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Citation	International Journal of Cardiology, 2005, v. 102 n. 1, p. 111-116
Issued Date	2005
URL	http://hdl.handle.net/10722/48558
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An affected pedigree member analysis of linkage between the dopamine D2 receptor gene TaqI polymorphism and obesity and hypertension

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Short title: DD2R gene linked to obesity and HT

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Abstract

Background: Dopamine modulates a variety of physiological functions including natriuresis and satiety. We have previously reported that the TaqI polymorphism of the dopamine D2 receptor (DD2R) gene is associated with both blood pressure and obesity indices in a normoglycaemic Hong Kong Chinese population. In this study, we present evidence confirming the linkage between this gene polymorphism, obesity and hypertension.

Methods: 274 siblings from 96 normoglycaemic hypertensive families were recruited, including 133 who were hypertensive. Central obesity was defined as a waist-to-hip ratio of ≥0.9 and ≥0.85 in males and females respectively, and was identified in 99 of the siblings. The DD2R gene TaqI polymorphism was identified with a polymerase chain reaction based restriction fragment length polymorphism protocol. The affected pedigree member linkage analysis (sib-pair program, version 0.99.9, by DL Duffy) was used to assess for linkage between this gene polymorphism, obesity and hypertension in 73 families with siblings discordant for hypertension.

Results: The A1 allele frequencies were similar in the 133 hypertensive, and 141 normotensive siblings, including the 99 centrally obese siblings at 0.431, 0.421 and 0.418, respectively. Affected pedigree member linkage analysis suggested that the DD2R gene TaqI polymorphism had evidence of linkage with blood pressure (t=-1.86, p=0.013), as well as with obesity (t=-1.58, p=0.007).

Conclusion: Our data in normoglycaemic Hong Kong Chinese supports that the DD2R gene TaqI polymorphism is a marker associated with the pathogenesis of obesity and hypertension.

Introduction

The catecholamine dopamine, a precursor of noradrenaline and adrenaline, is an endogenous neurotransmitter, which modulates a wide variety of physiologic functions including behaviour, ion transport, vascular tone, and blood pressure. There are reports of a deficiency in renal dopamine synthesis and/or secretion in various forms of human hypertension [1]. As endogenous renal dopamine plays an important role in maintaining body sodium homeostasis, renal dopaminergic deficiency may contribute to the development and maintenance of high blood pressure, at least in a proportion of subjects with essential hypertension [2]. Suppression of dopaminergic activity has been observed in young normotensive subjects with a family history of hypertension before the development of hypertension emerged [3]. Dopamine also plays a major role in the regulation of appetite [4]. Dopaminergic agonist drugs, such as dextroamphetamine, have been shown to suppress appetite and subsequently to reduce weight, whereas a major side effect of dopamine D2 receptor antagonists, such as haloperidol, is marked weight gain.

The dopaminergic system involves the interaction of dopamine with several specific dopamine receptors, which belong to a large family of G-protein-coupled receptors [5]. Biochemical and pharmacological studies have shown that the physiological actions of dopamine are mediated by interaction with two basic types of G-protein-coupled receptors, D1-like and D2-like, which stimulate and inhibit, respectively, the enzyme adenyl cyclase [6].

The human dopamine D2 receptor (DD2R) gene contains eight exons, spans at least 50 kilobases (kb), and has the unusual feature of a large (greater than 25 kb) intron (intron 1) separating the presumed promoter region from the protein-coding region [7]. The D2

receptor locus has been localised to the 11q22 to 11q23 region of the human genome. Grandy and colleagues cloned the human DD2R gene in rats and humans and described a TaqI polymorphism at the 3' end of the DD2R gene [8]. Previous studies showed that the allelic variants of the DD2R gene play a role in the regulation of body weight [9]. In Pima Indians, a genome wide scan provided strong evidence on chromosome 11q of a locus influencing susceptibility to obesity,[10]. Additionally, Hanson et al. found linkage between chromosome 11q and body mass index (BMI) and diabetes mellitus [11]. In a population-based study, we have previously reported this polymorphism to be associated with both obesity and blood pressure in normoglycaemic Chinese subjects, but in diabetics only the relationship with obesity was evident [12,13]. In this study we report additional data, in a different study group, supporting a relationship between this marker and blood pressure in an affected pedigree member analysis.

