

# Mitochondrial DNA Variant Discovery in Normal-Tension Glaucoma Patients by Next-Generation Sequencing

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**Purpose:** Normal-tension glaucoma (NTG) is a disease of late-onset, complex trait with multiple risk factors. In this study, we discovered a mitochondrial DNA variant in NTG patients using next-generation sequencing (NGS) .

**Methods:** DNA was extracted from the peripheral blood of NTG patients and normal control subjects. Sequencing of the entire mitochondrial DNA (mtDNA) using NGS revealed new genetic risk variants for NTG patients (discovery sample, n = 20) . For the candidate genetic variants, we performed a disease-gene association study in the independent case-control populations (validation sample; NTG, n = 196 and normal control, n=202) using Sanger sequencing.

**Results:** This study identified 148 different novel mtDNA-sequence changes. Of these, 21 sequence variants identified at a frequency greater than 15% were located in the ND2-ND6, RNR1, RNR2, COX1, COX3, ATP6, ATP8, and CYTB genes. Of the 21 candidate genetic variants, the frequencies of m.4883C>T (ND2 gene) , m.9540T>C (COX3 gene) and m.14766C>T (CYTB gene) were significantly different between NTG patients and controls (28.4% vs. 15.3%, P=0.002; 56.5% vs. 44.4%, P=0.020; and 3.1% vs. 0.0%, P=0.030, respectively) . The association with m.4883C>T in the ND2 gene resisted the Bonferroni correction for multiple tests. The NTG patients of T genotype in the m.4883C>T variant have more advanced visual field loss than those who carry the C genotype (P=0.009) .

**Conclusions:** This study reveals a spectrum of mtDNA variants in patients with NTG. Our results identified a synonymous change, m.4883C>T variant, which was more prevalent in the NTG cohorts than in the controls. This finding suggests that the identified variant may be a genetic risk factor for the development of NTG.

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