Int J Endocrinol Metab 2006; 4: 180-187

ORIGINAL ARTICLE

Insulin Gene Variable Number of Tandem Repeat Genotype, Early Growth and Glucose Metabolism in Adult Life

G. Eriksson J[a], Osmond C[b], J. Forsén[c], Kajantie E[d], JP Barker D[e], Laakso M[f]

[a]National Public Health Institute, Helsinki, Finland, [b]MRC Epidemiology Resource Centre, Southampton, UK, [c]National Public Health Institute, Helsinki, Finland, [d]National Public Health Institute, Helsinki, Finland, [e]Developmental Origins of Health and Disease Group, Southampton, UK, [f]University of Kuopio, Finland

The predisposition to type 2 diabetes is programmed early in life and genotypes promoting survival during nutritional adversity could increase the risk of type 2 diabetes. 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.

Materials and Methods: We assessed the association between the insulin gene VNTR genotypes, early growth and glucose and insulin metabolism in adult life in 488 subjects participating in the Helsinki Birth Cohort Study.

Results: Body size at birth did not differ significantly between the INS VNTR genotypes. One additional type III allele was associated with a 13 g decrease (95% CI -55 to 81 g; p=0.7) in birth weight. Fasting glucose concentration was highest in the carriers of the III/III genotype. The cumulative incidence of type 2 diabetes did not differ between the genotypes. Interactions between birth size and insulin VNTR genotype in relation to fasting glucose (p for interaction = 0.08 for birth weight, p=0.05 for birth length) and 2-hour insulin (p for interaction =0.04) were observed.

Conclusions: These interactions between body size at birth and genotype reflect interactions between the insulin VNTR gene and the intrauterine environment. Our findings are consistent with the hypothesis of developmental plasticity, where one genotype can give rise to different phenotypes dependent on the early environment.

Correspondence: Johan Eriksson, University of Helsinki, P.O.Box 41, 00014 University of Helsinki, Finland
E-mail: johan.eriksson@helsinki.fi

Key Words: Birth weight, Type 2 diabetes, insulin VNTR gene, Early growth

Received: 13/05/2006- **Accepted**: 02/10/2006

Introduction

The predisposition to type 2 diabetes is programmed early in life and body proportions at birth, during infancy and childhood modify the risk for developing the disease in later life.[1-4] In other words sub-optimal early growth is associated with permanent metabolic changes increasing the risk for later disease.

It has been suggested that certain genotypes promoting survival during nutritional adversity could also increase the risk of type 2 diabetes.[5] One candidate "thrifty genotype" is

the insulin gene on chromosome 11 p, and variation in the insulin gene variable number of tandem repeats (VNTR) polymorphism has been suggested to modify birth size and diabetes susceptibility.[5] 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 - with conflicting results - while there is little information on possible gene-early growth interactions in relation to type 2 diabetes.[5-16]

In the present study we have assessed the association between the insulin gene VNTR genotypes, early growth and glucose and insulin metabolism in adults.

Materials and Methods

The original birth cohort consisted of 7086 men and women, who were born as singletons at Helsinki University Central Hospital during 1924-1933, and who attended school in Helsinki and were still resident in Finland in 1971. Their birth records include birth weight and length at birth. Their heights and weights were measured serially between the ages of 7 and 15 years. The birth cohort and the clinical study design have been described in detail previously.[4,17] A total of 674 people from the original cohort who were known to be living in the greater Helsinki area were invited to attend a clinic. 500 of the men and women (74% of those invited) from the original study cohort attended a clinical examination which included a standard 75 g oral glucose tolerance test (OGTT) and 488 subjects who had DNA available were included in the present study.

The mean age at the time of investigation was 70±3 years. Plasma glucose and insulin concentrations were measured at zero, 30 and 120 minutes. Blood pressure was measured from the right arm after a 10 minute rest by a mercury sphygmomanometer. The mean of two measurements was used in the calculations.

Insulin resistance was estimated based upon the HOMA-IR-index calculated as: (fasting insulin x fasting glucose)/22.5. Beta-cell function was estimated using the HOMA-IS-index calculated as (20 x fasting insulin) / (fasting glucose – 3.5).[18]

Plasma glucose was measured by a hexokinase method.[19] Plasma insulin concentrations were determined by a two-site immunometric assay.[20]. Serum cholesterol and triglycerides concentrations were measured using standard enzymatic methods.[21,22]

The diagnosis of diabetes was based upon an OGTT as well as use of anti-diabetic medication. WHO 1999 criteria for glucose regulation were applied.