Methods

The study was approved by the Clinical Research Ethics Committee of the Chinese University of Hong Kong, and all subjects gave written informed consent. Families were recruited if the proband was found to be hypertensive and had siblings resident in Hong Kong. From 96 families with at least one hypertensive sibling, a total of 274 siblings were studied, of which 133 had hypertension. Most of the families had two or three siblings (64.6%) with a further 29.2% having four or five siblings. Blood pressure was measured using a semiautomatic sphygmomanometer (Critikon Dynamap 8100, Critikon Inc, CA, USA) by a trained research nurse, and was taken as the mean of readings taken 5 mins apart on two separate occasions in triplicate. The siblings defined as hypertensive had sitting blood pressure $\geq$140/90 mm Hg on no treatment or after stopping antihypertensive treatment for 4-8 weeks. Subjects with borderline high blood pressure levels between 130-139/80-89 mm Hg were excluded from the analyses.

Blood sampling was performed between 9-10 am after an overnight fast. At the same time, height and body weight were measured, and family history was ascertained by interview, including details of whether the subject had any relatives within the third degree who were hypertensive or diabetic. Families with siblings with diabetes or secondary hypertension were excluded. There were 99 siblings (69.9% hypertensive) with central obesity in the study defined by waist-to-hip ratio (WHR, ≥0.9 and ≥0.85 in males and females, respectively). The anthropometric and plasma biochemical parameters, after an overnight fast, were measured as described previously [12,13]. The 24 hour urinary dopamine levels were determined in a subset of 74 sibling pairs, using high performance liquid chromatography with electrochemical detection [14].

DNA was extracted from white blood cells. The DD2R gene TaqI polymorphism was examined by polymerase chain reaction (PCR) as described previously [12,13]. Briefly, the 310 bp fragment PCR product was then digested with 5 U TaqI restriction enzyme (Boehringer Mannheim, Germany) in a final volume of 20 µl for 6h at 65°C. The digestion products were visualised on a 2% agarose gel with ethidium bromide staining. The A1 allele remained undigested with the 310 bp fragment, the A2 allele produced bands 180 bp and 130 bp in size.

The affected-pedigree-member method (APM) is a nonparametric method that uses identity-by-state (IBS) status to test for linkage as indicated by increased marker similarity between affected-affected relative pairs. The APM method contrasts the null hypothesis of no association between marker variation and disease against a very general alternative hypothesis.

There are two subtypes of affected pedigree member (APM) linkage analysis, namely identity by state (IBS) and identity by descent (IBD). Sib-pair analyses usually require an unambiguous determination of the sib IBD relations at the marker locus. Such information is available only if the parents are available for study. In late-onset diseases such as hypertension, the parents are often not available and thus IBD cannot be determined. Weeks and Lange proposed the substitution with an IBS relationship as a method of solving this problem, and thus allowing sib-pair analyses to be performed in cases in which parents are unavailable. Additionally, the mode of disease inheritance is not required [15]. In this study, we used the APM IBS method (sib-pair program, version 0.99.9 (26th July 2000), by DL Duffy, http://www2.qimr.edu.au/davidD/)[16] to calculate a T statistic, to identify whether the centrally obese hypertensive members of a pedigree have an excess sharing of alleles of the DD2R gene polymorphism. Weighting functions were used in the analysis, which are dependent on the frequency of the allele, the rationale being that a match across a pair of individuals for a rare allele is more striking evidence for association between disease and genotype than would be the case for common alleles. Weeks and Lange proposed $f_y = 1/\sqrt{p_y}$ where p_y is the population frequency of the y th allele at the marker locus. This function represents a good compromise between ignoring (i.e. $f(p) = 1$) or strongly weighting (i.e. $f(p) = 1/(p)$) the allele frequency [15].

