A Novel Syndrome of Autosomal-Dominant Hyperinsulinemic Hypoglycemia Linked to a Mutation in the Human Insulin Receptor Gene

Kurt Højlund,1 Torben Hansen,2 Maria Lajer,2 Jan Erik Henriksen,1 Klaus Levin,1 Jørgen Lindholm,3 Oluf Pedersen,2 and Henning Beck-Nielsen1

Recently, various subtypes of familial hyperinsulinemic hypoglycemia with an autosomal-dominant inheritance have been etiologically characterized. In the present study, we have delineated the genetics and metabolic phenotype of a novel form of hypoglycemia in a large pedigree with an apparent autosomal-dominant transmission. After initial investigations of the proband, her mother, and a sister, the study was extended to 19 family members in three generations. Glucose tolerance was assessed by a 5-h oral glucose tolerance test (OGTT) and insulin sensitivity by euglycemic-hyperinsulinemic clamp in six affected family members and six control subjects. To identify the genetic cause of hypoglycemia, linkage analysis and mutation analysis of genomic DNA from all family members were performed. All affected family members were characterized by postprandial hypoglycemia, fasting hyperinsulinemia, and an elevated serum insulin-to-C-peptide ratio. The 5-h OGTT demonstrated hyperinsulinemic hypoglycemia, and the clamp studies showed reduced insulin sensitivity and clearance of serum insulin in affected family members compared with control subjects. Linkage analysis and subsequent mutation screening revealed a missense mutation (Arg1174Gln) in the tyrosine kinase domain of the insulin receptor gene that cosegregated with the disease phenotype (logarithm of odds [LOD] score 3.21). In conclusion, we report a novel syndrome of autosomal-dominant hyperinsulinemic hypoglycemia. The findings demonstrate the coexistence of severe postprandial hypoglycemia, fasting hyperinsulinemia, and impaired insulin clearance and suggest that hypoglycemia should be considered as a phenotype linked to heterozygote mutations in the insulin receptor gene. Diabetes 53:1592–1598, 2004

From the 1Diabetes Research Centre, Department of Endocrinology, Odense University Hospital, Odense, Denmark; the 2Steno Diabetes Center, Copenhagen, Denmark; and the 3Department of Medicine, Division of Endocrinology, Holstebro Hospital, Holstebro, Denmark.

Address correspondence and reprint requests to Kurt Højlund, MD, PhD, Diabetes Research Centre, Department of Endocrinology, Odense University Hospital, Kloevervaenget 6, DK-5000, Odense C, Denmark. E-mail: k.hojlund@dadlnet.dk.

Received for publication 1 October 2003 and accepted in revised form 8 March 2004.

GDR, glucose disposal rate; LOD, logarithm of odds; OGTT, oral glucose tolerance test.
© 2004 by the American Diabetes Association.

Until recently, familial persistent hyperinsulinemic hypoglycemia was considered a syndrome of early infancy with a recessive inheritance (1). In hundreds of cases, mutations in the β-cell sulfonylurea receptor (SUR1) gene or inward-rectifying potassium-channel (Kir6.2) gene have been identified (1–4). Recently, autosomal-dominant forms of familial hyperinsulinism were reported in case subjects with milder- and later-onset forms of hypoglycemia (5–10). In some families, gain-of-function mutations in the genes of glucokinase or glutamate dehydrogenase were found (7–9). In other families, an abnormal pyruvate-induced insulin release during exercise was demonstrated (10). In adults, endogenous hyperinsulinemic hypoglycemia is most frequently due to insulinoma (11). However, many sporadic and familial cases of hyperinsulinemic hypoglycemia in children and adults remain unexplained (5,6).

All known genetic defects giving rise to familial hyperinsulinemic hypoglycemia are characterized by inappropriate and excessive secretion of insulin (1–4,7–9,12). However, variability in any gene capable of increasing circulating levels of insulin may cause hyperinsulinemic hypoglycemia. Thus, paradoxical fasting hypoglycemia in infancy has been described in rare cases with leprechaunism and Rabson-Mendenhall’s syndrome caused by mutations in both alleles of the insulin receptor gene (13). In adults, mutations in the insulin receptor gene have almost exclusively been associated with severe insulin resistance (13).

