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RESEARCH LETTER

S. S. Fajans · G. I. Bell

# Phenotypic heterogeneity between different mutations of MODY subtypes and within MODY pedigrees

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To the Editor:
Contrary to currently held views [1], different mutations within the same MODY gene may be associated with differences in phenotype in diabetic as well as non-diabetic carrier subjects. This is illustrated by studies of apolipoproteins in different MODY1 pedigrees with various mutations of the gene encoding hepatocyte nuclear factor 4α (*HNF4A*). The mean plasma triglyceride concentration was significantly lower in 18 subjects (mean BMI 24.0) of the Michigan RW pedigree with the Q268X mutation (mean 0.80 mmol/l) [2] and in six subjects (mean BMI 24.0) from a Swedish family with the K99fsdelAA mutation (mean 0.64 mmol/l) [3] compared with 1.39 and 1.36 mmol/l, respectively, in control groups matched for BMI. The 18 RW subjects also had significantly lower lipoprotein(a) concentrations (mean 0.31 mmol/l) compared with the 24 control subjects (1.16 mmol/l). However, there were no significant differences in triglyceride or lipoprotein(a) concentrations between carriers and controls in 42 subjects (mean BMI 25.3) from 11 families with a variety of *HNF4A* mutations in a large European collection [4], although six subjects (mean BMI 25.2) with the R154X mutations in another study had elevated lipoprotein(a) levels [5]. Various other apolipoprotein fractions (AI, AII, CIII, total HDL-cholesterol) have been reported to be significantly lower in subjects with various *HNF4A* mutations [2, 4].

Different mutations in the gene encoding glucokinase (*GCK*/MODY2) have also been associated with differences in apolipoprotein levels. In 15 German MODY2 carriers (A232D mutation, 12 subjects; V154fsdelTG mutation, three subjects) (mean BMI 24.4), the mean triglyceride concentration was 0.84 mmol/l [6]. Two non-carrier subjects of the A232D pedigree had triglyceride levels of 1.17 and 1.25 mmol/l, suggesting that triglyceride levels may be lower in subjects with these two *GCK* mutations. The triglyceride level (mean 0.84 mmol/l) in the 15 MODY2 carriers is similar to that observed in 18 carriers of the RW/MODY1 pedigree (mean 0.80 mmol/l) [2]. In contrast, the triglyceride concentrations were normal in a very large series of primarily French MODY2 patients (mean BMI 22.0) [7]. We have recently studied a four-generation family (G pedigree) with a new *GCK* mutation, Leu 184 Pro (L184P). This pedigree includes affected individuals in three generations (ages 5–72 years). All are lean (mean BMI 21.3). In these six members, the mean triglyceride concentration was 0.68 mmol/l and the mean lipoprotein(a) concentration was 0.13 mmol/l, values that are lower than those in the RW/MODY1 pedigree. While the number of affected members in these various pedigrees is small, the results highlight the heterogeneity in apolipoprotein phenotypes seen in subjects with various *HNF4A* and *GCK* mutations. The variability could be due, at least in part, to different effects of the various mutations in each of these MODY genes on lipoprotein synthesis and metabolism but also to other genetic and environmental factors. Studies of larger numbers of pedigrees may determine if the variability between and within MODY families is larger than that between and within families in general.

The clearest evidence that different mutations in the same gene may have different effects on function and phenotype is found with glucokinase. Inactivating mutations are associated with MODY2 (heterozygous state) and permanent neonatal diabetes (homozygous or compound heterozygote), whereas activating mutations are associated with neonatal hypoglycaemia of infancy [8].

Our recent studies, as well as long-term studies, have also demonstrated that there is phenotypic heterogeneity among members of the same family with the same MODY mutation with regard to OGTT profiles. In three members of the MODY2 G pedigree (ages 6 and 45 [identical twins]

S. S. Fajans (✉)
Department of Internal Medicine,
University of Michigan Health System,
Ann Arbor, MI 48109, USA
e-mail: sfajans@umich.edu
Tel.: +1-734-9365039
Fax: +1-734-9369240

