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ORIGINAL INVESTIGATION

Monoamine oxidase A gene polymorphisms and enzyme activity associated with risk of gout in Taiwan aborigines

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Abstract Taiwanese aborigines have a high prevalence of hyperuricemia and gout. Uric acid levels and urate excretion have correlated with dopamine-induced glomerular filtration response. MAOs represent one of the major renal dopamine metabolic pathways. We aimed to identify the monoamine oxidase A (*MAOA*, Xp11.3) gene variants and MAO-A enzyme activity associated with gout risk. This study was to investigate the association between gout and the *MAOA* single-nucleotide polymorphisms (SNPs) rs5953210, rs2283725, and rs1137070 as well as between gout and the *COMT* SNPs rs4680 Val158Met for 374 gout cases and 604 controls. MAO-A activity was also measured. All three *MAOA* SNPs were significantly associated with gout. A synonymous *MAOA* SNP, rs1137070 Asp470Asp, located in exon 14, was associated with the risk of having gout ($P = 4.0 \times 10^{-5}$, adjusted odds ratio 1.46, 95% confidence intervals [CI]: 1.11–1.91). We also showed that, when compared to individuals with the *MAOA* GAT haplotype, carriers of the AGC haplotype had a 1.67-fold (95% CI: 1.28–2.17) higher risk of gout. Moreover, we found that *MAOA* enzyme activity correlated positively with hyperuricemia and gout (P for trend = 2.00×10^{-3} vs. normal control). We also found that *MAOA* enzyme activity by rs1137070 allele was associated with hyperuricemia and gout (P for trend = 1.53×10^{-6} vs. wild-type allele). Thus, our results show that some *MAOA* alleles, which have a higher enzyme activity, predispose to the development of gout.

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Introduction

Gout is characterized by elevated serum urate, which crystallizes as monosodium urate in and around the tissues of joints when it is beyond its physiologic solubility limit (Choi et al. 2005; Emmerson 1996; Terkeltaub 2003). The clinical manifestation of gout varies according to its severity from episodic attacks to recurrent painful attacks of acute inflammatory arthritis, tophaceous gout, chronic polyarticular arthritis, uric-acid urolithiasis, complicated with possible sequelae of renal impairment and failure.

Urate is synthesized mainly in the liver and is mainly excreted in the urine. Approximately, two-thirds of daily urate excretion is via the kidney. An estimated 85–90% of gout cases result from poor renal disposal of urate (Pascual and Perdiguero 2006). Urate transport depends on specific transporter molecules (URAT1 [urate transporter 1], SLC2A9 [urate voltage-driven efflux transporter 1], organic anion transport [OAT] family OAT1, OAT3) located within the membrane of the renal proximal tubule cells, which account for part of the urate transport system in the kidney (Anzai et al. 2008; Dalbeth and Merriman 2009; Hediger et al. 2005). However, the intrarenal apical-basolateral urate transport pathway remains unclear. High serum uric acid levels are independently associated with increased proximal tubular sodium reabsorption in men (Cappuccio et al. 1993). Familial juvenile hyperuricemic nephropathy disease, characterized by hyperuricemia with underexcretion, gout, and chronic renal failure, is believed to be caused by distal salt wasting and a compensatory upregulation of proximal tubule resorption of sodium and uric acid (Taniguchi and Kamatani 2008). Furthermore, this intrarenal signaling pathway could be likely explained by the fact that proximal tubular reabsorption of uric acid occurs by an active transport mechanism closely linked to, or identical with, the tubular reabsorption of sodium. Thus, understanding the molecular mechanisms of urate transport in the kidney has potential research and clinical implications.

