A Genome-Wide Linkage Scan of Insulin Level Derived Traits: the Amish Family Diabetes Study

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ABSTRACT

Objective: Serum insulin levels are altered in insulin resistance and insulin deficiency, states associated with development of type 2 diabetes. The goal of our study was to identify chromosomal regions likely to harbor genetic determinants of these traits.

Research Design and Methods: We conducted a series of genetic analyses, including genome-wide and fine-mapping linkage studies, based on insulin levels measured during an oral glucose tolerance test (OGTT) in 552 non-diabetic participants in the Amish Family Diabetes Study. Indices of insulin secretion included the insulinogenic index and insulin at 30 minutes post-glucose load (insulin 30), while indices of insulin resistance included HOMA-IR and fasting insulin. Insulin area under the curve (AUC), a measure of both insulin secretion and insulin resistance, was also examined.

Results: All traits were modestly heritable, with heritability estimates ranging from 0.1-0.4 (all p < 0.05). There was significant genetic correlation between fasting insulin and HOMA-IR ($\rho_G > 0.86$, p < 0.05), and insulin 30 and insulinogenic index ($\rho_G = 0.81$, p < 0.0001), suggesting that common genes influence variation in these pairs of traits. Suggestive linkage signals in the genome scan were to insulin 30 on chromosome 15q23 (LOD = 2.53, p = 0.00032), and to insulinogenic index on chromosome 2p13 (LOD = 2.51, p = 0.00034). Fine-mapping study further refined our signal for insulin 30 on chromosome 15 (LOD = 2.38 at 68 cM).

Conclusions: These results suggest that there may be different genes influencing variation in OGTT measures of insulin secretion and insulin resistance.

Abbreviations
AFDS: Amish Family Diabetes Study
AUC: area under the curve
BMI: body mass index
HOMA-IR: homeostatic assessment of insulin resistance
HbA1c: hemoglobin A1c
IFG: impaired fasting glucose
IGT: impaired glucose tolerance
LOD: logarithm of odds
OGTT: oral glucose tolerance test
STR: short tandem repeat
T2D: type 2 diabetes
Type 2 diabetes (T2D) is a classic example of a complex disease that results from the interaction of multiple genetic and environmental factors. One strategy to identify the genes regulating the T2D phenotype is to focus on related sub-clinical (intermediate) phenotypes, which are likely to be less genetically complex and involve fewer alleles. The pathophysiology of T2D involves defects in insulin sensitivity and/or insulin secretion thus making these measures excellent intermediate traits to study to dissect the genetic underpinnings of T2D. Circulating levels of plasma insulin, measured in either the fasting state or in response to a glucose load, vary considerably in nondiabetic individuals, with higher levels predicting future development of diabetes. Several indices of insulin secretion and insulin resistance can be derived from insulin and glucose levels measured at different time points during an oral glucose tolerance test (OGTT). OGTT-derived measures of insulin secretion include the insulinogenic index and insulin at 30 minutes following a 75 gram oral glucose load (insulin 30), while measures of insulin resistance include fasting insulin and the homeostatic model of insulin resistance (HOMA-IR). Insulin area under the curve (insulin AUC) during the OGTT reflects elements of both insulin secretion and insulin resistance.

Several studies have investigated the genetic epidemiology of fasting insulin levels and OGTT-derived indices (1; 2). Genome-wide scans have identified several chromosomal regions linked to these traits (3-12), but few have been replicated. The goal of this study was to characterize the genetic epidemiology of five insulin-related traits, including fasting insulin, insulin 30, insulinogenic index, HOMA-IR and insulin AUC. We first estimated their heritability, then assessed whether and to what degree these traits may share common genetic influence, and performed genome-wide and fine-mapping linkage analyses of these traits. We found that these insulin traits were significantly heritable and there may be different genetic influences underlying these OGTT-derived measures of insulin secretion and resistance. Furthermore, our genome scan provides evidence of linkage on chromosomes 2p and 15q to measures of insulin secretion.

Clinical characteristics of 552 nondiabetic subjects are shown in Table 1. The overall prevalence of IGT and/or IFG was 22% in this sample. Insulin resistance-related measures in those with IGT/IFG were significantly higher (p < 0.001) than in euglycemic individuals, whereas insulin secretion-related measures were similar between the two groups (data not shown).

