Am. J. Hum. Genet. 56:416–421, 1995

Homozygosity Mapping, to Chromosome 11p, of the Gene for Familial Persistent Hyperinsulinemic Hypoglycemia of Infancy

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Summary

Familial persistent hyperinsulinemic hypoglycemia of infancy (PHHI) is a rare, autosomal recessive disease of unregulated insulin secretion, defined by elevations in serum insulin despite severe hypoglycemia. We used the homozygosity gene-mapping strategy to localize this disorder to the region of chromosome 11p between markers D11S1334 and D11S899 (maximum LOD score 5.02 [$\theta = 0$] at marker D11S926) in five consanguineous families of Saudi Arabian origin. These results extend those of a recent report that also placed PHHI on chromosome 11p, between markers D11S926 and D11S928. Comparison of the boundaries of these two overlapping regions allows the PHHI locus to be assigned to the 4-cM region between the markers D11S926 and D11S899. Identification of this gene may allow a better understanding of other disorders of glucose homeostasis, by providing insight into the regulation of insulin release.

Introduction

Persistent hyperinsulinemic hypoglycemia of infancy (PHHI), also known as nesidioblastosis, is a glucose-metabolism disorder characterized by unregulated secretion of insulin and profound hypoglycemia. The pathophysiology of this disease remains obscure but is of considerable interest, as it may have important implications for the understanding of pancreatic β-cell development and regulation of insulin release. There is in vitro evidence that islet cells isolated from patients affected with PHHI have a decreased sensitivity to circulating glucose levels, analogous to that of fetal β-cells (Aynsley-Green et al. 1981; Kaiser et al. 1990), and are deficient in somatostatin (Aynsley-Green et al. 1981; Bishop et al. 1981; Rahier et al. 1984; Otonkoski et al. 1993). Histological evaluation of pancreatic specimens from affected patients has revealed combinations of ductulo-insular complexes, islet hypertrophy, and/or islet cell proliferation, all of which have been shown to be present, to a lesser degree, in the normal developing human pancreas (Jaffe et al. 1980; Gousdwaard et al. 1986; Rahier 1989). Hyperinsulinemic hypoglycemia also occurs in approximately one-third of neonates with the Beckwith-Wiedemann syndrome (Martinez-y-Martinez et al. 1992); it is unknown whether this syndrome and PHHI are variants of the same disease process. For individuals affected with PHHI, prompt treatment, with rapid resolution of hypoglycemia, is necessary to prevent permanent damage to the developing CNS (Jacobs et al. 1986; Bruining 1990). This treatment commonly involves use of drugs such as diazoxide and somatostatin analogues, which inhibit insulin secretion (Bruining 1990; Glaser et al. 1993; Thornton et al. 1993). Often near-complete pancreatectomy is required for definitive resolution of the hypoglycemia.

A number of familial cases of PHHI have been reported, and inheritance is in an autosomal recessive pattern (Woo et al. 1976; Becker et al. 1978; Mathew et al. 1988; Moreno et al. 1989; Glaser et al. 1990, 1994; Thornton et al. 1991; Woolf et al. 1991). The incidence of PHHI has been estimated at 1/50,000 live births in a randomly mating population (Bruining 1990). However, in a Saudi Arabian population, in which 51% of births occurred to parents who were first or second cousins, the incidence has been established as 1/2,675 live births (Mathew et al. 1988). This increased incidence in an inbred population is consistent with autosomal recessive inheritance.

When a condition with autosomal recessive inheritance is considered, the availability of affected children from consanguineous matings allows use of a strategy known as "homozygosity mapping" for localization of the disease gene. This approach is based on the premise that a rare disease in the affected progeny of a consanguineous mating is due to inheritance of two identical copies of the disease gene from the common ancestor, a situation termed "homozygosity by descent" (Lander and Botstein 1987). In addition, a relatively large region flanking the disease gene, calculated to be of a median length of 28 cM in first-cousin matings, will be homozygous by descent in most cases (Lander and Botstein 1987). Other regions of the genome

Received September 1, 1994; accepted for publication October 24, 1994.

