Research article

The A54T polymorphism at the intestinal fatty acid binding protein 2 is associated with insulin resistance in glucose tolerant Caucasians

Ken C. Chiu*1, Lee-Ming Chuang2 and Carol Yoon1

Address: 1Division of Endocrinology, Diabetes and Hypertension, Department of Medicine, University of California, Los Angeles, School of Medicine, Los Angeles, California, U.S.A and 2Department of Internal Medicine and Graduate Institute of Clinical Medicine, National Taiwan University Hospital, Taipei, Taiwan

E-mail: Ken C. Chiu* - kchiu@mednet.ucla.edu; Lee-Ming Chuang - leeming@ha.me.ntu.edu.tw; Carol Yoon - kclab@mednet.ucla.edu

*Corresponding author

Abstract

Background: An A54T polymorphism at the fatty acid binding protein 2 (FABP2) locus was found to be associated with insulin resistance in non-diabetic Pima Indians. To see whether this association is present in other populations, we performed a cross sectional study to examine the role of this polymorphism on insulin resistance in 55 healthy and normotensive Caucasian subjects with normal glucose tolerance. Insulin sensitivity (%S) and beta cell function (%B) were assessed using the Homeostasis Model Assessment (HOMA). Their genotypes were determined using a polymerase chain reaction-restriction fragment length polymorphism assay. The relationship between the genotypes and the phenotypes was examined.

Results: After genotyping, we identified 24 AA, 27 AT and 4 TT subjects. The TT subjects were combined with the AT subjects during the analysis due to its small sample size. No differences were noted in gender distribution, clinical features, and fasting lipid profile between the two genotypic groups (AA vs. AT/TT). The AT/TT group had a higher fasting plasma insulin concentration and a lower %S than the AA group (p = 0.0444 and p = 0.0461, respectively). However, no differences were noted in plasma glucose concentrations and %B. Univariate analysis revealed that this polymorphism explained 7.3% of the variation in %S. Multivariate analysis revealed that the polymorphism was an independent determinant for %S (p = 0.0434) and with body mass index accounted for 28.7% of the variation in %S. In contrast, this polymorphism had no impact on %B.

Conclusions: The A54T polymorphism at the FABP2 locus is a risk factor for insulin resistance in a Caucasian population.

Introduction

The Pima Indians have a very high prevalence for type 2 diabetes mellitus (or non-insulin-dependent diabetes mellitus, NIDDM) with evidence of strong familial aggregation [1]. In this population, insulin resistance is a major risk factor for the development of the disease [2], and maximal insulin action (i.e. glucose disposal rate at pharmacological insulin levels) was found to be determined by a co-dominantly inherited autosomal gene [3]. Initially, Bogardus and colleagues observed an association and linkage between insulin resistance and red cell antigens on chromosome 4q [4]. After the analysis of 128 sib-pairs using quantitative trait sib-pair analysis, they observed a significant linkage between maximal insulin action and the intestinal fatty acid-binding protein 2 (FABP2) gene and the annexin V (ANX5) gene on chromosome 4q [5].
It is well recognized that fatty acid metabolism is linked to insulin resistance [6,7]. Intestinal FABP2 contains a single ligand binding site that displays a high affinity for fatty acid [8]. Because it is a candidate gene at this locus, a search for a mutation was initiated and an Alanine (GCT) to Threonine (ACT) polymorphism at codon 54 was identified in Pima Indians [9]. The associations between this polymorphism and fasting insulin concentration, fasting fat oxidation, and glucose uptake during a hyperinsulinemic euglycemic clamp were identified in 137 non-diabetic Pima Indians [9].

Because NIDDM is a genetic disorder [10] and results from an imbalance between insulin sensitivity and beta cell function, we hypothesized that the A54T polymorphism of the FABP2 gene plays a role in the pathogenesis of insulin resistance, which is one of the key determinants for the development of NIDDM [2]. Since insulin sensitivity is affected by hypertension [11,12] and abnormal glucose tolerance [2], we examined the relationship of this polymorphism with insulin sensitivity in 55 healthy and normotensive Caucasians with normal glucose tolerance.