Dopamine plays a critical role in the regulation of different renal functions, including glomerular filtration, renin production, and sodium excretion (Zeng et al. 2007). Recently it has been shown that uric acid levels and urate excretion correlated with dopamine-induced glomerular filtration response (Sulikowska et al. 2008). In the proximal tubule, intrarenal dopamine, released within the tubule lumen and the peritubular space, serves as an autocrine/paracrine factor, locally modulating renal hemodynamic and/or excretory functions (Bianchi et al. 2003; Vindis et al. 2001). Many investigators have confirmed that dopamine decreases sodium reabsorption at the basolateral and apical membranes by inhibiting the Na^+–K^+ ATPase and the Na^+–H^+ exchanger through the activation of specific D1- and D2-like receptors (Jose et al. 1992; Pestana et al. 2001). The metabolism of dopamine involves mitochondrial monoamine oxidases (MAOs) and the cytosolic catechol-*O*-methyltransferase (*COMT*), since these enzymes degrade dopamine into 3,4-dihydroxyphenylacetic acid (DOPAC) and homovanillic acid (HVA) which can be easily filtrated through the tubule (Pestana et al. 2001). Two isoenzymes MAO-A and MAO-B are present in renal tubular epithelial cells. However, MAO-A is the predominant isoenzyme in the rat renal cell types involved in the deamination of the natriuretic hormone dopamine (Guimaraes and Soares-da-Silva 1998). Monoamine oxidases A (*MAOA*) and *COMT*, are believed to play a major role in regulating the renal dopamine activity (Pestana et al. 2001; Zeng et al. 2007). Although MAOs has been implicated in the development or the maintenance of mental retardation and neurodegenerative disorders (Cases et al. 1995), recent evidence has indicated that MAOs induces the production of injurious H_2O_2 in proximal tubule cells, which contributes to extracellular-regulated kinases (ERK) and c-Jun N-terminal kinase (JNK) activation and cell apoptosis, thereby promoting tissue injury (Kunduzova et al. 2002).

Taiwanese aborigines have a high prevalence of hyperuricemia and gout (Chang et al. 1997; Wang et al. 2004). In Taiwanese aborigines men 40 years or older, the prevalence of hyperuricemia is 40–60% and the prevalence of gout 5–20% (Chang et al. 1997). The direct causal mechanisms linking uric acid metabolism to the occurrence of gout in this susceptible population have not been unequivocally determined. At present there is no positive evidence for a direct role for X chromosome genes in most cases of gout. The goal of this study was to determine whether there is a correlation between some *MAOA* gene variants and gout. To this end, we examined in Taiwan aborigines the genotype distributions of *MAOA* gene variants in individuals with gout and in control individuals in a case–control study design and the relationship between these polymorphisms and MAO-A enzyme activity.

Methods

Subjects

From 2004 to 2007, a follow-up study of 374 gout participants (290 males and 84 females) was evaluated and a population-based study of 604 healthy controls (433 males and 171 females) was enrolled. As much as 514 participants (125 male and 41 female gouty patients; 52 male and 76 female hyperuricemia; 130 male and 90 female controls) could complete MAO-A enzyme levels testing. Gouty patients were diagnosed using criteria from the American College of Rheumatology (Wallace et al. 1977). Cases of gout were ascertained to satisfy 6 or more of the 11 criteria

and were confirmed by rheumatologist and primary care doctors in the local health center. Demographic and substance use information was collected by interview using a standardized questionnaire. Current/past smokers and drinkers (self-reported) were defined.

This study protocol was approved by Institutional Review Board of Kaohsiung Medical University and National Health Research Institutes. Written informed consent was obtained from all participants.

Uric acid levels determination

Hyperuricemia was defined by serum uric acid level exceeding 7.0 mg/dL and 6.0 mg/dL in men and women, respectively. An aliquot of plasma blood was stored at 4°C for routine blood tests, which included measurements of plasma total cholesterol, triglycerides, creatinine, and uric acid using an automated analyzer (Beckman LX-20, Palo Alto, California).

Genomic DNA extraction

Total genomic DNA was obtained from white blood cells using a genomic DNA extraction kit (PureGene DNA Purification Kit; Gentra Systems, Minneapolis, MN), and stored at −20°C until genotyping.

