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Letters

Observations

The polymorphism Gly574Ser in the transcription factor HNF-1α is not a marker of adult-onset ketosis-prone atypical diabetes in Afro-Caribbean patients

To the Editor: Type 1B diabetes or ketosis-prone atypical diabetes (KPAD) is a subtype of diabetes mostly described in patients of sub-Saharan African ancestry and characterized by insulin dependence at the time of presentation, without immunological markers seen in typical Type 1A diabetes (T1D), and frequently followed by absence of insulin requirements as in the case of Type 2 diabetes (T2D) [1, 2, 3]. The subsequent clinical course of KPAD, which could represent up to 12% of the sub-Saharan African diabetic population, is characterized by an alternance of near normoglycaemic remissions and relapses of insulin dependence without precipitating illness [3, 4]. Despite metabolic studies showing a beta-cell insulin secretory defect, no large genetic characterization has focused on this clinical subtype of diabetes.

Mutations in the gene encoding the transcription factor hepatocyte nuclear factor (HNF)-1α impair glucose-stimulated insulin secretion and cause maturity onset diabetes of the young (MODY) [5]. It has been reported that the missense mutation Gly 574 (GGC) to Ser (AGC) (Gly574Ser) in HNF-1α was a marker of children-onset KPAD [6]. In a cohort of six auto-antibody negative African American children they found that four patients (67%) were carrying the heterozygote mutation compared to only 7% of the healthy non diabetic African-American children [6].

In order to study the genetics of beta-cell dysfunction in the pathogenesis of KPAD, we gathered 80 unrelated black Afro-Caribbean diabetic patients admitted to hospital with the typical diagnosis of KPAD (83% of sub-Saharan origin, 17% of Caribbean origin). All patients had new onset diabetes with acute signs of insulinopenia (ketosis or diabetic ketoacidosis and weight loss), without precipitating illness, and requiring insulin therapy. Means ± SD age was 39±9.5 years, islet cell antibodies and anti-glutamic acid decarboxylase 65 antibodies were negative in all patients. Of the patients 65 (81%) underwent near normoglycaemic remission of insulin dependence as previously defined [4] within one month following admission. Our initial objective was to assess whether the Gly574Ser mutation in the HNF-1α gene was also a marker of adult-onset KPAD. In all patients, we amplified the coding region of exon 9 of the HNF-1α gene by polymerase chain reaction (PCR) using specific primers (forward primer: 5′-CCAAGCAGGTAAGGTCCAGG-3′; reverse primer: 5′-CACAGTGACGGACAGCAACAG-3′). PCR products were purified using centrifugal filter devices (Microcon PCR, Millipore, Bedford, Mass., USA) and both strands were sequenced using the BigDye Terminator kit (Applied Biosystems, Foster City, Calif., USA) and analyzed on a ABI Prism 310 sequencer (Applied Biosystems). The cohort of KPAD patients was compared to a cohort of unrelated T2D patients, T1D patients, and normoglycaemic control subjects of the same Afro-Caribbean background. Informed consent was obtained in all subjects and the study was approved by the institutional review board of Saint-Louis Hospital. We did not find any increased frequency of the Gly574Ser mutation in the KPAD cohort compared to the normoglycaemic control population [odds ratio 95% CI=0.85 (0.22–3.32)]. In addition, we did not find any association between the Gly574Ser polymorphism and the T2D or T1D diabetic cohorts. There was no difference between the Gly574Ser carriers and non-carriers respectively (Student's *t* test or χ^2) in the KPAD and T2D groups in terms of age of diabetes onset [KPAD (years): 33.9±6.9 vs 40.1±8.2; T2D: 40.2±8.8 vs 41.0±8.3; mean ± SD], existence of a family history of diabetes [KPAD: 40% vs 49%; T2D: 75% vs 71%], males/females ratio [KPAD: 80% vs 75%; T2D: 44% vs 50%] or BMI [KPAD (kg/m^2): 25.7±4.6 vs 28.2±4.8; T2D: 27.8±6.3 vs 28.4±6; mean ± SD] (Table 1).