**Results**

The clinical features of the studied subjects were shown in Table 1. Using the PCR-RFLP assay, we identified 24 AA, 27 AT, and 4 TT subjects. In this Caucasian population, the allele frequency was 68% for the A allele and 32% for the T allele. The distribution of genotypes was in compliance with the Hardy-Weinberg equilibrium (p = 0.8321).

Since there were only 4 TT subjects, they were pooled with the AT subjects during the analysis. There were no differences in clinical features between the two genotypic groups (AA vs. AT/TT) as shown in Table 2. Although the AT/TT subjects had a higher fasting plasma insulin concentration than the AA subjects (p = 0.0444), no differences were noted in fasting plasma glucose concentrations and postchallenged plasma glucose and insulin concentrations. We estimated insulin sensitivity (%S) and beta cell function (%B) using the average of the three fasting plasma glucose and insulin concentrations. While no difference was noted in %B, the AT/TT subjects were more insulin resistant (a lower %S) than the AA subjects (p = 0.0461).

Since a higher body mass index had been reported to be associated with this polymorphism [13], we were concerned that the observed differences could be the result of other confounding covariates. A multivariate analysis was performed to examine the influence of this polymorphism and other covariates (Table 3). This polymorphism and body mass index explained 28.7% of the variation in %S and this polymorphism was an independent determinant of %S (p = 0.0434). However, this polymorphism had no impact on %B. Age, gender and waist hip ratio accounted for 19.5% of the variation in %B.

---

**Table 1: Clinical features of the studied subjects**

|                      | Mean ± (n) | Std. Dev. | Minimum | Maximum |
|----------------------|------------|-----------|---------|---------|
| **N**                | 55         |           |         |         |
| **Gender**           | F/M        | 29/26     |         |         |
| **Age**              | year       | 28        | 6       | 39      |
| **Body mass index**  | kg/m²      | 24.52     | 3.87    | 34.26   |
| **Waist-hip ratio**  | cm/cm      | 0.81      | 0.09    | 1.03    |
| **Systolic blood pressure** | mmHg | 114       | 10      | 137     |
| **Diastolic blood pressure** | mmHg | 68        | 7       | 83      |
| **Oral glucose tolerance test** |               |           |         |         |
| Fasting plasma glucose | mM       | 4.72      | 0.35    | 5.55    |
| Plasma glucose at 30 minutes | mM   | 7.44      | 1.27    | 9.66    |
| Plasma glucose at 60 minutes | mM   | 7.14      | 1.44    | 10.20   |
| Plasma glucose at 90 minutes | mM   | 6.30      | 1.29    | 9.02    |
| Plasma glucose at 120 minutes | mM   | 5.98      | 1.06    | 7.60    |

* arithmetic means
Discussions
In this study, we found that the A54T polymorphism of the FABP2 was associated with insulin resistance and accounted for 7.3% of the variation in %S. Multivariate analysis confirmed that this polymorphism was an independent risk factor for insulin resistance. In contrast, this polymorphism had no impact on %B. Our observations confirm that the A54T polymorphism of the FABP2 affects insulin sensitivity, which was previously reported in Pima Indian and Japanese populations [9,14].

The FABP2 locus has been studied extensively. MNS red cell antigens, one of the few genetic markers available at that time, were initially found to be linked to insulin resistance in 86 non-diabetic Pima Indians from 31 nuclear families using a sib-pair analysis and they were also associated with insulin resistance in 132 non-diabetic Pima Indians [4]. With additional families and additional genetic markers, a significant linkage was identified between the FABP2 and ANX5 loci on chromosome 4q with insulin resistance in 123 non-diabetic subjects from 46 nuclear families [5]. Furthermore, the linkage of the FABP2 locus with insulin resistance (2-hour post-challenged insulin concentration) was also found in a Mexican-American population, which is genetically related to the Pima Indians [15]. However, sib-pair analysis failed to detect any linkage of the FABP2 locus or the A54T polymorphism with diabetes related phenotypes in other ethnic groups [16,17] as shown in Table 4A. Furthermore, no linkage was found between the FABP2 locus (Table 4B) and diabetes [18,19], lipodystrophic diabetes [20], or obesity [17]. As shown in Table 4C, the population association studies of the FABP2 locus with diabetes/impaired glucose tolerance were negative in UK, Finnish, and Welsh [21] and Japanese populations [22]. Subsequently, the A54T polymorphism was identified and was found to be associated with increased fatty acid binding protein, increased fat oxidation and increased insulin resistance in the Pima Indians [9]. Positive associations were mostly observed in quantitative association studies as shown in Table 4D. In addition to the original positive association between the A54T polymorphism and fasting plasma insulin concentration, fasting fat oxidation and glucose uptake in non-diabetic Pima Indians [9], positive association was also found with obesity [13,14], 2-hour post-challenged insulin concentration [14], and various lipid metabolism [13,28–30]. In the present study, we also demonstrated a positive quantitative association between this polymorphism and %S. However, numerous negative studies were also noted [23,24,29,31–33].

