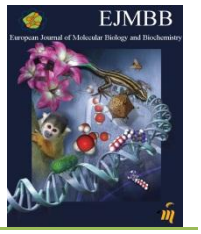
e - ISSN - 2348-2206
Print ISSN - 2348-2192

European Journal of Molecular Biology and Biochemistry

Journal homepage: www.mcmed.us/journal/ejmbb



STUDY OF CYP2A6 GENE POLYMORPHISM AMONG BETEL QUID CHEWERS OF EASTERN AND NORTH – EASTERN INDIA

[1]Adhikari Aniket and [2]De Madhusnata

[1]Research Scholar, [2]Professor, Ramakrishna Mission Seva Pratishthan, Vivekananda Institute of Medical Sciences, Department of Genetics, 99 Sarat Bose Road , Kolkata - 700026

Article Info

Received 23/02/2015
Revised 16/02/2015
Accepted 10/03/2015

Key words:- Oral cancer, Betel quid, CYP2A6 polymorphism.

ABSTRACT

Oral cancer is most common cancer in males and third most common in females, one of the main causative agents being use of chewing betel quid (BQ). Areca nut (Areca catechu), a major component of BQ, contains certain alkaloids that give rise to nitrosamines. CYP2A6 genetic polymorphism was studied among the Eastern and North eastern Indian population. In this present study subjects were screened from Department of E.N.T. & Oral and Maxillofacial surgery of RKMSP hospital, Kolkata and different areas of Eastern and North Eastern states of India. Polymorphism of CYP2A6 gene was studied from EDTA blood. Some of the cases had more than one addiction. It has been found that most of the subjects had betel quid chewing habit. Early metabolizers are susceptible to oral cancer where as in case of poor metabolizers chances are less. Betel quid has an immense role in changing the oral pathology and developing oral cancer.

INTRODUCTION

Betel quid is fourth most commonly used psychoactive substance after tobacco, caffeine and alcohol worldwide. The betel (*Piper betle*) is the leaf of a vine belonging to the Piperaceae family, which includes pepper and kava. It is valued both as a mild stimulant. The betel plant originated from South and South East Asia. Many Indian people chew betel quid (a combination of areca nut, betel leaf and lime paste). Users are easily identified due to black brown teeth and stain the tongue with oral mucosa [1,2]. Betel leaf contain large amount of carcinogens known as safrole. Betel quid (BQ) products, with or without tobacco, have been classified by the International Agency for Research on Cancer (IARC) as group I human carcinogens that are associated with an elevated risk of oral potentially malignant disorders (OPMDs) [3] and cancers of the oral cavity and pharynx.

Corresponding Author

Aniket Adhikari
Email: - aniket_adhikari@rediffmail.com

There are estimated 600 million BQ users globally. The Cytochrome p450 (*CYP*) families are divided into14 gene families of which CYP1, CYP2 and CYP3 are primarily active in the metabolism of a wide range of chemicals and these CYPs families are implicated in the metabolic activation of BQ and areca nut-specific nitrosamines [4].

CYPs are located on human chromosome19. The CYP2A6 gene consist of 350 kilobases located at 19q 12 – 19q 13.2 [5, 6, 7]. The CYPs that are known to exhibit polymorphism are CYP1A1, CYP2A6, CYP2C9 and CYP2E1.Out of this polymorphism of CYP1A1, CYP2A6, and CYP2E1gene have been studied in relation to susceptibility to head and neck cancers. Genetic defects in the CYP2A6 gene may also effect susceptibility to pre carcinogen in the environment. People are classified as EM known as early metabolizers and PM known as poor metabolizers based on genetic variation [8]. The PM phenotype are incapable of metabolizing the exogenous compound but EM phenotype are capable of metabolizing the exogenous compound [9,10].

Our present work based on case control study suggests that the CYP2A6 genetic polymorphism has an impact on susceptibility to oral cancer.

(A) Screening of Subjects

I) Camp in Eastern India, II) Camp in North East India and III) patients attending Maxillofacial and ENT department of RKMSP hospital.

I) Eastern India camp

220 subjects were screened at a camp held in Bankura, Purba Midnapur,Atghara .West Bengal. Out of whom 133 were betel quid chewers.

II) North East camp

56 subjects were screened at a camp held in Karimganj, Assam. Out of whom 33 were betel quid chewers.

III) RKMSP Hospital

2885 cases attending in one year at E.N.T OPD and Oral Maxillofacial OPD of RKMSP Hospital had other complications like auditory, nasal, throat & facial problem. 35 Patient were selected for our study.24 cases were betel quid chewers .Out of 35, 14 cases had pre-cancerous lesion, 13 cases had squamous cell carcinoma, 8 cases had pre-cancerous condition.

(B) Methods

i) Detailed history was taken from all cases by filling up questionnaire.

ii) Molecular study

PCR of different cases were performed with forward and reverse primer for case and control sample at 58° C for annealing temp with 35 cycle and total amount of PCR product is 26.5µL.