Blood samples were drawn for DNA analyses, and for 488 subjects the INS VNTR genotype was successfully determined. DNA samples were genotyped for the –23 bp A/T (SNP rs 689) diallelic polymorphism by the restriction enzyme HphI, using PCR. This polymorphism is in virtually complete linkage disequilibrium with the INS VNTR. The region of the promoter of the insulin gene was amplified with polymerase chain reaction (PCR) with the forward primer 5'-CGTCAGGTGGGCTCAGGGTT-3' and reverse primer 5'-ACAAAGGCTGCGGCTGGGTC-3' (PCR-product size 253). PCR amplification was conducted in a 10μL volume containing 50 ng genomic DNA, 5 pmol of each primer, 10 mmol/L Tris-HCl (pH 8.8), 50 mmol/l KCl, 1.5 mmol/L MgCl, 0.1% Triton X -100, 0.125 units of DNA polymerase (DynaZyme DNA Polymerase; Finnzymes, Finland), 200 μmol/L dNTP. PCR conditions were denaturation at 94°C for 4 min, followed by 35 cycles of denaturation at 94°C for 30 s, annealing at 65°C for 60 s, and extension at 72°C for 30 s with final extension at 72ºC for 4 min. Amplified product (253 bp) was digested with HphI (New England Biolabs, Beverly, MA), the restriction enzyme specific for the sequence GGTGA(N)8, in a 15μL volume containing 5 μl of PCR

product and 3,0 U HphI. The mixture was incubated at 37°C overnight to yield fragments of 104, 40 and 109 for the A/A genotype and 104 and 149 bp for the T/T genotype. The digested samples were separated on a 9% polyacrylamide gel (150V, 60 min). Separated DNA fragments were visualized by ethidium bromide staining.

Ethical approval was obtained from the Ethical Committee at the National Public Health Institute in Helsinki. All study subjects gave written informed consent.

Statistical methods: Data were analysed by tabulation of means and multiple linear and logistic regression. Levels of significance refer to analyses of continuous variables. Plasma glucose and insulin concentrations had skewed distributions and were log-transformed for analysis. We adjusted these values for age, sex and current body mass index. Regressions were done within birth size categories and within genotype. In the analyses for glucose and insulin metabolism, those 26 individuals known to be taking anti-diabetic drugs were excluded since these drugs are known to affect the parameters being measured. Of the 26 individuals taking anti-diabetic drugs 25 had the known INS VNTR genotype.

Results

The INS VNTR genotype distribution was I/I 64.3 % (n=314), I/III 29.5 % (n=144) and III/III 6.1 % (n=30). The genotypes were in Hardy-Weinberg equilibrium. Birth size, childhood growth and INS VNTR

Body size at birth did not differ significantly between the INS VNTR genotypes (Table 1). One additional type III allele was associated with 13 g decrease (95% CI -55 to 81 g; p=0.7) in birthweight. The lowest mean birthweight was seen in the III/III group, 80 g lower than the others, but this difference was not statistically significant (95% CI -91 to 252 g; p=0.4). Body weight, height and body mass index during school years (7-15 y), did not differ between the genotypes of the INS VNTR gene polymorphism. Because the association between this polymorphism and birthweight may be modified by postnatal growth, we assessed possible interactions between the effects of the genotype and weight, height and body mass index at 7 years on corresponding measurements at birth. No such interaction was found.

Glucose, insulin and lipid metabolism in adult life: Fasting plasma glucose concentration was highest in the carriers of the III/III genotype. One additional type III allele was associated with 3.2% increase in fasting glucose (95% CI 0.5 to 6.0%;p=0.02) (Table 1). Neither 30 nor 120 minutes glucose values differed between the genotypes. No differences were observed in insulin concentrations between the genotypes. The cumulative incidence of type 2 diabetes did not differ between the genotypes of the INS VNTR gene; the cumulative incidence being 21 % in the I/I group, 17 % in the I/III group and 23 % in the III/III group. Total cholesterol, HDL-cholesterol, LDL-cholesterol and triglyceride concentrations as well as systolic and diastolic blood pressure did not differ between the genotypes.