In this report, we describe a large family with several members in three generations suffering from postprandial episodes of neuroglycopenia (14). We aimed at characterizing glucose metabolism in affected family members by oral glucose tolerance test (OGTT) and euglycemic-hyperinsulinemic clamp studies and to identify the genetic defect responsible for the apparent dominant inheritance of hyperinsulinemic hypoglycemia in a large Danish pedigree.

**RESEARCH DESIGN AND METHODS**

A 21-year-old woman was referred because of severe hypoglycemia. Since her twelfth year, she has experienced episodes with blurred vision, loss of consciousness, and convulsions, which occurred 2–5 h postprandially, often in conjunction with exercise and relieved by food ingestion. After several admissions to emergency units, anticonvulsant therapy was given for 3 years despite the finding of a normal electroencephalogram. At the age of 20 years, hypoglycemia was documented by low capillary blood glucose concentrations in the range of 1.1 to 1.5 mmol/l during episodes with symptoms. The proband...
was nonobese, healthy looking, and showed no signs of severe insulin resistance, such as skin pigmentation or hirsutism. Her menarche was at the age of 14 years. She experienced irregular menses (anovulatory cycles) despite intermittent use of oral contraceptives until she was 20 years old, after which she had regular menstrual cycles. Fasting hyperinsulinemia (341 pmol/l), together with an elevated serum insulin to C-peptide ratio of 0.5 (normal range 0.1), was found. HbA1c and fasting circulating levels of glucose, lipids, insulin-like growth factors (IGFs), cortisol, glucagon, growth hormone, thyroid, and sex hormones were normal. Endoscopic ultrasonography of the pancreas revealed no tumors. Antibodies to insulin, islet cell, and GAD65 were absent. She completed a 72-h fast without symptoms of hypoglycemia despite low blood glucose concentrations (1.7–2.2 mmol/l) during the last 24 h of the fast. Despite high overnight fasting serum insulin levels (341 pmol/l), serum levels of insulin (12 pmol/l), C-peptide, and proinsulin declined to values within normal ranges after 60 h of fasting (15). The serum insulin to C-peptide ratio steadily declined throughout the 72-h fast, from 0.5 to 0.2. The counterregulatory release of cortisol, glucagon, and growth hormone during prolonged fasting was normal (15). She was treated with long-acting octreotide (20–30 mg/month), which significantly ameliorated postprandial symptoms of hypoglycemia and prevented severe neuroglycopenic attacks.

Several family members in three generations had symptoms suggestive of severe hypoglycemia (14). To determine the apparently genetic cause of hypoglycemia, we initially studied the mother, the maternal grandmother, and a sister of the proband (subjects II-9, I-1, and III-11, respectively) (Fig. 1), who all had low capillary blood glucose concentrations (<2.5 mmol/l) during episodes with symptoms suggestive of hypoglycemia. They had fasting hyperinsulinemia and an elevated serum insulin to C-peptide ratio (Table 1).

In contrast, examination of the sister (subject III-11), who had moderate symptoms of hypoglycemia, showed mild skin pigmentation in the axillae, increased total and free serum levels of testosterone, and polycystic ovary syndrome. In conclusion, we describe a family with autosomal-dominant hyperinsulinemic hypoglycemia, in whom a novel Arg1174Gln mutation in the insulin receptor gene was identified.

---

**TABLE 1**

Fasting levels of plasma glucose, serum insulin, and C-peptide in family members potentially affected by hyperinsulinemic hypoglycemia

