Evidence for Further Heterogeneity

Maturity-onset diabetes of the young (MODY) is a heterogeneous single gene disorder characterized by non–insulin-dependent diabetes, an early onset and autosomal dominant inheritance. Mutations in six genes have been shown to cause MODY. Approximately 15–20% of families fitting MODY criteria do not have mutations in any of the known genes. These families provide a rich resource for the identification of new MODY genes. This will potentially enable further dissection of clinical heterogeneity and bring new insights into mechanisms of β-cell dysfunction. To facilitate the identification of novel MODY loci, we combined the results from three genome-wide scans on a total of 23 families fitting MODY criteria. We used both a strict parametric model of inheritance with heterogeneous and a model-free analysis. We did not identify any single novel locus but provided putative evidence for linkage to chromosomes 6 (nonparametric linkage [NPL] score 2.12 at 71 cM) and 10 (NPL score 1.88 at 169–175 cM), and to chromosomes 3 (heterogeneity LOD [HLOD] score 1.27 at 124 cM) and 5 (HLOD score 1.22 at 175 cM) in 14 more strictly defined families. Our results provide evidence for further heterogeneity in MODY. Diabetes 52:872–881, 2003

Maturity-onset diabetes of the young (MODY) is characterized by β-cell dysfunction, no requirement for insulin in the first years of the disease, an autosomal dominant mode of inheritance, and an early age at onset of diabetes (<25 years) (1). The identification of MODY genes has helped explain the phenotypic heterogeneity associated with the disorder. MODY is a genetically diverse subgroup of diabetes, and to date six distinct MODY genes have been identified: these encode the glycolytic enzyme glucokinase (GCK) (2,3), hepatocyte nuclear factor (HNF)-1α (4), HNF-1β (5), HNF-4α (6), insulin promoter factor (IPF)-1 (7), and NeuroD1/BETA2 (8). The relative distribution of MODY1–6 depends on the population investigated, although in all studies mutations in GCK and HNF1α are the two most prevalent forms (9–11). Mutations in each gene result in distinct clinical and physiological characteristics (12). Glucokinase mutations present with stable mild fasting hyperglycemia throughout life as a result of reduced glucose sensing in the β-cell (13). In contrast, mutations in the transcription factors (HNF-1α, HNF-4α, HNF-1β, and IPF-1) cause a progressive β-cell failure that may become severe (14).

In several British (9), French (10), and Scandinavian (11) cohorts, ~15–20% of the MODY families are not linked to already known genes, which suggests the existence of additional MODY gene(s). Several studies have tested a series of a priori candidate genes for a role in MODYX families or other early-onset type 2 diabetes. Although sequence variants have been identified in these genes, none have been conclusively shown to cause MODY or predispose to type 2 diabetes. Genes studied include HNF3β (15), Pax-4 (16), Nkx2.2 (17), NeuroD4 (18),
Neurogenin-3 (19,20), PPAR\textsubscript{\alpha} (21), ACVR2B (22), EIF2AK3 (23), HNF6 (24), and GLUT2 (25).

The identification of new MODY genes will enable further dissection of the underlying clinical heterogeneity. It will also bring new insights into potential mechanisms of \(\beta\)-cell dysfunction and highlight potential candidate pathways or genes that could be excellent candidates for polygenic type 2 diabetes. Finally, the identification of new MODY genes will allow diagnostic genetic testing with further implications for predictive and preventive issues or guidelines in clinical practice.

Within a European consortium (named GIFT: Genomic Integrated Force for Type 2 Diabetes), we collected 23 European MODY families on strict criteria. In this study, we report a combined statistical analysis using both parametric and nonparametric linkage (NPL) methods and exploiting raw data from three genome-wide screens conducted separately, which aimed to identify new loci for early-onset diabetes in the European population.

