Association between temporomandibular joint osteoarthritis and mitochondrial DNA haplogroups in a Korean population

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The Doctoral Dissertation

submitted to the Department of Dentistry,

the Graduate School of Yonsei University

in partial fulfillment of the requirements for the degree of

Doctor of Philosophy in Dental Science

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December 2017

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Abstract

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The aim of this study was to investigate the association between temporomandibular joint (TMJ) osteoarthritis (OA) and mitochondrial DNA (mtDNA) haplogroups among Korean adults.

Unrelated patients diagnosed with TMJ OA (n=108) and 108 control subjects were recruited. Buccal swab samples were collected, from which DNA was extracted using the QIAamp® DNA Mini Kit. The extracted DNA was quantified, amplified, and then analyzed using a multiplex allele-specific PCR system to distinguish mtDNA haplogroups M, G, D, D4, D5, M7, M8, M9, M10, N, A, N9, R, F, and B, as well as the D4 subhaplogroups. After thermal cycling, the genotyping of PCR products was carried out using AB GeneMapper® ID Software.

The frequency of haplogroup M10 was higher in patients with TMJ OA than in the controls (p = 0.024). Subhaplogroup D4j, a subdivision of haplogroup D4 which is frequently identified in

Korea was also associated with an increased risk of TMJ OA (p = 0.044). On the other hand, the frequency of haplogroup D4 was lower in patients with TMJ OA than in the controls (p = 0.031).

The frequencies of haplogroups M10 and D4j were higher in TMJ OA patients, while haplogroup D4 was lower, which represent the first reported association between TMJ OA and mtDNA haplogroups. These results provide evidence that mtDNA haplogroups contribute to the pathogenesis of TMJ OA and finding new therapeutic approaches to TMJ OA. Polymorphisms of these mtDNA haplogroups could therefore be a promising target for ascertaining the pathogenesis of TMJ OA and finding new therapeutic approaches to TMJ OA.

Keywords: mtDNA, temporomandibular joint, osteoarthritis, alleles, genotype

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Ⅰ. INTRODUCTION

Temporomandibular disorder (TMD) is a collective term representing a group of clinical musculoskeletal problems of masticatory muscles, TMJs, and their associated tissues. TMD is classified into four categories: temporomandibular joint disorders including degenerative joint

diseases, masticatory muscle disorders, headaches, and diseases of associated structures (Peck et al. 2014; Schiffman et al. 2014). Temporomandibular joint (TMJ) osteoarthritis (OA) is a degenerative joint disease characterized by the deterioration of articular tissue with concomitant osseous changes in the condyle or articular eminence or both. The reported prevalence of TMJ OA has varied from 22% to 45% depending on the used methods and the subjects of the study. TMJ OA progressively increases with age and is much more common in women presumably related to the estrogen receptor. The clinical signs and symptoms of TMJ OA are joint pain, limited joint function, joint crepitation, and occlusal changes resulting from bony changes (Okeson 2007; Rando and Waldron 2012). History taking and physical examination are essential for the diagnosis of TMJ OA. Radiographic examinations, which reveal the bony changes including subchondral cysts, erosion, generalized bony sclerosis, and osteophyte, are used to confirm the diagnosis (Schiffman et al. 2014). The etiology of TMJ OA is multifocal and complex. The pathogenesis of TMJ OA remains controversial and unclear. Imbalance between chondrocyte-controlled reparative processes and degradative processes is considered an important etiologic factor of TMJ OA. TMJ has its own remodeling mechanism as the form of bony addition or resolution for adapting the applied force to the joints. Dysfunction of the remodeling process by overloading beyond the adaptive capacity of the joint degrades the articular tissue and induces cartilage breakdown. Excessive mechanical stress to the joint leads to the proteolysis of extracellular matrix components through the plasminogen activator system. Numerous mediators including interleukin (IL)-12, IL-1β, IL-6, tumor necrosis factor (TNF)-α, and monocyte chemoattractant protein (MCP)-1 are known to be involved in the pathogenesis of TMJ OA. These cytokines induce generation of matrix-degrading enzymes, prostaglandins, arachidonic acid, and isoprostanes. Reactive oxygen species (ROS) are generated as one of the by-product in these processes. The elevation of intracellular ROS is involved in the pathogenesis of TMJ OA through various aspects. ROS can

