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Complex Segregation Analysis of Familial Nasopharyngeal Carcinoma in Guangdong, China: Evidence for a Major Gene Transmission*

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Abstract: Nasopharyngeal carcinoma (NPC) has a striking geographic and ethnic distribution. It occurs with high frequency in southern China and Southeast Asia. Although familial aggregation has been frequently documented, and genetic susceptibility has been regarded as one of the most important cause of NPC, its mode of inheritance remains uncertain. To investigate the inheritance pattern of familial NPC in Guangdong, China, a complex segregation analysis using the regressive model as in REGD program of SAGE software was applied. 136 high risk families with two or more affected cases were investigated, which ascertained through a proband with NPC treated in Cancer Center of SUMS. The results suggest that the inheritance mode of NPC in this study population is compatible with autosomal dominant or codominant inheritance with reduced penetrance, and the former is the best fitting model. The results enhanced the evidence of the existence of major susceptibility gene, and give the necessary support for linkage analysis in familial NPC.

Keywords: nasopharyngeal carcinoma; complex segregation analysis

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1 Introduction

Nasopharygeal carcinoma (NPC) has a striking geographic and ethnic distribution. The incidence rates are generally low throughout most of the world ($< 10^{-6}$), making it a rare cancer among Caucasions of North America and Europe, but in southern China and Southeast Asia, it is high[1]. Rates for 100, 000 for Chinese males are approximately 18 in Singapore, 28 in Hongkong, and over 40 in parts of Guangdong[1,2].

Familial cluster of NPC has been widely documented for recent decades in Chinese population. A typical example is a family in Nanhai, GuangDong province, in which 13 of 49 family members have

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affected NPC[3]. An earlier survey for 1000 NPC patients who were treated in the Cancer Center, Sun Yat-sen University of Medical Sciences (SUMS), Guangdong province showed that approximate 10 percent of the patients have family history of cancer[3]. Some case-control studies on Southern China population have confirmed that the proportion of familial cases in NPC patients is significant higher than that in controls, and the proportions are remarkably similar, such as Hong Kong, 7.2%; Yulin, 6.0%; Guangzhou, 5.9% in first degree generations[4,5].

Although current knowledge has suggested that susceptibility gene may transmitted in families, until now few genetic epidemiological studies focusing on genetic transmission mode have conducted, the inheritance mode for NPC is still an unsettled issue. Coffin[6] has reported a white American family of Scandinavian descent, which includes five members with NPC in three generations and six with other malignant carcinoma. After segregation analysis, the result suggests that the susceptibility to NPC and other malignancies is transmitted as an autosomal codominant characteristic. For the result is just depend on a single large family, it is quite limited to generalize to general population. In Taiwan, a study based on 347 new NPC cases showed that the genetic mode is consistent with multifactorial inheritance mode, the value of heritability is 0.60 (95% confidence interval = 0.55 – 0.64)[7]. Until now there is no investigation on genetic mode in Chinese population.

For the purpose of investigating genetic transmission mode for NPC in Guangdong province, we collected 136 high risk families ascertained through a proband with NPC treated in Cancer Center of SUMS, each of the family has at least two or more NPC cases. Complex segregation analysis was carried out by using SAGE software. The result suggests that the inheritance mode of NPC in this study population is compatible with autosomal dominant or codominant inheritance with reduced penetrance, and the former is the best fitting model.

2 Subjects and methods

2.1 Subjects

From January 1999 to March 2000, we visited the NPC patients of incident or prevalent cases who were treated in the Cancer Center of SUMS. The center is located in Guangzhou, capital of Guangdong province. It is the largest center for cancer prevention and treatment in southern China. NPC patients from all areas of Guangdong province tend to come and be treated here. For this reason, the NPC cases in the hospital have a good representative around GuangDong provinces. Each patient we visited was questioned regarding his family history (first, second and third degree relatives), site and type of cancer. If he is unclear for someone, other family members who are familiar to that person are needed to recall. Therefore, the information is relatively veracity. In the end, one hundred and thirty-six families who have more than one affected family members were obtained. The patients whom we visited were regarded as a proband, all of them were pathologically confirmed.

