cytoplasmic GR. The GR gene is another candidate gene that could partly explain the associations between early growth and later health outcomes [28]. Certain haplotypes of the GR gene modify the association between birth size and adult phenotypes in the HBCS. These findings suggest that a common GR haplotype could modify the association of short length at birth with glucose tolerance in adult life [29]. Figure 2 shows that carriers of the GR gene haplotype 3 had the highest prevalence of impaired glucose tolerance and type 2 diabetes but only in the combination with a short birth length. The interaction between the effects of length at birth and GR haplotype on glucose regulation was highly significant (p = 0.02).

Conclusion

The findings described here could be interpreted as manifestations of gene early environmental interactions and illustrate the importance of the early environment in relation to risk factors for type 2 diabetes and related disorders. But what does this mean, can we take these findings further and make some clinical implications? Acknowledging the interactions between early growth and genotypes might help us to design individual therapies as well as plan lifestyle interventions. We need to take into account individual variability

Fig. 2. Prevalence of impaired glucose tolerance and type 2 diabetes according to length at birth and glucocorticoid receptor gene haplotype. *p = 0.007; p = 0.02 for interaction between birth length and GR haplotype on the cumulative incidence of glucose intolerance.
not only in the genetic setup but also in early growth phenotypes. Further studies focusing on growth during infancy and childhood – and potential interactions with high risk genotypes – are needed in this field.

References

Discussion

**Dr. R. Bergmann:** The peroxisome proliferator-activating receptor (PPAR)y2 gene is the master gene for the terminal differentiation of adipocytes, which is promoted by arachidonic acid [1]. Ailhaud and Guesnet [2] proposed that nutritional imbalances in n-6 and n-3 fatty acids during the last decades were determinants for the increasing prevalence of adiposity in childhood, i.e. gene–nutrition interactions.

**Dr. Eriksson:** I think it’s quite possible but we still know very little about these and there might be gene–nutrition interactions. Another aspect that is quite important when looking at the PPAR\$^y\$ gene is that it has an important co-activator, PGC-1 that influences its activity, consequently there could also be important gene–gene interactions. Anyway, this field is so new and we have not had the time yet to look at any gene–nutrition interactions, but we are certainly planning to do that. We have adult food frequency data on 2,000 individuals and we are also following them up prospectively.

**Dr. Batubara:** Did you say that in a person with a low birthweight or who is obese but carrying this Ala allele, the gene has a protective effect on diabetes type 2?

**Dr. Eriksson:** Yes. In our older cohort those with low birthweight and carrying the Ala allele were protected against the negative influence of a small birth size. However, life is obviously much more complicated and if you look at all the meta-analyses in relation to the PPAR\$^y\$ gene, they are not really consistent. In general you can say that people who carry the Ala allele are more insulin-sensitive and they are at a lower risk of getting type 2 diabetes.

**Dr. K. Bergmann:** One thing that impresses me very much is that with higher birthweight there is a lower risk of later diabetes type 2. In our own study and in several other studies, we see that a high birthweight is a great risk factor for later obesity, and obesity being the basis in about 95% of cases of type 2 diabetes, you should also find effects of high birthweight on this phenomenon.

**Dr. Eriksson:** This is a really important. When we are looking at birth size in relation to type 2 diabetes, we can study them both using epidemiological or clinical data. If we do this mainly on epidemiological data, we usually identify only those with the worse type of type 2 diabetes and they simultaneously have coronary heart disease. So
I think that is one reason why we see an association between a low birthweight and type 2 diabetes mainly from the epidemiological data. We have been looking at those people with a higher birthweight and what you say is completely true. Both people with low and high birthweight can develop type 2 diabetes, they do it through a different early growth pathway.

**Dr. Ogra:** There is a certain disparity between birthweight and type 2 diabetes. Clearly obesity does contribute to the development of type 2 diabetes. Are we looking at a heterogeneous population in type 2 diabetes? Is there any relationship to early colonization with different microbial flora or diet with type 2 diabetes or those who develop non-alcoholic hepatitis associated with type 2 diabetes? Are we looking at multiple triggers? Birthweight may be only one of those factors, and gene polymorphism may also be one of the factors in this whole process.

**Dr. Eriksson:** As a diabetologists we know that type 2 diabetes is extremely heterogeneous in adult life. We have been studying the different subtypes of diabetes that develop in those people born with lower birthweight compared to that seen among those born with a higher birthweight. There is a study on the Pima Indians that has clearly shown that gestational diabetes is a major and important risk factor for the high birthweight route [3]. There was another study done in schoolchildren in Taiwan that also showed a strong relationship between birth size and later risk of type 2 diabetes [4], and the risk associated with type 2 diabetes in the high birthweight group in Taiwan was mostly explained by a strong family history for type 2 diabetes.

**Dr. Thornburg:** Has anyone looked to see whether or not the effect of polymorphisms related to birthweight are actually due to genetic modifications through epigenetic means? It seems to me that this might be a possibility that hasn’t been ruled out yet.

**Dr. Eriksson:** It certainly hasn’t been ruled out and I very much agree with you that it could be a very likely explanation for this, but as far as I know nobody has looked yet at the human population.

**Dr. Ogra:** The PGC-1 gene, is this a polymorphism which has been identified for a long time or is it something very recent? We are seeing a tremendous increase in type 2 diabetes in certain population groups in the USA.

**Dr. Eriksson:** I am sorry to say that I don’t have the information on the distribution of the PGC-1 gene in various populations.

**Dr. Ogra:** What about the PPAR gene?

**Dr. Eriksson:** It is quite similarly distributed, at least in the Western population.

**References**


4 Wei JN, Sung FC, Li CY, et al: Low birth weight and high birth weight infants are both at an increased risk to have type 2 diabetes among schoolchildren in Taiwan. Diabetes Care 2003;26:343–348.