Table 2: Clinical features and glycemic parameters by the FABP2 genotypes

|                      | AA                | AT/TT              |
|----------------------|-------------------|--------------------|
|                      | Mean (n)          | (95% CI)           |
|                      | Mean (n)          | (95% CI)           |
| Gender               | F/M               | 15/9               | 14/17               |
| Age                  | year              | 28                 | 27                 |
|                      | (26,31)           | (25,29)            |
| Body mass index      | kg/m²              | 23.99              | 24.42              |
|                      | (22.52, 25.56)    | (23.03, 25.90)     |
| Waist-hip ratio      | cm/cm              | 0.80               | 0.80               |
|                      | (0.76, 0.84)      | (0.77, 0.83)       |
| Systolic blood pressure | mmHg              | 112                | 116                |
|                      | (109,116)         | (112,120)          |
| Diastolic blood pressure | mmHg              | 68                 | 68                 |
|                      | (65,71)           | (65,70)            |
| Triglycerides        | mg/dL              | 89                 | 73                 |
|                      | (66,110)          | (57.89)            |
| Total cholesterol    | mg/dL              | 166                | 152                |
|                      | (152,180)         | (141,163)          |
| HDL cholesterol      | mg/dL              | 50                 | 48                 |
|                      | (45,54)           | (43,54)            |
| LDL cholesterol      | mg/dL              | 98                 | 89                 |
|                      | (85,111)          | (79,99)            |
| Oral glucose tolerance test |              |                    |
| Fasting plasma glucose | mM                  | 4.68               | 4.75               |
|                      | (4.53, 4.83)      | (4.62, 4.89)       |
| Fasting plasma insulin | pM                 | 55                 | 65                 |
|                      | (48.63)           | (59.72)            |
| %B                   | 139                | 150                |
|                      | (118,163)         | (132,171)          |
| %S                   | 0.63               | 0.52               |
|                      | (0.54, 0.73)      | (0.47, 0.58)       |

1 geometric means; 2 p = 0.0444; 3 p = 0.0461.
Clearly there is substantial controversy surrounding this locus and the A54T polymorphism in the pathogenesis of insulin resistance and T2DM as described above. Disagreement also occurred in the original Pima Indian study. Although significant linkages were identified at the FABP2 locus with fasting insulin concentration (p = 0.0004) and with glucose uptake (p = 0.0008) in the Pima Indians [5], the differences regarding the A54T polymorphism with fasting insulin concentrations (p < 0.04) and glucose uptake (p < 0.04) were only marginally significant in the same population [9]. The significant linkage in the original sib-pair study [5] could be the combined results of a highly polymorphic marker of the FABP2 locus (5 alleles vs. 2 alleles for the A54T polymorphism) and less intrafamilial difference in insulin sensitivity as the result of familial clustering of insulin sensitivity. In contrast, the marginal difference reflected a very modest influence on insulin sensitivity of the A54T polymorphism in the Pima Indian population, which is consistent with our observation that this polymorphism only accounted for 7.3% of the variation in %S in this Caucasian population. Furthermore, since 1) insulin resistance is neither necessary nor sufficient for the development of T2DM, 2) this polymorphism has only a very modest influence on insulin sensitivity, and 3) beta cell dysfunction, on which this polymorphism has no influence in the present study, plays a key role in the development of overt diabetes [2], the population association studies and linkage studies are not able to detect the interaction between this polymorphism and the diabetes phenotype. In contrast, quantitative studies of diabetes-related phenotypes become more rewarding in detecting a polymorphism of a very modest effect as shown in Table 4D. The negative quantitative studies could be the result of other confounding factors, such as the inclusion of diabetic, impaired glucose tolerant or hypertensive subjects in the study. Therefore, we only enrolled glucose tolerant and normotensive subjects in the present study for the reasons described previously.