Heritability (h²) estimates for insulin related traits ranged from 0.12 to 0.36 (all p <0.05) (Table 1). We next examined the extent to which these traits share common genetic influences in order to assist our interpretation of subsequent linkage analyses. As shown in Table 2, high genetic correlations were observed between fasting insulin and HOMA-IR, suggesting that these two measures share very substantial genetic components (estimated \( \rho_G = 0.86, p <0.05 \)). These findings are not unexpected since HOMA-IR is derived from the fasting insulin. Insulin 30 had a strong genetic correlation with insulinogenic index (\( \rho_G = 0.81, p <0.001 \)). Insulin AUC was more genetically correlated with insulin 30 than with any other trait (\( \rho_G = 0.82, p <0.001 \)). There was no significant genetic correlation between fasting insulin and insulin 30 or the insulinogenic index.

Our genome-wide linkage analysis identified two chromosomal regions with suggestive evidence for linkage (defined as p <0.001, or LOD >2.07) to insulin secretion traits. The first region was for insulin 30...
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(LOD = 2.53, p = 0.00032), occurring at 73 cM on chromosome 15q23 (nearest marker: D15S131) (Figure 1a), which was also supported by the 2-point analysis of D15S131 (LOD = 2.82, p = 0.00016). The second region was for insulinogenic index at 121 cM on chromosome 2p13 (LOD = 2.51, p = 0.00034, nearest marker: D2S139) (Figure 1b), as supported by 2-point analysis of D2S139 (LOD = 1.45, p = 0.0049). Similar results were obtained when the analysis was performed without adjustment for BMI. Nine other chromosomal regions (on chromosomes 1q21, 2q21-q22, 6p24-p23, 7q11-q21, 7q31, 10q11, 11q21-q23, 12p13-p12, and 19p13) showed linkage signals to one or more insulin traits with LOD \geq 1.18 (p <0.01) (Table 3).

Bivariate linkage analysis for the two pairs of highly correlated insulin secretion traits was conducted. The maximum LOD score for (insulin 30 + the insulinogenic index) was 2.21 at 69 cM from the p-ter of chromosome 15. Insulin 30 + insulin AUC showed a lower LOD score (1.58) at 73 cM also on chromosome 15. These results suggest that the genes in this region may contribute more to the insulin 30 phenotype than to the other 2 traits. The complete genome scan results can be viewed in the electronic appendix (available at http://diabetes.diabetesjournals.org).

To follow-up on the linkage signal to insulin 30 on chromosome 15q, 14 additional STR markers were genotyped to increase the information content in the region. These markers reduced the marker density from 11.1 to 3.2 cM and further refined the linkage peak to near D15S153 (at 68 cM, LOD = 2.38), approximately 9 cM closer to the centromere compared to original genome scan results, which was well within the 1-LOD interval.

Insulin secretion and insulin sensitivity are important determinants of glucose homeostasis and diabetes. The current “gold standard” for quantifying insulin secretion is the acute insulin response to intravenous glucose (AIRg) test, and for insulin sensitivity, the hyperinsulinemic euglycemic clamp. Since it is not practical to obtain these labor intensive and costly phenotypes in large numbers of subjects for genetic studies, many have used surrogate measures of insulin secretion and insulin sensitivity. Previous studies have shown that the correlation between insulin-related indices from OGTT investigated in this study and the clamp were moderate (|r| = 0.3 – 0.7), but significant (13; 14). In contrast, Bergman et al. has shown that in African and Hispanic Americans, the \(\rho_G\) between fasting insulin and HOMA-IR to be high (0.96), while the \(\rho_G\) between fasting insulin and insulin sensitivity (SI) derived from an intravenous glucose tolerance test and that between HOMA-IR and SI were modest (\(\rho_G = -0.46\) and -0.48 respectively) (15). The authors interpreted these findings to mean that compared to SI, fasting insulin and HOMA-IR are not good proxy measurement of insulin resistance. However, another interpretation is that there may be differential genetic influence on insulin resistance among different populations or HOMA-IR and SI may be measuring different aspects of insulin resistance. Indeed, variation in the relative amount of hepatic versus insulin resistance has been demonstrated in individuals with T2D, and fasting glucose and insulin mark hepatic insulin resistance while SI may be a better marker of muscle insulin resistance (1; 2).