G. I. Bell
Department of Medicine, University of Chicago,
Chicago, IL, USA

years), the OGTT showed the characteristic pattern (MODY2 group 1; Fig. 1), i.e. a rapid decline in plasma glucose from peak levels to near-fasting levels at 2 h, although a few subjects had considerably higher plasma glucose levels during the OGTT [9]. The other three members of the G family (ages 14, 49 and 72 years) had OGTT profiles that were considerably higher, particularly at the 1.5 and 2 h times of the test (MODY2 group 2; Fig. 1). The two groups of three subjects each had identical fasting hyperglycaemia (7.6 mmol/l) and $HbA_{1c}$ levels of 6.3 and 6.4%, respectively. In addition, five of the six subjects had similar OGTT, fasting plasma glucose and $HbA_{1c}$ levels years to those decades earlier. Comparing the two groups, the first had a mean increase in concentration from fasting to 2 h of 0.8 mmol/l, and the second had a mean increase of 7.0 mmol/l. Peak levels during the OGTT for the two groups were 12.4 and 16.2 mmol/l, respectively. These differences could not be explained by lower increments and peak levels of insulin concentrations in the second group; they were actually slightly higher (Fig. 1). In comparison, two carriers of the RW/MODY1 pedigree (III-37 and V, age 13 years) [10], with stable OGTT over 4 years, and almost identical fasting plasma glucose levels (mean 7.7 mmol/l) at the time of each of seven OGTTs, the mean increment (fasting to 2 h) was 6.2 mmol/l and the mean maximum level was 14.2 mmol/l (MODY1; Fig. 1). Similar results were obtained for two carriers of the *HNF1A* MODY3 P pedigree (II-1 and II-3; *TCF1* mutation, IVS5nt-2A→G). Their mean fasting plasma glucose was 7.5 mmol/l, the increment (fasting to 2 h) was 7.0 mmol/l and the peak level was 14.4 mmol/l. In summary, these data indicate that the OGTT profile can vary within a MODY2 family, with some members having a typical profile [9] and others having a profile very similar to (at 2 h) or even higher (at 1 and 1.5 h) than those observed in the *HNF4A*/MODY1 or *HNF1A*/MODY3 subjects with similarly elevated fasting plasma glucose concentrations. Although the characteristic low OGTT profile is a good predictor of MODY2 [9], a higher profile in any individual subject may not predict the underlying genetic cause of MODY (MODY2 vs MODY1 or MODY3). However, a family history of the diabetic phenotype, including OGTT profiles and the nature of complications, can be useful in predicting the type of MODY before genetic testing.

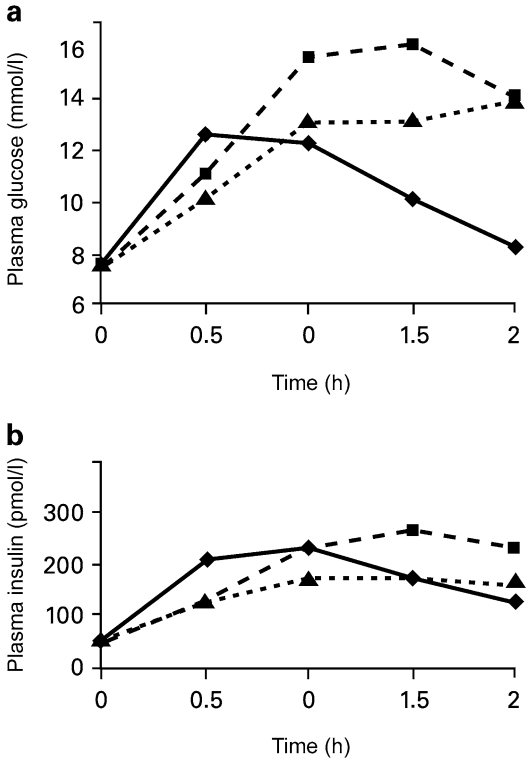


**Fig. 1** Oral glucose tolerance tests for subjects of the G pedigree with the novel *GCK* mutation L184P. Plasma glucose is shown in **a** and plasma insulin is shown in **b**. The subjects are arbitrarily divided into groups of three individuals to illustrate the heterogeneity of OGTT patterns. Group 1 (*diamonds, solid lines*) shows the classic MODY2 pattern while group 2 (*squares, dashed lines*) has a profile similar to or higher than that of subjects of the RW/MODY1 pedigree (*triangles, dotted lines*) chosen for having almost identical fasting plasma glucose concentrations (see text)

Finally, the clinical progression of the disease can vary between and within MODY families. The hyperglycaemia of *HNF4A*/MODY1 and *HNF1A*/MODY3 is progressive in severity over years and decades, while MODY2 shows very little progression over decades [9, 10]. The natural history of MODY1 and MODY3 may vary in different subjects: some are able to be treated with oral agents for many decades, but approximately 35% become insulin-requiring for the control of hyperglycaemia. Heterogeneity of phenotype may occur within the same family and within the members of the same sibship. As an example, the RW/MODY1 pedigree contains a sibship of 11 offspring (III-29 to III-39), seven of whom had diabetes diagnosed by routine testing in 1958 [10]. The severity of diabetes after 47 years of follow-up ranges from mild fasting hyperglycaemia (7.9 mmol/l), easily controlled with 100 mg of chlorpropamide (III-32), to severe insulin-requiring labile diabetes with minimal fasting and postprandial insulin concentrations (III-38) [10] that clinically resemble type 1 diabetes. The latter may be due to co-inheritance of additional unknown diabetogenic genes in the more severely affected insulin-requiring members of the sibship or due to unrecognised environmental factors.

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