Genotype analysis

One missense SNP of *COMT* was selected (rs4680 Val158Met, located in exon 4). Two *MAOA* SNPs were selected (rs2283725, located in intron 3; rs1137070 Asp470Asp, located in exon 14) from a public reference database based on the minor allele frequency of >0.10 and the structure of the haplotype block having similar recombination in the HapMap Chinese population. To allow determination of the extent of linkage disequilibrium (LD) beyond the boundaries of the gene, one SNP in the 5′ intergenic region was included (rs5953210, located in 5′ near gene). DNA samples were genotyped using the TaqMan SNP allelic discrimination using the ABI7900HT (Applied Biosystems, Foster City, California). As much as 10% of the samples were tested in duplicate with no genotyping errors detected.

Amine oxidase activity measurements

The MAO activity was investigated by measuring the production of hydrogen peroxide (H_2O_2)—and therefore resorufin—from *p*-tyramine using the Amplex Red MAO assay kit (Molecular Probe, Eugene, Oregon). The MAO-A inhibitor, clorgyline, and the MAO-B inhibitor, pargyline, were included to help confirm the identity of the enzyme responsible for the amine oxidase activity. The assay is based on the detection of H_2O_2 in a horseradish peroxidase—coupled reaction using 10-acetyl-3,7-dihydroxyphenoxazine (Amplex Red reagent). The Amplex Red reagent reacts with H_2O_2 in a 1:1 stoichiometry, and the resulting fluorescence signal is directly proportional to H_2O_2 production and therefore to amine oxidase enzymatic activity. Experiments were carried out according to the manufacturer's instructions, with a final substrate concentration of 2 mM.

Statistical analysis

Statistical analyses were performed with SAS version 9.1.3 (SAS Institute Inc, Cary, NC). The genotype frequency of control in women confirmed to the Hardy–Weinberg equilibrium (HWE $P \geq 0.05$). For haplotype analysis, we estimated haplotype frequencies using the Haploview 4.0 program for a subset of SNPs selected on the basis of individual association with a given trait. Continuous variables, such as MAO-A enzyme activity and plasma triglyceride concentrations that were not normally distributed were log-transformed to achieve normality before using statistical models. In these analyses, the dependent variables were gout and MAO-A enzyme activity. Independent variables were alleles of the individual *MAOA* SNPs. The association study analyses used gender-specific SNPs from a logistic regression model after adjusting for age, gender, log-transformed triglycerides, uric acid, creatinine, and smoking categories. Multiple testing-adjusted *P*-values using the stepdown Bonferroni method of Holm (considering three SNPs) were computed for multiple testing corrections. Men and women were analyzed together, as well as separately, to examine gender-specific effects. MAO-A enzyme activity was calculated using linear regression models with adjustment for age and gender. P values < 0.05 were considered statistically significant.

Results

The baseline characteristics of the 374 gout cases and the 604 controls are presented in Table 1. Gout cases were significantly higher in males, log-transformed triglycerides, uric acid levels, and higher cigarette use ($P < 0.05$) than control subjects. Three analyzed *MAOA* SNPs showed significant associations with gout ($P \leq 9.90 \times 10^{-4}$; Tables 2, 3). A synonymous *MAOA* SNP, rs1137070 Asp470Asp, located in exon 14, was the significantly associated with the risk of having gout: the at-risk rs1137070 C allele frequency was 71% in gouty males versus 60% in control males ($P = 0.002$); at-risk C allele was 71% in gouty females versus 59% in control females ($P = 0.007$). With

Table 1 Characteristics of gout and control subjects in Taiwan aborigines

Variable	Gout (n = 374)	Control (n = 604)	P value*
Age (years)	50.3 (15.3)	51.9 (16.9)	0.142
Gender (%)			
Male	290 (78)	433 (72)	0.043
Female	84 (22)	171 (28)	
Total Cholesterol (mg/dL)	183.4 (50.1)	180.5 (48.7)	0.367
Triglycerides (mg/dL)	269 (289)	224.3 (288.4)	0.020
Log (Triglycerides) (mg/dL)	5.3 (0.8)	5.1 (0.8)	<0.001
Uric acid (mg/dL)	9.4 (2.4)	7.5 (2.1)	<0.001
Creatinine (mg/dL)	1.2 (0.7)	1.0 (0.2)	<0.001
BMI (kg/m^2)	26.2 (4.4)	26.1 (4.3)	0.989
Alcohol use (%)			
Nondrinker	99 (26)	153 (25)	0.692
Drinker	275 (74)	451 (75)	
Cigarette use (%)			
Nonsmoker	159 (43)	338 (56)	<0.001
Smoker	215 (57)	266 (44)	