Data from normally distributed parameters are presented as means ± SD, whereas those parameters with a skewed distribution were logarithmically (base 10) transformed and are presented as geometric means with 95% confidence intervals of the mean. Differences in the levels of anthropometric and biochemical parameters between the hypertensive and normotensive siblings were assessed using the Student's t-test. Differences between group means were tested using analysis of covariance (ANCOVA),

which allowed for adjustment for age and gender. The χ^2 test was used to identify any differences in the genotype or allele distribution of the DD2R TaqI polymorphism between the normotensive and hypertensive populations and to assess for deviations from the Hardy-Weinberg equilibrium for each cohort. A p values less than 0.05 was indicative of statistical significance.

Results

The 274 study subjects, including 96 sibships and 193 discordant sib-pairs, were recruited. Of the 96 families, 40.6% had 2 siblings, with 24.0% having 3 siblings and 14.6% each had 4 or 5 siblings. They included 99 siblings (69.9% hypertensive) with central obesity and 133 siblings with essential hypertension. The hypertensive siblings generally had higher levels of the components of the metabolic syndrome, including indices of obesity and an adverse lipid profile (Table 1). Even though normoglycaemic subjects were recruited, levels of glycaemia were significantly higher in the hypertensive compared to normotensive siblings. The plasma electrolytes, sodium and potassium, were significantly higher and lower, respectively, and 24 hour urinary sodium excretion was also higher in the hypertensive subjects. Urinary dopamine output was 25% higher in the hypertensive compared to the normotensive siblings.

In our previous population study of the dopamine D2 receptor gene TaqI polymorphism, it was found that the frequency of the A1 allele was 46.8% in a total of 383 hypertensive and control Chinese subjects [13]. Compared to the earlier study there was no significant differences in the A1 allele frequency in the 133 hypertensive (43.1%, p>0.05), 141 normotensive (42.1, p>0.05) or the 99 centrally obese siblings (41.8%, p>0.05) and the allele frequencies were similar in these 3 groups.

Allele and genotype frequencies of all the subjects were consistent with the Hardy-Weinberg equilibrium. The anthropometric and biochemical data of subjects with the A2A2, A1A1 and A1A2 genotypes were compared by analysis of covariance (ANCOVA), with age and gender adjustment. Between the A1A2 and A1A1 groups, there were significant differences in WHR and triglycerides (p=0.003, p=0.007, respectively), with WHR and triglyceride values being higher in the A1A1 homozygote group (Table 2). There was a significant increasing relationship between 24 hour urinary dopamine levels and increasing proportions of the A1 allele.

Using the APM method, 44 hypertensive-hypertensive sib-pairs and 187 hypertensive-normotensive sib-pairs were analysed using three weighting functions. There was a tendency for linkage between the DD2R gene polymorphism and hypertension in the discordant sib-pairs, with T=-1.797, p=0.036 for weighting function $f(p) = 1$, T=-1.863, p=0.013 for weighting function $f(p) = 1/\sqrt{p}$ and T=-1.868, p=0.012 for weighting function $f(p) = 1/p$. Similarly when the 75 sib-pairs concordant and 173 sib-pairs discordant for central obesity were analysed, evidence of linkage was found between this gene polymorphism and central obesity in the discordant sib-pairs (T=-1.588, p=0.056, T=-1.575, p=0.007 and T=-1.503, p=0.006, respectively), but not in the concordant sib-pairs.

Discussion

Dopamine influences blood pressure regulation through both central and the peripheral mechanisms [17,18]. In this sibling study, all the subjects had a hypertensive family history, increasing the risk that the normotensive siblings may subsequently develop hypertension.

It is believed that obesity is a major factor contributing to the development of essential hypertension [19-21]. Obesity is associated with increased tubular sodium reabsorption, in part through enhanced activation of antinatriuretic renin-angiotensin and sympathetic systems [19,22], as reflected by elevated plasma sodium, and lower plasma potassium, the latter being reciprocally excreted [19,22]. Evidence that the dopaminergic system may be implicated in obesity is suggested from studies showing the effectiveness of amphetamine-like drugs in weight loss [23]. Furthermore, neuroleptics, which block the D2 dopamine receptor, have been shown to lead to body weight gain in clinical [24] and animal studies [25]. There was a clear relationship both between elevated blood pressure and increasing proportions of the A1 allele with increasing 24 hour urinary dopamine excretion. It is possible that counter-regulatory systems are responsible for the elevated levels of the natriuretic dopamine to attenuate the increased tubular sodium reabsorption associated with the obese state. Additionally the elevated dopamine levels may be in response to defective signal transduction, which has been reported in hypertensive subjects [2], and contrasts to other evidence suggesting a relative suppression of dopaminergic activity in young normotensive subjects with family history of hypertension before the development of hypertension emerged [3]. The DD2R TaqI polymorphism may therefore be in linkage disequilibrium with a mutation that modulates renal dopamine production, the major source of urinary dopamine.

