

Predictors of Success in Smoking Cessation Among Hospitalised Patients

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Introduction

The aim of this study was to determine the clinical factors affecting smoking abstinence in hospitalised patients receiving a smoking cessation intervention that is considered adequately intensive for effectiveness based on current evidence.¹⁻³

Materials and Methods

This prospective study was conducted in a university-affiliated urban hospital. The recruitment sites for the study were 4 general wards of the hospital. These 4 wards admitted patients from the cardiology and respiratory medicine departments. The participants recruited were current smokers, 19 years of age or older, of stable condition to receive the intervention, had no gross memory impairment, were literate and had access to a telephone for follow-up intervention.

A dedicated smoking counsellor was employed to contact patients within 3 days of admission, to ask if they would be willing to talk about smoking. Those who agreed received a 30-minute behavioural counselling session provided at the bedside. Beginning with an assessment of the patients' intentions concerning smoking cessation,^{4,5} the counselling was tailored accordingly. The intervention was based on 5 principles: (1) smoking cessation is a process, (2) individuals choose to quit smoking; they cannot be forced, (3) smoking interventions need to be individualised and stage-matched, (4) people perceive that they have the skills and ability to quit smoking if they are to be successful (smoking cessation self-efficacy), and (5) cessation efforts must be reinforced with follow-up.

The following were components of the intervention: (1) a bedside counselling session, (2) written self-help material, (3) a prompt in the medical records for physicians and (4) counselling via telephone after discharge. The counsellor reviewed the dangers of smoking and the benefits of quitting; assessed participants' knowledge and beliefs about, and potential barriers to smoking cessation; and provided counter-arguments to belief barriers. Behavioural self-management techniques to counter known relapse triggers, such as stress, the presence of other smokers, alcohol use and depression, were also discussed. Subjects were encouraged to set a firm quit date, preferably that same day; the focus was on making a decision to maintain abstinence in the hospital and after discharge. At the close of the session, the patients were given the booklet "Quit Kit",⁶ printed in whichever language (English, Chinese, Malay or Tamil) the patients preferred, and were asked to review it. A sticker was placed on each counselled patient's hospital notes to remind the staff and physician to advise smoking cessation at future contacts.

Patients who met the criteria for nicotine dependence based on the use of the modified Fagerstrom Tolerance Questionnaire,⁷ or who were noted to have severe withdrawal symptoms during hospitalisation, were offered nicotine replacement therapy. The smoking counsellor obtained prescriptions from primary physicians and instructed patients on the appropriate use of either the nicotine patch or inhaler. Verbal instructions on the use of these agents,

including a schedule for decreasing use after 8 to 12 weeks were provided.

Data collection procedures were like medical record extraction from the subject's medical records for current medical information, and for medical history and risk factor data through the use of a standardised data collection form. The baseline information collected include: (1) sociodemographic factors; (2) medical history; (3) smoking history (pack-years, usual and recent cigarette use, and number of prior quit attempts); (4) nicotine withdrawal symptoms; (5) readiness (i.e., intention) to stop smoking; and (6) patient beliefs about the relationship between smoking and their health. After discharge, participants received follow-up telephone counselling calls from the same smoking counsellor. These calls were made at fortnightly intervals during the first post-discharge month and then monthly intervals for the following 2 months. These telephone counselling and follow-up sessions continued the skills training initiated during the face-to-face counselling session, and each telephone counselling call lasted less than 30 minutes. Participants who had resumed smoking were encouraged to set new quit dates.

Participants were defined as being continuously abstinent if they reported that they had not smoked at all in the past week. They also had to have an expired carbon monoxide (CO) reading <10 ppm. Data at the 2-month follow-up were collected at the time of routine hospital visit after discharge. Patients unavailable for follow-up were excluded. Patients with self-confessed abstinence with refusal of expired CO testing during follow-up were considered to be smokers.

Univariate and multivariate analyses were performed to identify baseline characteristics that were associated with smoking cessation after hospital discharge. In the univariate analysis, the independent student t-test was used to compare continuous variables, whereas the chi-square test was used for categorical variables. Significant factors associated with cessation in the univariate analysis (i.e., $p < 0.05$) were included sequentially in the multivariate logistic regression model,⁸ starting from the most significant variable. The dependent variable was expired CO-validated one-week abstinence at 1 month after discharge. Data were analysed using Stata version 6.0.