<table>
<thead>
<tr>
<th>Subject no.</th>
<th>Age (years)</th>
<th>Symptoms of hypoglycemia/age of onset (years)</th>
<th>Plasma glucose (mmol/l)</th>
<th>Serum insulin (pmol/l)</th>
<th>Serum C-peptide (pmol/l)</th>
<th>Insulin-to-C-peptide molar ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td>I-1</td>
<td>80</td>
<td>Yes/24*</td>
<td>5.1</td>
<td>213</td>
<td>769</td>
<td>0.28</td>
</tr>
<tr>
<td>II-2</td>
<td>58</td>
<td>Yes/30*</td>
<td>5.1</td>
<td>114</td>
<td>415</td>
<td>0.28</td>
</tr>
<tr>
<td>II-6</td>
<td>49</td>
<td>Yes/25*</td>
<td>5.1</td>
<td>228</td>
<td>781</td>
<td>0.29</td>
</tr>
<tr>
<td>II-8</td>
<td>47</td>
<td>Yes/14*</td>
<td>4.8</td>
<td>248</td>
<td>746</td>
<td>0.33</td>
</tr>
<tr>
<td>II-9</td>
<td>42</td>
<td>Yes/15*</td>
<td>5.0</td>
<td>202</td>
<td>517</td>
<td>0.39</td>
</tr>
<tr>
<td>III-1</td>
<td>36</td>
<td>No/—</td>
<td>5.1</td>
<td>35</td>
<td>431</td>
<td>0.08</td>
</tr>
<tr>
<td>III-2</td>
<td>31</td>
<td>Yes/10*</td>
<td>4.4</td>
<td>470</td>
<td>1,323</td>
<td>0.36</td>
</tr>
<tr>
<td>III-3</td>
<td>34</td>
<td>No/—</td>
<td>5.5</td>
<td>63</td>
<td>1,055</td>
<td>0.06</td>
</tr>
<tr>
<td>III-4</td>
<td>27</td>
<td>No/—</td>
<td>4.7</td>
<td>44</td>
<td>643</td>
<td>0.06</td>
</tr>
<tr>
<td>III-6</td>
<td>7</td>
<td>Yes/7</td>
<td>4.3</td>
<td>75</td>
<td>285</td>
<td>0.26</td>
</tr>
<tr>
<td>III-7</td>
<td>20</td>
<td>Yes/3*</td>
<td>5.0</td>
<td>377</td>
<td>1,026</td>
<td>0.37</td>
</tr>
<tr>
<td>III-8</td>
<td>17</td>
<td>No/—</td>
<td>4.5</td>
<td>51</td>
<td>615</td>
<td>0.08</td>
</tr>
<tr>
<td>III-9†</td>
<td>23</td>
<td>Yes/12*</td>
<td>3.3</td>
<td>361</td>
<td>721</td>
<td>0.50</td>
</tr>
<tr>
<td>III-10</td>
<td>19</td>
<td>No/—</td>
<td>4.2</td>
<td>41</td>
<td>591</td>
<td>0.07</td>
</tr>
<tr>
<td>III-11</td>
<td>15</td>
<td>Yes/12</td>
<td>5.3</td>
<td>2,172</td>
<td>2,482</td>
<td>0.87</td>
</tr>
</tbody>
</table>

Subject numbers correspond to the numbers shown in Fig. 1. The reference intervals for plasma glucose, serum insulin, and C-peptide were 4.0–6.0 mmol/l, 12–77 pmol/l, and 130–760 pmol/l, respectively. *Affected family members who had experienced loss of consciousness; †proband.
**HYPOGLYCEMIA ASSOCIATED WITH INSULIN RESISTANCE**

TABLE 2
Clinical characteristics and metabolic parameters during euglycemic-hyperinsulinemic clamp studies

<table>
<thead>
<tr>
<th></th>
<th>Control subjects</th>
<th>Affected family members</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>n</strong></td>
<td>6</td>
<td>6</td>
</tr>
<tr>
<td><strong>Sex (female/male)</strong></td>
<td>1/5</td>
<td>1/5</td>
</tr>
<tr>
<td><strong>Age (years)</strong></td>
<td>44.0 ± 2.3</td>
<td>41.7 ± 5.6</td>
</tr>
<tr>
<td><strong>BMI (kg/m²)</strong></td>
<td>24.5 ± 0.8</td>
<td>25.4 ± 1.0</td>
</tr>
<tr>
<td><strong>HbA₁c (%)</strong></td>
<td>4.8 ± 0.1</td>
<td>5.7 ± 0.2‡</td>
</tr>
<tr>
<td><strong>Fasting plasma triglycerides (mmol/l)</strong></td>
<td>1.2 ± 0.4</td>
<td>1.3 ± 0.2</td>
</tr>
<tr>
<td><strong>Fasting cholesterol (mmol/l)</strong></td>
<td>5.2 ± 0.3</td>
<td>5.7 ± 0.4</td>
</tr>
</tbody>
</table>