**RESEARCH DESIGN AND METHODS**

**Subjects.** We studied 23 families fitting strict MODY criteria of having at least one affected subject diagnosed with type 2 diabetes \(\geq 25\) years and at least two generations of type 2 diabetes. An additional three families with characteristics falling just outside these criteria were included (families FR624, FR743, and DK19). Table 1 gives the clinical criteria for all subjects. All families were of European ancestry except DUK149 (East-Asian Jamaican). These families underwent three separate genome-wide linkage studies; 5 families were genotyped in Malmo, Sweden, and have been reported as part of a previous study of young-onset families from Sweden and Finland (26), 7 were genotyped in Oxford and Exeter, U.K., and 14 families were genotyped in Lille, France. These families consisted of 236 individuals of which 125 were considered affected (105 with diabetes, 11 with impaired glucose tolerance [IGT], and 9 with impaired fasting glucose [IFG]). Figure 1 shows the pedigrees, and Table 2 summarizes the family structures. Of the affected subjects in the five MODY families from the Swedish scan, 65% had HLA risk alleles (DQB02 and/or 0302). The same criteria for a subject to be considered affected were used among all participating groups as follows:

1) Diabetes was defined according the World Health Organization 1999 criteria: fasting plasma glucose \(>7.0\) mmol/l, 2-h plasma glucose \(\geq11.1\) mmol/l, or a previous diagnosis of diabetes with ongoing treatment with oral agents and/or insulin (27).

**TABLE 1**

<table>
<thead>
<tr>
<th>Phenotype table for subjects included in the study</th>
</tr>
</thead>
<tbody>
<tr>
<td>26 Families</td>
</tr>
<tr>
<td>n (M/F)</td>
</tr>
<tr>
<td>n status: D/IGT/IFG</td>
</tr>
<tr>
<td>Age at study (years)</td>
</tr>
<tr>
<td>BMI (kg/m(^2))</td>
</tr>
<tr>
<td>Treatment (%diet/OHA/Ins)</td>
</tr>
</tbody>
</table>

Data are \(n\) and median (interquartile range). D, diabetes; Ins, insulin; OHA, oral hypoglycemic agent. Genotype data was available from an additional 15 subjects, but these were coded as unknown affection status in the analysis due to uncertainties regarding their affection status.
IFG was defined as fasting plasma glucose \( > 6.1 \) and 2-h blood glucose \( < 7.8 \) mmol/l, and IGT was defined as fasting plasma glucose \( < 7.0 \) mmol/l and 2-h blood glucose \( \geq 7.8 \) mmol/l. Patients with IFG or IGT were considered affected only if they had the same status on two or more consecutive occasions of an oral glucose tolerance test. All Swedish/Finnish subjects classified as IGT had a 2-h blood glucose \( \geq 8.5 \) mmol/l. If subjects only reached these values on a single test, they were classified as status unknown. There were 20 patients with IGT or IFG among the three sets; all have first-degree relatives with diabetes and are of high risk to develop diabetes later in life (28).

**Mutation screening.** Exclusion of mutations in known MODY genes was performed using one or more of the following methods: 1) linkage exclusion (logarithm of the odds [LOD] scores less than \(-2.0\)) using microsatellite markers flanking known MODY genes (microsatellites included D12S366, D12S321, D12S807, D12S820, D12S342, D12S1349, and D12S395 for HNF-1; D20S170, D20S96, D20S119, ADA microsatellite, D20S17, and D20S197 for HNF-4; GCK1, GCK2, D7S667, D7S519, and D7S2506 for glucokinase; D17S1788, D17S927, and D17S800 for HNF-1; and D13S221, D13S1254, and D13S289 for IPF1); 2) forward and reverse direct sequencing of all exons and intron-exon boundaries of known MODY genes according to previously described methods (11,29,30); and 3) automated fluorescent single-strand conformation polymorphism or denaturing high-performance liquid chromatography technique, followed by sequencing of variant profiles (31). The presence of a A3243G mitochondrial DNA mutation was either excluded by previously described genetic methods (11) or by the absence of a history of maternal diabetes and deafness. In addition, the recently described \( \beta \)-cell-

<table>
<thead>
<tr>
<th>Table 2: Family structure</th>
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<tbody>
<tr>
<td>Affected</td>
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<tr>
<td>----------</td>
</tr>
<tr>
<td>14 Families</td>
</tr>
<tr>
<td>26 Families</td>
</tr>
</tbody>
</table>

Data are median (minimum-maximum).
specific alternative promoter and associated exon1D of HNF-4α (resulting in the splice variant HNF-4α7) was excluded by forward and reverse direct sequencing using a proband from each family and previously described methods (32).