Values are expressed as mean (standard deviation) unless otherwise stated

TC total cholesterol, *BMI* body mass index

* The P value was calculated continuous variables by the t test and by the χ^2 for the categorical variables

Table 2 Association between SNPs in *MAOA* and *COMT* genes and gout risk

SNP	Reference/ risk allele	Male				Allelic P-value*	Female[a]				Allelic P value
		Gout (n = 290)	RAF	Control (n = 433)	RAF		Gout (n = 84)	RAF	Control (n = 171)	RAF	
MAOA		A/a		A/a			AA/Aa/aa		AA/Aa/aa		
rs1137070 Asp470Asp	T/C	206/84	0.71	259/174	0.60	0.002	44/31/9	0.71	57/86/28	0.59	0.007
rs2283725	A/G	180/110	0.62	232/201	0.53	0.024	40/31/13	0.66	45/88/38	0.52	0.003
rs5953210	G/A	181/109	0.62	242/191	0.56	0.081	41/34/9	0.69	45/96/30	0.54	0.002
COMT		AA/Aa/aa		AA/Aa/aa			AA/Aa/aa		AA/Aa/aa		
rs4680 Val158Met	G/A	22/99/168	0.25	18/146/268	0.21	0.125	2/23/58	0.16	4/67/97	0.22	0.164

A risk allele, *a* non-risk allele, *RAF* risk allele frequency

* Allelic P value was calculated by χ^2 test

[a] The genotype frequency of control in women confirmed to the Hardy–Weinberg equilibrium

Table 3 Association between SNPs located in *MAOA* and gout risk

SNP	Gout		Control		Allelic P value	Stepdown Bonferroni	OR (95% CI)[a]
	Number	RAF[a]	Number	RAF			
MAOA	A/a		A/a				
rs1137070	325/133	0.71	459/316	0.59	4.00×10^{-5}	2.00×10^{-4}	1.46 (1.11–1.91)
rs2283725	291/167	0.64	410/365	0.53	2.80×10^{-4}	6.00×10^{-4}	1.38 (1.06–1.79)
rs5953210	297/161	0.64	428/247	0.55	9.90×10^{-4}	1.00×10^{-3}	1.34 (1.03–1.74)

A risk allele, *a* non-risk allele, *RAF* denotes risk allele frequency

[a] Odds ratio (OR) of SNP was adjusted for age, gender, log-transformed triglycerides, uric acid, creatinine, and cigarette use (yes/no), and the related 95% confidence intervals (CI)

gender-specific effects likely, we also showed the combined groups that SNP rs1137070 was the most significant associations with gout after adjusting covariates ($P = 4.00 \times 10^{-5}$, adjusted odd ratio 1.46, 95% CI: 1.11–1.91). We also showed that *COMT* rs4680 was not significantly associated with gout.

Table 4 Association between haplotype analysis across *MAOA* and gout risk

At risk haplotype (AGC) analysis indicates 3 SNPs of *MAOA* (rs5953210 A > G, rs2283725 G > A and rs1137070 C > T)

* *P* value was analyzed after 100,000 permutations

Haplotype	Gout Frequency	Control Frequency	χ^2	*P* value*	OR (95% CI)
G–A–T	0.27	0.36	11.51	1.60×10^{-3}	1.00
A–A–T	0.01	0.03	3.16	2.83×10^{-1}	0.48 (0.16–1.45
A–G–T	0.01	0.02	1.31	7.37×10^{-1}	0.76 (0.27–2.14
G–A–C	0.08	0.08	0.00	1.00×10^{1}	1.33 (0.84–2.13
A–G–C	0.61	0.50	16.03	8.00×10^{-5}	1.67 (1.28–2.17

Certain *MAOA* haplotypes were significantly associated with gout. We identified three SNPs (rs5953210 A > G, rs2283725 G > A, and rs1137070 C > T) in the *MAOA* gene to investigate the haplotypic effect of the studied SNPs on the risk of gout. Our results showed that, compared to individuals with *MAOA* GAT haplotype (gouty frequency 0.27 vs. control 0.36, $P = 1.60 \times 10^{-3}$), carriers of *MAOA* AGC haplotype (gouty frequency 0.61 vs. control 0.50, $P = 8.00 \times 10^{-5}$) had a 1.67-fold (95% CI: 1.28–2.17) increased risk of developing gout (Table 4). The odds ratio of at-risk haplotype was slightly larger than the effects of the single SNP, implying that *MAOA* blocks may be inherited more frequently in gout cases.

