

## ABSTRACT

MITOCHONDRIAL DNA MUTATION RELATED TO DIABETES MELITUS  
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Mutation in the mitochondrial DNA (mtDNA) is known as a monogenic causative factor for A3243G mtDNA mutation in the pathomechanism of type 2 diabetes mellitus (T2DM). A point mutation at nucleotide position G3316A and T3394C in the mtDNA NADH dehydrogenase 1 (ND1) gene has been reported in T2DM, categorized as Single Nucleotide Polymorphism (SNP), however, those two SNPs has been also found in normal population. The role of mtDNA mutation is still not yet studied widely among Indonesian population. We therefore investigated the contribution of mtDNA mutation and diabetes mellitus (DM).

Blood DNA was screened from 451 of T2DM cases collected from DM patients at Dr. Soetomo Hospital during 2001-2003. The A3243G was detected using the Polymerase chain reaction (PCR) and digested with *Apal* restriction enzyme. The G3316A and T3394C were also detected using PCR and digested with *HaeIII* restriction enzyme. Our results indicate the absence of A3243G mutation in the study population. Fortunately we found two pedigrees harboring G3316A and two pedigrees with T3394C point mutation. Family studies of those pedigrees showed that DM with those G3316A and T3394C had a significant odds ratio 5,2 (95 % CI: 1,222 – 22,134) and 3,185 (95 % CI: 1,025 – 9,893), respectively, compared to the sample taken from the same social and environmental background. Healthy individuals with G3316 and T3394C mutation carrier have a low normal pancreatic  $\beta$ -cell function as shown by Homeostasis Model Assessment  $\beta$  - Cell (HOMA-B score), thus, it is important to conclude that prediabetic stage of mutation carrier have a deficient  $\beta$  cell pancreas function which is prone to develop into DM in the next future especially if there is any other risk factors such as obesity, sedentary life, dyslipidemia, age greater than 45, and hypertension. The clinical manifestation of DM with G3316A and T3394C are uncontrolled T2DM with various macro and micro angiopathy.

We suggest that there are two types of mtDNA mutation associated with DM. The first are pathogenic mutations that lead to severe defect in oxidative phosphorylation (OXPHOS), represented by A3243G, and thus causal for DM. The second are SNPs that presumably alter tissue capacity for OXPHOS in such a way contributing to the polygenic T2DM as a predisposing factor. We provided evidence that firstly, A3243G mtDNA point mutation may not play an important role in the pathogenesis of T2DM in Surabaya or Indonesia, and secondly, a conclusion could be made that is G3316A and T3394C are SNPs that have a role as polygenic components to the pathomechanism of DM.

**Keywords:** *mitochondrial DNA mutation, monogenic, polygenic, diabetes mellitus, maternally inherited, single nucleotide polymorphism, A3243G, G3316A, T3394C.*