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0002-9297/95/5602-0009$02.00

will also be homozygous by descent, but such regions will vary among affected children. For an informative, tightly linked marker, the calculations of Lander and Botstein revealed that three first-cousin matings, each with a single affected offspring, will provide a LOD score >3.0, the accepted threshold for linkage (Lander and Botstein 1987). Ten or more nonrelated nuclear families with affected pairs of siblings would be required to generate a similar score (Farrall 1993). Given the current availability of highly informative polymorphic markers closely and evenly spaced throughout the genome (Buetow et al. 1994; Gyapay et al. 1994; Matise et al. 1994), searching for regions of homozygosity in progeny of consanguineous matings provides an efficient strategy to localize rare autosomal recessive disorders when patient samples are in limited supply.

We used this homozygosity mapping strategy to localize the gene for familial PHHI in progeny of five consanguineous families of Saudi Arabian origin. Recently, Glaser et al. (1994) reported linkage of PHHI to chromosome 11p14-15.1, an assignment supported by our work. Taken together, our results and those of Glaser et al. (1994) narrow the region in which a gene important in the control of insulin secretion should be sought.

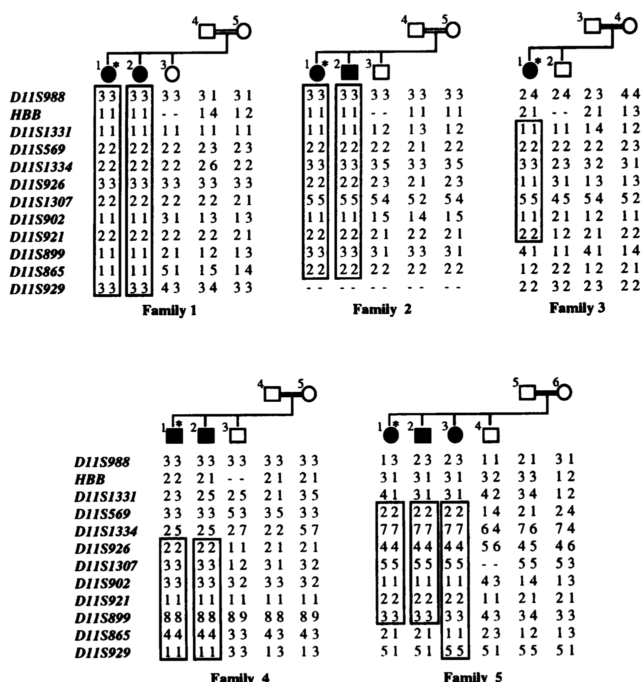

Figure 1 Simplified pedigrees and genotypes, in the region of homozygosity, of members included in the PHHI homozygosity mapping analysis. In families 1, 2, and 4, the parents are first cousins. In families 3 and 5, the parents are second cousins. Those affected individuals marked with an asterisk (*) have been reported elsewhere (Mathew et al. 1988). Dashes (-) indicate that genotype was not determined. Regions of homozygosity in affected children are boxed.

Subjects and Methods

Families

Five independent affected families were recruited from the patient population of the Arabian American Oil Company (ARAMCO) Hospital Medical Services Organization, in eastern Saudi Arabia, after institutional approval was received. The incidence of PHHI has been established in this Saudi Arabian population as 1/2,675 live births, and the rate of first- or second-cousin marriages as 51% (Mathew et al. 1988). As designated in figure 1, families 1, 2, and 4 are first-cousin matings, and families 3 and 5 are second-cousin matings. In each case, diagnosis of PHHI was based on established criteria (Aynsley-Green et al. 1981) and was made by one of the authors (P.M.M.). In all children analyzed, the disease was clinically manifested by age ≤3 d, except in the affected child of family 3, who presented at age 8 d. None of the patients analyzed were the infants of diabetic mothers, had hydrops fetalis, or exhibited features of the Beckwith-Wiedemann syndrome. All affected children had elevated insulin levels in the face of profound symptomatic hypoglycemia (glucose levels <20 mg/dl in all cases) and increased glucose utilization. A nearly complete (95%) pancreatectomy was required in all patients, for definitive resolution of hypoglycemia, except for those of family 4, whose parents refused to consent to the surgical procedure. These two patients were maintained on medical therapy with diazoxide for 5 and 8 years, respectively, with eventual resolution of the hypoglycemia. Histopathologic examination of all operative specimens revealed diffuse nesidioblastosis, which was confirmed with immunohistochemical studies. Previously reported children (Mathew et al. 1988) are identified in figure 1.