damage to the joint, cause inadequate lubrication, produce cytokines related to the pathogenesis of TMJ OA, and induce various cellular responses leading to the chondrocyte apoptosis (Tanaka et al. 2008; Vos et al. 2012; Wang et al. 2015).

Mitochondria are membrane-enclosed organelles in the cytoplasm of eukaryotic cells. Mitochondrial proteins are encoded by nuclear DNA (nDNA) and mitochondrial DNA (mtDNA). mtDNA, a double-stranded closed molecule of 16,569 base pairs, encodes 13 peptides for the mitochondrial respiratory chain, 2 ribosomal RNAs and 22 transfer RNAs. mtDNA has non-coding regions with control elements at displacement loop (D-loop). D loop contains the mtDNA replication origin and promoters for mitochondrial RNA transcription, and contains three hypervariable segments with high polymorphism. The damage derived from long-term exposure to ROS and the lack of a repair system of mtDNA contribute to the higher mutational rate than nDNA. mtDNA is inherited exclusively through the maternal line, point mutations of mtDNA have accumulated and radiated to the maternal lineages. Due to these characteristics, mtDNA has been used for the studies of human migration, medicine and forensics. Mitochondria play important roles in biosynthetic pathways, calcium homeostasis, thermogenesis, cell death by apoptosis, and signal transduction pathways. Mitochondria generate more than 80% of the essential energy of the cell by converting nutritional molecules into ATP via oxidative phosphorylation (OXPHOS). Mitochondrial dysfuctions affect various human diseases including aging, neurodegenerative diseases, metabolic diseases, infectious diseases, and cancer (Scatena et al. 2012; Wallace 2010).

The individual groups characterized by the combination of single-nucleotide polymorphisms (SNPs) in the mtDNA sequence are called mtDNA haplogroups. The mtDNA haplogroup of a population reflects its geographic or historical origin, and these haplogroups have been used to map human migrations and understand genetic differences among populations (Merriwether et al. 1991; Torroni et al. 1996; Wallace 2010). Koreans are geographically a northeastern Asian group,

but genetically both a southeastern and northeastern Asian population. Koreans were classified into the East Asian phylogeny, and mtDNA haplogroups M, G, D, D4, D5, M7, M8, M9, M10, N, A, N9, R, F, and B are commonly used in Korea (Fig 1) (Lee et al. 2013). The haplogroup D4, which is the most prevalent in Koreans was subdivided into derived subhaplogroups; D4a, D4b, D4e, and D4j (Lee et al. 2006b; Lee et al. 2013; Umetsu et al. 2005). The maternal lineages of Koreans are homogenous at the peninsular level with the exception of Jeju Island due to a shared national history in the relatively small territory. The exception may result from geographical location and different cultural factors (Hong et al. 2014; Hong et al. 2015).

