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Distribution of COL9A2 and COL9A3 Gene Polymorphism in Male Chinese Singaporean – A Pilot Observational Study

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ABSTRACT The association between allelic variants and lumbar disc degenerative disease (DDD) has been investigated in Europe and Northern Asia. However, this has not been investigated in Southeast Asia. This observational study aims to compare the distribution of COL9A2 and COL9A3 gene polymorphism among male Chinese Singaporeans with and without lumbar DDD. COL9A2 gene polymorphism was investigated in p326 (tryptophan 2, Trp2 and glutamine 2, Gln2, alleles) and p335 (valine 2 or Val2 allele). COL9A3 gene polymorphism was investigated in p17 (glycine 3 or Gly3 allele) and p103 (tryptophan 3 or Trp3 allele). The Val2 allele was significantly decreased in the group with lumbar DDD ($p < 0.05$). No significant difference in allelic distributions of Trp2, Gln2 and Gly3 was found. The Trp3 allele was absent from all the subjects. The presence of at least one Val2 allele appears to have a protective effect against DDD. However, these should be interpreted with caution, given the limitations. Further investigations are warranted in order to verify such genetic predisposition prior to the potential development of preventative or therapeutic strategies in the near future.

INTRODUCTION

Degenerative Disc Disease (DDD) is a common musculoskeletal condition with strong genetic determinants (Seki et al. 2006). It often leads to physical impairment, requiring surgery and it contributes significantly to health costs and work disability in individuals and as well as the society (Paassilta et al. 2001; Seki et al. 2006; Solovieva et al. 2006). The environmental factors contributing to DDD are generally well known while research into genetic contributions is limited (Frymoyer 1988). In recent years, association between allelic variants in the collagen IX genes and DDD was reported (Annunen et al. 1999; Paassilta et al. 2001; Solovieva et al. 2002). Collagen IX is a heterotrimer of three alpha chains, 1(IX), 2(IX) and 3(IX) encoded by the genes COL9A1, COL9A2 and COL9A3 respectively (Karppinen et al. 2002; Zhang et al. 2008). Recent studies have suggested an association between COL9A2 and COL9A3 gene polymorphisms with DDD in the Finnish (Annunen et al. 1999; Paassilta et al. 2001), Greek (Kales et al. 2004), Japanese (Higashino et al. 2007) and Southern Chinese (Jim et al. 2005) individuals.

However, this has not been investigated in Southeast Asia, particularly Singapore. Whether there is a difference between ethnic Chinese from Hong Kong and Singapore may be questioned by some and yet a phenotypic difference has been demonstrated in nasopharyngeal carcinoma (NPC), in that the incidence of NPC varies greatly among ethnic groups from Kwantung and Fukien Provinces in Southern China (Clifford 1970; Ho 1972). Similarly, it is assumed that ethnic Chinese from both Hong Kong and Singapore are likely to share similar genetic background, yet a striking difference has been shown in cardio-

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vascular mortality between ethnic Chinese living in both cities (Zhang et al. 2008). In view of these findings, there is still a plausible difference in genetic background between ethnic Chinese from both cities.

Worldwide, the high prevalence of symptomatic DDD accounts for a major proportion of musculoskeletal disease burden (Jim et al. 2005). Clarifying the genetic predisposition to DDD will improve the understanding of the development and treatment of this disease. As such, the aim of this study is to compare the distribution of COL9A2 and COL9A3 gene polymorphism in symptomatic male Chinese Singaporeans with and without lumbar degenerative disc disease (DDD).

MATERIALS AND METHODS

Consecutive symptomatic male Chinese Singaporean patients who have had pain over their low back and/or lower limb with duration of at least 1 month were recruited from the specialist outpatient clinic (SOC) within the period Aug 08 – Dec 08. These subjects were excluded if they were present with pain over low back/lower limbs secondary to non-degenerative causes, for example, rheumatoid arthritis, traumatic spondylolisthesis etc. Subjects also completed a physical activity questionnaire (International Physical Activity Questionnaire IPAQ) short form (Criag et al. 2003).