The most convincing evidence that supports the A54T polymorphism as a causal mutation is from a functional study of mutated FABP2 [9]. FABP2 plays a role in the absorption and intracellular transportation of dietary long-chain fatty acids [8]. Thr54-containing FABP2 has a twofold greater affinity for long-chain fatty acids than the Ala54-containing FABP2 [9]. As predicted by the proposed [6,7] and subsequently proven [34] "Randle's cycle", an increased concentration of fatty acid inhibits glucose uptake in muscle and results in insulin resistance. Furthermore, two interventional studies showed that this A54T polymorphism affected lipid metabolism during interventions [35,36], as shown in Table 4E.

In summary, we examined the role of the A54T polymorphism in the pathogenesis of insulin resistance in 55 glucose tolerant and normotensive healthy Caucasians. We found that this polymorphism had an independent, but very modest influence (7.3%) on insulin sensitivity (%S), which was assessed by the HOMA. However, it had no impact on beta cell function (%B). To our knowledge, this is the very first report of a positive association between this polymorphism and insulin sensitivity in a Caucasian population.

### Table 3: Multivariate analysis

| Dependent Variable | Covariate Entered | Covariate Removed | r² | P |
|--------------------|-------------------|-------------------|----|---|
| %S                 | Body mass index   | 0.0002            | 0.287 | 0.0434 |
|                    | FABP2 polymorphism|                   |      |     |
|                    | Waist-hip ratio   | 0.1045            |      |     |
|                    | Gender            | 0.5313            |      |     |
|                    | Systolic blood pressure | 0.8157 |      |     |
|                    | Age               | 0.8560            |      |     |
|                    | Diastolic blood pressure | 0.8909 |      |     |
| %B                 | Age               | 0.0109            | 0.195 |     |
|                    | Gender            | 0.0169            |      |     |
|                    | Waist-hip ratio   | 0.0671            |      |     |
|                    | Systolic blood pressure | 0.2636 |      |     |
|                    | Body mass index   | 0.2684            |      |     |
|                    | FABP2 polymorphism| 0.3215            |      |     |
|                    | Diastolic blood pressure | 0.3371 |      |     |
Table 4: Published studies of FABP2 and A54T

| Subjects/description                      | Genetic marker | Result | Phenotype                                                                 | Ref |
|-----------------------------------------|----------------|--------|---------------------------------------------------------------------------|-----|
| **A. Sib-pair study**                   |                |        |                                                                           |     |
| Non-diabetic Pima Indians               | MNS red cell antigen | +      | maximal insulin-stimulated glucose uptake + insulin action index - fasting insulin | [4] |
|                                         | ANX5           | +      | maximal insulin-stimulated glucose uptake                                  | [5] |
|                                         | FABP2          | +      | maximal insulin-stimulated glucose uptake + fasting insulin                |     |
| Non-diabetic Mexican Americans          | FABP2          | +      | 2-h post challenge insulin levels                                          | [15]|
| Pondicherian Tamil Indians              | A54T           | -      | diabetes, body mass index, waist/hip ratio, insulinemia, glycemia, triglyceride, total cholesterol | [16]|
| French families with morbid obesity     | FABP2          | -      | body mass index, adult life body with gain fasting leptin, insulin, glycerol, free fatty acid | [17]|
| **B. Linkage study**                    |                |        |                                                                           |     |
| Mexican American diabetic pedigrees     | FABP2          | -      | diabetes                                                                  | [18]|
| French diabetic pedigrees               | FABP2          | -      | diabetes                                                                  | [19]|
| Pedigrees with lipodystrophic diabetes  | FABP2          | -      | lipodystrophic diabetes                                                   | [20]|
| French families with morbid obesity     | FABP2          | -      | obesity                                                                   | [17]|
| **C. Population association study**     |                |        |                                                                           |     |
| UK, Finnish and Welsh population        | FABP2          | -      | diabetes/impaired glucose tolerance                                        | [21]|
| Pima Indian population                  | A54T           | -      | diabetes                                                                  | [9] |
| Japanese population                     | FABP2          | -      | diabetes/impaired glucose tolerance                                        | [22]|
| Aboriginal Canadians population         | A54T           | -      | diabetes                                                                  | [28]|
| Canadian Inuit population               | A54T           | -      | coronary artery disease                                                   | [26]|
| Diabetic and nondiabetic Finnish population | A54T         | -      | coronary artery disease                                                   | [27]|
| Japanese population                     | A54T           | -      | diabetes                                                                  | [23]|
| Japanese population                     | A54T           | -      | diabetes                                                                  | [24]|
| African Americans population            | A54T           | -      | diabetes, obesity, hypertension                                            | [25]|
| **D. Quantitative association study**   |                |        |                                                                           |     |
| Non-diabetic Pima Indians               | A54T           | +      | fasting insulin, fasting fat oxidation + glucose uptake                   | [9] |
Subjects and Methods