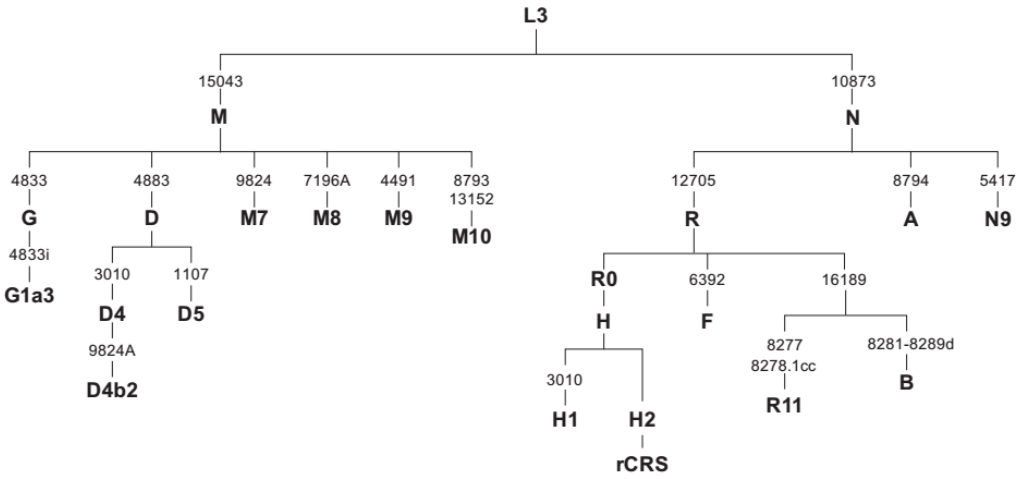

Figure 1. The mtDNA haplogroups in the East Asian mtDNA phylogenetic tree (Lee et al. 2013)

In OA, mitochondrial dysfunction compromises the function of chondrocytes, increases inflammatory responsiveness to cytokines of the chondrocytes, and induces the apoptosis of chondrocytes (Blanco et al. 2011; Rego-Perez et al. 2008; Soto-Hermida et al. 2014).

Studies have investigated the association between OA and mtDNA haplogroups, and specific mtDNA haplogroups are known to contribute to the progression or prevention of OA. Patients with haplogroup J showed a significantly decreased risk and less severe progression of knee OA and hip OA in a Spanish population, while those with haplogroup U showed more severe progression of knee OA (Rego-Perez et al. 2008; Rego et al. 2010). Patients with haplogroup T in knee OA and haplogroup TJ in knee or hip OA showed slower progression of OA (Soto-Hermida et al. 2014; Soto-Hermida et al. 2015). In a southern Chinese population, patients carrying the haplogroup G showed an increased risk of knee OA occurrence and more severe progression of knee OA than controls, while carriers of haplogroup B showed a lower susceptibility to the occurrence of OA (Fang et al. 2014). However, the implications of the findings of these studies to TMJ OA are dubious due to the difference between TMJ and other joints of the body, and different distribution of mtDNA haplogroups. The biomechanics of the TMJ differs from those of other load-bearing synovial joints, and TMJ is related to the growth center of the mandible. The TMJ provides the simultaneous and combined movement of two joints continuously, and the articular disc is covered by a dense fibrocartilage rather than a hyaline cartilage as in most synovial joints (Scrivani et al. 2008; Stankovic et al. 2013).

There has been no report about TMJ OA, which shares some common features of the pathogenesis of OA and there has been no study of OA in Korea as well. In consideration of this background and to understand how mtDNA influences TMJ OA, we investigated the association between TMJ OA and mtDNA haplogroups in a Korean population.

Ⅱ. SUBJECTS AND METHODS

1. Subjects

The study recruited 108 unrelated TMJ OA patients, comprising 95 women and 13 men, from the Department of Orofacial Pain and Oral Medicine at Yonsei dental hospital. Their mean age was 41.80 years, and their age range was from 19 to 75 years. Patients were diagnosed with TMJ OA according to Diagnostic Criteria for Temporomandibular Disorders (Schiffman et al. 2014). The diagonosis was confirmed when bony changes including subchondral cysts, erosion, generalized sclerosis, and osteophyte were observed in computed tomography. Subjects younger than 19 years and with systemic disease that can induce bony changes in TMJ such as, rheumatoid arthritis were excluded.

Age- and sex-matched control subjects (n=108) were recruited from both the Department of Orofacial Pain and Oral Medicine at Yonsei Dental Hospital; and the Department of Oral Medicine at Sahmyook Adventist Dental Hospital. The control subjects did not have any TMJ symptoms, had not been diagnosed with TMJ OA, showed no pathologic bony changes in radiographic examination, and had no other known degenerative diseases.