Interactions between birth size and INS VNTR genotype: We assessed whether there were interactions between birth size and the INS VNTR genotype in relation to glucose and insulin metabolism in adult life (Table 2). In Table 2, people with the III allele have been combined to form one group. There was an interaction between birth size and genotype in relation to fasting glucose (p for interaction = 0.08 for birth weight, p=0.05 for birth length) but no interaction was seen in relation 2-hour glucose or fasting insulin concentrations. A birth weight genotype interaction was observed in relation to 2-hour insulin (p for interaction =0.04). Plasma insulin concentrations fell with increasing birth weight among men and women with the III allele. Those with the III allele and the high-

est birth weight (> 3500 g) had the lowest 2 hour insulin concentration. No genotype birth size interactions were observed in relation to type 2 diabetes.

Glucose and insulin levels in newly diagnosed untreated type 2 diabetics according to INS VNTR genotype

We assessed glucose and insulin response during the OGTT in those 73 subjects whose OGTT fulfilled type 2 diabetes criteria but who received no medication for the disorder (Table 3). Because of the smaller number of subjects, hetero- and homozygous carriers of type III allele are grouped together in this analysis. Among type III allele carriers fasting (p=0.003) and 30 min (p=0.01) glucose levels were significantly higher and HOMA-IS lower (p=0.02) compared with the carriers of the I/I genotype.

Table 1. Body size at birth, during childhood and in adult life and clinical metabolic characteristics in adult life (70 years). Subjects with drug treated diabetes were excluded from the analyses for glucose and insulin metabolism.

	I/I	I/III	III/III	P value
	(N=296)	(N=137)	(N=30)	(for trend)
Birth weight (g)	3350±495	3366±408	3254±442	0.70
Birth length (cm)	49.9±1.8	50.0±1.7	49.5±1.9	0.93
BMI at 7 years (kg/m^2)	15.4±1.2	15.3±1.2	15.4±1.2	0.91
Adult BMI (kg/m^2)	27.6±4.4	27.7±4.4	27.9±4.1	0.71
fP-glucose (mM/L) *	5.5±1.2	5.7±1.2	5.9±1.3	0.02
P-glucose 30' (mM/L) *	9.4±1.2	9.4±1.2	9.7±1.3	0.61
P-glucose 120' (mM/L) *	8.1±1.4	7.5±1.4	8.4±1.5	0.37
FS-insulin (pmol/L)*	68±1.7	67±1.8	74±1.5	0.71
S-insulin 30' (pmol/L) *	453±1.8	472±1.8	475±1.9	0.48
S-insulin 120' (pmol/L) *	515±1.9	452±2.0	476±2.1	0.12
HOMA-IR index *	16.7+1.8	17.0+1.9	19.4+1.6	0.31
HOMA-IS*	684+1.9	643+1.9	654+2.0	0.40
Cholesterol (mmol/L)	6.0+1.1	6.1+1.2	6.0+1.0	0.50
LDL-cholesterol (mmol/L)	3.8+0.9	3.9+1.0	3.7+1.0	0.76
HDL-cholesterol (mmol/L)*	1.4+1.3	1.4+1.3	1.4.+1.4	0.79
Trigycerides (mmol/L) *	1.28+1.5	1.31+1.5	1.47+1.7	0.12
Systolic BP (mmHg)	159+21	160+21	159+23	0.81
Diastolic BP (mmHg)	88+10	90+10	88+10	0.19
Diabetes prevalence (%)	21 %	17 %	23 %	0.84

* Means and standard deviations are geometric (following log transformation); Birth and childhood characteristics adjusted for gender; BMI adjusted for age and gender; all other variables adjusted for age, gender and adult BMI

Table 2. Fasting glucose (upper) and 120 minutes insulin concentrations (lower) in relation to birth weight and INS VNTR genotype. Numbers in brackets indicate number of subject per cell.