This mutation has been exclusively reported in diabetic patients from African ancestry [6, 7, 8] and has never been observed in people from European or Asian descent. In all studies, there was no increased frequency of this mutation in the adult-onset T2D African-American population (4–7%) [6, 7] or sub-Saharan African populations (18%) [6] studied compared to control subjects. In a recent study a 16% frequency of the Gly574Ser mutation in a T2D population of 69 subjects

Table 1. Frequency of Gly574Ser polymorphism of the HNF-1α gene in various African diabetic groups

Population	Genotypes		
	Gly/Gly	Gly/Ser	Ser/Ser
KPAD (*n*=80)	75 (93.7%)	5 (6.3%)	0 (0%)
T1D (*n*=12)	11 (91.7%)	1 (8.3%)	0 (0%)
T2DM (*n*=81)	72 (88.9%)	9 (11.1%)	0 (0%)
Non-diabetic (*n*=55)	51 (92.7%)	4 (7.3%)	0 (0%)

Study groups are represented by phenotypes. The mean age ± SD in the non diabetic group is 47±8.6 years. Results are expressed in number of people (and percent) of a given genotype. Differences in respective frequency of the Gly574Ser in the KPAD, T1D, T2D groups compared to the control group (χ^2) are non significant ($p>0.05$)

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from Dakar, Senegal, was reported but the study did not include any control group [8]. In fact, this control population can be extrapolated from the initial study by Boutin et al. [6] in which their background population came from the same city (Dakar) and the frequency of the Gly574Ser allele was as high as 33%. Indeed, in our group, 9 of 18 (50%) patients carrying the Gly574Ser allele come from Senegal. This high frequency in Senegal could reflect a founder effect of this mutation in this particular country. Contrary to these previous studies, our diabetic and control populations were all widely distributed around 11 countries of West Africa and three different Caribbean islands. Therefore the 7.2% frequency of the Gly574Ser heterozygous genotype is probably very representative of the sub-Saharan African non diabetic populations.

In conclusion, we gathered a cohort of 80 patients with the pure clinical phenotype of KPAD. The Gly574Ser polymorphism of the HNF-1α gene does not seem associated with this form of diabetes. Further genetic studies are needed to determine the involvement of transcription factors or other candidate genes in the beta-cell dysfunction of KPAD.

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No interactions between polymorphisms in the β_3-adrenergic receptor gene and the PPAR-γ gene on the risk of the insulin resistance syndrome in the Danish MONICA cohort

Keywords Insulin resistance syndrome, type 2 diabetes, genetics, polymorphism, transcription factors.

To the Editor: Multiple mechanisms, including genetic components, are thought to contribute to the pathogenesis of the insulin resistance syndrome (IRS). The genetic factor probably results from the effect of a cluster of variations at multiple genetic loci and genetic interaction, i.e. amplification of allelic effect in the presence of variants at other loci, is likely to be present further illustrating the complexity. The prevalent Ala allele of the Pro12Ala polymorphism of the peroxisome proliferator-activated receptor-γ (PPAR-γ) gene is associated in many studies with increased insulin sensitivity and a decreased risk of Type 2 diabetes [1]. In line with these observations, we recently showed an association of the Ala/Ala genotype and a decreased propensity to develop the IRS in the Danish Monitoring of trends and determinants in Cardiovascular diseases (MONICA) study population [2]. The Trp64Arg variant in the β3-adrenergic receptor (BAR) gene, another candidate gene for obesity and insulin resistance, has in many studies been linked to features of the IRS. However, many investigations have failed to show such associations. Reasons for these disparities might be insufficient statistical power, ethnic differences and genetic heterogeneity. Interestingly, results from a recent study in Mexican Americans suggest a model in which these two genetic risk factors, having no or modest effect when expressed alone, interact in a synergistic manner on the development of obesity and insulin resistance [3]. We have examined the effect of the Trp64Arg variant expressed alone and in combination

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