Typing of DNA Markers

The search for a region of consistent homozygosity in the genome of affected individuals was performed, using polymorphic repeat markers of heterozygosity >.7. All primer sequences for the polymorphic markers used have been published (Litt et al. 1993; Buetow et al. 1994; Gyapay et al. 1994) and are available in the Genome Data Base. Initial screening was performed with selected primer pairs from the Weber screening set (version 3a), which were obtained from Research Genetics and were spaced, on average, ~30 cM apart. Chromosome 11 was considered a candidate because of the well-described association between Beckwith-Wiedemann syndrome, which maps to the 11p15.5 region (Koufos et al. 1989; Ping et al. 1989; Weksberg et al. 1990, 1993; Richard et al. 1993), and hyperinsulinemic hypoglycemia (Pettenati et al. 1986; Martinez-y-Martinez et al. 1992; McKusick 1992).

Genomic DNA was extracted from whole blood, according to the manufacturer's instructions, using a model 341 nucleic acid–purification system with a double purge for PCR-quality DNA, from Applied Biosystems. Purified genomic DNA (40–60 ng) was amplified in a 25-μl PCR-

reaction mixture containing 250 μM each of dATP, dGTP, dCTP, and dTTP, 1 × PCR buffer (20 mM Tris-HCl, pH 8.4; and 50 mM KCl), 1.5 mM $MgCl_2$, 1–2 units of *Taq* DNA polymerase (GIBCO BRL), at 0.4 μM concentration of each primer pair, and 0.04 μM forward primer end-labeled with [^{32}P]λγ-ATP. After denaturation at 94°C for 4 min, amplification was performed with 30 cycles at 94°C for 40 s, 55°C for 30 s, and 72°C for 30 s, followed by a final extension at 72°C for 5 min (Perkin Elmer Thermal Cycler 480) or, if nonspecific amplification was a problem, with a "touch-down" protocol (Mellersh and Sampson 1993; Keats et al. 1994) composed of 10 cycles at 94°C for 40 s, annealing that began at 66°C and decreased by 1°C per cycle for 30 s, and at 72°C for 30 s, followed by 20 cycles at 94°C for 40 s, 56°C for 30 s, and 72°C for 30 s, followed by a final extension at 72°C for 2 min in a 60-well thermocycler with a hot-bonnet attachment (MJ Research). An equal volume of formamide-loading dye (95% formamide, 20 mM EDTA, 0.05% bromophenol blue, and 0.05% xylene cyanol) was added to each reaction mixture, and 4–5 μl were subjected to electrophoresis through a 7% denaturing sequencing gel, over 2–3 h. After the gels were dried, the DNA fragments were visualized by exposure for 2–24 h onto X-ray film.

Statistical Analysis of DNA Linkage

Two-point linkage analysis was carried out, using the LINKAGE program package (Lathrop et al. 1984). An autosomal recessive disease with 100% penetrance was assumed. The marker allele and haplotype frequencies were estimated from the data. However, results were not dependent on allele frequencies, as reanalysis with equal allele frequencies assumed produced equivalent results. The disease allele frequency in the Saudi Arabian population was derived from the study by Mathew et. al. (1988).

Table 1

Two-Point Linkage Analysis between PHHI Locus and Markers on Chromosome 11p

	LOD Score at θ =				
Marker	.00	.10	.20	.30	.40
D11S988	−∞	−.21	.07	.06	−.01
HBB	−∞	.99	.79	.45	.15
D11S1331	−∞	−.13	.27	.23	.09
D11S569	−∞	1.83	1.31	.73	.24
D11S1334	3.42	2.64	1.75	.96	.33
D11S926	5.02	3.60	2.30	1.19	.37
D11S1307	4.14	2.96	1.92	1.04	.37
D11S902	4.48	3.25	2.10	1.08	.33
D11S921	2.82	2.06	1.35	.72	.23
D11S899	3.68	2.87	1.93	1.06	.38
D11S865	−∞	1.95	1.41	.77	.24
D11S929	−∞	1.26	.93	.53	.19