Subjects
Through the advertisement in the campus newspaper of this institution, healthy subjects without a prior history of diabetes and hypertension were invited to participate in the study. None of the participants were receiving medical treatment on a regular basis. Subjects were instructed to fast for at least 14 hours before the study visit. On the morning of the visit, subjects were admitted to the General Clinical Research Center of this institution as outpatients. An indwelling angiocatheter was inserted into an antecubital vein. All subjects had fasting blood samples drawn at -15, -10, and -5 minutes. A blood sample for the fasting lipid profile was obtained at -15 minutes. Fasting plasma glucose and insulin concentrations were calculated as the average of the three fasting samples. After an oral administration of 75-gm glucose, postchallenged blood samples were drawn at 30, 60, 90, and 120 minutes for glucose and insulin measurements. A total of 55 Caucasian subjects were enrolled in the study. They were glucose tolerant (fasting plasma glucose < 6.1 mM, interval plasma glucose < 11.1 mM, and 2-hour plasma glucose < 7.8 mM), and normotensive (systolic blood pressure < 140 mmHg and diastolic blood pressure < 90 mmHg). Plasma glucose and insulin concentrations were assayed as described previously [37].

Insulin sensitivity (%S) and beta-cell function (%B) were estimated based on the Homeostasis Model Assessment (HOMA) as described elsewhere [38,39]. They were calculated from the average of three fasting plasma glucose and insulin concentrations (mM and mU/L, respectively) using the following formulae: %S = 22.5 / (insulin x fasting plasma triglyceride).
Genomic DNA was extracted from peripheral leukocytes using the method described previously [40]. A polymerase chain reaction-restriction fragment length polymorphism (PCR-RFLP) assay was developed for genotyping. The genomic DNA fragment flanking the A54T polymorphism (PCR-RFLP) assay was developed for genotyping. The genomic DNA fragment flanking the A54T polymorphism was amplified using two primers flanking exon 2 of the FABP2 gene: CTACCGAGTTTTCTCCACC and AATTTAACATCAATGAAATAGAC. Polymerase chain reaction (PCR) was carried out in an 11-µl reaction volume containing 0.5 pM of each primer, 0.2 mM dNTP, 2 mM MgCl₂, 5% glycerol, 0.275 U Taq polymerase, 50 mM KCl, 10 mM Tris-HCl pH 8.3, and 0.1 µg of genomic DNA. The region of interest was amplified by an initial denaturation at 94°C for 5 minutes, 35 cycles of denaturation at 94°C for 30 seconds, annealing at 60°C for 30 seconds, and extension at 72°C for 30 seconds, and concluded with a final extension at 72°C for 10 minutes. Then, 5 µl of the PCR product (375 base pairs) was digested in a 15-µl reaction volume containing 1 U of Hha I (New England Biolabs Inc., Beverly, Massachusetts, USA) with the buffer supplied by the vendor. The digested PCR products were resolved on 2.0% agarose gels. Hha I digested the wild type, Alanine (GCT), which yielded two products, 200 and 175 base pairs (A allele). The G to A substitution (Threonine, ACT) destroyed the Hha I site (T allele).

