with BE and that this complex dissociates on specimen dilution with water or saline solution. This may be similar to the reported masking effects of benzalkonium chloride (VisineTM) with the enzyme-multiplied immunomassay technique and TDxTM (Abbott Laboratories) assays for 9-carboxy-tetrahydrocannabinol; the drug is proposed to partition into micelles formed by benzalkonium chloride so that it is not accessible to antibodies (3). The matrix components of different slide lots may vary in our experiments and affect dissociation of the complex between BE and binding components in urine. Intermolecular association may provide a mechanism for interference with selected components in lateral flow assay, accounting for interference with BE but not benzodiazepine and opiate detection. Because the two urine specimens from the above individual tested positive for cocaine, opiates, and benzodiazepine, that person was excluded from the drug study.

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References


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Are Glucokinase Mutations Associated with Low Triglycerides?

To the Editor:

Mutations in the glucokinase gene lead to an impaired sensing of blood glucose by the pancreatic β cell, causing an autosomal dominant form of type 2 diabetes, maturity-onset diabetes of the young type 2 (MODY2). Usually, MODY2 patients present with high fasting blood glucose (6–12 mmol/L) from an early age (1). This situation should significantly increase their risk for diabetic complications (2), but whereas other forms of diabetes typically lead to macrovascular complications, MODY2 patients rarely develop diabetes-related problems (3).

In a family with autosomal dominant diabetes, we identified a novel C→A substitution in the glucokinase gene at nucleotide position 695 [A232D (pancreatic isoform), A231D (liver isoform)] in all affected individuals (Fig. 1). Codon 232 is highly conserved among nine different species. The mutation was not detected in 192 control chromosomes. Studied mutations around codon 232 (T228M and G261R) cause the lowest glucokinase activities of all mutations tested to date and suggest similar effects of A232D (4).

On the basis of our findings, we determined that individuals 0307 and 0309 were probably misdiagnosed with type 1 diabetes and individuals 0301 and 0304 with gestational diabetes. However, individual 0305 was an unaffected mutation carrier, which is not uncommon for MODY.

High hemoglobin A1c [HbA1c; reference interval, 4.3–6.1% by HPLC (Variant II; Bio-Rad)] should be associated with high triglycerides because it is an indicator of poor metabolic control (5). However, despite high HbA1c affected individuals of our MODY2 family showed even lower fasting triglyceride concentrations (Fig. 1A) than the unaffected family members (7 unaffected individuals, including 1 unaffected mutation carrier, vs 10 affected mutation carriers; individual 0206 received fenofibrate and was not considered); the mean (SD) values for affected vs unaffected family members were as follows: cholesterol, 5.71 (1.17) vs 5.62 (1.12) mmol/L; LDL-cholesterol, 3.44 (0.94) vs 3.30 (0.91) mmol/L; HDL-cholesterol, 1.85 (0.34) vs 1.58 (0.33) mmol/L. In another MODY2 family, Dresden-7 (V154fsdelTG; Fig. 1B), we made the same observation (6). In both families, the difference for triglycerides was significant (P = 0.025, two-sided test; 7 unaffected and 13 affected individuals), but we had no homozygous mutation carrier and too few cases to make a general statement.

It is possible that glucokinase mutations lead to lower triglycerides, even within their reference interval (0.35–2.30 mmol/L). Glucokinase mutations impair glycolysis, which is responsible for delivering glyceroldehyde 3-phosphate as the later glycerol backbone of triglycerides (4). Transgenic mice overexpressing glucokinase develop hypertriglyceridemia in addition to other effects, indicating a direct link between glucokinase activity and triglyceride regulation (7). There is evidence that serum concentrations of triglycerides are directly correlated with rates of progression of coronary artery disease and other macrovascular complications (8–10). In the studied family, and in concordance with the much lower frequency of diabetic complications in known MODY2 families, only one individual (0205) had a macrovascular event (myocardial infarction).

In conclusion, impaired glucokinase activity could lead to particularly low triglycerides in the circulation. The contribution of triglycerides...
Fig. 1. Glucokinase mutations in families D_0000_7302 (A; A232D) and Dresden-7 (B; V154fsdelTG).

Black-shaded symbols represent MODY2 patients. Individuals 0206 (A) and 1.2 (B) had classic type 2 diabetes but were not MODY2 cases (dark-gray-shaded symbols). Individual 0305 (A) was a mutation carrier for A232D but had no clinical signs of type 2 diabetes (light-gray-shaded symbol). MN in circles/rectangles indicates a heterozygous mutation; NN indicates the wild-type genotype. Genotyped microsatellite markers on chromosome 7 are given on the left. The disease haplotype is shown in black. The sequence with the mutation (exon 7, forward strand) is shown for individual 0305 and the wild-type sequence for individual 0306. The location of the glucokinase gene is indicated by an arrow in the haplotype of individual 0401. CA/AM, current age/age at manifestation; BMI, body mass index; T2D, type 2 diabetes; OHA, oral hypoglycemic agents; CHD, coronary heart disease; GD, gestational diabetes; NE, diabetic neuropathy; FF, fenofibrate therapy.
to the development of diabetic complications warrants further investigation.

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Precision of Computed Spectrophotometric Scans for Heme Pigments in Subarachnoid Hemorrhage Makes Interpretation Reliable

To the Editor:

A previous contribution to this journal (1) has rightly highlighted the difficulties associated with making a precise determination of heme pigments in suspected subarachnoid hemorrhage. In the United Kingdom, it is recommended that net bilirubin absorbance (NBA) is determined by zero-order spectrophotometry (2).

Viljoen et al. (1) reported large CVs at or near the cutoff of 0.007 absorbance units (AU; 22% at 0.0062 AU and 17% at 0.007 AU); their calculations were based on manual drawing of a predicted baseline and measurement of net absorbance by use of a ruler. This imprecision therefore has an impact on clinical decision-making. It is clear that positive NBA measurements calculated in this manner may lead to a high proportion of false-negative reports, with disastrous consequences, or, on the other hand, a high proportion of false positives, leading to unnecessary angiographic procedures used to locate the site of the aneurysm.

In our laboratory, we have demonstrated that the precision of NBA measurement is excellent at clinically relevant cutoff values if an appropriate spectrophotometer aided by computer software for analysis of scanned data is used.

We obtained cerebrospinal fluid (CSF) samples from patients with a negative or equivocal computed tomography scan by the standard lumbar puncture procedure. Samples were centrifuged for 5 min at 1831g as soon as possible after lumbar puncture. An undiluted CSF sample was scanned on a frequently serviced (6-month intervals) Unicam UV300 spectrophotometer (ThermoSpectronic) from 360 to 600 nm at a scan speed of 240 nm/min with a 2-nm bandwidth. Data collection points were set at 0.5-nm intervals. Pure water was used as blank along the entire wavelength range. Data were collected and subsequently analyzed with Vision 32 software (ThermoSpectronic). The use of this software allows simple postscan manipulation of the collected data. The zero-order trace was first subjected to high smoothing without loss of resolution. A predicted baseline was drawn by placement of cursors at the desired wavelengths with an accuracy of 0.5-nm steps.

CSF specimens used for the imprecision study were chosen to give a range of NBAs that might be encountered near the medical decision cutoff point of 0.007 AU. Eight CSF samples with a mean NBA in the range 0.0042–0.0973 AU were

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