Table 2

Two-Point Linkage Analysis between the PHHI Locus and Markers On Chromosome 11p, Disregarding Consanguinity in the Pedigrees

	LOD Score at θ =				
Marker	.00	.10	.20	.30	.40
D11S988	−∞	−.09	.17	.16	.06
HBB	−∞	.77	.60	.33	.10
D11S1331	−∞	−.07	.24	.19	.06
D11S569	−∞	1.22	.95	.54	.16
D11S1334	2.43	1.82	1.22	.65	.19
D11S926	2.91	2.17	1.43	.75	.22
D11S1307	2.31	1.67	1.06	.53	.14
D11S902	3.33	2.47	1.61	.82	.23
D11S921	2.01	1.53	1.04	.56	.17
D11S899	2.43	1.76	1.13	.57	.16
D11S865	−∞	1.22	.87	.46	.13
D11S929	−∞	.40	.37	.22	.07

Results

A region of homozygosity on the short arm of chromosome 11 was found in both affected children of family 1, with marker D11S988. Further genotype analysis in the region revealed that each of the 10 individuals affected with PHHI was homozygous at all four loci tested between, and including, D11S926 and D11S921 (fig. 1). These homozygous regions varied in length among the affected children and extended <35 cM. Flanking this region of consistent homozygosity, heterozygous genotypes were found at marker D11S1334 for the two affected children of family 4 (individuals 1 and 2) and at marker D11S899 for the affected child of family 3 (individual 1); thus, homozygosity mapping defined a region of <5 cM (Gyapay et al. 1994) extending between, but excluding, markers D11S1334 and D11S899.

We used two-point linkage analysis to assess linkage between PHHI and the loci within this region of homozygosity. LOD score calculations with consanguinity included in the analysis supported linkage for each of the six markers between, and including, D11S1334 and D11S899 (table 1). The maximum LOD score achieved was 5.02 ($\theta = 0$), with marker D11S926. When consanguinity was ignored in the analysis, statistically significant linkage was established only with marker D11S902, with a maximum LOD score of 3.33 ($\theta = 0$) (table 2). Marker D11S921 revealed two alleles in the individuals analyzed and was fully informative only in family 5; at least one parent was uninformative in the remaining families, and both parents were uninformative at this marker in family 4 (fig. 1). This is the most likely explanation for the lack of statistical significance for marker D11S921.

Because recombination appears to be an unusual event

Table 3

Haplotypes Constructed for Markers D11S926 through D11S899

Family and Haplotype	Marker Number[a]				
	D11S926	D11S1307	D11S902	D11S921	D11S899
1:					
A[b]	3	2	1	2	1
B	3	2	3	2	2
C	3	1	3	1	3
2:					
D[b]	2	5	1	2	3
E	1	2	4	2	3
F	3	4	5	1	1
3:[c]					
G	1	5	1	2	4
H	3	4	2	1	1
I	1	5	1	2	1
J	3	2	1	2	4
4:					
K	1	1	3	1	8
L[b]	2	3	3	1	8
M	1	2	2	1	9
5:					
N[b]	4	5	1	2	3
O	5	5	4	1	4
P	6	3	3	1	3

[a] The numbers represent qualitatively different alleles.
[b] Affected individuals in each family are homozygous for this haplotype.
[c] The single affected individual is heterozygous for haplotypes I and G.

in the region between markers D11S926 and D11S899, haplotypes were constructed using these markers and were tested for linkage. Sixteen haplotypes were found (table 3). In four of the five families, all affected individuals were homozygous for a haplotype, the structure of which differed in each family. In family 3, the single affected individual was heterozygous for two haplotypes, which differed only at marker D11S899. The maximum LOD score for linkage of the haplotypes with the disease locus was 5.58 ($\theta = 0$) (table 4).

Discussion

Homozygosity mapping, even using a limited number of families, provided a strategy to establish linkage of the rare disease familial PHHI to a region of <5 cM on chromosome 11p. Taking consanguinity into account in the linkage analysis substantially increased the LOD scores over those obtained without this consideration, confirming that knowledge of consanguinity provided additional linkage information.