Results

Of the 268 patients included in the study over a 6-month recruitment period, 227 (84.7%) were men; the mean age was 56 years. The baseline characteristics of the patients are shown in Table I. The number of patients with cardiology and respiratory diagnoses were 137 (51.1%) and 123 (45.9%), respectively. The baseline smoking history of the patients are as follows: mean ($\pm$ SD) age started smoking was 18.7 ± 7.5 years; mean duration of smoking was 37.4 ± 15.3 years; median number of cigarettes was 15 (range, 1 to 80). All patients had considered that smoking worsened their condition.

All patients survived to hospital discharge. Two patients died before the 2-month follow-up and were excluded from the analysis. At 2 months after hospital discharge, 108 patients were continuously non-smoking and 106 were still smoking. Fifty-two patients had

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TABLE I: BASELINE CHARACTERISTICS OF SUBJECTS

Variable	No. of subjects (n = 268)
Sex	
Female	41 (15.3)
Male	227 (84.7)
Race	
Chinese	186 (69.4)
Malay	39 (14.6)
Indian	36 (13.4)
Others	7 (2.6)
Highest education level	
Nil	54 (20.2)
Primary	112 (41.8)
Secondary	89 (33.2)
Diploma/Degree	13 (4.9)
Marital status	
Single	33 (12.3)
Married	209 (78.0)
Divorced/Separated/Widowed	26 (9.7)

TABLE II: UNIVARIATE ANALYSIS OF DEMOGRAPHIC AND CLINICAL FACTORS ASSOCIATED WITH SMOKING CESSATION

Variable	Still smoking (n = 106)	Quit smoking (n = 108)	p value ¹
Mean age (SD) [y]	55.8 (15.2)	56.7 (15.1)	0.675
Sex			
Female	17 (16.0%)	16 (14.8%)	0.804
Male	89 (84.0%)	92 (85.2%)	
Race			
Chinese	73 (68.9%)	77 (71.3%)	0.562
Malay	15 (14.2%)	17 (15.7%)	
Indian	14 (13.2%)	13 (12.0%)	
Others	4 (3.8%)	1 (0.9%)	
Marital status			
Single	16 (15.1%)	10 (9.3%)	0.212
Married	79 (74.5%)	91 (84.3%)	
Divorced/Separated/Widowed	11 (10.4%)	7 (6.5%)	
Highest education level			
Nil	20 (18.9%)	19 (17.6%)	0.547
Primary	42 (39.6%)	51 (47.2%)	
Secondary	39 (36.8%)	31 (28.7%)	
Diploma/Degree	5 (4.7%)	7 (6.5%)	
Requirement of intensive care			
No	86 (81.1%)	77 (71.3%)	0.091
Yes	20 (18.9%)	31 (28.7%)	
Hospitalisation			
Initial	10 (9.4%)	2 (1.9%)	0.016
Recurrent	96 (90.6%)	106 (98.2%)	
Principal diagnoses			
Cardiology	54 (50.9%)	65 (60.2%)	0.174
Respiratory	52 (49.1%)	43 (39.8%)	
Mean duration of hospitalisation (SD) [days]	4.8 (3.4)	5.3 (4.0)	0.348

¹ Independent t-tests were used to compare means of continuous variables, whereas the chi-square test was used for categorical variables.

defaulted on their follow-up and were not contactable. These 52 patients were also not considered in the analysis. Hence, the smoking cessation rate at 2 months after discharge was 50.5%.

Univariate analysis of factors that may affect smoking cessation are shown in Tables II and III. There is no significant difference in demographic and clinical factors between quitters and non-quitters, except a significantly greater proportion of patients admitted for the first time for their medical condition quit smoking 2 months after hospital discharge ($p = 0.016$). For factors related to smoking, successful quitters had an older age of onset of smoking ($p = 0.005$), were smoking fewer cigarettes per day ($p = 0.016$) and had made more numbers of attempt to quit ($p < 0.001$). There were also significantly greater proportions of patients in higher stages of readiness to stop smoking ($p < 0.001$), preferring to quit “cold