2.2 Statistical methods

The analyses were done using the REGD program of the Statistical Analysis for Genetic Epidemiology (SAGE) software that fits regressive logistic models[8]. The parameters of the model were estimated by the method of maximum likelihood, which include transmission probabilities ($\tau_{AA}, \tau_{AB}, \tau_{BB}$), baseline paremeters ($\beta_{AA}, \beta_{AB}, \beta_{BB}$), and residual familial effects of parents (δ_p).

A major gene effect was assumed to result from segregation at a single locus having two alleles, A

and B. Allele A was associated with the affected states. A represents the risk factor. The B allele represents multiple nondisease-associated alleles with the same inheritance pattern. Random mating and Hardy-Weinberg equilibrium for population frequencies were assumed.

The transmission of the types AA, AB and BB from parents to children was modeled. Mendilian transmission define the probability that an A allele is transmitted from parents to children, and the probabilities ($\tau_{AA}, \tau_{AB}, \tau_{BB}$) are set as 1, 0.5 and 0, for AA, AB and BB parents, respectively. For a non-transmitted environmental model, these transmission probabilities are assumed equally ($\tau_{AA} = \tau_{AB} = \tau_{BB} = q_A$). The most general transmission model allowed the transmission parameters τ_{AA}, τ_{AB} and τ_{BB} to maximize independently between zero to one.

A likelihood ratio test (LRT) was used to select the most parsimonious model, which is minus twice the difference in the $\log_e$ likelihood ($\ln L$) between models before and after reducing parameters. The likelihood of general unrestricted model is first calculated and then compared with a variety of models with one or more parameters restricted. To test a hypothesis, $-2\ln L$ of the general model is subtracted from $-2\ln L$ of the restricted model of interest. The difference is distributed asymptotically as a χ^2 with $(n-k)$ df, where n is the number of parameters estimated in general model and k the number in the hypothesis tested. However, if the value of a parameter under the null hypothesis is at the boundary of the parameter space, the LRT statistic does not follow a simple chi-square distribution. Akaike[9] information criteria (AIC) was applied to the data when more than one model fit the data, in order to determine which was the most parsimonious model.

3 Results

The data set consists of 1127 individuals in 136 familial NPC families. The number of all affected individuals is 328, among whom, 203 affected members are male, 125 are female. Within 136 families, there were 192 nuclear families. Of 192 nuclear families, there were 125 (65.1%) multiplex affected families.

The results of segregation analyses performed under REGD, Table 1 presents six models with the maximum likelihood estimates of the parameters for NPC. In the general model, the estimates of gene frequency, transmission probabilities, baseline parameters, and residual familial effects were all arbitrary. The environmental hypothesis was rejected when a comparison was made between the environmental model, in which all transmission probabilities were fixed to be equal to gene frequency, and the general transmission model ($P < 0.01$). The no major gene model ($P < 0.01$) were rejected as compared to the general model. The Mendelian model ($P < 0.01$) of recessive inheritance was also rejected. Among six models, a dominant and a codominant model fit the data well, for the dominant model is with a lowest value of the Akaikes's information criterion (AIC), and it is the best fitting model. The penetrance of allele gene AA or AB is approximately 72.54%, and gene BB 3.69%.

Tab.1 Complex segregation analysis for 136 poly nasopharyngeal carcinoma pedigrees

Parameter	Hypothesis					
	Mendelian inheritance			Non-major gene	environment	General
	Dominant	Recessive	Codominant			
q_A	0.00841	0.30807	0.00812	–	0.33109	0***
τ_{AA}	1.0*	1.0*	1.0*	–	0.33109**	1.0***
τ_{AB}	0.5*	0.5*	0.5*	–	0.33109**	0.17
τ_{BB}	0.0*	0.0*	0.0*	–	0.33109**	0.0***
β_{AA}	0.97159	−0.42113	6.46669	−2.02454	−2.12546	0.44760
β_{AB}	0.97159**	−5.25776	1.75399	−2.02454**	−2.03332	−1.62585
β_{BB}	−3.26283	−5.25776**	−2.95871	−2.02454**	−1.99167	−3.40762
δ_p	−1.34405	−2.28975	−1.23981	−0.76205	−0.76209	−1.20377
−2ln	1012.56	1024.53	1016.27	1035.34	1035.34	1010.73
χ^2	1.83	13.8	5.54	24.61	24.61	–
df[1)]	1−5	1−5	1−5	4−7	2−5	–
P[2)]	>0.05	<0.01	>0.05	<0.01	<0.01	–
AIC	1020.56	1032.53	1024.27	1039.34	1043.34	1028.73