Plasma glucose (mmol/l) | 5.3 ± 0.1 | 5.1 ± 0.1 | 5.6 ± 0.2 | 5.3 ± 0.1 | 3.5 ± 0.1  
Serum insulin (pmol/l)  | 18 ± 2    | 328 ± 17‡ | 177 ± 30§| 1,313 ± 127‡| 24.5 ± 0.3  
Serum C-peptide (pml/l)| 403 ± 46  | 465 ± 83  | 553 ± 64 | 527 ± 101 | 54.3 ± 0.4  
Total GDR (mg·min⁻¹·m⁻²) | 77 ± 4 | 346 ± 33‡ | 76 ± 2 | 200 ± 34§ | 0.5 ± 0.1  
Glucose oxidation rate (mg·min⁻¹·m⁻²) | 45 ± 6 | 117 ± 52‡ | 48 ± 6 | 100 ± 143 | 0.5 ± 0.1  
Nonoxidative glucose metabolism (mg·min⁻¹·m⁻²) | 32 ± 5 | 229 ± 28‡ | 27 ± 5 | 100 ± 24§ | 0.5 ± 0.1  
Insulin sensitivity (ml/min per pmol/l) | 1.85 ± 0.23 | — | — | 0.23 ± 0.07* | 0.5 ± 0.1  
Insulin clearance (ml·min⁻¹·m⁻²) | — | 885 ± 132 | — | 192 ± 45* | 0.5 ± 0.1  

Data are means ± SE. *P < 0.01 (affected family members versus control subjects); ‡all HbA₁c values were in the normal range (4.3–6.4%); §P < 0.05 (basal versus clamp); †P < 0.05 (affected family members versus control subjects).

**RESULTS**
Characterization of affected family members. In 10 family members in three generations, the disease phenotype was characterized by episodes of hypoglycemia (Fig. 1 and Table 1), which ranged from moderate symptoms of hypoglycemia in 2 family members to episodes with loss of consciousness in 8 and convulsions causing admission to emergency units in 5. The proband and subjects II-9 and III-3 were treated with anticonvulsant therapy for years without effect. Reported age of onset was between 3 and 30 years, and all affected family members were shown to have fasting hyperinsulinemia and an elevated serum insulin–to–C-peptide ratio between 0.28 and 0.87 (Table 1). These traits were distributed in an autosomally dominant pattern of inheritance (Fig. 1). All affected family members had normal fasting plasma glucose concentrations.

**Five-hour OGTT, euglycemic-hyperinsulinemic clamp, and exercise study.** After an overnight fast, affected family members (subjects II-1, II-6, II-8, II-9, III-7, and III-9) and control subjects had a standard 75-g OGTT. Venous blood samples were drawn every 30 min for 5 h for measurement of plasma glucose and serum insulin. Total glucose disposal rate (GDR), hepatic glucose production, and rates of glucose and lipid oxidation were assessed in affected family members (subjects II-2, II-6, II-8, II-9, III-2, and III-7) and in control subjects by euglycemic-hyperinsulinemic clamp studies (2-h equilibration period followed by 3-h insulin infusion, 40 mU/min per m²) combined with indirect calorimetry as described previously (17,18). Nonoxidative glucose metabolism was calculated as the difference between GDR and glucose oxidation. Insulin sensitivity and clearance were calculated from the clamp as: 1) insulin sensitivity = ΔGDR/(Δinsulin · glucoseclamp) and 2) insulin clearance = insulin infusion rate/Δinsulin · (C-peptideclamp/C-peptidebasal). Hepatic glucose production and the levels of plasma glucose, serum insulin, and blood lactate before and during exercise were determined in the mother of the proband after an overnight fast using the tracer-dilution method as described in detail previously (19). After a 2-h resting period that allowed for tracer equilibration, she performed moderate exercise at 50% VO₂max for 30 min and intense exercise at 70% VO₂max for 30 min on an ergometer bicycle. Plasma glucose, serum insulin, and C-peptide concentrations were measured as described elsewhere (15). Data are presented as means ± SE. Statistical significance was tested using Student’s t test for unpaired data.

**Linkage analysis and mutation analysis.** DNA was isolated from peripheral blood from 19 family members to perform studies of genetic linkage to chromosomal loci known to cause hyperinsulinemia and/or hypoglycemia. The initial linkage study was done using fluorescently labeled polymorphic microsatellite markers flanking the insulin receptor gene located on chromosome 19. The markers (D19S894, D19S216, D19S905, and D19S884) were chosen from the ABI Prism Linkage Mapping Set, version 2 (Applied Biosystems, Torrance, CA). The 22 exons and the intron/exon boundaries of the insulin receptor gene were examined by direct sequencing (20). Linkage calculations were performed using the computer program Linkmap in the Fastlink package (ftp://fastlink.nih.gov/pub/fastlink) (21).
tent with hyperinsulinemic hypoglycemia. Four of six affected family members reported symptoms of hypoglycemia during nadir levels of plasma glucose, and one of these lost consciousness (subject I-1) during OGTT. The proband and her maternal grandmother (subject I-1) had impaired glucose tolerance.