Fifty-four subjects (mean age 28.12 years, SD 12.3, confidence interval [CI] 24.8 to 31.4 years) consented while 6 subjects declined invitation to participate in this study. These patients then underwent MRI examinations, which were carried out at the Department of Diagnostic Radiology using a 1.0 or 1.5 Tesla Magnetic Resonance scanner (Siemens, Erlangen, Germany). The scans were scored mainly based on the sagittal T2-weighted turbo spin echo sequences (TR = 4000 milliseconds, TE = 112 milliseconds, slice thickness = 4mm), although the rest of the magnetic resonance sequences in the routine clinical study were also referred to during reading.

DDD was diagnosed on the basis of signal changes in the intervertebral discs of lumbar spine (Schneiderman et al. 1987). The grade of disc degeneration was determined based on a previous study (Jim et al. 2005), in which Grade 0 indicated no signal change, Grade 1 a slight decrease in signal intensity in the nucleus pulposus, Grade 2 a generalized hypointense nucleus and Grade 3 a hypointense nucleus with disc space narrowing using Schneiderman's classification (Schneiderman et al. 1987). The construct validity of such classification using MRI was demonstrated when it was 99% accurate in predicting normality or abnormality as determined by discography (Schneiderman et al. 1987). Individuals with five Grade 0 discs or having one Grade 1 disc of the lumbar spine were assigned as "Normal" (Jim et al. 2005). These subjects acted as the control group in this observational study. The rest with more than one Grade 1 or greater disc of the lumbar spine were assigned as "DDD". All the MRI scans were analyzed by only one experienced radiologist (L.L.C.) who was blinded to the clinical history of these subjects.

Three milliliters (ml) of blood were drawn from each patient and genomic DNA was extracted from the blood followed by amplification using QIAamp® DNA Mini Kit. The isolated DNA samples were then stored at 4 degrees Celsius (°C) until further procedures analyzed the DNA sequence for COL9A2 genotype variations. COL9A2 gene polymorphism was investigated in p326 (tryptophan 2, Trp2 and glutamine 2, Gln2, alleles) and p335 (valine 2 or Val2 allele) (Table 1). Polymerase chain reaction primers were designed to amplify exon 19 of the human COL9A2 genes. A GeneAmp PCR system 9700 was used with the following amplification conditions, that is, an initial denaturation at 95 °C for 3 minutes, 35 cycles of 95 °C for 30 seconds, 60 °C for 45 seconds, 72 °C for 1 minute, and a final extension at 72 °C for 10 minutes. The polymerase chain reaction products were subjected to conformation via gel electrophoresis. Products were then purified using QIAquick® PCR Purification Kit. Sequence variations observed as heteroduplexes were examined using a ABI PRISM 3100 Sequencer and BigDye Terminator Sequencing Kit (Applied Biosystems, Foster City, CA).

COL9A3 gene polymorphism was investigated in p17 (glycine 3 or Gly3 allele) and p103 (tryptophan 3 or Trp3 allele) (Table 1). Here, a probe which contained primers (Taqman®, SNP Genotyping Assays Pre-Designed, Small-Scale, Applied Biosystems, USA) was used. Allelic discrimination was then examined using a 7500 Fast Real-Time PCR System (Applied Biosystems, Foster City, CA). TaqMan probe primer set and Genotyping Master Mix were used for

Table 1: Analysis of the Collagen IX gene sequence variations

Gene	*Nucleotide variation*	*Primers 5'-3'*	*Product Size (bp)*	*Detection Method*
COL9A2	exon 19, p326, 1st codon C > T (*Trp2*)	Forward: TGGATCTCAGTTTCCCTACCTG	246	Sequencing
		Reverse: CAAGAGGTGGTGATTGAGCAAGAGC	246	Sequencing
	exon 19, p326, 2nd codon G > A (*Gln2*)		246	Sequencing
	exon 19, p335, 1st codon C > G (*Val2*)			
COL9A3	exon 1, p17, 2nd codon A > G (*Gly3*)	TaqMan® SNP genotyping assays, Applied Biosystems assay ID- C_16188902_10	245	Allelic discrimination
	exon 5, p103, 1st codon C > T (*Trp3*)	assay ID- C_25600748_20	244	

