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Brief Communication

Mitochondrial and Nuclear Mitochondrial Variants in Allergic Diseases

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ABSTRACT

The mitochondrial genome encodes core catalytic peptides that affect major metabolic processes within a cell. Here, we investigated the association between mitochondrial DNA (mtDNA) variants and allergic diseases, including atopic dermatitis (AD) and asthma, alongside heteroplasmy within the mtDNA in subjects with allergic sensitization. We collected genotype data from 973 subjects with allergic sensitization, consisting of 632 children with AD, 498 children with asthma, and 481 healthy controls by extracting DNA from their blood samples. Fisher's exact test was used to investigate mtDNA and nuclear DNA variants related to mitochondrial function (MT-nDNA) to identify their association with allergic diseases. Among the 69 mtDNA variants, rs28357671 located on the *MT-ND6* gene displayed statistically significant associations with allergic diseases (Bonferroni-corrected $P < 7.25E-4$), while 6, 4, and 2 genes were associated with allergic sensitization, AD, and asthma, respectively ($P < 0.0002$), including *NLRX1*, *OCA2*, and *CHCHD3* among the MT-nDNA genes. Heteroplasmy of mitochondrial DNA associated with allergic sensitization was evaluated in a separate cohort of patients consisting of 59 subjects with allergic sensitization and 52 controls. Heteroplasmy was verified when a patient carried both alleles of a mitochondrial single-nucleotide polymorphism (SNP) when clustered. One of the 134 mitochondrial SNPs showed heteroplasmy at a level of 0.4313 when clustering was applied. The probe sequence located at mitochondrial position 16217 and within the D-loop, which acts as a major control site for mtDNA expression. This is the first study to evaluate the association between mitochondrial DNA variants and allergic diseases. A harmonized effect of genes related to mitochondrial function may contribute to the risk of allergic diseases.

Keywords: Mitochondrial DNA; heteroplasmy; atopic dermatitis; asthma; association

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INTRODUCTION

The mitochondrial genome encodes core catalytic peptides that form the major proteins of the electron transport chain. Associations between mitochondrial DNA (mtDNA) variants and metabolic traits, including body mass index and waist hip ratio, have recently been reported.[1] Several studies have reported the connection between allergic diseases and metabolic conditions.[2] Moreover, some studies have suggested a unifying mitochondrial link between these interlinked morbidities.[3,4] Mitochondrial dysfunction occurs in allergic diseases, including both alteration in mitochondrial structure[5] and function.[6]

Mitochondrial heteroplasmy is an important factor for many conditions, including neurological diseases[7] and drug toxicities.[8] Heteroplasmy is the mixed population of wild-type and mutated mtDNA within a cell, caused by potent oxygen free radicals and lack of protective histone proteins within the mitochondria.[9] Since mutated and wild-type mtDNA can easily coexist in a single cell or a single sample, mtDNA variants can influence an individual's predisposition to complex diseases in a continuous manner through heteroplasmy.

Here, mtDNA and nuclear DNA variants related to mitochondrial function (MT-nDNA) were investigated to identify their associations with allergic diseases, including atopic dermatitis (AD) and asthma. We also looked into heteroplasmy within the mtDNA in subjects with allergic sensitization.

MATERIALS AND METHODS

Different cohorts were used to study the mtDNA/MT-nDNA variants and mitochondrial heteroplasmy. Each cohort and analysis are described as follows.

Identification of the mtDNA and MT-nDNA variant associations: cohort description

We collected genotype data from 973 subjects with known allergic sensitization and 481 healthy controls to identify the mtDNA and MT-nDNA variants associated to allergic diseases. Subjects with allergic sensitization comprised 632 subjects with moderate-to-severe AD and 498 subjects with persistent asthma. Of these subjects, 475 had only AD, 341 had only asthma, and 157 had both. Allergic sensitization was defined by specific IgE levels of greater than 0.7 kUA/L to at least one of the following allergens: egg white, milk, peanut, soybean, wheat, *Dermatophagoides pteronyssinus*, *Dermatophagoides farinae*, Alternaria species, and *Blattella germanica*. AD was diagnosed by pediatric allergists (SCORing Atopic Dermatitis; SCORAD ≥ 30) and asthma was confirmed on the basis of consistent respiratory symptoms verified by physicians. The presence of either a bronchodilator response of ≥12% increase in the forced expiratory volume in 1 second (FEV1), or bronchial hyperresponsiveness defined as a decrease in FEV1 of ≥20% with inhalation of <16 mg/mL methacholine was considered as asthma. Controls had neither allergic diseases nor allergic sensitization. Each subject provided written informed consent. The study was approved by the Institutional Review Board of Severance Hospital (Seoul, Korea; IRB No. 4-2004-0036).