Our systematic genetic analyses of plasma insulin levels during a 3-hour OGTT and indices derived from these measures provide insights likely to be useful in the search for genetic influences on insulin secretion and sensitivity. We demonstrate modest levels of heritability for a number of insulin secretion related traits that have not previously been reported, such as insulin AUC, insulinogenic index and insulin 30. The level of heritability for fasting insulin levels in the Amish was relatively low (h^2 =
0.13) compared to values reported in Caucasians (0.37 – 0.47) (16; 17), African Americans (0.28) (17), Mexican Americans (0.38 – 0.53) (4; 18), Pima Indians (0.26) (19) and Asians (0.43) (20), although not much different from that estimated in African Americans and Hispanics from the Insulin Resistance and Atherosclerosis Study \( (h^2 = 0.08 – 0.17) \) (15; 21).

As expected based upon that fact that HOMA-IR is derived from the fasting insulin, both of these traits are phenotypically and genetically highly correlated. These two traits may reflect relatively more of the insulin resistance phenotype. HOMA-IR is commonly used in epidemiological studies as a proxy measurement of insulin resistance, yet it did not appear to be more informative, compared to fasting insulin, in our genetic analysis. This is likely due to the fact that fasting insulin is a primary component of the HOMA-IR calculation, particularly in nondiabetic subjects for whom there is less variation in glucose levels. Our results suggest that a simpler measurement (fasting insulin) may serve as good as a more complicated composite measurement (HOMA-IR) for genetic studies of insulin resistance. On the other hand, insulin 30 shared a significant genetic component with the insulinogenic index, both measures thought to be more related to insulin secretion. Importantly, there was no significant genetic correlation between fasting insulin and insulin 30, suggesting that these two traits are likely to have different genetic influences. These findings are consistent with the biological concept that defects in insulin sensitivity and insulin secretion are genetically distinct.

From our genome-wide linkage analysis, we identified two chromosomal regions, 15q23 for insulin 30 and 2p13 for insulinogenic index, with suggestive evidence of linkage. For the linkage signal for insulin 30 on chromosome 15q, the 1-LOD support interval is a 31.4 cM region defined by markers D15S117 and D15S158. Within this interval, there are 302 genes [263 named, 59 predicted (NCBI Build 35.1)]. Several genes within our region of linkage on 15q23 may potentially be associated with beta cell development and function. Some of the candidate genes in this region are involved with hormone secretion \( (SCAMP2, SCAMP5) \) (22; 23), others are growth factors \( (NRG4) \) (24), while others such as \( ISL2 \) are homologous to proteins known to be involved in beta cell development \( (ISL1) \) (25). For the linkage signal for insulinogenic index on chromosome 2p, the 1-LOD support interval is a 26 cM region defined by markers D2S139 and D2S347. Within this interval, there are 194 genes [167 named, 27 predicted]. A number of candidate genes for beta cell development or function lie within the 1 LOD region including two genes encoding secretory vesicle associated membrane proteins \( VAMP5, VAMP8 \).

It is somewhat surprising that there was little overlap of linkage signals for insulin 30 and insulinogenic index on chromosomes 2 and 15 given that genetic correlation was high. However, these traits were not perfectly correlated and thus may not have an identical genetic basis. Furthermore, gene-by-gene or gene-by-environment interactions, which were not accounted for in estimates of genetic correlation, may contribute to the lack of significant overlapping linkage signals in these regions.