amplification under standard conditions. Initially, the pre-PCR conditions read at 60°C for 1 minute, followed by 95°C for 10 minutes. Subsequently, there were 40 cycles of 95°C for 15 seconds and 60°C for 1 minute. After amplification, the post-PCR conditions read at 60°C for 1 minute. These procedures enabled us to compare the distribution of COL9A2 and COL9A3 gene polymorphism in symptomatic male Chinese Singaporeans with and without clinically diagnosed lumbar (DDD).

The study protocol was approved by The Institutional Review Board (IRB) of Singapore General Hospital.

Data Analysis

Descriptive statistics were calculated for age, height, weight, amount of time spent on sitting (mins per wk), IPAQ score and grade of disc degeneration. Data were checked for normality and homogeneity of variance and paired t tests were used. Where data were neither of normal distribution or homogeneity of variance, non-parametric equivalents were used (using SPSS 16.0 for Windows, SPSS Inc, Chicago, IL 60606). Frequencies were also determined for all nominal data. Chi-square statistic was used where significant difference was required (p set at 0.05).

RESULTS

Out of the 54 subjects who consented to participate in this study, thirty-four subjects were diagnosed with DDD (mean age 30.74 years, SD 14.1, 95% confidence interval [CI] 25.8 to 35.7 years) and 20 were found to have normal MRI results (the control group) (mean age 23.35 years, SD 7.46, 95% confidence interval [CI] 19.9 to 26.8 years) (Table 2). Compared to the control group, there was significantly greater extent of disc degeneration over the L4/5 and L5/S1 levels in the DDD group (Table 2).

Table 2: Characteristics of subjects (N = 54)

Characterstics	*Normal MRI[1] findings (N=20)*	*MRI[1] with findings (N=34)*	*DDD[2] Significance (p)*
Age, yrs (SD)	23.35 (7.5)	30.74 (14.1)	0.05
Height, m (SD)	1.72 (0.1)	1.74 (5.3)	0.098
Weight, kg (SD)	68.05 (12.2)	72.4 (13.3)	0.259
Sit mins per wk	72941.5 (2199.4)	73905.93 (2256.9)	0.089
IPAQ[3] score	6270.98 (6409.4)	5873.9 (8150.8)	0.667
Mean grade of disc degeneration (SD)			
- L1/2[4]	0.20 (0.4)	0.12 (0.4)	0.220
- L2/3[5]	0.20 (0.4)	0.24 (0.7)	0.121
- L3/4[6]	0.20 (0.4)	0.44 (0.9)	0.452
- L4/5[7]	0.15 (0.4)	1.74 (1.2)	<0.001
- L5/S1[8]	0.35 (0.6)	1.97 (1.2)	<0.001

[1] MRI: Magnetic Resonance Imaging
[2] DDD: Degenerative Disc Disease
[3] IPAQ: International Physical Activity Questionnaire
[4] L1/2: Level of disc between the first and second lumbar vertebrae
[5] L2/3: Level of disc between the second and third lumbar vertebrae
[6] L3/4: Level of disc between the third and fourth lumbar vertebrae
[7] L4/5: Level of disc between the fourth and fifth lumbar vertebrae
[8] L5/S1: Level of disc between the fifth lumbar vertebra and first sacral vertebra