**Euglycemic-hyperinsulinemic clamp.** In the basal state, no difference in GDR, glucose oxidation, or nonoxidative glucose metabolism (glucose storage) was observed between the groups, and in both groups insulin infusion significantly increased GDR, glucose oxidation, and glucose storage (Table 2). However, insulin-stimulated GDR and glucose storage were significantly reduced in affected family members (Fig. 3). Hepatic glucose production and lipid oxidation were significantly suppressed by insulin infusion in both groups (P < 0.05). Neither in the basal state nor after insulin stimulation did hepatic glucose production or lipid oxidation differ (data not shown).

**Exercise study.** The mother of the proband completed the exercise study without developing symptoms suggestive of hypoglycemia. Plasma glucose and serum insulin levels (~150 pmol/l) remained constant during both moderate and intense exercise, whereas hepatic glucose production almost doubled during moderate exercise and rose to ~300% of resting values during intense exercise (Fig. 4). Blood lactate increased from 0.7 to 5.8 mmol/l during moderate exercise and further to 11.6 mmol/l during intense exercise.

**Linkage analysis and mutation analysis.** The linkage analysis showed complete cosegregation of a specific haplotype in the insulin receptor region with the disease phenotype. In the proband, sequencing of the insulin receptor gene revealed several previously described polymorphisms and a heterozygous point mutation at codon 1174 of exon 20 (CGG→CAG), resulting in a substitution of the positively charged amino acid Arg with the uncharged Gln. Genotyping of the family members showed that all affected family members and none of the unaffected family members harbored the Arg1174Gln variant. Subsequent linkage analysis revealed a significant logarithm of odds (LOD) score at 3.21, supporting the hypothesis that the Arg1174Gln mutation is disease causing (Fig. 1).

**DISCUSSION**

We report a novel syndrome of autosomal-dominant hyperinsulinemic hypoglycemia expressed in three generations of one family. Consistent with other dominant forms of hyperinsulinism, the clinical presentation of this syn-

---

**FIG. 2.** Prolonged OGTT in control subjects (A) and carriers of the Arg1174Gln mutation (B). Data represent plasma glucose and serum insulin levels (mean ± SE) at four time points corresponding to the start of the test (I), to peak plasma glucose levels (II), to nadir plasma glucose levels (III), and to the end of the test (IV), respectively. The times of peak and nadir plasma glucose levels are indicated by vertical lines and intercept times (italized numbers). Insulin levels were higher in the Arg1174Gln group at all time points (P < 0.01). *P < 0.05 and **P < 0.01 for the comparison of time with control subjects. #P = 0.01 for the comparison of plasma glucose levels with the control subjects.

**FIG. 3.** Whole-body GDR in control subjects and carriers of the Arg1174Gln mutation. Whole-body GDR is presented as glucose oxidation (■) and nonoxidative glucose metabolism (□) during basal and insulin-stimulated (clamp) steady-state conditions. Data represent mean ± SE. GDR, glucose oxidation, and nonoxidative glucose metabolism increased in both groups in response to insulin (all P < 0.05). #P = 0.01 for GDR and *P < 0.05 for nonoxidative glucose metabolism in Arg1174Gln group versus control subjects.
Hypoglycemia associated with insulin resistance