The study was approved by the Institutional Review Board of the Yonsei University Dental Hospital (2-2013-0029) and Public Institutional Bioethics Committee designated by the Ministry of Health and Welfare (P01-201507-31-003), and written informed consent was obtained from all subjects.

2. Genotyping of mtDNA haplogroups

Buccal swab samples were collected from the 108 patients and 108 controls. DNA was extracted using the QIAamp® DNA Mini Kit (Qiagen, Hilden, Germany) according to the manufacturer's instructions. Extracted DNA was quantified using the Quantifiler® Duo DNA Quantification Kit (Applied Biosystems, Foster City, CA, USA) or the NanoDrop 2000c spectrophotometer (Thermo Fisher Scientific, Waltham, MA, USA). DNA samples were amplified using a multiplex allele-specific PCR (ASP) system to distinguish mtDNA haplogroups M, G, D, D4, D5, M7, M8, M9, M10, N, A, N9, R, F, and B. Multiplex ASP was applied to a 10 μL reaction volume containing 100 pg of extracted DNA, 2.5 U of AmpliTaq Gold® DNA polymerase (Applied Biosystems), 1.0 μL of Gold ST*R 10x buffer (Promega, Madison, WI, USA), and an appropriate concentration of each primer. Primer information given in Table 1 was based on the study by Lee et al (Lee et al. 2013). The haplogroup D4 were subdivided into haplogroups D4a, D4b, D4e, and D4j by using other primers based on the study by Lee et al (Lee et al. 2006a). Thermal cycling was conducted on a PTC-200 DNA engine (MJ Research, Waltham, MA, USA) and SimplyAmp™ Thermal Cycler (Applied Biosystems) under the following conditions: 95℃ for 11 min; followed by 28 cycles of 94℃ for 20 s, 60℃ for 1 min, and 72℃ for 30 s; with a final extension at 60℃ for 45 min. PCR products were mixed with the GeneScan™ 500 LIZ® Size Standard (Applied Biosystems) and analyzed by capillary electrophoresis using the ABI PRISM 3130xl Genetic Analyzer (Applied Biosystems) and GeneScan 3.7 software (Applied Biosystems). The PCR products at each locus were genotyped using AB GeneMapper® ID Software Version 3.2 (Applied Biosystems) and an allelic ladder.

Table 1. Allele-specific primer sets of the multiplex allele-specific PCR system to determine East Asian mtDNA haplogroups (Lee et al. 2013)

