Online Appendix

Rationale for the selection of *HNF1A, HNF4A*, and *GCK*, for testing in the SEARCH population

We tested for MODY mutations in the three most common genes which account for approximately 99% of all MODY that is not associated with syndromic features.[1] There is strong evidence from our and other series that testing other genes would not add significantly to the number of cases that would be found; this evidence is detailed below. ***IPF1* mutations** were initially described in a single family [2] and have not been described in any other MODY families since, despite testing in large series of French, Japanese and UK MODY subjects.[1,3-4] ***HNF1B* mutations** are very rare in MODY [5] and in all the cases found in the UK series,[1] the patients had renal disease (usually renal cysts) and other features of a multi-system syndrome including female genital malformations, hyperuricemia, pancreatic atrophy, and abnormal liver function tests.[6] ***NeuroD1* mutations** are very rare with only one convincing description of a mutation in an Icelandic pedigree;[7] mutations in this gene have not been associated with MODY in large international series.[8-10] **Mutations in *CEL*** result in exocrine pancreatic dysfunction as well as MODY and have only been seen unequivocally in 2 MODY families,[11] despite testing in 240 MODY families in which the genetic etiology is unknown.[12] In summary, the extreme rarity of mutations in the genes not tested - even in well selected series of MODY patients - means that testing them in this large unselected population of children with diabetes would be extremely unlikely to result in any additional cases.

In addition, HNF1A, HNF4A and GCK are the only three MODY subtypes for which the detection of MODY will result in a change of treatment, as there are specific treatments that apply to persons with these three MODY genes but not to persons with any of the very rare subtypes. On the basis of the prevalence and the implications of identifying persons with these mutations, the European clinical practice guidelines recommend that MODY genetic testing be performed only for these three subtypes unless there are clear non-diabetes related features suggesting other very rare causes.[13] Therefore in clinical diagnostic laboratories, we do not test for the other genes in cases of diabetes alone.

Online references

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Table 1: *HNF1A*, *HNF4A* and *GCK* mutations identified by genetic testing in SEARCH

Patient	Mutation (Nucleotide description)	Novel missense mutation or in-frame deletion
HNF1A		
1	G31D (c.92G>A)	
2	G31D (c.92G>A)	

3	G52A (c.155G>C)	Yes
4	R54X (c.160C>T)	
5	E59X (c.175G>T)	
6	T82M (c.245C>T)	
7	P112L (c.335C>T)	
8	R114H (c.341G>A)	
9	R159W (c.475C>T)	
10	Q182X (c.544C>T)	
11	R200Q (c.599G>A)	
12	R203H (c.608G>A)	
13	I242T (c.725T>C)	Yes
14	S249P (c.745T>C)	
15	V259F (c.775G>T)	
16	R263C (c.787C>T)	
17	W267S (c.800G>C)	Yes
18	P291Q (c.872C>A)	Yes
19	P291fsinsC (c.872dup)	
20	P291fsinsC (c.872dup)	
21*	P291fsinsC (c.872dup) and *HNF4A* R127W (c.379C>T)	
22**	Y322C (c.965A>G) (+) L389V (c.1165T>G)	
23	G375V (c.1124G>T)	Yes
24	L502V (c.1504C>G)	Yes
25	R583Q (c.1748G>A)	
26	K226del (c.676delAAG)	Yes
HNF4A		
1	R80Q (c.239G>A)	
2	R104fsinsAGdelC(c.310delCinsAG)	
3	R127W (c.379C>T)	
4	R168Q (c.503G>A)	Yes
5	L260P (c.779T>C)	Yes
6	E276X (c.826G>T)	
7	V395I (c.1183G>A)	Yes
GCK		
1	K15M (c.44A>T)	Yes
2	V62A (c.185T>C)	
3	I130T (c.389T>C)	
4	V182M (c.544G>A)	
5	G178E (c.533G>A)	
6	M202T (c.605T>C)	
7	V226M (c.676G>A)	
8	R250C (c.748C>T)	
9	V335fsdelG (c.1003delG)	
10	A387E (c.1160C>A)	
11	V389D (c.1166T>A)	
12	IVS4-2A>T (c.484-2A>T)	
13	R422L (c.1265G>T)	Yes
14	G385fsdelG (c.1155delG)	

*Mutations in both *HNF1A* and *HNF4A*; **Two different mutations in *HNF1A*