SUPPLEMENTARY DATA

Summary of Clinical Issues in MODY

I. *Definition*
   a. A genetically heterogeneous disorder due to mutations in the heterozygous mutations in at least 11 different genes
   b. Onset of diabetes early in life: childhood, adolescence, young adulthood
   c. Autosomal dominant inheritance
   d. Primary defect in insulin secretion [in MODY1 (*HNF4A*) there may also be transient neonatal hyperinsulinemia and hypoglycemia]

II. *Phenotypic Expression and Natural History of MODY*
   a. Recognition at a young age:
      i. Often under age 25 years
      ii. 7 – 13 years or younger, if sought by oral glucose tolerance testing in younger generations
   b. Not progressive or progressive:
      i. Non-progressive hyperglycemia from birth (MODY2)
      ii. Hyperglycemia responsive to diet and/or oral anti-hyperglycemic agents for years to decades (MODY1 and MODY3)
      iii. May progress to insulin-requiring diabetes (not insulin-dependent or ketosis-prone with rare exception) (MODY1 and MODY3)
      iv. May progress rapidly from young age onward (MODY1 and MODY3)

III. *Distinguishing Clinical Characteristics Between MODY and Type 2 Diabetes*
   a. Mode of inheritance
      i. MODY: Monogenic, autosomal dominant
      ii. Type 2 diabetes: Polygenic
   b. Age of onset or diagnosis
      i. MODY: Childhood, adolescence, usually <25 years, if looked for
      ii. Type 2 diabetes: Usually 40-60 years; however, may occur in obese adolescents
   c. Family history
      i. MODY: Multi-generational
      ii. Type 2 diabetes: Rarely multi-generational
   d. Penetrance
      i. MODY: 80-95 %
      ii. Type 2 diabetes: Variable (10-40 %)
   e. Body habitus
      i. MODY: Not obese, occasional obesity in some families
      ii. Type 2 diabetes: Usually obese
   f. Dysmetabolic syndrome
      i. MODY: Absent
      ii. Type 2 diabetes: Usually present

IV. *Clinical Implications of Genetic Heterogeneity of MODY*
   a. MODY1 and MODY3:
      i. Progressive clinical course in terms of hyperglycemia, with increasing treatment requirements.

ii. Development of microvascular, macrovascular and neuropathic complications of diabetes in a frequency similar to that seen in type 2 diabetes, if matched for duration and degree of hyperglycemia
Most likely determined by the degree of glycemic control

b. MODY2:
   i. Mild to moderate elevation in plasma glucose levels from birth
   ii. Not progressive
   iii. Complications rare
c. MODY5:
   i. Progressive clinical course in terms of hyperglycemia, with increasing treatment requirements
   ii. Presence of renal cysts and other renal abnormalities as well as genital abnormalities and abnormal liver function
d. Molecular genetic diagnosis has important implications for clinical management of MODY subtypes and prognosis

V. MODY: Clinical Strategies

a. Genetic testing and diagnosis are feasible for young subjects at risk for MODY, and have important prognostic implications
b. Genetically susceptible subjects can be counseled to have periodic evaluation of glucose tolerance beginning at a young age
c. Attainment of normoglycemia beginning at the time of appearance of metabolic abnormalities can prevent vascular and neuropathic complications

VI. Estimated Prevalence of MODY

a. 1% - 2% of all diabetic patients

The above summary addresses MODY due to mutations in *HNF4A* (MODY1), *GCK* (MODY2), *HNF1A* (MODY3) and *HNF1B* (MODY5), the most common genetic causes of MODY.

SUPPLEMENTARY DATA

Supplementary Table 1. Genetic causes of MODY (adapted from Online Mendelian Inheritance in Man - http://www.ncbi.nlm.nih.gov/omim?term=MODY)

MODY subtype	Gene name	Gene symbol	Gene function	Other
MODY1	Hepatocyte nuclear factor-4α	*HNF4A*	Transcription factor	Macrosomia and neonatal hypoglycemia
MODY2	Glucokinase	*GCK*	Glycolytic enzyme	
MODY3	Hepatocyte nuclear factor-1α	*HNF1A*	Transcription factor	
MODY4	insulin promoter factor 1/ Pancreas-duodenum homeobox protein 1	*IPF1/PDX1*	Transcription factor	
MODY5	Hepatocyte nuclear factor-1β	*HNF1B*	Transcription factor	Renal cysts and diabetes
MODY6	Neurogenic differentiation 1	*NEUROD1*	Transcription factor	
MODY7	Kruppel-like factor 11	*KLF11*	Transcription factor	
MODY8	Carboxyl-ester hydrolyase/Bile salt-stimulated lipase	*CEL*	Lipase	MODY with exocrine dysfunction
MODY9	Paired box gene 4	*PAX4*	Transcription factor	
MODY10	Insulin	*INS*	Insulin	
MODY11	Tyrosine kinase, B-lymphocyte specific	*BLK*	Transcription factor	

SUPPLEMENTARY DATA

Supplementary Figure 1. The RW pedigree modified from references 24, 26 and 35. This partial pedigree focuses on the proband (III-5 and noted with arrow) and his descendants. Genetic studies have shown that individuals II-1 and III-2 also transmitted the *HNF4A* mutation (Q268X) responsible for MODY1. Individuals shown in red have MODY1, those shown in black could have MODY1 or type 2 diabetes (genetic studies of the descendants of III-3 and III-6 indicate that they likely had type 2 diabetes), those shown in green have inherited the Q268X and have impaired glucose tolerance, and those shown in blue have inherited the Q268X mutation but have not yet developed diabetes because of their young age. One individual (V-10) has type 1 diabetes (shown in yellow). The *HNF4A* genotype (if known) is shown below the symbol: N/N and N/M (N/Q268X). The age-at-diagnosis of diabetes or age at last test is shown at the top left of the symbol. All of the individuals in generations I-III are deceased as are individuals IV-1 and -8. The complications observed in members of generation III are shown: MI, myocardial infarction; PVD-A, peripheral vascular disease and amputation; R, retinopathy; R-B, retinopathy and blindness; PVD-A-G, peripheral vascular disease, amputation and gangrene; Np, nephropathy; and N, neuropathy. The repository numbers assigned to immortalized cells lines stored at the Corriell Institute for Medical Research are shown below the symbol.