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Identification of mtDNA and MT-nDNA variant associations: genotyping and analysis

DNA was extracted from blood samples of pediatric patients, and genome wide SNP and genetic variant information was sought by Illumina Human Core Exome 24 kit version 1.0 (Illumina, Inc., San Diego, CA, USA). Since all subjects were Korean and unrelated, additional correction was not conducted. Subject ancestry evaluation was performed using GRAF-pop 2.3.1[10] to verify Asian descent in all subjects (**Supplementary Fig. S1A**). Kraja *et al.* [1] provided a list of 2,282 nuclear genes that may contribute to mitochondria function. The "MT-nDNA candidates" were curated for their study using protein co-localization within the mitochondria and text mining. We used PLINK[11] (http://pngu.mgh.harvard.edu/purcell/plink/) to extract the mtDNA and MT-nDNA genes from the whole genome SNP data. Missingness per marker and per individual was set at under 0.05 and Hardy-Weinbeg Equilibrium threshold was 0.0001. SNPs with a minor allele frequency over 0.01 were included and Fisher's exact test was used to evaluate the associations. We evaluated mitochondrial gene-nuclear gene interactions by calculating the odds ratio considering both risk alleles of the mtDNA and MT-nDNA. Using the allele counting method for the risk allele in rs28357671 (MT-ND6) and each MT-nDNA, the total number of risk alleles present in the case and control groups were used to calculate the additive effect.

Investigating mitochondrial heteroplasmy: cohort description

Heteroplasmy associated with allergic sensitization was evaluated in a cohort of patients consisting 59 subjects with allergic sensitization and 52 controls. Allergic sensitization was confirmed using the same standards as before. All subjects were Korean and unrelated. Asian descent was confirmed in all subjects using GRAF-pop 2.3.1[10] (**Supplementary Fig. S1B**).

Investigating mitochondrial heteroplasmy: genotyping and analysis

We used genotype data from the Illumina Infinium Global Screening Array 24 kit on adult blood samples. Heteroplasmy occurs due to somatic mutation by environmental factors or errors made during DNA replication; thus, adults have accumulated more clinically relevant mtDNA mutations than children.[12] The reliability of Illumina genotyping array data has been confirmed to estimate high level heteroplasmy and a method established to evaluate the heteroplasmy levels was used.[13] The study was approved by Severance Hospital (Seoul, Korea; IRB No. 2015-2537-001).

RESULTS

Subject characteristics

Table 1 shows the subjects' characteristics consisting of 1,454 subjects for the mtDNA and MT-nDNA variant analysis and 111 subjects for mitochondrial heteroplasmy analysis. For the subjects in the mtDNA and MT-nDNA variant analysis, the mean age was 6.2 years for subjects with allergic sensitization, 4.8 years for those with AD, and 8.6 for those with asthma. Total serum immunoglobulin E (IgE) and blood eosinophil levels were much higher in subjects with allergic sensitization than in controls. However, the mean age for the mitochondrial heteroplasmy analysis was 45.5 years in subjects with allergic sensitization, focusing only on adult subjects.

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Table 1. Subject characteristics

Characteristics	mtDNA variant associations				Mitochondrial heteroplasmy	
	Allergic sensitization	AD	Asthma	Control	Allergic sensitization	Control
No. subject	973	632	498	481	59	52
Age (yr)	6.2 ± 4.2	4.8 ± 4.2	8.6 ± 2.9	15.6 ± 10.7	45.5 ± 13.4	44.9 ± 15.0
Male sex	653 (67.1)	416 (65.8)	337 (67.7)	219 (45.5)	45 (76.3)	31 (59.2)
Total serum IgE (kU/L)	929.2 ± 1,130.0	1,054.0 ± 1,295.8	827.6 ± 877.2	40.7 ± 34.7	430.8 ± 689.2	24.1 ± 18.2
Blood eosinophils (/mm^3)	807.0 ± 1,095.6	948.6 ± 1,314.1	578.0 ± 363.1	172.8 ± 135.0		
SCORAD		53.9 ± 16.5				