TABLE III: UNIVARIATE ANALYSIS OF FACTORS ASSOCIATED WITH SMOKING CESSATION

Variable	Still smoking (n = 106)	Quit smoking (n = 108)	p value ¹
Mean age started smoking (SD) [y]	17.4 (6.7)	20.3 (8.0)	0.005
Mean years of smoking (SD)	37.9 (15.6)	36.4 (15.2)	0.086
Median number of cigarettes smoked per day at baseline (range)	17 (2-60)	10 (1-40)	0.016 ^f
Median number of quit attempts (range)	0 (0-10)	1 (0-3)	<0.001 ^f
Stage of readiness to quit			
Action	0 (0.0%)	1 (0.9%)	<0.001
Contemplation	71 (67.0%)	100 (92.6%)	
Pre-contemplation	35 (33.0%)	7 (6.5%)	
Preferred method of quitting			
Sudden cessation	78 (73.6%)	97 (90.1%)	0.002
Reduction	28 (26.4%)	11 (9.9%)	
Nicotine dependence score			
Low	49 (46.2%)	76 (70.4%)	<0.001
High	57 (53.8%)	32 (29.6%)	
Smoking history in family			
No	69 (65.1%)	73 (67.6%)	0.699
Yes	37 (34.9%)	35 (32.4%)	

^f Number of cigarettes smoked and number of quit attempts were analysed on the log scale, due to skewness of distribution.

¹ Independent t-tests were used to compare means of continuous variables, whereas the chi-square test was used for categorical variables.

TABLE IV: MULTIVARIATE ANALYSIS OF FACTORS ASSOCIATED WITH SMOKING CESSATION USING LOGISTIC REGRESSION METHOD

Covariate	OR	95% for OR	p value ¹
Preferred method of quitting			
Reducing	1		
Nicotine replacement therapy	0.87	(0.27-2.78)	0.811
Cold turkey	8.33	(1.72-50.00)	0.009
Nicotine dependence score			
High	1		
Low	2.78	(1.37-5.56)	0.004
Cases/first-timers			
No	1		
Yes	8.35	(1.64-42.63)	0.011

¹ p values from Wald test.

turkey” ($p = 0.002$) and with low nicotine dependence score (Fagerstrom test for nicotine dependence ≥ 5 points; $p < 0.001$) among successful quitters. Multivariate analysis showed that a low nicotine dependence score (odds ratio 2.78, 95% CI: 1.37-5.56, $p = 0.004$), determination to quit by the “cold-turkey” method compared to reducing (odds ratio 8.33, 95% CI: 1.72-50.00, $p = 0.009$) and initial hospitalisation (odds ratio 8.35, 95% CI: 1.64-42.63, $p = 0.011$) were the main independent predictors of positive outcome (Table IV).

Discussion

In a systematic review on interventions for smoking cessation in hospitalised patients,¹ the analyses by diagnosis suggested that there was an increase in cessation rate in patients with cardiovascular diagnosis given an intervention, while the effectiveness of interventions in patients with a respiratory diagnosis was unclear. Our results did not show any significant increase in cessation rate in patients with cardiovascular diagnosis and respiratory diagnosis. Patients with different clinical diagnoses do not appear to respond in different ways to the intervention. Although different diagnoses may provide greater or less motivation to make a quit attempt, other factors are likely to be more determining.

Another critical factor of the hospitalisation that may influence outcome was whether the hospitalisation episode was the first for the patient’s medical problem. To our knowledge, this is the first study

that has shown that, among hospitalised smokers, quit rates for smoking cessation intervention provided for patients during the initial hospitalisation are higher than those given to patients with repeated admissions. It may be that patients are more receptive to the intervention during and following their first hospitalisation for the medical illness compared to repeated hospitalisation for the same illness. If this is so, it may have significance in designing future hospital-based cessation programmes targeting the most receptive patients in order to achieve the best possible outcomes.

Biological factors, such as experiencing nicotine withdrawal symptoms and the level of nicotine dependence, affect cessation rates in the general population and are also likely to play a substantial role in successful cessation among hospitalised patients. In the present study, a low nicotine dependence score was an independent predictor of smoking cessation. However, the introduction of nicotine replacement therapy (NRT) does not seem to have significantly affected quit rates among hospitalised patients in general. Taylor et al¹⁰ permitted the use of nicotine gum or patch for participants who met the criteria for nicotine dependence or who had severe withdrawal symptoms. There was no significant difference between the quit rate of the NRT group and that of the group without NRT.