Haplogroup	SNP locus	Primer	Sequence (5^0–3^0) [a]	Final	Amplicon size
M	15043	15043G	aaaGCCTCTTCCTACACATCTG**G**	0.18	75
		15043A	GCCTCTTCCTACACATGGG**A**	0.26	72
		15043R	6FAM-TGCCGATGTTTCAGGTTTCT	0.26	
G	4833	4833A	ttaCCCAGAGGTTACCCAATGC**A**	0.80	99/102
		4833A-A	ttaCCCAGAGGTTGCCCAATGC**A**	0.40	99
		4833A-B	tGTCCCAGAAGTTACCCAATGC**A**	0.07	99
		4833G	aCCCAGAGGTTACCCAAGTC**G**	0.55	97
D	4883	4883C	6FAM-GGAGAGATTTGGTATATGATTGAGCT**G**	0.80	
		4883T	6FAM-GAGGGAGAGATTTGGTATATGATTGAAAT**A**	0.50	
D4	3010	3010G	TTAATAGCGGCTGCACCTT**C**	0.20	121
		3010A	aaTTTAATAGCGGCTGCACAAT**T**	0.20	124
		3010F	6FAM-GACCAACGGAACAAGTTACCC	0.20	
D5	1107	1107T	CACTATGCTTAGCCCTAACCCT	0.12	142
		1107C	aaCCACTATGCTTAGCCCTAAACC**C**	0.09	145
		1107R	6FAM-CGGGGTTTATCGATTACAGAAC	0.12	
M7	9824	9824T	ACAGGCTTCCACGGGCT**T**	0.30	71
		9824C	taaACAGGCTTCCACGGAGT**C**	0.24	74
		9824A	attaCACAGGCTTCCACGGTCT**A**	0.16	76
		9824R	PET-ATTAGTTGGCGGATGAAGCA	0.30	
M8	7196A	7196C	aatGGGCATTCCGGATAGGTC**G**	0.30	96
		7196A	GGGCATTCCGGATAGACC**T**	0.18	93
		7196F	PET-CAAACCTACGCCAAAATCCA	0.30	
M9	4491	4491G	atCCTGCAAAGATGGTAGAGTAGATTA**C**	0.11	114
		4491A	CTGCAAAGATGGTAGAGTAGAGGA**T**	0.18	111
		4491F	PET-AAGGTCAGCTAAATAAGCTATCGG	0.18	
M10	13152	13152A-B4	aCTAGCAGAAAACAGCCCCCTA**A**	0.16	130
		13152A	CCTAGCAGAAAATAGCCCCCTA**A**	0.60	130
		13152G	aaaCCTAGCAGAAAATAGCCCAGT**G**	0.08	133
		13152R	PET-ACTTGAAGTGGAGAAGGCTACG	0.60	
N	10873	10873T	aGTTGTTGATTTGGTTAAAAAATAGGAGA**A**	0.10	81
		10873C	TGTTGATTTGGTTAAAAAATAGTCG**G**	0.45	78
		10873F	VIC-ACATAATTTGAATCAACACAACCAC	0.45	
M10	8793	8793C-	CCTCCTCGGACTCCTTCCC*C*	0.16	93
A	8794	8794C	ttCCTCCTCGGACTCCTGCATC	0.26	95
		8794T	taattaCTCCTCGGACTCCTGGCTT	0.12	98
		8794R	VIC-ATCACTGCGCCYGCTCATA	0.26	
N9	5417	5417G	GGTGGGTTTTGTATGTTCACAC	0.34	125
		5417A	atGGGTGGGTTTTGTATGTTCCAAT	0.14	128
		5417F	VIC-TAGCCACCATCACCCTCCT	0.34	
R	12705	12705C	GGTAACTAAGATTAGTATGGTAATTAGGCA**G**	0.11	76
		12705T	ttCGGTAACTAAGATTAGTATGGTAATTAGTAAA	0.23	79
		12705F	NED-AAACTCAGACCCAAACATTAATCAG	0.23	

F	6392	6392T	aaCCTCTATCTTAGGGGCCATGAA**T**	0.60	102
		6392C	CTCTATCTTAGGGGCCATC**AC**	0.50	99
		6392R	NED-AGGACGGATCAGACGAAGAG	0.60	
B	8281-8289d	9 bp-F	NED-AGGGCCCGTATTTACCCTAT	0.11	123/132
		9 bp-R	TTTAGTTGGGGCATTTCACTG	0.11	

[a] The mismatched bases to the rCRS are underlined. Two or three alleles of the SNP at the 3^0 end of allele-specific primers are indicated in bold. Base substitutions due to mutations specific for other haplogroups are indicated in italics. The tails are written in lower case.

3. Statistical Analysis

Statistical analyses were performed using SPSS (version 23.0, IBM Corporation - Armonk, NY, USA). The age and sex distributions were compared between patients and controls using the *t*-test. Haplogroups of the TMJ OA group and control group were compared using the chi-square test, and probability values of $p<0.05$ were considered statistically significant.