Hypoglycemia was hypoglycemia with a later age of onset than that observed in recessive forms of hyperinsulinism (1–10,12). Despite low blood glucose concentrations during prolonged fasting, symptoms of hypoglycemia appeared to occur only in the postprandial state, which contrasts with the recessive forms of hyperinsulinism in which only fasting hypoglycemia has been reported (1–4). On the other hand, hypoglycemia occurs in both the fasting and postprandial states in the dominant form of hyperinsulinism caused by gain-of-function mutations in the glucokinase gene (7,8). In the dominant exercise-induced form of hyperinsulinism, fasting hypoglycemia does not occur in the resting state (10). Thus, distinction between these syndromes based solely on the clinical presentation seems difficult. However, in contrast to all of the recessive and dominant forms of hyperinsulinism reported previously (1–10,12), hyperinsulinemia in the present syndrome of hypoglycemia seems to be associated with decreased degradation rather than increased secretion of insulin, as evidenced by increased fasting levels of serum insulin despite normal levels of serum C-peptide and reduced clearance of exogenous insulin during clamp studies. It might therefore be questioned whether the present syndrome of autosomal-dominant hyperinsulinemic hypoglycemia should be categorized within the group of persistent hyperinsulinemic hypoglycemia of infancy.

Before linkage analysis, other possible candidates in the pathogenesis of hyperinsulinemic hypoglycemia were studied. However, no disease-causing defects in the genes of insulin, SUR1, and Kir6.2 were found. In addition, normal serum ammonium levels in carriers of the Arg1174Gln mutation make gain-of-function mutations in the glucokinase gene less likely. The normal exercise-induced increase in hepatic glucose production supports that increases in insulin levels rather than liver glycogen storage disease cause hypoglycemia. Although only hypoglycemia was clinically apparent in affected family members, the presence of hyperinsulinemic hypoglycemia during a prolonged OGTT and the reduced insulin sensitivity during euglycemic-hyperinsulinemic clamp studies demonstrated the coexistence of severe hypoglycemia and moderate insulin resistance. Together with the finding of an elevated insulin-to-C-peptide ratio and decreased insulin clearance, these data suggested a mutation in the insulin receptor gene.

Identification of a missense mutation (Arg1174Gln) in the tyrosine kinase domain of the insulin receptor gene, which cosegregated with the disease phenotype (LOD score 3.21), supports the hypothesis that the insulin receptor mutation is disease causing. Furthermore, the absence of this mutation in 64 alleles from normal nondiabetic subjects (22) and in 164 alleles from Danish Caucasian patients with late-onset type 2 diabetes (data not shown) indicates that this mutation is not a common polymorphic variant of the receptor protein. Due to the heterotetrameric (α2β2) structure of the insulin receptor, 25% of the receptors are expected to be formed by wild-type alleles, 50% by hybrids of wild-type and mutant alleles, and 25% by mutant alleles alone (13). Two normal β-chains are required for tyrosine kinase activity, which might explain the dominant expression of the Arg1174Gln mutation (13). Hypoglycemia has not been reported in insulin resistance in adults before and, hence, must be considered a novel phenotype linked to heterozygote mutations in the insulin receptor gene.

The Arg1174Gln mutation has previously been reported in three women with the type A syndrome of insulin resistance (22,23) and in an apparently healthy man (24,25), which suggests that the genetic background determines the severity of insulin resistance and whether hypoglycemia is seen or not. Thus, in the study of Møller et al. (22) two paternal aunts had features of severe insulin resistance and two paternal uncles had type 2 diabetes. However, the Arg1174Gln mutation was documented in neither these paternal relatives nor in the father (22). Furthermore, the vast majority of patients with features of the type A syndrome have normal insulin receptors (22,26). No evidence of linkage between insulin receptor mutation and the type A syndrome has ever been provided. For these reasons, it might be argued that other factors (genetic or other) were responsible for the presence of hyperglycemia and extreme insulin resistance (type A syndrome) rather than postprandial hypoglycemia and moderate insulin resistance in the three women previously reported (22,23) with the Arg1174Gln mutation. In the present study, six men and four women with the Arg1174Gln mutation suffered from episodes of hypoglycemia. Only one family member with less severe symptoms of hypoglycemia presented with signs of type A insulin resistance, and none in three generations had
diabetes, which suggests a selection bias of patients previously screened for insulin receptor mutations.