Table 3: Distribution of COL9A2 and COL9A3 gene polymorphism

Gene	*MRI findings*						*χ^2 and p*	
	Normal		*DDD*		*Total*			
	N	*%*	*N*	*%*	*N*	*%*	*χ^2*	*P*
COL9A2 p326 1st codon (*Trp2*) (*n* = 54)								
C/C	17	36.2	30	63.8	47	87.0	1.036	0.596
T/T	0	0.0	1	100.0	1	1.9		
C/T	3	50.0	3	50.0	6	11.1		
COL9A2 p326 2nd codon (*Gln2*) (*n* = 54)								
G/G	5	35.7	9	64.3	14	25.9	1.975	0.373
A/A	1	14.3	6	85.7	7	13.0		
G/A	14	42.4	19	57.6	33	61.1		
COL9A2 p335 1st codon (*Val2*) (*n* = 54)								
C/C	10	27.0	27	73.0	37	68.5	8.413	0.015
G/G	0	0.0	2	100.0	2	3.7		
C/G	10	66.7	5	33.3	15	27.8		
COL9A3 p17 2nd codon (*Gly3*) (*n* = 54)								
A/A	19	38.0	31	62.0	50	92.6	0.268	0.604
G/G	0	0.0	0	0.0	0	0.0		
A/G	1	25.0	3	75.0	4	7.4		
COL9A3 p103 1st codon (*Trp3*) (*n* = 54)*								
C/C	20	37.0	34	63.0	54	100.0	-	-
T/T	0	0.0	0	0.0	0	0.0		
C/T	0	0.0	0	0.0	0	0.0		

*Chi-square statistics was not computed since Trp3 allele was absent from all the subjects in this study.

The Val2 allele was present in both groups (DDD: 20.6%, control 50.0%, $p < 0.05$) (Table 3). Distributions of Trp2, Gln2 and Gly3 were 11.8%, 73.5% and 8.82% for DDD respectively and 15.0%, 75.0% and 5.0% for controls respectively. No significant difference in allelic distributions was found between the two groups (Table 3). The Trp3 allele was absent from all the subjects.

DISCUSSION

To date, this is the first paper to report on the significant difference in the distribution of the Val2 allele frequency among symptomatic controls (50%) and subjects with DDD (20.6%). Interestingly, none of the Val2 subjects with DDD have moderate or severe disc degeneration. Such Val2 allele frequency was also found in 7% of Finnish patients with discogenic sciatica, 8% in healthy controls and as well as 5% of controls with osteoarthritis (Paassilta et al. 2001). The mechanism by which Val for Leucine (Leu) substitution could contribute to DDD remains open to speculation. Both Val and Leu are hydrophobic and generally buried in folded proteins. It was reported that matrix acidity in a disc microenvironment of Sprague-Dawley rats caused a decrease in proliferation and viability of mesenchymal stem cells and was associated with a change in cell morphology (Wuertz et al. 2009). However, the pH of both Val and Leu are 5.96 and 5.98 respectively. In addition, Leu has an additional methylene group in its side chain compared with Val. We do not know if such difference in quarternary structures would alter the function of collagen IX or interfere with the covalent bonds between collagen IX and cartilage fibrils of collagen II which results in a change in the mechanical property of the intervertebral disc. The influence of Val2 allele on DDD merits further investigation.

No significant difference in Trp2, Gln2 and Gly3 allelic distributions was found between the control and DDD groups in this study. With the exception of Trp2 allele, Gln2 and Gly3 allelic distribution were not reported across the literature. The Trp2 allele was present in three subjects without DDD (out of 20) and four subjects with DDD (out of 34), all of whom were in the

age group 18-29 years. This infers a lack of association between DDD and Trp2 in the age group 18-29 years, which is consistent with finding reported by Jim and co-workers (Jim et al. 2005). Trp2 allele was found in 4% of affected Finnish individuals but none in their asymptomatic controls (Annunen et al. 1999). Here, recruitment of subjects was based on patients with symptoms of sciatica, which may have different underlying causes (Jim et al. 2005). However, the Trp2 allele was reported to be absent from the Greek patients (Kales et al. 2004). The Trp2 allele was also reported to be present in 20% of the Southern Chinese population (Jim et al. 2005). The presence of Trp2 allele was reported to be a significant age-dependent risk factor for DDD as affected Trp2 individuals, especially those at 40 to 49 years, had a 2.4 fold increase in the risk of developing DDD (Jim et al. 2005). It was further suggested that Trp2 mutation in collagen IX could render the intervertebral disc structurally weaker and therefore more vulnerable to stress from repeated loading. More recently, Trp2 was reported to be present in 21.4% of Japanese patients who had low back pain and/or sciatica (Higashino et al. 2007). Similarly, their result also suggested that Trp2 allele was an age-dependent risk factor for DDD particularly in patients under 40 years old. They reported that patients under 40 years with the Trp2 allele had a 6 fold increase in the risk of developing more severe disc degeneration. It is conceivable that the Trp2 allele could be expressed differently at different stages of the life span in an individual, although further study in this area would be warranted.