Population studies have clearly documented the relationship between obesity and hypertension [26]. Even modest weight gain over a period of a few weeks can elevate blood pressure in experimental animals and humans, and weight loss reduces blood pressure in hypertensive, as well as normotensive subjects [27].

In this study, the DD2R gene TaqI polymorphism showed evidence of linkage with central obesity and hypertension in our hypertensive families. The linkage of obesity with an increased prevalence of the A1 allele may suggest that either the mutation causing the TaqI polymorphism or a mutation in linkage disequilibrium with the TaqI polymorphism is associated with a decrease in the function of the DD2R gene [28]. Linkage results from the cosegregation of two loci in sets of related individuals and therefore represents the relationship between the two loci of interest. This contrasts with association studies that assess the relationship in unrelated individuals between the states of the two loci. Therefore, when the disease gene is not used as the marker, linkage of the two loci does not infer association between states of the two loci in the population. Linkage, the more sensitive approach, in the absence of association, as in the current study, suggests the TaqI polymorphism is at least 50 kb away from the gene of interest.

Obesity is a metabolic disorder with multiple pathophysiological consequences, including insulin resistance, increased renal sodium reabsorption, and development of hypertension [19]. It is now well established that a particular obesity phenotype is uniquely associated with the propensity to develop hypertension and other cardiovascular risk factors. In the mid-1950s, Jean Vague, a French clinician, noted that the cardiovascular and metabolic complications of obesity were most common in those individuals with the upper body fat distribution pattern [29]. Vague's observations drew little comment until the 1980s, when epidemiological surveys, particularly from Scandinavia, using WHR as a convenient surrogate for body fat distribution, confirmed a relationship between abdominal or upper body obesity and cardiovascular risk [30,31]. Cardiovascular risk factors, including hypertension, thus track with the upper body or abdominal form of obesity, and now are considered part of the metabolic syndrome [32].

In the current study the increased central adiposity as indicated by the greater WHR in those subjects with the homozygous A1 genotype may be mediating the similar significant increases in triglyceride levels.

Dopamine regulates appetite and behaviour through dopaminergic neurones. Studies in genetically heterogeneous human populations have shown weak associations between DDR2 gene variants and obesity [9,33-35]. Reports of the DD2R Ser311Cys and TaqI polymorphisms in Pima Indians, suggested a weak association with the former polymorphism, but neither polymorphism accounted for the previously reported linkage with BMI on chromosome 11 in Pima Indians [36]. In this sibling-based study, we found some evidence of linkage between this gene polymorphism and blood pressure and WHR, but not BMI, supporting findings from the previous population studies in Hong Kong [13]. In Chinese populations, obesity is a major predictor of hypertension, rather than for example insulin resistance, which although increased in the hypertensive siblings is largely determined by obesity [13,20]. However, we previously reported that the A2 allele was associated with increased blood pressure and lower indices of obesity [13]. It would also suggest that possibly more than one dopaminergic mechanism is involved in the regulation of these parameters. The relationship with urinary dopamine may mediate the relationship with blood pressure, yet the dopaminergic reward system most likely controls the association with obesity [2,4].

In conclusion, the DD2R gene TaqI polymorphism showed some evidence of being in linkage disequilibrium with the central obesity and hypertension in these discordant sibling pair from hypertensive families of Hong Kong Chinese. The A1 allele of this gene polymorphism was related to the higher WHR in our hypertensive families in agreement with our findings from population-based studies.