**Genome scan technology.** Genotyping data were pooled from three different genome scan studies, consisting of 14 (from France), 7 (from U.K.), and 5 (from Sweden) families.

**French genome-wide scan.** Genotyping was performed using 445 microsatellite markers with an average spacing of 10 cM. After electrophoresis on an ABI 377 DNA sequencer, semiautomated fragment sizing was performed by use of GENESCAN and GENOTYPER software (ABI). Each genotype was reviewed independently by two members of the research team to confirm the accuracy of allele calling. Incompatibilities were searched for with the PED-CHECK 1.1 program (33) and inconsistencies resolved. For nonresolvable errors, genotypes for families or subfamilies involved were deleted.

**U.K. genome-wide scan.** Genotyping was performed using 400 dinucleotide repeat markers with an average spacing of 10 cM. Electrophoresis was performed on a MegaBACE 1000 capillary array sequencer (Molecular Dynam-
FIG. 2—Continued.
ics; Amersham Pharmacia Biotech, Sunnyvale, CA). We reviewed and manually edited only those genotypes receiving a quality score <2.0 (of a possible 10), indicating a lower confidence in the automated genotype provided by the software. Mendel checking (testing for co-dominant inheritance of marker alleles) was performed with PedCheck version 3.0 (33). Before linkage analysis, Mendel conflicts due to misinterpretation of traces were resolved through rescoring in Genetic Profiler. The Swedish Finnish Genome-Wide Scan has been described in detail elsewhere (26).

Strategy of data pooling. We analyzed our data by generating combined marker maps and combining raw genotyping data from the three different genome-wide scans as recommended (34).

Marker maps were created using the Marshfield Marker map and subsequently the obtained marker order was tested in MAP-O-MAT, which is a web-based program that runs CRI-MAP on Centre d’Etude du Polymorphisme Humain (CEPH) families; for details, see the Appendix of this article. A total of 757 unique markers were put into a map with an average distance of 4.7 cM between unique markers (note that for any given family average spacing between markers remained at ~10 cM, as no further genotyping was performed). Kosambi map distances were used. Markers used in more than one genome screen were coded as two separate markers with 0.01 cM distance between them.

Statistical analysis. All genotype data were rechecked for Mendelian segregation using the PEDMANAGER software (M.P. Reeve and M.J. Daly, personal communication). As the extent of genetic homogeneity was largely unknown, we decided ad hoc that four analyses should be performed in our pooled data sets. Two groups of families were used: all 26 families and a subset of 14 families fitting more strict criteria for autosomal dominant inheritance. These more strict minimum criteria were as follows: two members with age at diagnosis at <25 years and two consecutive generations of diabetes or one member with an age of diagnosis at 25 years and three consecutive generations of diabetes. Families fitting this criteria but including bilineal inheritance were also excluded. The subset of 14 families were FR30, FR538, FR694, FR725, IT884, IT485, ES7, SW1168, SW20631, SW20655, SW20663, DUK149, DUK89, and DUK156. These two sets of 14 and 26 families were pooled data sets. Two groups of families were used: all 26 families and a subset of 14 families from the Swedish genome scan, but none of these quite reached the empirical level for declaring suggestive linkage. HLOD scores using the previously described parametric model for MODY reached a maximum of 0.81 at 80 cM for chromosome 6 and 0.38 at 174 cM for chromosome 10.

RESULTS

Figure 2 shows the multipoint NPL Z-scores for all 26 families, the multipoint HLOD scores for the subset of 14 strictly defined families, and the peak multipoint LOD scores >1.0 for individual families. In the set of 14 families with the strictest MODY criteria, we extracted on average 60% of the inheritance information.

Analysis of all 26 families. The analysis of all 26 families revealed NPL Z-scores exceeding the nominally significant threshold of P = 0.05 on chromosome 6 (69–82 cM from pter; GATA29C09-D6S460, max NPL score 2.18 at 80 cM) and chromosome 10 (169–175 cM from pter; D10S212-D10S109 max NPL score 1.90 at 172 cM), although neither of these quite reached the empirical level for declaring suggestive linkage. HLOD scores using the previously described parametric model for MODY reached a maximum of 0.31 at 80 cM for chromosome 6 and 0.38 at 174 cM for chromosome 10. There was a high frequency of affected subjects with high-risk HLA alleles in the five families from the Swedish genome scan, but none of these families showed evidence for linkage to the HLA region. There were no differences in phenotypic characteristics (age at onset, BMI, or treatment) between families contributing to different loci. In addition, we analyzed these 26 families by individual scan, but this did not result in any HLOD scores reaching genome-wide significance.