Thus far, genome-wide linkage studies of diabetes-related traits, including insulin traits, have been reported in several ethnic groups (3-8). Studies conducted in Japanese and Mexican Americans have also revealed linkage to T2D on chromosome 15q. In a Japanese study (7), a suggestive linkage signal to T2D was observed on 15q13-q21 \( (MLS = 2.19) \), whose 1-LOD region overlaps with the 1-LOD region for the linkage to insulin 30 in the Amish. A small linkage
signal to T2D (two-point MLS for D15S119 = 1.50) was also observed in the same region in a study of Mexican Americans (8). On the other hand, evidence for replication of our linkage on chromosome 2p13 to insulinogenic index (LOD = 2.51, or empirical p = 0.00034, at 121 cM) is more limited. A meta linkage analysis utilizing information from 4 ethnic groups of the NHLBI Family Blood Pressure Program (3) reported suggestive linkage signals to both fasting insulin and HOMA-IR (LOD = 2.3 – 2.6, or empirical p = 0.03 – 0.06, at ~113 - 117 cM on the Amish map). We also observed LOD scores ≥ 1.18 (corresponding to an empirical p <0.01) on 9 other chromosomal regions. Several of these regions of linkage have also been reported in the literature. In a recent study, Freedman et al. (6) observed suggestive linkage to both fasting insulin and HOMA-IR in African Americans at the same location on chromosome 19p (LOD = 2.3, near D19S1034, at ~10 cM on the Amish map) where we observed a modest linkage signal to fasting insulin (LOD = 1.3 at 10 cM). We did not observe evidence for linkage to regions on chromosomes 3p (4), 19q (5), or 20p (6) previously reported to harbor loci for insulin traits we examined.

In summary, we observed evidence for linkage of insulin traits to regions of chromosome 2p13 and 15q23, both regions with a number of beta cell candidate genes. Further examination of these regions through linkage disequilibrium mapping and positional candidate gene analysis will be necessary to identify the genes and their functional variants, which should be relevant not only to their influences on insulin levels, but also to susceptibility to T2D.

RESEARCH DESIGN AND METHODS

Our study was based on 691 members of the Amish Family Diabetes Study. Details of subject recruitment have been previously reported (26). The study protocol was approved by the Institutional Review Board at the University of Maryland Baltimore, and informed consent was obtained from each participant.

Phenotypes. After an overnight fast, a standard 3-hr OGTT with blood sampling every 30 minutes was administered to subjects without a prior history of diabetes. Plasma glucose and insulin concentrations were assayed with standard protocols. Fasting glucose levels ranged from 3.81 to 6.83 mmol/l in this population. Total insulin AUC during the 3-hr OGTT was calculated using the trapezoid method. HOMA-IR index was calculated as [fasting insulin (mU/l) x fasting glucose (mmol/l)]/22.5. The insulinogenic index was calculated as: [(insulin 30 – fasting insulin)/(glucose 30 - fasting glucose)]. Criteria for the diagnosis of T2D, impaired glucose tolerance (IGT) and impaired fasting glucose (IFG) were adapted from American Diabetes Association recommendations. As the development and treatment of T2D can significantly alter insulin levels, only nondiabetic subjects were included in the analysis (n = 552).

Genotypes. We typed 357 short tandem repeat (STR) markers on 22 autosomes using DNA from leukocytes. These markers were from the ABI Prism Linkage Mapping Set (Perkin-Elmer). Overall genotyping rates across all STRs were 96.3 ± 2.4% complete. The marker order and sex-averaged inter-marker distances (mean: 9.7 cM) were estimated from our data using CRI-MAP (27). The mean marker heterozygosity was 0.75 (0.33 to 0.91). Based on initial linkage analysis results, 14 additional STR markers were genotyped on chromosome 15 (between 14 and 101 cM) for a fine-mapping study.

Statistical analysis. Values for traits with a significantly skewed distribution were transformed by their natural logarithm, and extreme outliers (value deviating from the mean by >3 s.d.) were excluded from analysis (n = 0 – 4, depending on trait). Furthermore,
to reduce the computational complexity, we divided the single large pedigree into 27 smaller pedigrees (n = 3 – 118) for analysis. Results from all analyses were adjusted for sex-specific age and age^2, and BMI.