Conclusion

Among a cohort of patients hospitalised with cardiac or respiratory

diagnoses and receiving smoking cessation intervention, initial hospitalisation, low dependence on nicotine and motivation to quit by sudden cessation are the main independent predictors of positive outcome. Patients with different clinical diagnoses do not appear to respond in different ways to the intervention.

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Special Poster Presentation

Caregiver Stress in Activities of Daily Living-dependent Elderly Aged More Than 65 Years

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Introduction

The Asia-Pacific region has more than half of the world's population. Over the next 25 years, this region would contribute significantly to a worldwide doubling of people who are more than 65 years of age.¹ People would have a longer lifespan, a result of good socio-economic progress and improvement in modern medicine. With longer lifespan, the proportion of frail elderly with disabilities as a result of birth, accidents, chronic illnesses and even ageing would only increase. Faced with the challenges of providing sufficient and adequate care for the elderly, many governments have begun the process of devolving health-related care from institutions onto the communities and homes.²⁻⁴ Singapore is in a similar situation, with an expected 19% of her population, or 796,000 people, aged >65 years old in 2003. About 10% of the elderly needs assistance in basic activities of daily living (ADL).⁵

The family has been the traditional caregiver for the frail elderly.^{6,7} This form of care is now under threat as family size decreases and more women, traditionally the caregivers, entered the workforce.

Caregiver provides direct care, like bathing, and indirect care, like

running errands. Psychodynamic issues are involved in this type of relationship that may precipitate feelings of resentment and depression. Stress on the caregiver will only increase as the care recipient grows older with functional decline, dwindling financial resources and less family members to share the care burden.⁷

Caregiver stress could be expressed in somatic complaints,⁸ hypertension, poorer immune functions, coronary heart disease,⁹ physical and financial burdens.⁷ The caregiver may be able to cope, as in the "adaptation" hypothesis, or suffer, as in the "wear and tear" model,^{10,11} with dire consequences for the frail elderly: neglect, abuse and, finally, institutionalisation.

In this study, we attempt to assess caregivers' issues associated with caring for community-dwelling ADL-dependent elderly.

Materials and Methods

This study is part of a larger community-based study on the health of elderly in Singapore. This study was conducted in November and December in 2002 in Toa Payoh Central. This area has an estimated 9000 households with about 11% elderly population, which is close

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to the national population estimate. Of the 2300 households randomly selected by the Department of Statistics, Singapore, a final 265 elderly participated in that study after taking into consideration households that declined, uninhabited, uncontactable and appropriate one-step replacement for elderly-absent households. Of the 54 ADL-dependent (based on Barthel Index) elderly with caregivers, only 76% (n = 41) of caregivers participated in the caregiver section.

The Zarit Burden Interview¹² was used to assess the impact of the elderly's disabilities on the caregiver's physical, emotional, social and financial well-being. An estimate of the degree of burden could be made on the total score (0-20: little or no burden; 21-40: mild to moderate burden; 41-60: moderate to severe burden and 61-88: severe burden). Issues of utilisation of support services (day care centres, day rehabilitation centres, home medical or nursing services and home help services) and finances were explored. Statistical analysis was performed using SPSS version 11.0.

Results

The elderly were generally older than the general study population: 75.2 years versus 71.7 years for male and 77.4 years versus 73.4 years for female. More females (n = 31) were present and this could be attributed to their longer life expectancy. The average Barthel Index was 75.5 for male and 70.8 for female. Most stayed with their children (82.9%, n = 34), while 12.2% (n = 5) stayed with their spouse and 2.4% (n = 1) stayed alone. Majority of the caregivers were children (51.2%, n = 21); spouse and maids, 19.5% (n = 8) each. The mean Zarit Burden Interview score was 17.9 ± 14.1 . Majority [53.7% (n = 22)] of caregivers expressed little or no burden; 39% (n = 16) had mild to moderate burden; 7.3% (n = 3) had moderate to severe burden; and none had severe burden. Up to 87.5% (n = 35) of caregivers felt sometimes that they should do more for the elderly and, similarly, up to 82.9% (n = 34) felt sometimes that they could do a better job in caring. Only 4.9% (n = 2) of caregivers utilised community support services, while up to 32.5% (n = 13) were not aware of their existence. Between 65% and 78% (n = 26 to 32) were aware, but not using the services. About 82.1% (n = 32) of caregivers spent up to \$600 monthly on nursing the elderly; 82.1% (n = 32) of the households surveyed had <\$3000 in total monthly income. Children were the main financial source (57.5%, n = 23), followed by self (15%, n = 6) and spouse (10%, n = 4). Insurance was notably absent as a source of income.