Birth weight (g)	< 3000	- 3500	> 3500	P value
Genotype				
Fasting glucose (mmol/L)				
I/I	5.6 (65)	5.6 (150)	5.4 (99)	0.18
I/III and III/III	5.7 (30)	5.7 (85)	5.8 (59)	0.61
p-value	0.60	0.34	0.08	
p-value for interaction				0.08
120 min insulin (pmol/mL)				
I/I	530 (65)	526 (150)	488 (99)	0.37
I/III and III/III	567 (30)	460 (85)	400 (59)	0.005
p-value	0.65	0.17	0.09	
p-value for interaction				0.039

Table 3. Glucose and insulin levels in newly diagnosed type 2 diabetic subjects according to the INS VNTR genotype

	I/I	I/III and III/III	P value
	(48)	(N=25)	
fP-glucose (mmol/L)*	6.4±1.3	7.6±1.3	0.003
P-glucose 30' (mmol/L)*	11.1±1.2	12.6±1.2	0.01
P-glucose 120' (mmol/L)*	12.7±1.3	14.2±1.4	0.30
FS-insulin (pmol/L)*	79±1.8	84±1.7	0.99
S-insulin 30' (pmol/L)*	369±1.8	357±2.0	0.73
S-insulin 120' (pmol/L)*	647±2.2	594±2.4	0.51
HOMA-IR index*	22.4+1.9	28.4+1.8	0.21
HOMA-IS*	588+1.9	430+2.0	0.02

* Means and standard deviations are geometric (following log transformation)

Discussion

In the present study, no significant associations between INS VNTR genotype, birth size and childhood body size were observed. The III/III genotype was associated with higher fasting glucose levels. A significant birth size genotype interaction in relation to insulin secretion was observed; carriers of the

III allele with the highest birth weight showed the lowest insulin values at 120 minutes after an oral glucose tolerance test.

The insulin gene variable number of tandem repeats locus has two main alleles in Caucasians, i.e. class I and class III, and is of great interest since it has been shown to influence transcription/expression of the insulin gene.[5,23] Interestingly class I alleles have been associated with smaller body size at birth, increased postnatal weight gain and increased insulin secretion in obese children.[5-7] In other words, variations in the insulin gene VNTR have been suggested to modify birth size and diabetes susceptibility. The insulin VNTR gene has mostly been studied in relation to early growth, with conflicting results, while there is little information on possible gene-early environmental interaction in relation to glucose metabolism in later life.[5-16]

Previously in the ALSPAC cohort the INS VNTR genotype was found to be associated with size at birth.[10] However, another UK study of 1184 infants did not observe any significant associations between birth weight and INS VNTR genotypes.[14] Contrary to the findings in the ALSPAC cohort in a study of 418 PIMA Indian children the III/III genotype was associated with a small body size at birth but no association with type 2 diabetes was found.[10] More recent findings from the Northern Finland Birth Cohort study were unable to find any significant associations between the INS VNTR genotypes and body size at birth in 5646 subjects.[11]

The allele frequency in the present study is in accordance with previously published findings, although the I/I genotype frequency is slightly higher compared to some published findings.[5,23] Those with the III/III genotype had a birth weight ~100 g lower compared with the other genotypes. In men from Hertfordshire, UK, who were of similar age to the subjects in the present study, no significant association between birth weight and the INS VNTR genotype was found.[24] The underlying reasons for the discrepancy between previous studies remain unknown although study-design and sample size issues could be of importance. The vast majority of published studies have been unable to report any significant associations between birth weight and INS VNTR genotype, mainly consistent with findings from the Helsinki Birth Cohort Study.

The III allele and III/III genotype have previously been associated with insulin resistance and other features of the metabolic syndrome, type 2 diabetes and obesity.[5-7,9,23,25] Fasting insulin levels have been found to be higher in infants with the III/III genotype compared with those with the I/I genotype. Likewise both insulin sensitivity and insulin secretion have been proposed to be associated with the INS VNTR genotype during infancy.[9] Contrary to these reports young subjects, homozygous for class I VNTR alleles, have been reported to secrete more insulin than those with other genotypes and to be more prone to the development of juvenile obesity.[6] In girls with precocious pubarche the I/I and I/III genotypes had a phenotype characterised by insulin resistance.[7] In the present study, no associations between the genotypes and fasting insulin and estimates of insulin sensitivity were observed.