Statistical analysis:
Variables, which failed the Normality test, were logarithmically transformed before analysis. They were age, body mass index, waist-hip ratio, plasma insulin concentrations, %S, and %B. The relationship between the variables and parameters of interest (%B or %S) was determined by using univariate analysis. A multivariate analysis using a stepwise-regression strategy was employed to examine the effect of covariates on the parameter of interest (%S or %B). The continuous covariates were age, body mass index, waist-hip ratio, and systolic and diastolic blood pressure. The categorical covariates were gender and the FABP2 polymorphism. Backward stepwise option with alpha-to-enter of 0.10 and alpha-to-remove of 0.10 was employed to exclude covariates that had much less or no influence on the parameter under analysis, one at a time starting from the one that had least impact, which was based on the p value (the highest p value). Stepwise regression analysis was stopped when all the p values of all covariates, that were examined, were less than 0.10. Since a very close linear relationship was noted between systolic and diastolic pressure (r² = 0.3586, p < 0.0001) and also between body mass index and waist-hip ratio (r² = 0.3014, p < 0.0001), they were removed from the multivariate analysis based on their p values as indicated in each analysis. A nominal P value of less than 0.05 was considered significant. SYSTAT 8.0 for Windows from SPSS, Inc. (Chicago, Illinois) was used for the statistical analysis.

Acknowledgements
We thank Mohammad F. Saad, M.D. and the staff of the General Clinical Research Center at the University of California, Los Angeles for their continued support. We also thank George P. Tsai, Sonya Wilsterman, Jennifer M. Ryu, Jennifer L. McCormick, and Jennifer E. McCarthy for their laboratory assistance. The work was supported in parts by grants from USPHS M01RR00885 (UCLA-GCRC), NIH/NIDDK R01DK52337-01 (KCC), Diabetes Action Research and Education Foundation (KCC), and American Diabetes Association (KCC).

References
1. Knowler WC, Pettitt DJ, Saad MF, Bennett PH: Diabetes mellitus in the Pima Indians: incidence, risk factors and pathogenesis. Diabetes Metab Rev 1990, 6:1-27
2. Saad MF, Knowler WC, Pettitt DJ, Nelson RG, Charles MA, Bennett PH: A two-step model for development of non-insulin-dependent diabetes. Am J Med 1991, 90:229-235
3. Bogardus C, Liljola S, Nyomba BL, Zurlo F, Svinnum B, Espósito-Del Puente A, et al: Distribution of in vivo insulin action in Pima Indians as mixture of three normal distributions. Diabetes 1989, 38:1423-1432
4. Bogardus C, Liljola S, Ward R, Degregorio M, Mott D, Ferraro R, et al: Association and linkage between insulin resistance and MNS red cell antigens in Pima Indians. Diabetes 1991, 40(S1):297A.
5. Prochazka M, Liljola S, Taal JF, Knowler WC, Mott DM, Spraul M, et al: Linkage of chromosomal markers on 4q with a putative gene determining maximal insulin action in Pima Indians. Diabetes 1993, 42:514-519
6. Randle PJ, Hales CN, Garland PB, Newsholme EA: The glucose fatty acid cycle: its role in insulin sensitivity and the metabolic disturbances of diabetes mellitus. Lancet 1963, 1:785-789
7. Randle PJ: Carbohydrate metabolism and lipid storage and breakdown in diabetes. Diabetologia 1966, 2:237-247
8. Lowe JB, Sacchettini JC, Laposata M, McQuillan JJ, Gordon J: Expression of rat intestinal fatty acid-binding protein in Escherichia coli. Purification and comparison of ligand binding characteristics with that of Escherichia coli-derived rat liver fatty acid-binding protein. J Biol Chem 1987, 262:5931-5937
9. Baier LJ, Sacchettini JC, Knowler WC, Eads J, Paolasso G, Tataranni PA, et al: An amino acid substitution in the human intestinal fatty acid binding protein is associated with increased fatty acid binding, increased fat oxidation, and insulin resistance. J Clin Invest 1995, 95:1281-1287
10. Pernmutt MA, Chiu KC, Ferrer J, Glasser B, Inoue H, Nestorowicz A, et al: Genetics of type II diabetes. Recent Prog Horm Res 1998, 53:201-216
11. Ferrannini E, Natali A, Capaldo B, Lethorwa M, Jacob S, Yki-Jarvinen H: Insulin resistance, hyperinsulinemia, and blood pressure: role of age and obesity. European Group for the Study of Insulin Resistance (EGIR). Hypertension 1997, 30:1144-1149
12. Ferrannini E, Buzigoli G, Bonadonna R, Giorgio MA, Oleggini M, Grazislidi L, et al: Insulin resistance in essential hypertension. N Engl J Med 1987, 317:350-357
13. Hegele RA, Harris SB, Hanley AJ, Sadiqian S, Connelly PW, Zinman B: Genetic variation of intestinal fatty acid-binding protein associated with variation in body mass in aboriginal Canadians. J Clin Endocrinol Metab 1996, 81:4334-4337
14. Yamada K, Yuan X, Ishiyama S, Koyama K, Ichikawa F, Koyanagi A, et al: Association between Ala54Thr substitution of the fatty acid-binding protein 2 gene with insulin resistance and intra-
abdominal fat thickness in Japanese men. Diabetologia 1997, 40:706-710