Discussion

In this study, the majority of caregivers [92.7% (n = 38)] were not overstretched in their roles as expressed in the Zarit Burden Interview score. Possible contributing factors may be due to:

- The emotional, social and physical well being of the caregivers were not threatened significantly. As the current caregivers are the baby boomers from the 1960s' cohort, the burden of parental care could be shared among the siblings.
- The elderly in this study were not severely ADL-dependent, and, hence did not pose a strain on the type of care required.
- Attitude of caregivers – not many had expressed a need to do more for the elderly, nor the necessity to do a better job in caring for the elderly.

The caregivers may need to have a mindset change with regards to care for the elderly. The attitude of ageism need to be corrected. Medical and nursing needs may change with time and may become more sophisticated; similarly, expectations of better educated elderly may increased. It would be appropriate to educate and train the caregivers to recognise such changes in the elderly and to respond appropriately. With appropriate input, the functional decline of the elderly could be stabilised or even improved upon.¹³ On the perception

of higher stress burden of caregivers are factors such as greater involvement in provision of care, especially of elderly with higher level of disabilities, increased duration of care, lack of personal and social resources, lack of family support and lower family income.¹⁴⁻¹⁶

Of particular concern would be a group of elderly who stayed with their spouses only. Spousal care may become more prominent as more elderly opted to stay away from their children in years to come.¹⁷ The spouses themselves are particularly at risk of stress, as they too grow old, with the attendant functional decline and less family support as the family unit becomes smaller.⁷

Paid help, in the form of maids, may become a prominent source of care for the elderly. They are usually untrained and need to be equipped with skills in order to fulfil the caregiver role. They would need to be orientated to the peculiar cultural aspects of the local population in order to better relate and play a more effective role in caring for the elderly. Formal caregivers would, in time, play a more prominent role as the availability of informal caregivers (usually family members) declined.¹⁸

Financial concerns were raised in 12% (n = 5) of caregivers who answered the Burden Interview. This could be due to the fact that an estimate of 20% (\$600/\$3000) of the household income may be spent on caring for the elderly at home. Also, 17.5% (n = 7) of caregivers had expressed concerns that the financial source may not be regular. The causes for the latter statement may be related to job security, especially in the current economic down cycle of the late 1990s and early 2000s, increasing medical expenses and decreased contribution from a decreasing family size. Currently, the efforts of the caregivers are not fully recognised financially and they may have to give up their jobs.

More studies would be needed to evaluate the causes for poor utilisation of community support resources. These could be attributed to the cost of utilisation, proximity, mobilisation, transportation, time constraints, attitudes of caregivers and care recipients, and type and appropriateness of facilities available. More effective communication to the caregivers, care recipients and even primary care personnel may be needed.

There are positive effects on caregivers with the appropriate matching of community support resources.¹⁴ These include respite care, better home care management, network with other potential available resources, professional help advice, reduce family breakdown and chance of partial employment. The main objective of such resources would be to reduce caregiver burden through assisting and supplementing the caregiver in his/her role.

The WHO Study Group on home-based long-term care⁶ has summarised that home care of the sick is not just fulfilling a physical need, but a social responsibility and an element in development of the individual and society. While allowing the frail elderly to reap the advantages of home care, the needs of caregivers should not be neglected. The caregiver should receive societal support in order to effectively perform his/her role so that the frail elderly may receive the best benefits. If the caregiver is not well managed, the latter may become another victim of poor health who needs help himself/herself.

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Special Poster Presentation

Interleukin-4 Receptor α Subunit (IL-4RA) Gene Polymorphisms and Singapore Childhood Minimal Change Disease

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Introduction

Minimal change nephrotic syndrome (MCNS) is a glomerular disease that is characterised by heavy proteinuria and a relapsing/remitting course, without histological evidence of classical inflammatory immune-mediated injury.¹ It is the most common cause of nephrotic syndrome in Singapore children. Although its pathogenesis remains to be elucidated, there is strong evidence that it is a primary immune disease associated with immunoregulatory imbalance between Th1 and Th2 cytokines.²

We have demonstrated that gene expression of interleukin-13 (IL-13) was upregulated in both CD4+ and CD8+ T-cells in children with steroid-responsive nephrotic syndrome in relapse, compared to remission, and this was associated with increased intra-cytoplasmic IL-13 production by CD3+ cells,³ and elevated serum total IgE levels during relapses. Moreover, the elevated serum total IgE levels found in patients in nephrotic relapse correlated significantly with the increase in CD3+ IL-13 producing-cells. Other studies have also indicated an important functional role of IL-13 in the pathogenesis of MCNS. Recently, IL-13 has also come to be appreciated as a critical mediator both functionally and genetically in some immune disorders such as allergic disease.