1) Degree of freedom (df) expressing in range (for the estimation of some parameters is at boundary);

2) Goodness of fit test for restricted model compared with general model;

* Parameter values fixed by a given model and not estimated in the model;

* * Parameter value fixed consistent with last parameters, not be estimated independently;

* * * Estimated value at boundary;

q_A The frequency of allele A which associated with affected disease (NPC);

τ_{AA} The probability that a parent with genotype AA transmits an allele A to an offspring, similar for τ_{AB}, τ_{BB};

β AA The baseline parameter for subpopulation with AA genotype, similar for β_{AB}, β_{BB};

δ_p Residual familial effects of parents.

4 Discussion

Familial aggregation for NPC and its related genetic susceptibility were determined and have been frequently reported, but until now, investigating on the mode of inheritance is very limited. Guangdong is one of the areas with the highest incidence of NPC around the world, and approximately 10% of NPC patients history was reported to have family by cancer center of SUMS[3]. Recently, a new study obtained a much higher percentage than that one (not press). Therefore, exploring the mechanism of familial cluster and using the fruit to guide cancer treatment and prevention, especially using it in the high risk population in Guangdong province seems to be impressive. Meanwhile, the information of this complex analysis can be used to the linkage analysis and providing important genetic model and parametric value on parametric based linkage methods.

In the study, 136 high risk families which have more than one affected members and include 328 cases in total of 1127 individuals were investigated. Complex segregation analysis, the most widely used method for testing inheritance mode, was used to determine the most plausible explanation for the familial cluster of NPC. We rejected an environmental model and no major gene model, a recessive

model of single-gene Mendelian hypothesis was rejected too. Our results suggest that the inheritance mode of NPC in our population is compatible with autosomal dominant or codominant inheritance with reduced penetrance. Arecent a study in Taiwan advanced multifactorial inheritance model for NPC, but the conclusion was based on a simple segregation analysis, which just evaluate weather the proportion of affected and unaffected offspring in families is consistent with Mendelian expectations. Differently, complex segregation analysis can be applied to any pedigree structure, can consider more complicated pattern of transmission and environmental perturbations.

In the course of data collection, the method of subject selecting has a direct effect on the outcome of segregation analysis. Our study included a random clinic patient population which were selected solely by family history, and only those who have family history of NPC were selected to become our study subjects, those without family history were excluded. Therefore the result can only be valid in a population with multiplex families, in other words, in a population of high NPC prevalence families, and sporadic cases were not taken into consideration. More over, we must emphasize that our sample was not random sample of NPC patients, the subjects were just recruited from one hospital, not population. This referral bias may have affected our results such that the finding may not be applicable to all NPC populations. But our study is still going on, in which, not only cases with positive family history, but also sporadic cases without family histories were in collection. With the increase of the study sample, and with the collection of other verified important risk factors of NPC, more precise result of segregation analysis will be obtained.

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723.

广东家族性鼻咽癌复合分离分析的研究：主基因传递的证据

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摘 要：鼻咽癌具有显著的地理差异和种族差异．该病在中国南方和东南亚地区高发．虽然家族聚集现象已被多次报道，且遗传易感性被认为是鼻咽癌发病中最重要的危险因素之一，但是它的遗传模式目前还不清楚．为了研究广东家族性鼻咽癌的遗传模式，作者采用了SAGE软件的REGD程序进行了复合分离分析．文章对136个高危家系进行了研究，这些家系中均具有两个或以上鼻咽癌患者．先证者来自于在中山医科大学肿瘤中心诊治的患者．结果提示该研究群体的遗传模式复合常染色体显性或共显性遗传模式，常染色体显性遗传模式的拟合最佳．该结果增加了主基因存在的证据，为家族性鼻咽癌的连锁分析提供了重要的支持．

关键词：鼻咽癌；复合分离分析

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