Data expressed as number (%) or mean ± standard deviation.
mtDNA, mitochondrial DNA; AD, atopic dermatitis; SCORAD, SCORing Atopic Dermatitis.

mtDNA and MT-nDNA variant associations

Among the 69 mtDNA genes remaining after QC, rs28357671 located on the *mitochondrially encoded NADH:ubiquinone oxidoreductase core subunit 6* (*MT-ND6*) gene displayed a statistically significant association (Bonferroni-corrected $P < 7.25E-4$) with allergic sensitization, AD, and asthma (**Table 2**). rs28357671 showed more association with allergic sensitization ($P = 3.84E-07$) than with AD ($P = 3.03E-06$) or asthma ($P = 5.61E-05$). The odds ratio (OR) for rs28357671 was between 0.23 and 0.25 for the allele C. Among 2,282 MT-nDNA genes, 6, 4, and 2 were associated with allergic sensitization, AD, and asthma respectively ($P < 0.0002$) (**Table 2**). *NLR family member X1* (*NLRX1*) and *OCA2 melanosomal transmembrane protein* (*OCA2*) were associated with both allergic sensitization and AD. Association to *TAL bHLH transcription factor 2* (*TAL2*), *adaptor related protein complex 2 subunit beta 1* (*AP2B1*), *Cbl proto-oncogene* (*CBL*), and *solute carrier family 2 member 1* (*SLC2A1*) were unique to allergic sensitization, while *solute carrier family 8 member A1* (*SLC8A1*) and *family with sequence similarity 107 member B* (*FAM107B*) were unique to AD. *Coiled-coil-helix-coiled-coil-helix domain* containing *3* (*CHCHD3*) was associated with asthma. Regarding mitochondrial gene-nuclear gene interactions, in half of the cases the interaction OR was greater than the MT-nDNA OR. rs4245191, which is located within the gene *NLRX1*, showed notable increases in OR for both allergic sensitization and atopic dermatitis with a difference of 0.377 and 0.396 respectively.

Table 2. Mitochondrial variants and nuclear mitochondrial variants related to allergic diseases

Variables	SNP	Gene symbol	BP*	Risk allele	Case frequency	Control frequency	*P* value	OR	Interaction OR†
mtDNA									
Allergic sensitization	rs28357671	*MT-ND6*	14178	T	0.98144	0.92516	3.84E-07	4.277	
AD	rs28357671	*MT-ND6*	14178	T	0.98254	0.92516	3.03E-06	4.552	
Asthma	rs28357671	*MT-ND6*	14178	T	0.97988	0.92516	5.61E-05	3.939	
MT-nDNA									
Allergic sensitization	rs10816292	*TAL2*	9:108423366	T	0.4596	0.3826	0.000119	1.372	1.347
	rs7179419	*OCA2*	15:28307179	G	0.3771	0.3044	0.000119	1.383	1.326
	rs28384428	*AP2B1*	17:33913989	G	0.1881	0.132	0.000125	1.523	1.256
	rs4245191	*NLRX1*	11:119052826	A	0.8832	0.8306	0.00013	1.542	1.919
	rs6589722	*CBL*	11:119085783	T	0.8849	0.8326	0.000158	1.545	1.915
	rs841852	*SLC2A1*	1:43401499	G	0.8443	0.7875	0.00018	1.463	1.757
AD	rs4245191	*NLRX1*	11:119052826	A	0.8883	0.8306	0.000108	1.621	2.017
	rs7179419	*OCA2*	15:28307179	G	0.3825	0.3044	0.000131	1.416	1.345
	rs404005	*SLC8A1*	2:40396078	G	0.6463	0.5672	0.000178	1.394	1.489
	rs11259210	*FAM107B*	10:14633723	A	0.6258	0.5468	0.000182	1.386	1.473
Asthma	rs358734	*C3orf33*	3:155483319	C	0.5875	0.5011	0.000131	1.418	1.407
	rs7808471	*CHCHD3*	7:132716502	C	0.1596	0.1021	0.000172	1.671	1.227

AD, atopic dermatitis; BP, base pair position; OR, odds ration; mtDNA, mitochondrial DNA; MT-nDNA, nuclear DNA variants related to mitochondrial function; SNP, single-nucleotide polymorphism.
*BP correspond to GRCh38/hg38 genome assembly; †Interaction OR is the odds ratio calculated by the additive effect of rs28357671 (*MT-ND6*) and each MT-nDNA SNP.