Whether the genetic polymorphisms of IL-13 or its receptors are associated with nephrotic syndrome has thus triggered much attention. We have found that the 3 single nucleotide polymorphisms (SNPs) in the IL-13 gene were correlated with the long-term outcome of MCNS in Singaporean Chinese children (unpublished data). As IL-13 acts through the IL-4 receptor α subunit (IL-4RA), a common receptor with IL-4, this study aimed firstly to examine the genetic variations of IL-4RA in Singaporean Chinese children and, subsequently, to assess its association with atopy, steroid-response and long-term outcome in children with MCNS.

Materials and Methods

A total of 65 unrelated Singapore Chinese children with MCNS were included in this study. Their mean age at initial diagnosis was 4 years (range 1 to 14 years). According to the criteria from the International Study of Kidney Disease in Children (ISKDC),^{4,5} 33 children were defined as steroid-dependent, 25 were steroid-responsive (infrequent relapsers), while 6 were steroid-resistant. Clinical parameters of atopy, namely asthma, eczema, recurrent

TABLE I: GENOTYPE FREQUENCIES OF IL-4RA (EXON 11) POLYMORPHISM

Polymorphism	Genotype	Controls n (%)	MCNS n (%)	P value
E375A	EE	76 (83.5%)	51 (78.5%)	0.42
	EA	15 (16.5%)	14 (21.5%)	
	AA	0	0	
L389L (1417G/T)	GG	81 (89.0%)	55 (85.0%)	0.42
	GT	10 (11.0%)	10 (15.0%)	
	TT	0	0	
C406R	CC	75 (82.4%)	51 (78.5%)	0.54
	CR	16 (17.6%)	14 (21.5%)	
	RR	0	0	
L408L (1474T/C)	TT	75 (82.4%)	51 (78.5%)	0.54
	TC	16 (17.6%)	14 (21.5%)	
	CC	0	0	
R473H	RR	90 (98.9%)	63 (97.0%)	0.38
	RH	1 (1.1%)	2 (3.0%)	
	HH	0	0	
S478P	SS	75 (82.4%)	51 (78.5%)	0.54
	SP	16 (17.6%)	14 (21.5%)	
	PP	0	0	
Q551R	QQ	64 (75.3%)	46 (70.8%)	0.77
	QR	18 (21.2%)	17 (26.1%)	
	RR	3 (3.5%)	2 (3.1%)	
S727A	SS	90 (98.9%)	64 (98.5%)	0.83
	SA	1 (1.1%)	1 (1.5%)	
	AA	0	0	

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TABLE II: PAIRWISE LINKAGE DISEQUILIBRIUM BETWEEN IL-4RA SNPs AT EXON 11

	E375A	L389L	C406R	L408L	S478P	1902
E375A		109.31	134.63	141.00	141.00	19.61
L389L	0.83		105.08	105.08	105.08	13.39
C406R	0.97	0.80		141.00	141.00	23.02
L408L	0.97	0.80	1.00		141.00	23.02
S478P	0.97	0.80	1.00	1.00		23.02
Q551R	0.45	0.37	0.49	0.49	0.49	

Above diagonal, Δ ; below diagonal, χ^2 ; $\chi^2 > 9.49$, $p < 0.05$

TABLE III: REFERENCE ALLELE FREQUENCIES OF IL-4RA SNPs AT EXON 11 IN DIFFERENT CLINICAL COURSES

Clinical courses	E375A A (%)	L389 (1417G/T) G (%)	Q551R A (%)
Control	91.8	91.2	85.9
MCNS total	89.2	92.3	83.8
Steroids			
Responsive	92.0	94.0	90.0
Dependent	84.8	89.4	74.2 *
Resistant	100.0	100.0	100.0
Atopy			
With atopy	86.7	93.3	80.0
Without atopy	90.0	92.0	85.0
Outcome (≥ 5 years of follow-up)			
Complete remission	88.3	90.0	86.7
Relapsing	88.7	93.5	79.0

urticaria and allergic rhinitis, were noted in the children, of whom 15 were atopic. Of the 61 children who were followed up for at least 5 years, 30 were in complete remission, while 31 were still relapsing. 91 healthy Chinese children formed the control group. Informed consent was obtained from the parents prior to blood sampling, and this study had been approved by the Ethics Committee of National University Hospital.