Analysis of 14 strict criteria families. The analysis of the 14 families defined using more strict criteria and using the previously described parametric model for MODY

FIG. 2—Continued.
TABLE 3

<table>
<thead>
<tr>
<th>Individual family maximum LOD score</th>
<th>within the four regions of linkage</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chr. 3</td>
<td>Chr. 5</td>
</tr>
<tr>
<td>D3S1282-D3S2459</td>
<td>D3S400-D5S498</td>
</tr>
<tr>
<td>FR30</td>
<td>2.24</td>
</tr>
<tr>
<td>DUK149</td>
<td>1.55</td>
</tr>
<tr>
<td>SW20663</td>
<td>0.98</td>
</tr>
<tr>
<td>FR725</td>
<td>1.21</td>
</tr>
<tr>
<td>FR4912</td>
<td></td>
</tr>
<tr>
<td>SW20655</td>
<td>0.65</td>
</tr>
<tr>
<td>SW10110</td>
<td>0.71</td>
</tr>
<tr>
<td>FR743</td>
<td></td>
</tr>
<tr>
<td>DUK03</td>
<td></td>
</tr>
</tbody>
</table>

revealed a maximum HLOD score of 1.81 at 117 cM on chromosome 3 (HLOD >1.0, α = 0.36 from 91–122 cM; D3S1287-D3S2459). The only other HLOD >1.0 was observed on chromosome 5 (HLOD 1.37, α = 0.50 at 172 cM; D5S400-D5S498). NPL Z-scores for these 14 families exceeding the nominally significant threshold of P = 0.05 were obtained on chromosome 3 (HLOD >1.0), chromosome 6 (HLOD >1.0, maximum Z-score 2.84 at 102 cM), chromosome 10 (HLOD >1.0, maximum Z-score 2.04), chromosome 6 (70–75 cM, maximum Z-score 2.07), and chromosome 10 (169–175 cM, maximum Z-score 1.61), although only one of these, on chromosome 3, exceeded the empirical Z-score of 2.8 for declaring suggestive linkage. The addition of four extra markers (D3S3683, D3S1303, D3S1267, and D3S1269) in the chromosome 3 region reduced the HLOD to 1.27 at 124 cM and the NPL linkage score to 2.78 at 97 cM.

The maximum LOD score possible for an individual family using the parametric model described was 2.24 (family FR30), and therefore none of the families in our study reached the required LOD score of ≥3.0 for declaring significance. Table 3 gives details of the families contributing to the evidence for linkage at each of the peaks identified in the genome scan. In our study, two families were capable of exceeding LOD scores of 2.0 and a further 13 families were capable of exceeding LOD scores of 1.0. We did not observe any significant clustering of individual family LOD scores (if so this would have resulted in significant HLOD scores), but a few results from individual families are worth noting (Table 4). Two of the three largest families FR30 and DUK149 are linked to chromosome 3 with their maximum LOD scores; FR30 has a maximum LOD of 2.24 at 106 cM, and DUK149 has a maximum LOD of 1.55 at 147 cM. There was some degree of overlap between these results, but the addition of four extra markers, while narrowing the region of overlap of multipoint linkage scores, revealed that no single marker showed evidence for linkage to both families. In addition, two families, FR571 and DUK32, have LODs >1.0 at 10 cM from pter of chromosome 22.

DISCUSSION

We have performed the first large genome-wide scan of MODY families not linked to any of the six known genes. Our results are consistent with further heterogeneity ex-