Interestingly, the Trp3 allele was similarly absent in this and other studies involving Asians (Jim et al. 2005; Higashino et al. 2007). However, this allele was identified as a common predisposing factor in the Finnish patients (12.2% of the patients with sciatica and 4.7% of their asymptomatic controls had this allele) (Paassilta et al. 2001). The presence of at least one Trp3 allele increased the risk of developing DDD by about 3 fold. The Trp3 allele was also reported to be present in 8.6% of the Greek patients with surgically and radiologically proven herniated discs and 4.9% of their asymptomatic controls (Kales et al. 2004). Rather than selection bias, such difference in allelic frequency could be due to ethnic differences, implying that the Trp3 allele is not a common risk factor for DDD in the Southern Chinese population (Jim et al. 2005), Japanese (Higashino et al. 2007) and possibly male Chinese Singaporean population.

Several limitations in this study deserve consideration. Firstly, the small sample size in this study could limit external validity. The baseline genetic equilibrium based on the Hardy-Weinberg equilibrium model could not be achieved in this pilot study. Secondly, with reference to the distribution of Val2 allele, it is worthwhile taking note of the total number of allele "G" in the control group (n=10) and lumbar DDD group (n=9) (Table 3). From a statistical point of view, that is, based on a 2x2 Chi^2 test (Yates Chi), the total number of allele "G" in the control group is not statistically greater than the lumbar DDD group (χ^2 =1.6614, p= 0.1974). Thirdly, participants in the control group had significantly less disc degeneration at the lower lumbar levels than those in the DDD group, likely to be linked to the latter being significantly older than the former (Table 2). We did not statistically adjust for potentially confounding factors such as age and level of disc degeneration because of the small sample size. Fourthly, this pilot case-control study may not be the most appropriate research design. Although some temporal relationship can be assumed to exist between gene polymorphisms and development of symptomatic DDD, given that expression of some allele, such as the Trp2 allele, may differ during the lifespan, a prospective cohort design could be considered. Lastly, the significant difference between the control and lumbar DDD group for the distribution of Val2 allele at 19 p335 of COL9A2 gene may be due to linkage disequilibrium with other loci, statistical fluctuation or even type I error. Therefore, the results from this pilot observational study require further investigation in order to verify genetic predisposition.

In conclusion, the distribution of Val2 allele was significantly decreased in subjects with DDD. The presence of at least one Val2 allele at exon 19 p335 of COL9A2 gene appears to have a protective effect against DDD. These findings should be interpreted with caution, given the limitations. Nevertheless, this study has established preliminary evidence of different distributions of Val2 allele in symptomatic male Chinese Singaporeans with and without radiologically diagnosed DDD.

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Appendix 1: Schneiderman's classification (Schneiderman et al. 1987)
Definition of MRI signal intensity

Term	*Definition*
Normal	Normal height and signal intensity
Intermediate	Speckled pattern or heterogenous decreased signal intensity
Marked	Diffuse loss of signal
Absent	Signal void

Definition of discographic patterns

Term	*Definition*
Normal	Normal disc appearance
Herniated	Protrusion of contrast beyond the normal disc margin
Degenerated	Loss of height, even distribution of contrast throughout the disc rather than centralization in nucleus, or fissuring
Degenerated herniated	Degenerated but with protrusion of contrast beyond normal disc margin