Assessment of highly sensitive C-Reactive Protein levels as diagnostic discriminator of Maturity Onset Diabetes of the Young due to *HNF1A* mutations
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Online Appendix
Supplementary Subjects and methods

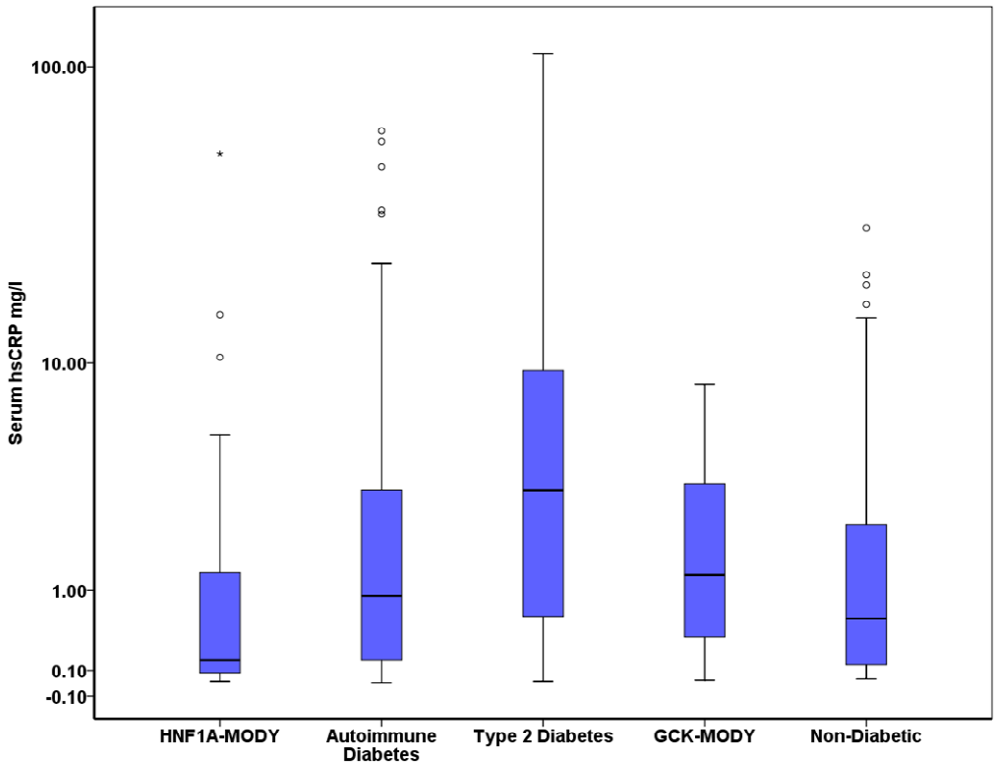
Subjects were ascertained in Oxfordshire and Berkshire, UK and those with MODY from these and other counties in the South of England. The MODY samples comprise subjects with a mutation (confirmed by sequencing in a certified UK diagnostic centre) in either *HNF1A* (n=31 from 19 families) or *GCK* (n=24 from 11 families). The individuals with MODY were recruited from patients known to our clinical service, family members of those patients or patients from other hospitals identified by the Genetic Diabetes Nurse network. Twenty seven of the HNF1A-MODY subjects had diabetes, one had IGT and 3 were normoglycaemic. Twenty-nine of the HNF1A-MODY cases carry known pathogenic mutations: the remaining two have novel missense alleles which have not been identified in >400 ethnically matched normal chromosomes. Cosegregation analyses are ongoing, but the phenotype provides strong reassurance that these are pathogenic: the first patient was diagnosed with apparent type 1 diabetes 10 years previously, but was able to stop insulin, the other has a 30 year history of type 2 diabetes controlled for 26 years on oral agents, and a father diagnosed with diabetes at age 20. OGTT data were available on the non-diabetic HNF1A-MODY mutation carriers.

