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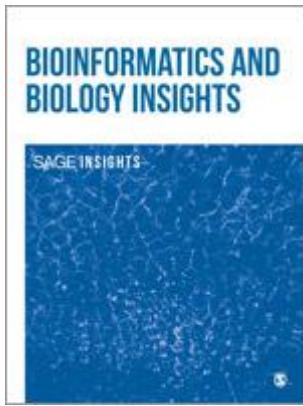
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# Bioinformatics Study of Mm.9053G>A Mutation at the ATP6 Gene in Relation to Type 2 Diabetes Mellitus and Cataract Diseases

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**ABSTRACT:** The mitochondrial disease often associated with various illnesses in relation to the activity of cells metabolites and the synthesis of adenosine triphosphate (ATP), including alteration in the mitochondrial DNA. The mutation of m.9053G>A at the ATP6 gene was found in patients with type 2 diabetes mellitus (DM type 2) and cataract. Therefore, this mutation is predicted to be clinical features of the 2 diseases. ATP6 gene encodes protein subunit of ATPase6, a part of ATP synthase, which is important in the electron transfer and proton translocation in intracellular respiration system. This study aims to investigate the mutation effect of m.9053G>A at the ATP6 gene (S167N) to the structure and function of ATPase6 using bioinformatics method. The structure of ATPase6 was constructed using homology modeling method. The crystal structure of bovine's ATP synthase (Protein Data Bank ID 5FIL) was used as a template because of high sequence similarity (77%) and coverage (96%) of the input sequence. The effect of mutation was investigated at the proton translocation channel of ATPase6. It is predicted that the channel was disrupted due to changes in electrostatic potential from serine to asparagine. Furthermore, molecular docking suggests that water binding on the proton translocation channel in the S167N mutant was different from the wild type. The result of this study is hoped to be useful in the development of a new genetic marker for DM type 2 and cataract.

**KEYWORDS:** ATP6, diabetes mellitus, cataract, bioinformatics, proton translocation

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## Introduction

Mitochondria are organelles of eukaryotic cells which play an important role in producing energy in the form of adenosine triphosphate (ATP) by ATP synthase complex.<sup>1</sup> The complex of ATP synthase in mammals is composed of 2 parts, which are F<sub>1</sub> that has a catalytic site for ATP synthesis and hydrolysis and F<sub>0</sub> that has proton channel to translocate proton across the mitochondrial membrane.<sup>2</sup> Two subunits of F<sub>0</sub>, ie, ATPase6 (subunit a) and ATPase8 (A6L), are coded by mitochondrial DNA (mtDNA), whereas the rest of subunits are coded by nuclear DNA.<sup>3</sup> Therefore, mutations in mtDNA, especially that of subunits a and A6L, would affect the cell metabolism in producing energy that is crucial for all organs in human body.<sup>4</sup> There are 2 mutations of mtDNA which are related to type 2 diabetes mellitus (DM type 2) that complicated with cataract disease, ie., A3243G and C12258A.<sup>5</sup> Thus, mitochondrial disorder-related diseases are interesting to be studied. In 2014, World Health Organization reported that Indonesia is the fifth and the second largest country regarding a number of diabetes and cataract cases, respectively.

In 2010, Maksum reported 6 mutations in mtDNA which specifically occurred in patients having type 2 DM and cataract. Among the mutations, m.9053G>A was located at respiration complex protein, ATPase6, and was found to be unrelated

to neuromuscular diseases, eg, myopathy and deafness.<sup>6</sup> ATPase6 plays a role as proton translocation channel in the mitochondrial matrix through the rotation of F<sub>0</sub> ring and hence triggers the change of catalytic site of F<sub>1</sub> for ATP synthesis.<sup>7</sup> Maassen et al<sup>8</sup> suggested that mitochondrial disorder was related to diabetes due to the decreasing of insulin secretion as a result of the low concentration of ATP.

This study aims to investigate the changes of structural properties of ATPase6 due to m.9053G>A mutation (S167N) using bioinformatics methods. The structure of ATPase6 was built using homology modeling technique. Furthermore, the electrostatic properties of protein were calculated using Adaptive Poisson-Boltzmann Solver (APBS) program. The water affinity on the proton translocation channel was predicted using molecular docking by AutoDock Vina.

## Methods

### Homology modeling of human ATPase6

A structure of bovine mitochondrial ATP synthase, resolved by electron microscopy, was used a template for homology modeling (Protein Data Bank [PDB] ID 5FIL).<sup>9</sup> The sequence of the human ATP6 gene was retrieved from



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