All analyses were conducted using a pedigree-based variance components method. We first estimated heritability then genetic correlation. Bivariate modeling was used to partition the phenotypic correlation (ρ_P) between a given pair of quantitative traits into their additive genetic (ρ_G, i.e. genetic correlation) and random environmental (ρ_E) components (28). For linkage analyses, the effect of a quantitative trait locus was estimated by modeling the covariance in a trait between individuals to be a function of the probability that they inherited both alleles at the marker locus from a common ancestor. Both two-point and multipoint analyses were performed, and statistical significance was evaluated by likelihood ratio tests using the SOLAR program (29). Multipoint identity-by-descent matrices were computed using the Kosambi function in the LOKI program (30). As the variance components methods can be susceptible to significant violations of the multivariate normality assumption, we used simulations to estimate the empirical probability of obtaining false evidence for linkage. We derived the distribution of nominal LOD scores under the null hypothesis of no linkage by simulating 10,000 unlinked markers, dropping them through the pedigrees, and conducting linkage analysis with each of the 10,000 markers for each of the insulin traits. The probability of obtaining a false positive result was defined as the proportion of replicates for which we obtained a specified LOD score or higher. The p-values obtained from the simulation study were then back-converted into LOD scores by first converting them into corresponding χ^2 values, and then dividing the χ^2 values by (2 × ln 10). All LOD scores from QTL analyses presented in this report were obtained from this simulation.

ACKNOWLEDGEMENTS

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REFERENCES


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**Table 1.** Plasma levels (mean ± SD) of traits in non-diabetic study subjects by sex*.

<table>
<thead>
<tr>
<th>Trait</th>
<th>Male (n = 262)</th>
<th>Female (n = 290)</th>
<th>h² ± SE §</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (yrs)</td>
<td>46.0 ± 14.5</td>
<td>44.1 ± 14.6</td>
<td>--</td>
</tr>
<tr>
<td>BMI (kg/m²)</td>
<td>26.3 ± 3.6</td>
<td>28.0 ± 5.5</td>
<td>0.40 ± 0.08 ‡</td>
</tr>
<tr>
<td>Fasting glucose (mmol/l)</td>
<td>5.09 ± 0.49</td>
<td>5.02 ± 0.47</td>
<td>0.48 ± 0.09</td>
</tr>
<tr>
<td>Glucose 30 (mmol/l)</td>
<td>8.21 ± 1.76</td>
<td>8.21 ± 1.52</td>
<td>0.31 ± 0.08</td>
</tr>
<tr>
<td>Fasting insulin (mU/l)</td>
<td>10.3 ± 3.8</td>
<td>11.0 ± 6.4</td>
<td>0.12 ± 0.07 †</td>
</tr>
<tr>
<td>Insulin 30 (mU/l)</td>
<td>49.1 ± 29.7</td>
<td>54.6 ± 39.3</td>
<td>0.19 ± 0.10 †</td>
</tr>
<tr>
<td>Insulinogenic index (U/g)</td>
<td>0.75 ± 0.72</td>
<td>0.87 ± 0.80</td>
<td>0.36 ± 0.11 †</td>
</tr>
<tr>
<td>HOMA-IR (mU·mmol/l²)</td>
<td>42.2 ± 17.1</td>
<td>43.7 ± 20.1</td>
<td>0.13 ± 0.06 †</td>
</tr>
<tr>
<td>Insulin AUC (mU/l·hr)</td>
<td>99.9 ± 54.8</td>
<td>145.1 ± 87.8</td>
<td>0.28 ± 0.10 †</td>
</tr>
</tbody>
</table>

* See reference (25) for additional characteristics of the Amish Family Diabetes Study.

Due to missing data points, sample sizes ranged from 552 for fasting insulin to 486 for insulin AUC.

† *P* < 0.05; ‡ *P* < 0.001

§ Heritability ± standard error, adjusted for effects of BMI, sex-specific age and age²
Table 2. Correlation coefficients* among insulin traits§.