Moreover, we found that MAO-A enzyme activity correlated positively with hyperuricemia (8.88 ± 0.05 AU [arbitrary unit], $P = 0.084$) and gout (9.00 ± 0.06 AU, $P = 0.003$) compared with control individuals (8.72 ± 0.07 AU) (Bonferroni post-hoc test after adjustment of covariates; P for trend $= 2.00 \times 10^{-3}$). We also observe that MAO-A enzyme activity by rs1137070 C allele correlated positively with hyperuricemia (8.94 ± 0.05 AU, $P = 3.50 \times 10^{-3}$) and gout (9.06 ± 0.06 AU, $P = 9.25 \times 10^{-5}$) compared with control individuals of wild-type T allele (8.59 ± 0.09 AU) (Bonferroni post-hoc test after adjustment of covariates; P for trend $= 1.53 \times 10^{-6}$; Fig. 1). Our results suggest that variant of the SNP rs1137070 located within *MAOA* functional domain could affect enzyme activity in the renal/circulation system.

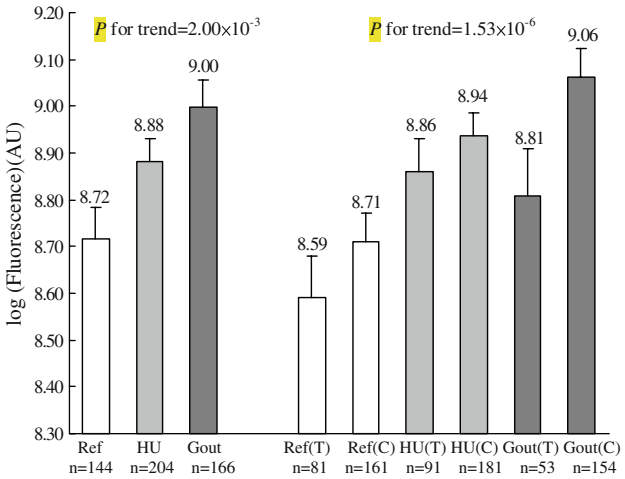

Fig. 1 Association of MAO-A enzyme activity and rs1137070 allele with hyperuricemia (HU) and gout compared with normal control (Ref) after adjustment for age and gender. *Error bars* indicate standard errors; *AU* arbitrary unit

Discussion

The pathogenesis of gout remains obscure. Genetic studies may provide important insights on the etiology of hyperuricemia and may help determine the risk of developing gout. With the strong male predominance of gout it is tempting to speculate that a defective gene or genes on the X chromosome may be involved. In this study, we found that there is a relationship between three common polymorphisms (risk allele frequency 62% to 71% in gout cases) within the *MAOA* (Xp11.3) gene and gout risk in Taiwanese aborigines. Indeed, we showed that the *MAOA* SNPs were associated with a 1.34 to 1.46-fold risk of developing gout and a risk of developing gout was also detected in subjects carrying the AGC haplotype (OR = 1.67). These results indicate that certain polymorphisms in the *MAOA* gene may be crucial in the development of gout.

Proximal tubule cells are the major source of renal dopamine synthesized from circulating filtered *L*-DOPA (*L*-3,4-dihydroxy-phenylalanine) to decarboxylation of *L*-DOPA by the cytosolic aromatic *L*-amino acid decarboxylase (AADC) (Pestana et al. 2001). Interestingly, sodium promotes the delivery of *L*-DOPA to sites of uptake in renal tubules. Newly formed dopamine in the proximal tubule is not stored; therefore, it can leave the cell and activate specific D1- and D2-like receptors, thereby leading to inhibition of sodium transport (Fig. 2a; Pestana et al. 2001).