15. Mitchell BD, Kammerer CM, O’Connell P, Harrison CR, Manire M, Shipman P, et al: Evidence for linkage of postchallenge insulin levels with intestinal fatty acid-binding protein (FABP2) in Mexican-Americans. Diabetes 1995, 44:1046-1053

16. Lepræstre F, Vionnet N, Budhan S, Dina C, Powell KL, Gaenin E, et al: Genetic studies of polymorphisms in ten non-insulin-dependent diabetes mellitus candidate genes in Tamil Indians from Pondicherry. Diabetes Metab 1998, 24:244-250

17. Clement K, Dina C, Basdevant A, Chastang N, Pelloux V, Lahloù N, et al: A sib-pair analysis study of 15 candidate genes in French families with morbid obesity: indication for linkage with islet 1 locus on chromosome 5q. Diabetes 1999, 48:398-402

18. Stem MP, Mitchell BD, Blangero J, Reinhart L, Krammerer CM, Harrison CR, et al: Evidence for a major gene for type II diabetes and linkage analyses with selected candidate genes in Mexican-American pedigrees. Diabetes 1993, 42:563-568

19. Vionnet N, Hani EH, Lesage S, Philipps A, Hager J, Varret M, et al: Genetics of NIDDM in France: studies with 19 candidate genes in affected sib pairs. Diabetes 1997, 46:1062-1068

20. Vigersouc C, Khalilouf E, Bourrut C, Robert JJ, de Kerdatan M, Tuni-ana-Rufi N, et al: Genetic exclusion of 14 candidate genes in lipoatrophic diabetes using linkage analysis in 10 consanguineous families. J Clin Endocrinol Metab 1999, 82:3438-3444

21. Humphreys P, McCarthy M, Tuomilehto J, Tuomilehto-Wolf E, Stratton I, Morgan R, et al: Chromosome 4q locus associated with insulin resistance in patients with familial combined hyperlipidemia. J Clin Endocrinol Metab 1999, 84:119-124

22. Yagi T, Nishi S, Hinata S, Murakami M, Yoshimi T: A population association study of four candidate genes (hexokinase II, glucagon-like peptide-1 receptor, fatty acid binding protein-2, and apolipoprotein C-II) with type 2 diabetes and impaired glucose tolerance in Japanese subjects. Diabet Med 1996, 13:902-907

23. Ito K, Nakatani K, Fujii M, Katsuki A, Tsuchihashi K, Murata K, et al: Codon 54 polymorphism of the fatty acid binding protein gene and insulin resistance in the Japanese population. Diabet Med 1999, 16:119-124

24. Hayakawa T, Nage Y, Nohara E, Yamashita H, Takamura T, Abe T, et al: Variation of the fatty acid binding protein 2 gene is not associated with obesity and insulin resistance in Japanese subjects. Metabolism 1999, 48:655-657