Ⅲ. RESULTS

The clinical characteristics of the 216 subjects (108 patients and 108 controls) are summarized in Table 2. The age distribution did not differ significantly between TMJ OA group and control group (p = 0.932). Fifteen haplogroups (M, G, D, D4, D5, M7, M8, M9, M10, N, A, N9, R, F, and B) and four D4 subgroups (D4a, D4b, D4e, and D4j) with unclassified haplogroup D4 were identified. The frequency of haplogroup M10 was higher in TMJ OA group than in control group (p = 0.024) (Table 3). The list of D4 subhaplogroups in Table 4, indicates that the frequency of haplogroup D4j was also higher in TMJ OA group than in control group (p = 0.044). The frequency of haplogroup D4 was lower in TMJ OA group than in control group (p = 0.031) (Table 4).

Table 2. Characteristics of the study groups

	TMJ OA	Control	Total
Sex			
Males (*n*)	13	13	26
Females (*n*)	95	95	190
Total (*n*)	108	108	216
Age, years (mean ± SD values)	41.8 ± 17.5	41.6 ± 17.6	

Table 3. Haplogroup distributions in TMJ OA group and control group

Haplogroup	TMJ OA	Control	*p*
M	4 (3.7)	1 (0.9)	0.175
G	7 (6.5)	13 (12.0)	0.159
D	0 (0.0)	1 (0.9)	0.316
D4	22 (20.4)	29 (26.9)	0.262
D5	8 (7.4)	6 (5.6)	0.580
M7	11 (10.2)	4 (3.7)	0.061
M8	7 (6.5)	9 (8.3)	0.603
M9	3 (2.8)	3 (2.8)	1.000
M10	5 (4.6)	0 (0.0)	0.024
N	1 (0.9)	1 (0.9)	1.000
A	12 (11.1)	10 (9.3)	0.653
N9	7 (6.5)	10 (9.3)	0.448
R	1 (0.9)	0 (0.0)	0.316
F	11 (10.2)	13 (12.0)	0.665
B	9 (8.3)	8 (7.4)	0.801
TOTAL	108 (100)	108 (100)	

Data are *n* (%) values

Table 4. D4 subhaplogroup distributions in TMJ OA group and control group

Haplogroup	TMJ OA	Control	*p*
D4	5 (22.7)	14 (48.3)	0.031
D4a	4 (18.2)	8 (27.6)	0.248
D4b	7 (31.8)	6 (20.7)	0.774
D4e	2 (9.1)	1 (3.4)	0.561
D4j	4 (18.2)	0 (0.0)	0.044
Total	22 (100)	29 (100)	

Data are *n* (%) values.

Ⅳ. DISCUSSION

The regional distribution of human mtDNA has been influenced by environmental factors. mtDNA play important roles in cell survival through physiological functions of OXPHOS including ATP production for performing work and heat generation for maintaining body temperature. For adaptation to new climate and dietary condition, the balance between ATP production and heat generation is influenced by the efficiency of OXPHOS coupling. Tightly coupled OXPHOS would generate more ATP and minimal coupling efficiency of OXPHOS would produce more heat. The high mutational rate and accumulation of these mutations through maternal lineage of mtDNA contribute to the mtDNA variations (Mishmar et al. 2003; Ruiz-Pesini et al. 2004).

Mitochondria are important regulators of cell function and survival. Dysfunction of mitochondria can induce damage to the cells, functional failure, degeneration, and cell death. Mitochondrial medicine, which addresses the involvement of mitochondria in diseases, has been extensively developed and studied for several diseases. Degenerative diseases, aging, cancer, and other diseases can result from reduction of mitochondrial energy production, and elevation of mitochondrial ROS production. Based on these understandings, new approaches of the treatment targeting mitochondrial dysfunction are studying for several diseases (Koene and Smeitink 2009; Scatena et al. 2012; Singer 2014; Wallace 20101; Wallace et al. 1998).