Therefore, there are at least two plausible pathway mechanisms that may account for gout occurrence (Fig. 2b). The first relates to the dopaminergic system that plays an important role in the regulation of blood pressure, sodium homeostasis, and kidney function. MAOs represents one of the major renal dopamine metabolic pathways (Fernandes and Soares-da-Silva 1994). Several studies suggest that reduced renal dopamine production is associated with a decrease in renal function and lack of dopamine may

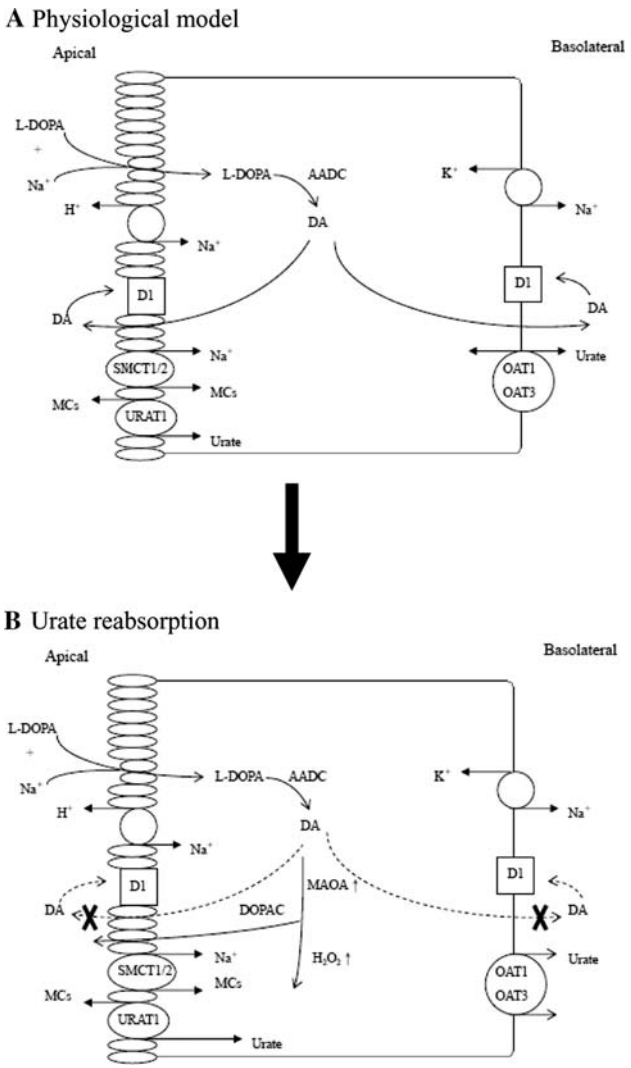

Fig. 2 Proposed model of impaired urate excretion and uric acid levels in response to dopamine (DA) metabolism by monoamine oxidase A (*MAOA*) within renal tubular proximal epithelial cells. **a** Physiological model. Renal DA is synthesized intracellularly from decarboxylation of *L*-DOPA (3,4-dihydroxy-*L*-phenylalanine) by cytosolic aromatic *L*-amino acid (AADC) after co-transport with sodium. Newly formed DA can exit the cell by inhibiting specific D1 receptor and blockage of sodium channels (Na^+–K^+ ATPase and Na^+–H^+ exchanger) that increase sodium excretion. **b** Urate reabsorption. Metabolism of DA by *MAOA* leads to increased formation of dihydroxyphenylacetic acid (DOPAC) and degradation products of hydrogen peroxide (H_2O_2), indirectly increasing urate reabsorption with sodium retention since uric acid levels and urate excretion correlate with dopamine-induced glomerular filtration response. Urate can enter into cell by apical route through scaffolding proteins effectively exchange for intracellular monocarboxylates (MCs) via apical located *SMCT1/2* (sodium-dependent monocarboxylates transporter 1/2) and *URAT1* (urate transporter 1). OAT1 and OAT3 (organic anion transporters 1/3) contribute to basolateral urate uptake