25. Lei HH, Coresh J, Shulidner AR, Boerwinkle E, Brancafl F: Variants of the insulin receptor substrate-1 and fatty acid binding protein 2 genes and the risk of type 2 diabetes, obesity, and hyperinsulinemia in African-Americans: the Atherosclerosis Risk in Communities Study. Diabetes 1999, 48:1868-1872

26. Mandelcom R, Connelly PW, Boright A, Young TK, Hegele RA: F5 Q506 mutation and the low prevalence of cardiovascular disease in Canadian Inuit. J Invest Med 1998, 46:232-235

27. Saarinen L, Pulkkinen A, Kareinen A, Heikkinen S, Lehto S, Laakso M: Variants of the fatty acid-binding protein 2 gene are not associated with coronary heart disease in nondiabetic subjects and in patients with NIDDM. Diabetes Care 1998, 21:849-850

28. Hegele RA, Connelly PW, Hanley AJ, Sun F, Harris SB, Zinman B: Common genomic variants associated with variation in plasma lipoproteins in young aboriginal Canadians. Arterioscler Thromb Vasc Biol 1997, 17:1060-1066

29. Piigiamake I, Rissanne J, Heikkinen S, Karjalainen L, Laakso M: Codon 54 polymorphism of the human intestinal fatty acid binding protein 2 gene is associated with dyslipidemias but not with insulin resistance in patients with familial combined hyperlipidemia. Arterioscler Thromb Vasc Biol 1997, 17:1039-1044

30. Boullu-Sanchis S, Lepræstre F, Heddlein G, Donnet JP, Schaffer P, Froguel P, et al: Type 2 diabetes mellitus: association study of five candidate genes in an Indian population of Guadeloupe, genetic contribution of FABP2 polymorphism. Diabetes Metab 1999, 25:150-156

31. Rissanne J, Piigiamake I, Heikkinen S, Kekeleainen P, Kuusisto J, Laakso M: The Ala54Thr polymorphism of the fatty acid binding protein 2 gene does not influence insulin sensitivity in Finnish nondiabetic and NIDDM subjects. Diabetes 1997, 46:711-712

32. Vidgren HM, Piigiaa F, Laakso M, Uusitupa M: Threonine allele in codon 54 of the fatty acid binding protein 2 gene does not modify the fatty acid composition of serum lipids in obese subjects. Eur J Clin Invest 1997, 27:405-408

33. Sipileainen R, Uusitupa M, Heikkinen S, Rissanen A, Laakso M: Variants in the human intestinal fatty acid binding protein 2 gene in obese subjects. J Clin Endocrinol Metab 1999, 82:2629-2632

34. Kelley DE, Molan M, Simonneau JA, Mandarino LJ: Interaction between glucose and free fatty acid metabolism in human skeletal muscle. J Clin Invest 1993, 92:91-98

35. Agren J, Valve R, Vidgren H, Laakso M, Uusitupa M: Postprandial lipemic response is modified by the polymorphism at codon 54 of the fatty acid-binding protein 2 gene. Arterioscler Thromb Vasc Biol 1998, 18:1606-1610

36. Hegele RA, Wolfever TM, Story JA, Connelly PW, Jenkins DJ: Intestinal fatty acid-binding protein variation associated with variation in the response of plasma lipoproteins to dietary fibre. Eur J Clin Invest 1997, 27:857-862

37. Chiu KC, McCarthy JE: The insertion allele at the angiotensin I-converting enzyme gene locus is associated with insulin resistance. Metabolism 1997, 46:395-399

38. Levy JC, Matthews DR, Hermans MP: Correct homeostasis model assessment (HOMA) evaluation uses the computer program. Diabetes Care 1998, 21:219-219

39. Matthews DR, Hosker JP, Rudenski AS, Naylor BA, Treacher DF, Turner RC: Homeostasis model assessment: insulin resistance and beta-cell function from fasting plasma glucose and insulin concentrations in man. Diabetologia 1985, 28:412-419

40. Chiu KC, Province MA, Permutt MA: Glucokinase gene is genetic marker for NIDDM in American blacks. Diabetes 1992, 41:843-849