In subgroup analysis of men from the Hertfordshire study the III/III genotype was associated with a higher risk for impaired glucose regulation.[24] In the same cohort the III/III genotype was weakly associated with 2 hour insulin concentrations during the oral glucose tolerance test. These findings resemble those in the present study, where the carriers of the III/III genotype had higher fasting glucose levels and a decreased insulin response to an oral glucose load. Studies published in this field are quite discordant. A large Finnish birth cohort study recently published, failed to find any significant associations between INS VNTR allele and anthropometric and biological measures obtained in early adulthood. The differences compared with our findings may be due to later age at study in the present study. Furthermore it could be that some of the interactions identified will

become evident only in the presence of disturbances in glucose metabolism accompanying later age.

In order to focus upon potential gene-environmental interactions in relation to defects in glucose regulation we assessed insulin and glucose levels in 73 subjects with type 2 diabetes diagnosed by OGTT but who received no medication. In this subgroup, individuals with the III allele had higher fasting and 30 minutes glucose concentrations while their HOMA-IS was lower. Thus the III allele of the INS VNTR polymorphism seems to be associated with impairment in insulin secretion at least in elderly subjects with increased insulin demands. Based upon analysis done in the whole study group the impact of the III allele was most prominent among those with the highest birth weight.

We have previously reported associations between the PPAR-γ2 gene and body size at birth with regard to insulin sensitivity and type 2 diabetes.[4,26,27] We have now shown corresponding interactions between birth size and the insulin VNTR gene on insulin and glucose metabolism in later life. This interaction between birth size and genotype reflects an interaction between the gene and the intrauterine environment. It is consistent with the hypothesis of developmental plasticity, where one genotype can give rise to different phenotypes dependent on the environment during development.

Acknowledgements

Grants support: British Heart Foundation, Academy of Finland, Finska Läkaresällskapet, Finnish Diabetes Foundation, Sohlberg Foundation, Finnish Foundation for Cardiovascular Research.

References

1. Hales CN, Barker DJ, Clark PM, Cox LJ, Fall C, Osmond C, et al. Fetal and infant growth and impaired glucose tolerance at age 64. BMJ 1991; 303:1019-22.
2. Lithell HO, McKeigue PM, Berglund L, Mohsen R, Lithell UB, Leon DA. Relation of size at birth to non-insulin dependent diabetes and insulin concentrations in men aged 50-60 years. BMJ 1996; 312 : 406-10.
3. Forsén T, Eriksson J, Tuomilehto J, Reunanen A, Osmond C, Barker D. The fetal and childhood growth of persons who develop type 2 diabetes. Ann Intern Med 2000; 133: 176-82.
4. Eriksson JG, Lindi V, Uusitupa M, Forsen TJ, Laakso M, Osmond C, et al. The effects of the Pro12Ala polymorphism of the peroxisome proliferator-activated receptor-gamma2 gene on insulin sensitivity and insulin metabolism interact with size at birth. Diabetes 2002; 51: 2321-4.
5. Dunger DB, Ong KK, Huxtable SJ, Sherriff A, Woods KA, Ahmed ML et al. Association of the INS VNTR with size at birth. ALSPAC Study Team. Avon Longitudinal Study of Pregnancy and Childhood. Nat Genet 1998; 19: 98-100.
6. Le Stunff C, Fallin D, Schork NJ, Bougneres P. The insulin gene VNTR is associated with fasting insulin levels and development of juvenile obesity. Nat Genet 2000; 26: 444-6.
7. Ibanez L, Ong K, Potau N, Marcos MV, de Zegher F, Dunger D. Insulin gene variable number of tandem repeat genotype and the low birth weight, precocious pubarche, and hyperinsulinism sequence. J Clin Endocrinol Metab 2001; 86: 5788-93.
8. Le Stunff C, Fallin D, Bougneres P. Paternal transmission of the very common class I INS VNTR alleles predisposes to childhood obesity. Nat Genet 2001; 29: 96-9.
9. Bazaes RA, Petry CJ, Ong KK, Avila A, Dunger DB, Mericq MV. Insulin gene VNTR genotype is associated with insulin sensitivity and secretion in infancy. Clin Endocrinol (Oxf) 2003; 59: 599-603.
10. Lindsay RS, Hanson RL, Wiedrich C, Knowler WC, Bennett PH, Baier LJ. The insulin gene variable number tandem repeat class I/III polymorphism is in linkage disequilibrium with birth weight but not Type 2 diabetes in the Pima population. Diabetes 2003; 52: 187-93.
11. Bennett AJ, Sovio U, Ruokonen A, Martikainen H, Pouta A, Taponen S, et al. Variation at the insulin gene VNTR (variable number tandem repeat) polymorphism and early growth: studies in a large Finnish birth cohort. Diabetes 2004; 53: 2126-31.