Mitochondria play important roles in the aging process and cell death, and the etiology and pathogenesis of various diseases. In the pathogenesis of OA, the alteration of mitochondrial function in the chondrocytes enhances chondrocyte proliferation and apoptosis in the joint (Blanco

et al. 2011; Hwang and Kim 2015; Kim et al. 2010). Some studies involving in European and Chinese populations have found significant associations between OA and mtDNA haplogroups. It is reported that the European mtDNA haplogroup U was associated with an increased risk of OA and haplogroups J and T were involved in protection from the incidence and severity of OA. Haplogroup U may be related to defects in ATP synthesis of chondrocyte, which lead to a severe progression of OA. Some of mutations of haplogroups J and T may reduce ROS production and oxidative stress in the pathogenesis of OA, so haplogroup J and T could have protective effect for OA (Rego-Perez et al. 2010; Rego-Perez et al. 2008; Soto-Hermida et al. 2014; Soto-Hermida et al. 2015). In the study of a southern Chinese population, haplogroup G increased the risk of OA by increasing the mtDNA deletion and mitochondrial ROS generation. Haplogroup B4 exhibited protective effects on chondrocytes by decreasing ROS levels and cell apoptosis (Fang et al. 2014). Spanish population belongs to the European-Caucasian population and the Chinese population belongs to the eastern Asian population, so different haplogroups are known to be involved in the pathogenesis of OA in these studies. The mechanism of the effect on the pathogenesis of OA is unknown, similar biologic roles seem to be indicated.

The pathogenesis of TMJ OA is multifocal and complex, remains unclear, and has been mostly based on studies of OA in other joints. As increased loading to the joint over its capacity continues, the remodeling mechanism breaks down and degradation of the articular tissue dominates regeneration. As the result, the destructive bony changes of the joint occur. The hypoxia-reperfusion theory has also been proposed to explain the pathophysiology of TMJ OA. Mitochondria generate ROS, one of the by-products of OXPHOS. ROS are involved in the pathogenesis of TMJ OA via damage to the articular tissues and various cellular responses leading to chondrocyte (Milam 2005; Tanaka et al. 2008; Vos et al. 2012; Wang et al. 2015). Haplogroups M10 and D4j might play an important role in the pathogenesis of TMJ OA through unknown

mechanism. It appears to be related to the OXPHOS and affect to the chondrocytes of the TMJ. Also, haplogroup D4 could be related to reduce ROS production and mitochondrial oxidative stress, and prevent apoptosis of chondrocyte. To verify this hypothesis, further functional analysis of SNPs of these haplogroups will be needed.

The frequencies of each mtDNA haplogroup obtained in this study were similar to the previously reported study in a Korean population by Lee et al (Lee et al. 2006a). The frequency of haplogroup M10 in Koreans is 1.5% and haplogroup D4j in Korean is 10.3% among haplogroup D4. However, the frequency of haplogroup M10 in this study was 4.6% in TMJ OA group and there was none in control group. Haplogroup D4j was 18.2% of haplogroup D4 and no one in control group. We can assume that haplogroups M10 and D4j strongly affect to the pathogenesis of TMJ OA based on the finding of relatively high frequencies of haplogroups M10 and D4j in the TMJ OA group. To clarify this hypothesis, larger scale study and research for revealing the role of mtDNA into the pathogenesis of TMJ OA are needed.

We identified only four D4 subhaplogroups (D4a, D4b, D4e, and D4j) in this study, and the D4 haplogroup was not specified for 19 subjects (5 patients and 14 controls). The mitochondrial genome variation is so large that the frequency of some haplogroups is only a few percent. Due to the difficulty of specifying all subgroups of the D4 haplogroup, we used four subhaplogroups that are identified frequently in Korea. It is reported that around 10% of haplogroup D4 was not classified, so we can regard unspecified D4 as one of the haplogroups. (Lee et al. 2006a)

mtDNA could vary in different racial groups including within the same country through interactions with environmental factors. (Ruiz-Pesini et al. 2004) Regional distribution of mtDNA haplogroups has been influenced by climate selection for human adaptation to different global environments. These mtDNA variants interact with environmental factors including climate and seasonal variation, and cultural factors including nutritional and social customs (Brand 2000;

Mishmar et al. 2003; Ruiz-Pesini et al. 2004). We did not find any association between TMJ OA and haplgroups G and B which were related to OA in Chinese study (Fang et al. 2014). Thus, haplogroups M10, D4j, and D4 might not be associated with TMJ OA in other countries or even in different studies of the same country.