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Table 1 Biochemical and anthropometric measurements for the 193 discordant hypertensive and normotensive sibling-pairs

	Hypertensives (n=133)	Normotensives (n=141)	P value
Age (years)	41.7±8.3	38.1±6.7	<0.001
Gender (% male)	49.6	29.8	<0.001
Mean SBP (mm Hg)	148±13	115±9	<0.001
Mean DBP (mm Hg)	91±9	67±8	<0.001
Weight (kg)	69±13	60±10	<0.001
Height (m)	1.58±0.08	1.59±0.08	0.433
Waist circumference (cm)	87.4±10.0	78.9±8.5	<0.001
Hip circumference (cm)	100.5±7.6	96.6±5.8	<0.001
Waist-to-hip ratio	0.87±0.07	0.82±0.06	<0.001
Body mass index (kg/m^2)	27.2±3.8	23.8±3.2	<0.001
Total cholesterol (mmol/L)	5.5±1.0	5.0±1.0	<0.001
Triglycerides (mmol/L)	1.3 (1.2-1.5)	1.2 (1.37-1.1)	<0.001
HDL-cholesterol (mmol/L)	1.3±0.4	1.4±0.4	<0.001
LDL-cholesterol (mmol/L)	3.5±0.8	3.2±1.0	<0.001
Glucose (mmol/L)	5.2±0.9	4.9±0.4	<0.001
Plasma insulin (mmol/L)	52.5 (44.5-61.9)	41.0 (36.2-46.4)	<0.001
Insulin-glucose product	264 (223-312)	201 (177-228)	<0.001
Plasma sodium (mmol/L)	141.7±1.9	141.1±1.5	<0.001
Plasma potassium (mmol/L)	4.2±0.5	4.3±0.4	<0.001
24h urinary sodium (mmol/d)	191.6±84.3	176.3±71.5	0.048
24h urinary potassium (mmol/d)	48.4±17.5	46.8±20.6	0.294
24h urinary dopamine (mmol/d)	1559 (1420-1711)	1272 (1125-1440)	<0.001
DD2R A1 allele frequency (%)	43.1	42.1	0.852

Mean±SD, median (95%CI)

Table 2 Demographic characteristics of subjects according to A1A2, A2A2 or A1A1 genotype of the DRD2 gene

Characteristics	DRD2 gene TaqI polymorphism genotypes		
	A2A2 (n=89)	A1A2 (n=136)	A1A1 (n=49)
Age (range, years)	40±8 (25-58)	39±7 (23-58)	40±7 (27-54)
Gender (% male)	34.8	40.4	44.9
Systolic blood pressure (mm Hg)	133±22	129±22	134±17
Diastolic blood pressure (mm Hg)	80±17	78±16	82±13
Weight (kg)	64.4±11.6	64.7±12.7	65.5±12.4
Body mass index (kg/m^2)	25.5±3.72	25.1±3.94	25.6±3.68
Waist-to-hip ratio	0.85±0.07	0.85±0.07	0.87±0.07[*]
Total cholesterol (mmol/L)	5.19±1.01	5.14±1.05	5.44±1.11
Triglycerides (mmol/L)	1.1(1.0-1.3)	1.0(1.12-1.09)	1.5(1.2-1.8)[*]
HDL-cholesterol (mmol/L)	1.34±0.40	1.34±0.34	1.24±0.38
LDL-cholesterol (mmol/L)	3.26±0.97	3.30±1.01	3.37±0.82
Glucose (mmol/L)	5.0±0.4	5.0±0.8	5.1±0.8
Plasma insulin (mmol/L)	50.7(42.9-60.0)	43.0(37.7-49.0)	48.0(39.2-58.0)
Insulin-glucose product	252 (211-301)	214 (186-247)	240 (193-298)
Plasma sodium (mmol/L)	141.3±1.4	141.2±1.7	141.6±1.5
Plasma potassium (mmol/L)	4.3±0.4	4.2±0.4	4.2±0.4
24h urinary sodium (mmol/d)	171.5±65.8	187.1±83.2	183.2±70.2
24h urinary potassium (mmol/d)	48.0±27.2	44.3±15.4	47.1±14.0
24h urinary dopamine (mmol/d)	1240 (1079-1425)	1434 (1302-1579)	1702 (1462-1981)[**]

Mean±SD, median (95%CI); [*]p<0.05 when A1A1 versus A1A2 genotype. [**]p<0.05 when A1A1 versus A1A2 and A2A2 genotypes.