12. Hansen SK, Gjesing AP, Rasmussen SK, Glumer C, Urhammer SA, Andersen G, et al. Large-scale studies of the HphI insulin gene variable-number-of-tandem-repeats polymorphism in relation to Type 2 diabetes mellitus and insulin release. Diabetologia 2004; 47: 1079-87.
13. Heude B, Dubois S, Charles MA, Deweirder M, Dina C, Borys JM, et al. VNTR polymorphism of the insulin gene and childhood overweight in a general population. Obes Res 2004; 12: 499-504.
14. Mitchell SM, Hattersley AT, Knight B, Turner T, Metcalf BS, Voss LD, et al. Lack of support for a role of the insulin gene variable number of tandem repeats minisatellite (INS-VNTR) locus in fetal growth or type 2 diabetes-related intermediate traits in United Kingdom populations. J Clin Endocrinol Metab 2004; 89: 310-7.
15. Meigs JB, Dupuis J, Herbert AG, Liu C, Wilson PW, Cupples LA. The insulin gene variable number tandem repeat and risk of type 2 diabetes in a population-based sample of families and unrelated men and women. J Clin Endocrinol Metab 2005; 90: 1137-43.
16. Guja C, Guja L, Nutland S, Rance H, Todd JA, Ionescu-Tirgoviste C. Strong association of insulin gene INS-VNTR polymorphisms with type 1 diabetes in the Romanian population. Rom J Intern Med 2004; 42: 313-23.
17. Eriksson JG, Forsén T, Tuomilehto J, Jaddoe VW, Osmond C, Barker DJ. Effects of size at birth and childhood growth on the insulin resistance syndrome in elderly individuals. Diabetologia 2002; 45: 342-8.
18. Wallace TM, Levy JC, Matthews DR. Use and abuse of HOMA modelling. Diabetes Care 2004; 27: 1487-95.
19. Kunst A, Draeger B,Ziegenhorn J. In UV-Methods with hexokinase and glucose-6--phosphate dehydrogenase, Bergmeyer HU (eds) Methods of Enzymatic Analysis. 3rd. Ed.; Weinheim Verlag Chemie, Dearfield, Deerfield Germany. 1984;163-72
20. Sobey WJ, Beer SF, Carrington CA, Clark PM, Frank BH, Gray IP, et al. Sensitive and specific two-site immunoradiometric assays for human insulin, proinsulin, 65-66 split and 32-33 split proinsulins. Biochem J 1989; 260: 535-41.
21. Lie AF, Schmitz JM, Pierre KJ, Gochman N. Cholesterol oxidase-based determination by continuous flow analysis of total and free cholesterol in serum. Clin Chem 1976; 22: 1627-30.
22. Fossait P, Prencipe L. Serum triglycerides determined colorimetrically with an enzyme that produces hydrogen peroxide. Clin Chem 1982; 28: 2077-80.
23. Bennett ST, Todd JA. Human type 1 diabetes and the insulin gene: principles of mapping polygenes. Annu Rev Genet 1996; 30: 343-70.
24. Ong KKL, Phillips DI, Fall C, Poulton J, Bennett ST, Golding J, et al The insulin gene VNTR, type 2 diabetes and birth weight. Nat Gen 1999; 21: 262-3.
25. Vankova M, Vrbikova J, Hill M, Cinek O, Bendlova B. Association of insulin gene VNTR polymorphism with polycystic ovary syndrome. Ann N Y Acad Sci. 2002; 967: 558-65.
26. Eriksson J, Lindi V, Uusitupa M, Forsen T, Laakso M, Osmond C, et al. The effects of the Pro12Ala polymorphism of the PPARgamma-2 gene on lipid metabolism interact with body size at birth. Clin Genet 2003; 64: 366-70.
27. Eriksson JG, Osmond C, Lindi V, Uusitupa M, Forsen T, Laakso M, et al. Interactions between peroxisome proliferator-activated receptor gene polymorphism and birth length influence risk for type 2 diabetes. Diabetes Care 2003; 26: 2476-7.