TABLE 4

<table>
<thead>
<tr>
<th>Family</th>
<th>Peak multipoint LOD score*</th>
<th>Chromosome</th>
<th>Position (cM from pter)</th>
<th>Nearest marker</th>
</tr>
</thead>
<tbody>
<tr>
<td>FR725 (2.45)</td>
<td>1.74</td>
<td>2</td>
<td>27</td>
<td>D2S168</td>
</tr>
<tr>
<td>FR743 (1.54)</td>
<td>1.36</td>
<td>2</td>
<td>186</td>
<td>D2S335</td>
</tr>
<tr>
<td>FR30 (2.24)</td>
<td>2.24</td>
<td>3</td>
<td>106</td>
<td>D3S3681</td>
</tr>
<tr>
<td>DUK149 (1.58)</td>
<td>1.55</td>
<td>3</td>
<td>145</td>
<td>D3S1292</td>
</tr>
<tr>
<td>FR571 (1.24)</td>
<td>1.23</td>
<td>9</td>
<td>85</td>
<td>D3S283</td>
</tr>
<tr>
<td>FR253 (1.50)</td>
<td>1.46</td>
<td>1</td>
<td>199</td>
<td>D1S238</td>
</tr>
<tr>
<td>SW1168 (1.27)</td>
<td>1.26</td>
<td>17</td>
<td>53</td>
<td>D17S1293</td>
</tr>
<tr>
<td>DUK32 (1.45)</td>
<td>1.33</td>
<td>22</td>
<td>10</td>
<td>D22S539</td>
</tr>
</tbody>
</table>

*Computed using GH 2.0 and by assigning genotypes to family members to mimic complete segregation: a gene frequency of 0.0095 was used and the frequency of the linked allele was set at 0.01 in a single point analysis. The parametric model previously used to identify the MODY3 locus was used (36).
117 cM), chromosome 5 (~173–175 cM), chromosome 6 (~70–75 cM), and chromosome 10 (~169–175 cM). Family FR30 was part of a previous genome-wide study using different markers that led to the mapping of the MODY3/HNF1α gene on chromosome 12q22 (38); family FR30 had a positive individual LOD score (Z >2.0) at D14S72 (the current genome-wide scan used a new optimized set of markers that by chance did not include this marker). A haplotype analysis with additional markers in the more centromeric region on chromosome 14q11 pointed out four markers cosegregating with diabetes in this family (39). In the current genome scan the closest marker (D14S261) to this region did not reveal any noteworthy evidence for linkage because of lack of complete informativeness within the FR30 pedigree. This indicates that with a 10-cM genome scan and uninformative markers in individual families, linkage may be missed.

To test the hypothesis of genetic heterogeneity within all families, we have also considered taking out the two large families showing linkage to chromosome 3p with their maximum LOD scores and repeated both parametric and NPL analyses in order to search for any other chromosomal location with a linkage peak rise. Only one HLOD >1.0 near the start of chromosome 12p came up in the 24 families set (after excluding FR30 and DUK149).

A search of the locations of known β-cell transcription factors did not reveal any close correlation between locations and linkage results in individual families. The exception to this was family FR253, which was linked to the region of chromosome 1 containing the LMX1 (LIM-homebox transcription factor 1) gene (LOD 1.48). LMX1 (OMIM: 600298) binds to the insulin promoter to stimulate insulin gene transcription (40). Family FR571 was linked to the region of chromosome 20 harboring the HNF-3β and Nkx2.2 genes, but the coding regions of these genes have already been excluded in this family (15). Family SW1168 was linked to the HNF-1α/NIDDM2 locus (4,36,41) with its maximum LOD score (1.27). It is possible that this family has a mutation in an unknown regulatory element of HNF-1α or another mutation mechanism that has not been identified using conventional mutation screening techniques.

No other genome-wide scans of MODY families have been published (with the exception of the five Swedish families in this study that were part of a young-onset type 2 diabetes genome-wide scan) (26), and so we cannot look for regions of linkage overlapping with ours using the same phenotype. Additional early-onset families with type 2 diabetes have been identified (42,43), and our regions will provide starting places for any future genome-wide screens of MODYX or early-onset type 2 diabetic families. One set of families of relevance to our study is the 32 multigenerational families with diabetes segregating in an autosomal dominant pattern identified by Doria et al. (43). An analysis of 90 cM of chromosome 12 using these families identified linkage (NPL Z-score 2.9) to chromosome 12q15 that was explained predominantly by four multigenerational families (44). We did not observe any notable evidence for linkage to this region; in the analysis of all 26 families the NPL Z-scores in this region were all negative and the HLOD 0.0. In the analysis of the subset of 14 families, the NPL Z-score was 0.48 at 88 cM (P = 0.30), and HLOD scores were 0.0.