RESULTS

Table 1: Detailed history of subjects of different areas

PLACE	NO	AGE GROUP (in years)						Addiction			No BQ Addiction	Tea Drinker	Non Tea Drinker
		Below 30	31-40	41-50	51-60	61-70	Above 70	Smoking	Alcohol	Betel Quid			
NORTH EAST CAMP 1. Assam, Karimganj	56	1	2	12	24	11	6	9	6	33	23	40	16
1) EASTERN INDIA CAMP	34	5	20	8	1	0	0	16	14	19	15	34	0
2) 1) Bankura,Dhulai	46	22	13	3	6	2	0	28	29	36	10	40	6
2)East Midnapur, Bibhisanpur	89	28	18	21	15	6	1	27	3	56	33	73	16
3) North 24 Pgs, Atghara 4)Narrah, Bankura	51	8	13	12	8	6	4	14	5	22	29	49	2
RKMSP	35	2	7	8	11	7	0	20	8	24	11	29	6
TOTAL	311	66	73	64	65	32	11	114	65	190	121	265	46

Note: Some cases had more than one addiction.

Table 2. Poor metabolizer and Early metabolizer of different area

Area	No of betel quid chewers	Poor metabolizer	Early metabolizer
Karimganj , Assam	33	60%	40%
Dhulai, Bankura	19	16%	84%
Bibisanpur, East Midnapore	36	42%	58%
Atghara,North 24 Pgs	56	90%	10%
RKMSP Hospital	22	13%	87%
Narrah, Bankura	24	18%	82%

Early metabolizers are susceptible to oral cancer where as in case of poor metabolizers chances are less.

DISCUSSSION

Oral cancer is one of the leading cancers in most Asian countries [11]. India has largest betel quid consuming population in the world.The habit of chewing betel quid is due to low cost, easily available and also as a mood elevator in the day to day busy scheduled life. CYP2A6 gene deletion reduces oral cancer risk in betel quid chewers in Sri Lanka [12]. Poor metabolizer are less prone to oral cancer than early metabolizer due to CYP2A6 gene polymorphism. Subjects who have polymorphism in CYP2A6 are poor metabolizer and showed band in PCR.

Early matabolizer had normal CYP2A6 gene and showed no band in PCR.

CONCLUSION

The substances which are present in the betel quid not only have the cytotoxic, mutagenic property but it also involved in genetic, enzymatically and molecular mechanism in the development of carcinogenesis. In our study it has been found that more than 50% cases from North Eastern states were poor metabolizer, whereas more than 50% cases of Eastern region (except North 24 Pgs) were early metabolizer.

ACKNOWLEDGEMENTS

The authors thank to the Secretary, Ramakrishna Mission Seva Pratishthan, for kind permission to use the laboratory for this work and Department of Maxillofacial and ENT Department of RKMSP Hospital.

REFERENCES

1. Raghavan B, Barua HK. (1958). Areca nut: India's popular masticatory – History, Chemistry and Utilization. *Econ Botany*, 12, 315 - 345.
2. Marshal M. (1987). An overview of drugs in Ocenia. In: Lindstrom L, editor. Drugs in Western Pacific Socities: relations of substance. Lanham, *Md: University Press of America*, 13 -50.
3. IARC, (2004). *IARC* Betel Quid and Areca – Nut Chewing and some Areca-Nut-Derived Nitrosamine, Volume 85, IARC Monographs on the Evaluation of Carcinogenic Risks to Humans, IARC, Fairbanks, Alaska, USA .
4. Raunio H, Pasanen M, Maenpaa J, Hakkola J and Pelkonen O. (1995). Expression of extra hepatic cytochrome P450 in humans; in Advances in Drug metabolism in Man pp 233- 238 eds G M Pacifici and G N Fracchia (Luxembourg European Commision).
5. Fernandez-Salguero P, Gonzalez F. J.(1995).The CYP2A gene subfamily: species differences, regulation, catalytic activities and role in chemical carcinogenesis. *Pharmacogenetics*, 5, S123–S128.
6. Hoffman S.M.G., Fernandez-Salguero P, Gonzalez FJ, Mohrenweiser HW. (1995). Organization and evolution of the cytochrome P450 CYP2A-2B-2F subfamily gene cluster on human chromosome 19. *Journal of Molecular Evolution*, 41(6), 894–900.
7. Tricker AR. (2003) .Nicotine metabolism, human drug metabolism polymorphisms, and smoking behaviour, *Toxicology*, 183(1–3), 151–173.
8. Ingelman-Sundberg M. (1997). The Gerhard ZbindenMemorial Lecture. Genetic polymorphism of drug metabolizing enzymes. Implications for toxicity of drugs and other xenobiotics. *Archives of Toxicology. Supplement*, 19, 3–13.
9. Namakura K, Yokoi T, Inoue K, Shimada N, Ohashi N, Kume T, and Kamataki T. (1996). CYP2D6 is the principal cytochrome P450 responsible for the metabolism of the histamine H_1 antagonist promethazine in human liver microsomes. *Pharmacogenetics*, 6, 449 -457.
10. Gonzalez FZ. (1996). The CYP2D subfamily. In C Ioannides, (ed.), Cytochrome P450, metabolic and toxicological aspects. *CRC Press, New York*, 183 -211.
11. Lin Sc, Chen YJ, Kao SY, Hsu MT, Lin CH, Yang SC, et al. (2002). Chromosomal changes in betel associated oral squamous cell carcinoma and their relationship to clinical parameters. *Oral Oncol*, 38, 266 -273.
12. Zeki T, Itsuo C, Masaki F,Toshiyuki S, Norikata A, Hiroshi Y, Figen S, Malsantha M, Hiroshi K, Tetsuya K. (2002). *Carcinogenesis*, 23(4), 595-598.