Our results confirm and extend a recent report that mapped familial PHHI, in 15 nuclear families, to the interval between markers D11S926 and D11S928 (Glaser et al. 1994). That 6.6-cM region overlaps the 5-cM interval between markers D11S1334 and D11S899 described here. Comparison of the boundaries of these two overlapping regions allows the PHHI locus to be assigned to the 4-cM region between the markers D11S926 and D11S899, further narrowing the area in which the PHHI gene should be sought (fig. 2). In addition, 12 of the 15 multiplex families described by Glaser et al. were of Ashkenazi-Jewish origin. Therefore, taken together, these reports demonstrate genetic homogeneity, as linkage to this 11p region occurs in both a Saudi Arabian population and an Ashkenazi-Jewish population.

The Beckwith-Wiedemann syndrome has been localized to the region encompassing the HBB locus to 11pter on chromosome 11p (Weksberg et al. 1993). The PHHI locus was excluded at marker HBB and >13 cM centromeric to

Table 4

LOD Score Summary for Haplotypes Constructed from Markers D11S926 through D11S899

LOD Score at θ =				
.00	.10	.20	.30	.40
5.58	4.22	2.85	1.58	0.56

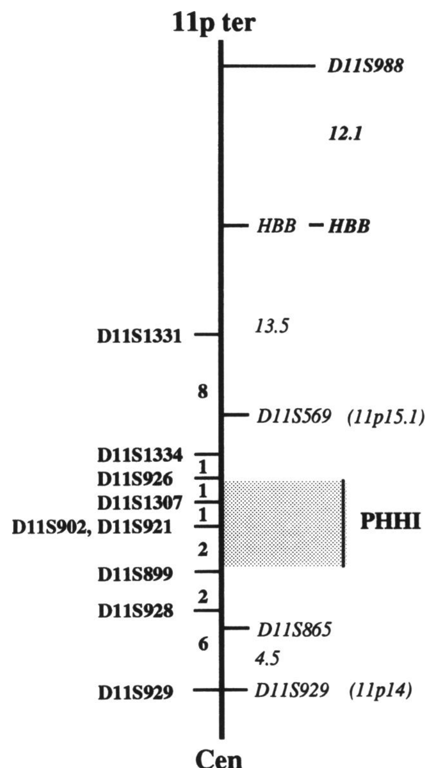

Figure 2 Genetic map of the chromosome 11p markers referred to in the PHHI homozygosity mapping analysis. The markers on the left, in boldface, are from the Généthon sex-averaged map (Gyapay et al. 1994). The shaded area, extending between, but not including, markers D11S926 and D11S899, represents the region to which PHHI can be assigned by combining the data reported here with those of Glaser et al. (1994). On the right, in italics, is the localization of markers D11S929, D11S865, D11S569, and HBB, according to the sex-averaged chromosome 11 map of Litt et al. (1993). Also on the right, in boldface italics, is the localization of D11S988 relative to HBB, according to the sex-averaged map of Buetow et al. (1994). Distances are represented in centimorgans.

it at marker D11S569 (LOD scores <−2), thereby excluding the region to which familial Beckwith-Weidemann syndrome has been mapped. Despite this, clarification of whether a relationship exists between these two disorders awaits identification of the genes responsible for each disease.

The gene responsible for PHHI is likely to have an important role in the regulation of insulin release and normal pancreatic β-cell development. Therefore, in addition to elucidating the pathophysiology of PHHI, identification of this gene may allow for a better understanding of other disorders of glucose homeostasis, such as some forms of diabetes mellitus.

Acknowledgments

We are grateful to the Saudi ARAMCO Medical Services Organization; to Robert F. Gagel and Alan Yahanda for helpful discussions and review of the manuscript; and to Jeff Fairman for technical advice. In addition, we thank all of the participating family members, without whom this study would not have been possible. P.M.T. was supported by U.S. Public Health Service award 1 T32 DK07696-01/05. This work was supported in part by an M. D. Anderson Cancer Center clinical research grant and NIH grant DK46660-01DDK. P.M.M. was employed by Saudi ARAMCO during the time the study was conducted and the paper was written.

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