Genomic DNA was extracted and screened for genetic variants of the IL-4RA gene using a direct polymerase chain reaction (PCR)-sequencing method. The exon 11, from which most of SNPs have been reported, was amplified by PCR. The primers were 5' CTGGAAAATCAGCATGGT 3' for sense, 5' TGGCTTGAG CTCTGAGCA 3' for anti-sense. PCR amplifications were carried out in 25 μ L volumes containing approximately 40 ng genomic DNA, 50 ng upstream or downstream primers, 200 μ M dNTP, 0.5 units Taq polymerase. The amplification procedure consisted of 35 cycles with the following parameters: denaturation at 94°C for 1 minute, annealing at 55°C for 1 minute and extension at 72°C for 1.5 minutes. Before sequencing, the PCR products were purified with QIAquick PCR purification kit (QIAGEN, Germany). ABI Prism dRhodamine Terminator Cycle Sequencing Ready Reaction Kits (PE Applied Biosystems, USA) were then used for double-strand sequencing of the PCR products. Sequencing was performed on a GeneAmp PCR 9700 system (PE Applied Biosystems, USA). The products were then analysed on an Applied Biosystems Genetic Analyser 3100 (PE Applied Biosystems, USA).

Genotype frequencies were tested for the Hardy-Weinberg equilibrium using Pearson chi-square (χ^2) test, and the difference in the allele and genotype frequencies between cases and controls was analysed by χ^2 as well as Fisher's exact test. Linkage disequilibrium between different polymorphisms was assessed by delta (Δ). Statistical significance was defined as $p < 0.05$.

Results and Discussion

As in shown in Table I, we detected 8 SNPs in exon 11 of IL-4RA in Singaporean Chinese children, all of which were in Hardy-

Weinberg equilibrium. All these SNPs had been reported in other populations,⁶ but the genotype frequencies varied greatly. The reasons for the variation may be due to the different populations, distinct diseases studied as well as different standards for controls. As R473H and S727A were rare mutations in Singaporean Chinese, they were left out from further analysis. For the other 6 SNPs, we found that E375A, C406R, L408L and S478P were in almost complete linkage disequilibrium ($\Delta \geq 0.97$, $p < 0.01$), thus only E375A was used for further assessment (Table II). Our results did not demonstrate any significant difference in genotype (Table I) or allele (Table III) frequencies for E375A, L389L, Q551R, between the normal controls and MCNS in Singaporean Chinese children. These results are in agreement with reports from other populations,^{7,8} suggesting that these SNPs at exon 11 of IL-4RA do not predispose to MCNS.

We further stratified the patients into different subgroups according to steroid-responsive, atopy and long-term outcome (at least 5 years of follow-up), and evaluated their association with IL-4RA gene variation. As shown in Table III, we found that the Q551 allele frequency was significantly reduced in steroid-dependent MCNS, as compared to non-steroid-dependent MCNS (odds ratio 0.49, 95% CI 0.09-0.96, $p < 0.05$) and controls (odds ratio 0.59, 95% CI 0.25-0.99, $p < 0.05$). Among the SNPs of IL-4RA, Q551R has been the most frequently studied, and 551R allele has been found to be strongly associated with atopy⁹ and severe asthma¹⁰ in Caucasian populations. Functional studies suggested that 551R could produce a receptor with enhanced signal transduction *in vitro*.⁹

Conclusion

In this study on children with MCNS, we found that Q551R significantly correlated with steroid-response, with the 551R allele predisposing to steroid-dependency. These findings suggest that the genetic variants of IL-4RA, especially 551R may be used as a marker for the clinical course following steroid therapy in Singaporean Chinese children with MCNS. Further study needs to be done to elucidate the underlying mechanisms.

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