<table>
<thead>
<tr>
<th></th>
<th>Fasting insulin</th>
<th>HOMA-IR</th>
<th>Insulin 30</th>
<th>Insulinogenic index</th>
</tr>
</thead>
<tbody>
<tr>
<td>HOMA-IR</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>$\rho_P$</td>
<td>0.92 ± 0.00</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>$\rho_G$</td>
<td>0.86† ± 0.08</td>
<td></td>
<td>0.50 ± 0.04</td>
<td>0.75 ± 0.02</td>
</tr>
<tr>
<td>$\rho_E$</td>
<td>0.93 ± 0.004</td>
<td>0.52 ± 0.03</td>
<td>0.18 ± 0.34</td>
<td>0.34 ± 0.04</td>
</tr>
<tr>
<td>Insulin 30</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>$\rho_P$</td>
<td>0.34 ± 0.04</td>
<td>0.28 ± 0.04</td>
<td>0.75 ± 0.02</td>
<td></td>
</tr>
<tr>
<td>$\rho_G$</td>
<td>0.41 ± 0.27</td>
<td>0.16 ± 0.29</td>
<td>0.81‡ ± 0.08</td>
<td></td>
</tr>
<tr>
<td>$\rho_E$</td>
<td>0.34 ± 0.08</td>
<td>0.34 ± 0.08</td>
<td>0.75 ± 0.04</td>
<td></td>
</tr>
<tr>
<td>Insulinogenic index</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>$\rho_P$</td>
<td>0.62 ± 0.03</td>
<td>0.59 ± 0.03</td>
<td>0.75 ± 0.02</td>
<td></td>
</tr>
<tr>
<td>$\rho_G$</td>
<td>0.52 ± 0.23</td>
<td>0.32 ± 0.29</td>
<td>0.82‡ ± 0.10</td>
<td></td>
</tr>
<tr>
<td>$\rho_E$</td>
<td>0.66 ± 0.05</td>
<td>0.65 ± 0.05</td>
<td>0.74 ± 0.04</td>
<td></td>
</tr>
</tbody>
</table>

* $\rho_P$: phenotypic correlation; $\rho_G$: genetic correlation; $\rho_E$: random environmental correlation.

§ All $\rho_G$ and $\rho_E$ are with $p < 0.001$.

† $P < 0.05$; ‡ $P < 0.001$
Table 3. LOD scores > 1.18 (p < 0.01) for each insulin-related trait from multipoint linkage analyses.

<table>
<thead>
<tr>
<th>Chromosome</th>
<th>Trait</th>
<th>Position (cM)</th>
<th>Nearest STR marker</th>
<th>LOD score</th>
</tr>
</thead>
<tbody>
<tr>
<td>1q21</td>
<td>HOMA-IR</td>
<td>145</td>
<td>D1S420</td>
<td>1.19</td>
</tr>
<tr>
<td>2p13</td>
<td>Insulinogenic index</td>
<td>121</td>
<td>D2S373</td>
<td>2.51</td>
</tr>
<tr>
<td>2q21-q22</td>
<td>Fasting insulin</td>
<td>315</td>
<td>D2S125</td>
<td>1.58</td>
</tr>
<tr>
<td>6p24-p23</td>
<td>Insulinogenic index</td>
<td>10</td>
<td>D6S344</td>
<td>1.18</td>
</tr>
<tr>
<td>7q11-q21</td>
<td>HOMA-IR</td>
<td>105</td>
<td>D7S669</td>
<td>1.88</td>
</tr>
<tr>
<td>7q31</td>
<td>Fasting insulin</td>
<td>125</td>
<td>D7S657</td>
<td>1.36</td>
</tr>
<tr>
<td></td>
<td>Insulin AUC</td>
<td>142</td>
<td>D7S657</td>
<td>1.54</td>
</tr>
<tr>
<td>10q11</td>
<td>Insulinogenic index</td>
<td>75</td>
<td>D10S220</td>
<td>1.19</td>
</tr>
<tr>
<td>11q21-q23</td>
<td>Insulin 30</td>
<td>115</td>
<td>D11S1358</td>
<td>1.29</td>
</tr>
<tr>
<td>12p13-p12</td>
<td>Fasting insulin</td>
<td>35</td>
<td>D12S364</td>
<td>1.27</td>
</tr>
<tr>
<td>15q23</td>
<td>Insulin 30</td>
<td>73</td>
<td>D15S131</td>
<td>2.53</td>
</tr>
<tr>
<td>19p13</td>
<td>Fasting insulin</td>
<td>10</td>
<td>D19S216</td>
<td>1.32</td>
</tr>
</tbody>
</table>
Figure 1a. Multipoint linkage analysis results on chromosome 15 for insulin at 30 minutes
Figure 1b. Multipoint linkage analysis results on chromosome 2 for the insulinogenic index.