It could be argued that the Arg1174Gln carriers in the present study harbor a second mutation in linkage disequilibrium with the insulin receptor mutation and, thus, that we have not proven that the Arg1174Gln variant is the molecular cause of hypoglycemia. Indeed, the identified linkage block, which extends both proximal and distal to the markers D19S894 and D19S884, has a size of at least 3.7 Mb and contains >100 genes. We cannot exclude a potential contributing effect of a different variant in this linkage block. However, none of these ~100 genes have previously been associated with hypoglycemia. In addition, the physiologic studies showed both insulin resistance and reduced clearance of insulin, which are known consequences of a functional mutation in the tyrosine kinase domain of the insulin receptor gene (13). It is therefore unlikely that mutations in other genes in the linkage block could explain the occurrence of hyperinsulinemic hypoglycemia to the same extent. Another possibility is that other variants in the insulin receptor gene might be modifying the phenotypic expression. Thus, neither we nor the previous reports (22,23) have addressed the possibility of variants affecting the promoter or other noncoding regions of the insulin receptor gene. Such additional variants might be segregating in this family or, in the previous cases, with the Arg1174Gln variant described in the literature.

Previous studies on the Arg1174Gln mutation have shown normal insulin binding to and normal numbers of insulin receptor on the plasma membrane but diminished rates of internalization and degradation of the insulin–insulin receptor complex, probably due to a 70% reduction in insulin-stimulated tyrosine kinase activity (22–25,27,28). Furthermore, insulin-mediated glycogen synthesis and GLUT4 translocation were impaired (27,28). In agreement with these data, we found reduced insulin clearance and decreased insulin sensitivity, the latter primarily caused by a reduction in glucose storage. Surprisingly, insulin receptor substrate-1 and its association with phosphoinositide-3-kinase was stimulated by insulin in cells transfected with the Arg1174Gln mutation (27,28), indicating that insulin signaling through some pathways may be intact and that the effects of this mutation may differ in various tissues.

A divergence in insulin signaling may explain the coexistence of insulin resistance and hypoglycemia, the main physiologic phenotypes of the Arg1174Gln mutation in this family. Thus, another naturally occurring mutation in the tyrosine kinase domain of the insulin receptor gene (Arg1152Gln) selectively impairs insulin action in skeletal muscle but not in liver (29,30). In addition, only glucose storage and not glucose oxidation was impaired by the Arg1152Gln mutation (29,30), as observed with the Arg1174Gln mutation in this family. Although, hypoglycemia was not reported in patients with the Arg1152Gln mutation, these data support the possibility that inappropriately high serum insulin levels in the postprandial state may suppress hepatic glucose production even at low blood glucose levels and thereby cause hypoglycemia. Such a temporary imbalance between glucose output and uptake could be due to different effects of this mutation in various tissues, e.g., liver and muscle. Probably, this is mediated by a direct effect of insulin on the ~25% fully functional insulin receptors, but an effect of hyperinsulinism on the ~75% insulin receptors without tyrosine kinase activity in certain tissues cannot be excluded (27,28). In children with complete absence of functional insulin receptors (leprechaunism) paradoxical fasting hypoglycemia has been related to an effect of insulin on type 1 IGF receptors (31). However, type 1 IGF receptors disappear from the liver in adult life (32) and because both type 1 IGF receptors and insulin receptor/IGF-I receptor hybrids bind insulin with a much lower affinity than insulin receptors (33), it is unlikely that these receptors contribute further to hypoglycemia in adults assumed to have ~25% fully functional insulin receptors. Studies of mice (34) with tissue-specific knockout of the insulin receptor indicate a role for insulin signaling in both pancreatic β-cells and brain. Dysfunction of these tissues in Arg1174Gln carriers may also contribute to disturbances in glucose homeostasis.

In summary, we report a novel syndrome of autosomal-dominant hyperinsulinemic hypoglycemia with onset in adolescence to adulthood and linked to a mutation Arg1174Gln in the insulin receptor kinase, which has previously been associated with severe insulin resistance. These findings confirm the coexistence of severe postprandial hypoglycemia, impaired insulin clearance, and insulin resistance and support the hypothesis that mutations in the insulin receptor may affect insulin action differently in various tissues.

ACKNOWLEDGMENTS
This work was supported in part by grants from the Danish Diabetes Association, the Novo Nordisk Foundation, and the Institute of Clinical Research, Odense University Hospital.

We thank Klaus Brusgaard for the examination of the SUR1 and Kir6.2 genes, Michel Egel-Mitani and Knud Vad for the sequencing of the insulin gene, and Hans Elberg for assistance with linkage analysis. We gratefully acknowledge the superior technical assistance of Lone Hansen, Charlotte B. Olsen, and Karin Dyrgaard.

REFERENCES
HYPOGLYCEMIA ASSOCIATED WITH INSULIN RESISTANCE