contribute to the inability to maintain sodium balance and an increase in blood pressure (Pestana et al. 2001). Renal excretion of uric acid is reduced in situations in which renal tubular reabsorption of sodium is increased (Feig et al. 2008). Urinary excretion of free dopamine (DOPAC) and HVA is markedly higher in patients who have recovered graft function than in those with acute tubular necrosis. In patients with recovered graft function, the daily urinary excretion of DOPAC (MAOs catalyzes the formation of DOPAC), but not that of HVA (COMT catalyzes the formation of HVA), increases progressively until day 12 and then remains constant (Pestana et al. 2001). Therefore, it has been suggested that MAOs play an important role in determining renal dopamine activity and urate reabsorption with sodium retention.

Our findings indicate that MAO-A enzyme activity correlates positively with hyperuricemia and gout. Decreased activity of the dopaminergic system may result in increased MAO-A enzyme activity and enhanced metabolism in the renal tubules. Increased MAO-A enzyme activity may preserve tubular units or may result in reduced renal blood flow with increased sodium reabsorption in these residual tubular units. Paradoxically, diuretics induce hyperuricemia by increasing urate reabsorption. It has been noted that hyperuricemia occurs when diuretics produce sufficient salt and water loss that results in volume contraction; this stimulates solute reabsorption at the proximal tubule, and this effect is corrected by administration of fluids (Pascual and Perdiguero 2006). Thus, the effects of MAO-A activity is in part related to increased urate reabsorption, which is due to enhanced reabsorption of sodium during dopamine degradation.

A second plausible mechanism relates to dopamine degradation by MAOs which generates hydrogen peroxide. Hydrogen peroxide may not be fully scavenged by intracellular antioxidants in proximal tubule cells (Pizzinat et al. 1999). A number of observations show that hydrogen peroxide combines with other reactive oxygen species (ROS), resulting in the activation of various signal transduction processes (serine/threonine phosphorylation; Monteiro and Stern 1996), and activation enzymes (ERK and JNK), and transcription factor (NF-κB, nuclear factor-κB; Vindis et al. 2001). These pathways may exert proliferative effects on proximal tubule cells and promoting apoptosis or cell necrosis (Bianchi et al. 2003; Kunduzova et al. 2002; Pestana et al. 2001; Vindis et al. 2001). Uric acid is also believed to affect tubular dysfunction and participate in tubulointerstitial damage (Feig et al. 2008).

Interestingly, the polymorphism at *MAOA* shows long-standing balancing selection (Tajima's $D = 1.86$ and Fay and Wu's H statistic test = 1.49, $P < 0.05$) which reveals nine persons of Taiwanese aboriginal, potentially acting on *MAOA*-related phenotypes (Gilad et al. 2002). Uric acid is a potent antioxidant and free radical scavenger (Choi et al. 2005; Johnson et al. 2008). Thus, it is interesting to notice that early hunter–gatherer societies, whether to offset the metabolic thrift (sufficient sodium retention which leads to

reduced water loss into the urine) in more MAO-A activity delivery correspondingly more ROS generated so the innate ability to counterbalance free radical production became imperative and increased ability to hunt. This could indicate preexisting equilibrium between ROS generation and antioxidant protection, where they naturally conserve more uric acid than the normal general population. Its success is reflected in the higher prevalence of susceptible alleles for *MAOA* with up to 71% (rs1137070 risk allele frequency). Whatever the reason for the maintenance of a balanced variant, it is interesting to note that variation of *MAOA* may fit a previously proposed hypothesis whereby alleles that confer resistance to physical activity and prevent renal damage in ancient settings are now associated with susceptibility to gout disease.

Limitations to our study is that we have no replication of the racial-specific diversity data across other races/ethnics. However, the isolation of the Taiwanese aboriginals has increased their genetic homogeneity, thus facilitating the search for gout susceptibility genes.

In conclusion, our results indicate that *MAOA* gene and MAO-A enzyme activity are associated with increased susceptibility to gout in Taiwanese aborigines. Additional studies are needed to verify this possibility and to elucidate the role between *MAOA* gene functional variant and the pathophysiology of gout.

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