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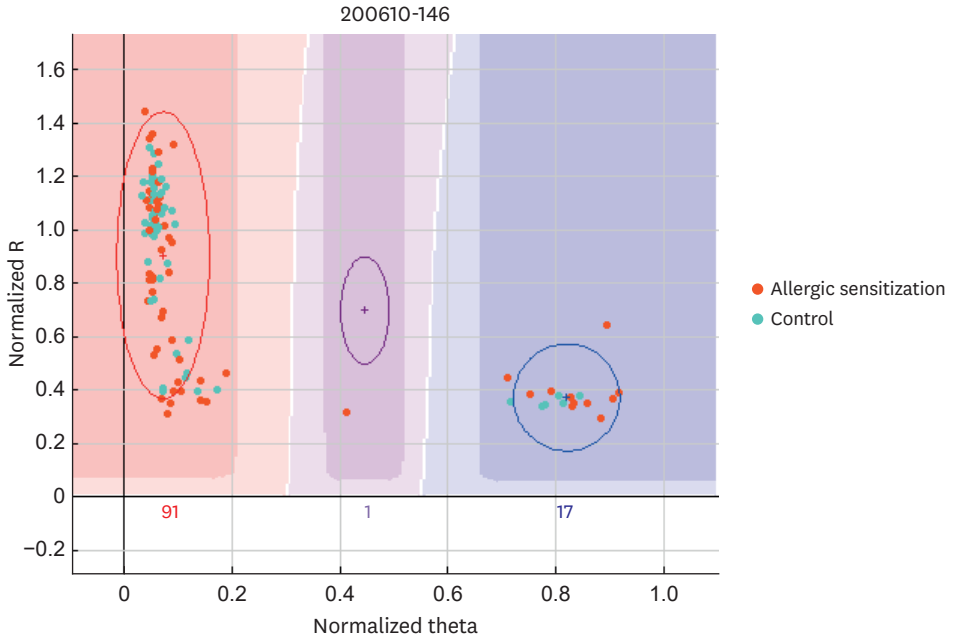

Figure. Clustering results for position 16217 on mtDNA genotype data. Polar coordinates display the cluster using the normalized theta and R values to denote the X and Y axis. Normalized theta represents the angle of deviation from the pure allele 1 signal, and normalized R represents the intensity of allele 2.
mtDNA, mitochondrial DNA.

Mitochondrial heteroplasmy

Of the 134 mitochondrial SNP probes, only 1 showed heteroplasmy when clustering was applied to the genotype data (**Figure**). The probe sequence is located at mitochondrial position 16217 and is within the D-loop, which acts as a major control site for mtDNA expression, containing the leading-strand origin of replication and the major promoters for transcription.[14] Out of all the 111 subjects studied, 108 had genotype data on the specific probe sequence. Of 91 individuals with genotype T, 45 (49%) exhibited allergic sensitization, while the remaining 46 (51%) did not. Furthermore, of 17 individuals with genotype C, 11 (65%) exhibited allergic sensitization but 6 (35%) did not. The association between allergic sensitization and controls on heteroplasmy was not significant as revealed by Fisher's exact test ($P = 0.2972$). The individual with heteroplasmy was one exhibiting allergic sensitization with a heteroplasmy level of 0.4313.

DISCUSSION

Here, we found that rs28357671 is an mtDNA variant on the *MT-ND6* gene and is highly associated with allergic diseases including AD and asthma. We also observed several nuclear genes that may contribute to mitochondrial function.