Several genome-wide screens have been completed in common type 2 diabetes, and some of these have focused on younger-onset families or stratified results by age at onset. These include studies in North European populations and have identified, through ordered subset analysis (computation of linkage in increasing numbers of families ranked according to a potential confounding phenotype, such as age at onset or BMI) or stratification, regions linked to type 2 diabetes in patients diagnosed at an earlier age.

These include regions on chromosome 4 and 20 (45) in Ashkenazi Jews, chromosome 6 in Finnish subjects ranging in age at diagnosis from 29 to 44 years (46), chromosome 5 in Swedish subjects (47), chromosome 3 in French subjects diagnosed with type 2 diabetes before 45 years of age (48), chromosomes 5 and 22 in U.K. subjects from families where the average age at diagnosis was <45 years (49), and chromosomes 1, 5, 7, 8, 11, 15, and 21 in Swedish/Finnish subjects (26). Although it is not clear from all these studies the exact ages at diagnosis, most appear to represent subjects diagnosed under the age of 45 years. These regions may therefore be of some relevance to our study (interquartile range of diagnosis 21–49 years). Of these regions of interest, we have some degree of overlap with the U.K. study and the Lindgren et al. study. The region identified on chromosome 5 in the U.K. sib-pair study (maximum NPL 2.46 at 171 cM) coincides with our chromosome 5 region (maximum NPL 1.83 and HLOD 1.22 at 175 cM in 14 families). In addition, this region also has a maximum NPL score of 2.4 at 162 cM in 26 Swedish/Finnish young-onset families, although these 26 families include the five analyzed in our combined scan. For the chromosome 22 region (maximum NPL 2.63 at 22 pter), we observed an NPL score of 1.59 at 10 cM in all 26 families. The families in our study showing positive NPL scores in these regions are a mixture of French and U.K. Although this overlap of results should be interpreted with caution, as multiple tests have been performed they will be of interest if replicated in further studies of young-onset subjects.

In conclusion, using data from three genome-wide scans of MODYX families, we have not identified a single major novel locus but provided evidence for further heterogeneity in this important form of diabetes in childhood and in young adults.

ACKNOWLEDGMENTS

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We are grateful to the patients and their families for their participation in our efforts to study the causes of MODY. We thank Marju Orho-Melander from the Swedish team. From the French team, we thank Philippe Gallina and Dr. Christine Bellamé-Chantelot for their contribution to family collection. From the U.K. team, we thank Amer- sham Parmacia Biotech for the funding of part of the study and acknowledge the MegaBACE Genotyping R&D team, especially David Shen, for their work in the early stages of this project. We also thank our colleagues at the Wellcome Trust Center for Human Genetics for their support, espe-
cally the Genotyping Core, Dr. Helen Williamson, who
donated all PCR primers, and Prof. Mark McCarthy. Sa-
mantha Mason and Dr. Simon Fisher gave advice on
specific PCR protocols.

APPENDIX

Electronic-database information.

Accession numbers and URLs for data in this article are as
follows:

1. ONline Mendelian Inheritance in Man (OMIM), http://
w w w . n c b i . n l m . n i h . g o v / o m i n / for MODY1 [MIM#601283],
MODY2 [MIM#601407], MODY3 [MIM#600496], MODY4
[MIM#151690], MODY5 [MIM#100640], and MIDD
[MIM#229300].

The GENEHUNTER software is found at Whitehead
Institute for Biomedical Research/MIT Center for Genome
software/gzh2/.

More detailed information about the GIFT collaboration can be
found at http://www.gift.med.ic.ac.uk, and a
description of the GIFT database can be found on http://

Marker map order was obtained from http://research.
marshfieldclinic.org/genetics/Map_Markers/mapmaker/
MapFormFrames.html, and marker order and distances
were tested in MAP-O-MAT, http://compgen.rutgers.edu/
mapomat and http://www.ncbi.nlm.nih.gov/cgi-bin/
Entrez/ncbi.

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Froguel P, Bell GI: Mutations in the hepatic nuclear factor 1 alpha gene in

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Bell GI: Mutation in hepatocyte nuclear factor-1b gene (TCF2) associated

Signorini S, Stoffel M, Bell GI: Mutations in the hepatocyte nuclear factor
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Re...