Our study had the limitation of the sample being small compared to the number of haplogroups and recruited subjects only in Seoul, Korea. Even the maternal lineages of Koreans are homogenous, large-scale study on a nationwide basis are needed. Also, multinational studies of the effect of mitochondria on TMJ OA are necessary to fully elucidate the relationships between TMJ OA and mtDNA haplogroups.

Ⅴ. CONCLUSION

This is the first study to examine and identify the association between TMJ OA and mtDNA haplogroups in a Korean population. The frequencies of haplogroups M10 and D4j were higher in TMJ OA patients than in the control group. While, the frequency of haplogroup D4 was lower in TMJ OA patients than in the control group. Polymorphisms of these mtDNA haplogroups could therefore be a promising target for ascertaining the pathogenesis of TMJ OA and finding new therapeutic approaches to TMJ OA.

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ABSTRACT (in Korean)

한국인에서 턱관절 골관절염과 미토콘드리아 DNA 하플로그룹의 연관성

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전 영 미

턱관절 골관절염은 턱관절에서 발생하는 골변화를 동반하는 퇴행성 관절질환으로 발생 원인은 불명확하지만 미토콘드리아의 기능장애와 연관이 있다는 보고가 있다. 골관절염과 미토콘드리아 DNA (mtDNA) 하플로그룹의 연구는 그 연관성이 보고된 바 있으나, 턱관절 골관절염에 관한 연구는 없는 실정이다. 이에 본 연구에서는 한국인에서 턱관절 골관절염과 mtDNA 하플로그룹의 연관성을 확인하고자 한다.

턱관절 골관절염으로 진단된 환자 108 명과 대조군 108 명을 모집하였다. 면봉을 이용하여 구강상피세포를 채취하고 QIAamp® DNA Mini Kit(Qiagen, Hilden, Germany)를 이용하여 DNA 를 추출하였다. 추출된 DNA 는 haplogroups M, G, D, D4, D5, M7, M8, M9, M10, N, A, N9, R, F, B, 그리고 하플로그룹 D4 를 세분화하기

위하여 정량 및 증폭을 시행한 후 multiplex allele-specific PCR system 과 AB GeneMapper® ID 소프트웨어를 사용하여 분석하였다.

턱관절 골관절염 환자에서 하플로그룹 M10 의 빈도가 대조군에 비하여 통계적으로 유의하게 높게 나타났다(p = 0.024). 또한, 한국인에서 가장 흔하게 발견되는 하플로그룹인 D4 의 하위그룹 중에서는 하플로그룹 D4j 가 턱관절 골관절염 환자에서 통계적으로 유의하게 증가된 경향을 보였다(p = 0.044). 또한 하플로그룹 D4 의 빈도는 턱관절 골관절염 환자에서 대조군에 비하여 통계적으로 유의하게 낮게 나타났다 (p = 0.031).

이 연구는 턱관절 골관절염과 mtDNA 하플로그룹과의 연관성을 밝힌 첫번째 연구로, 이 연구 결과를 바탕으로 향후 mtDNA 하플로그룹을 턱관절 골관절염의 병인론 및 치료의 연구에 유용하게 사용할 수 있을 것으로 사료된다.

핵심되는 말 : 미토콘드리아 DNA, 측두하악관절, 골관절염, 하플로그룹, 유전자형