The C allele at rs28357671 was suggested to elicit a protective effect against allergic sensitization, although the case frequency and control frequency were fairly low. The *MT-ND6* gene is a core subunit of the mitochondrial membrane respiratory chain NADH dehydrogenase. It functions in the transfer of electrons from NADH into the respiratory chain while coupling the flow of electrons to the pumping of protons. Although it has been studied in allergic diseases, there was a difference in expression levels in blood early

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in Alzheimer's disease.[15] All mtDNAs encode genes related to the process of oxidative phosphorylation, which ensues the production of mitochondrial reactive oxygen species (ROS).[16] ROS promotes mitochondrial membrane transition pores or affects mitochondrial biogenesis, triggering proinflammatory action and tissue injury.[17] In asthma, excess ROS in bronchial epithelial cells can cause airway hyper-responsiveness and epithelial cell damage.[18] An imbalance between mtDNAs, such as *MT-ND6*, may be involved in the derangement of oxidative phosphorylation and ATP production within cells, and might generate ROS.

Of the 2 MT-nDNA genes that are associated with allergic sensitization and AD, *NLRX1* is localized in the mitochondria and amplifies nuclear factor-κB and JNK pathways by inducing ROS production. Suppression of *NLRX1* was observed in chronic obstructive pulmonary disease, which has a substantial overlap with asthma with regard to its pathophysiological characteristics.[19] Moreover, *NLRX1* exhibited an increase in OR when its interaction with *MT-ND6* was considered, implying ROS imbalance within the mitochondria by gene-gene interactions. *OCA2* is an integral membrane protein involved in tyrosine transport. Interestingly, tyrosine is related to various pathological mechanisms of AD, including the irregularly high expression of immunoreceptor tyrosine-based inhibitory motif domain on CD4+ T cells in AD patients.[20] A combined effect of the MT-nDNA and mtDNA genes is expected to contribute in allergic sensitization and associated diseases.

CHCHD3, a nuclear gene encoding an inner mitochondrial membrane scaffold protein, was associated with asthma. *CHCHD3* contributes to maintaining the integrity of crista which is a fold created by the mitochondrial inner membrane.[21] It also engages in essential mitochondrial functions, including oxygen consumption and protein import. Reduced mitochondrial crista occurs in asthmatic airway remodeling in murine airway epithelium when observed through transmission electron microscopy.[22,23] This suggests that *CHCHD3* mutation in asthmatic patients might be related to mitochondrial structural changes and dysfunction, such as ROS production and inflammation. Other genes that have not been mentioned are novel genes that lack previous research with regard to mitochondrial function and allergic diseases. Further research is needed to understand the effect of these variants.

The mitochondrial position 16217 has shown heteroplasmy in allergic sensitization subjects. This nucleotide position encodes multiple regulatory proteins and has association with endometriosis with regard to the identical nucleotide change, from T to C.[24] It has been suggested that endometriosis is caused by oxidative stress by inducing an imbalance between ROS and antioxidants, leading to inflammatory responses. The underlying mechanism for allergic sensitization may be similar to that of endometriosis with respect to inflammation induction. Mitochondria resequencing arrays or mitochondria-targeted sequencing data are required in further studies to confirm the finding in other cohorts.

In conclusion, we identified *MT-ND6*, an mtDNA gene related to oxidative phosphorylation, which is highly associated with allergic diseases. MT-nDNA, such as *NLRX1*, *OCA2*, and *CHCHD3*, were also associated with AD, asthma, or allergic sensitization. Heteroplasmy was evaluated in subjects with allergic sensitization, and a patient was identified with a high level of heteroplasmy at an SNP in the displacement loop. Replication of mitochondrial genetic variants and a functional study to confirm mitochondrial dysfunction and ROS production in regard to genetic variants can further enhance the interpretation of our study. We pose the possibility of mtDNA variants leading to mitochondrial disruption or imbalance in ROS production, which induces inflammation in allergic diseases. This is the first study

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to evaluate the association between mitochondrial DNA variants and allergic diseases. Considering the MT-nDNA candidates associated with allergic sensitization, a harmonized effect of genes related to mitochondrial function may contribute to the risk.

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SUPPLEMENTARY MATERIAL

Supplementary Fig. S1

Ancestry inference using GRAF-pop on the cohort for (A) mtDNA and MT-nDNA variant study (n = 1,454) and (B) mitochondrial heteroplasmy study (n = 135). The X and Y axis denotes the GDs calculated for ancestry inference. Subjects are primarily consisted of East Asian descent with less than 1% of other Asian descent.

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