The remaining diabetic subjects were selected from the Young Diabetes in Oxford (YDX) study, comprising subjects diagnosed with diabetes ≤ 45 years of age recruited from either primary (n=84) or secondary (n=471) care. We included individuals with classical type 1 diabetes, (n=275), Latent Autoimmune Diabetes of Adulthood (LADA, n=41) and type 2 diabetes (n=240). Type 1 diabetes was defined as permanent insulin treatment since diagnosis with additional evidence of severe β-cell dysfunction (C-peptide ≤0.09nmol/l or HOMA %B < 10%), positive Glutamic acid decarboxylase antibodies (>14 WHO units/ml) or both. LADA was defined as diabetes diagnosed after 18 years of age with positive GAD antibodies where there had been no requirement for insulin treatment within 3 months of diagnosis. Diabetic subjects not requiring permanent insulin treatment at diagnosis and with negative GAD antibodies were classified as having type 2 diabetes. Subjects in this last category either did not meet clinical criteria for MODY diagnostic testing or had been tested and were negative for mutations in *HNF1A*, *HNF4A* (n=18) or *GCK* (n=7).

Non-diabetic subjects (n=198) were recruited from the Oxford Biobank (http://www.oxfordbrc.org/research/chronic-disease-cohorts/102/), a population-based collection of healthy adults aged 30-50 recruited for translational medicine studies.
One HNF1A-MODY subject, 5 type 1 diabetic subjects, 5 LADA subjects and 35 of the type 2 diabetic subjects were of non-European ethnicity (20 Asian, 18 Black, 1 Chinese, 7 mixed or other).

For all subjects, clinical details, anthropometry and blood samples were collected. The study was approved by the Oxfordshire Local Research Ethics Committee and all subjects gave informed consent.

Supplementary Figure 1:
Box plots of all hsCRP values. Box shows median and interquartile ranges, whiskers show adjacent values (the most extreme data points not considered outliers) and symbols are outliers. HsCRP levels are plotted on a $\log_{10}$ scale.



Supplementary Table 1
Calculations of sensitivity and specificity for the listed criteria for identifying HNF1A-MODY cases from type 2 diabetes diagnosed ≤45 years based on our dataset.

Criteria Used	Sensitivity	Specificity
hsCRP ≤1 mg/l	79%	62%
hsCRP ≤0.4 mg/l	71%	77%
hsCRP ≤0.2 mg/l	52%	89%
Diabetes diagnosed up to 25 yrs of age, 2 generations diabetes	58%	94%
Diabetes diagnosed up to 30 yrs of age	71%	76%
Diabetes diagnosed up to 25 yrs of age, 2 generations diabetes OR hsCRP ≤0.2 mg/l	79%	83%
Diabetes diagnosed up to 30 yrs of age OR hsCRP ≤0.2 mg/l	88%	75%

Supplementary Table 2
Calculations of positive test rate and detection rate for identifying HNF1A-MODY cases from apparent type 2 diabetes using the sensitivities and specificities derived from the study

Criteria Used	% of apparent type 2 diabetes subjects positive for criteria	Pick-up rate of HNF1A-MODY cases from those positive for criteria	% of HNF1A-MODY cases missed (1-sensitivity)
hsCRP ≤ 1 mg/l	40%	8%	21%
hsCRP ≤ 0.4 mg/l	25%	11%	29%
hsCRP ≤ 0.2 mg/l	13%	17%	48%
Diabetes diagnosed up to 25 yrs of age, 2 generations diabetes	8%	29%	42%
Diabetes diagnosed up to 30 yrs of age	24%	11%	29%
Diabetes diagnosed up to 25 yrs of age, 2 generations diabetes OR hsCRP ≤ 0.2 mg/l	20%	16%	21%
Diabetes diagnosed up to 30 yrs of age OR hsCRP ≤ 0.2 mg/l	28%	13%	12%