

Research Article

Association between GRK 5 polymorphism and poorly controlled asthma-A prospective Cross sectional study in South Indian population

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ABSTRACT

Background: Asthma is a chronic inflammation of the airways which are characterized with chest tightness, wheezing, cough and dyspnoea. Despite the presence of effective asthma treatments several patients have bronchial asthma that's inadequately controlled. Several reasons are quoted for this poor management like patient non-compliance to treatment, poor inhalation technique, lack of response to medications, hazards and genetic influence. Various genes are been researched for identifying the genetic factor. One of such unexplored genes is GRK 5 gene. This gene controls the kinase and turns off the receptor which results in decreased effect on administration of beta agonism. **Methods:** Study aimed in finding out if GRK5 polymorphism has higher proportion of occurrence in poorly controlled bronchial asthmatic patients and to study the other risk factors associated with poorly controlled asthma. This was a cross sectional study

with 160 patients. After getting informed consent from the patients they were divided into two groups (Well and Poor control) based on a self administered questionnaire – Asthma control test. Blood was obtained from these study participants and their genetic analysis was performed. **Results:** The prevalence of this polymorphism was found to be 14% in our population. But its association with poor control of asthma was not found to be statistically significant ($p=0.822$). Risk factors like known allergic history to dust, smoking history, climatic variation, history of GERD, regularity of treatment were all found to have statistical significance for poor control of asthma. In our study risk factors like progressing age, female sex, environmental hazard exposure, and exposure to pets were not statistically significant for poor controlled asthma. **Conclusion:** The current study did not demonstrate a significant association between GRK5-Leu41 polymorphism and poor control of asthma.

Key words: Asthma, poor control, GRK 5 polymorphism

INTRODUCTION

The NAEPP National asthma program defines asthma as, chronic inflammatory disease of the respiratory system involving several cells and its components. In vulnerable people, inflammation causes perennial events of coughing, chest tightness, dyspnoea, and wheezing. The episodes are sometimes related to airflow disturbance that is reversible by treatment or reverses spontaneously. Studies done in numerous countries shows, the prevalence of bronchial allergic reaction as 15-30 %¹ & incidence about 3.5-20 % of the people in all countries².

Despite the presence of effective asthma treatments and evidence-based management guidelines specializing in asthma management, several patients have bronchial asthma that's inadequately controlled³.

In addition, this data is supplemented in consideration with genetic modifiers of environmental exposures on expression of asthma. Various genetic alterations, SNP (single nucleotide polymorphism) are known within the factors affecting asthma and its effective management. E.g. ADRB2 gene, IL17, TNF alpha, ADAM 33, DPP10, GRPA, etc⁴.

One among such polymorphism that has not been effectively explored is GRK5 (G protein coupled receptor kinase 5). This study is to seek out if there's an association between GRK 5 polymorphism and poor control of asthma.

METHODOLOGY

STUDY CENTRE

The study was done in the Department of Pharmacology, PSG Institute of Medical Sciences and Research and the Department of Pulmonology, PSG Hospitals, in

collaboration with the PSG Centre for Molecular Medicine and Therapeutics (CMMT).

STUDY SUBJECTS

Inpatients and outpatients of Respiratory Medicine and Pulmonology department with clinical diagnosis of asthma from February 2013 to July 2014

STUDY DESIGN

The study was a cross sectional study. After obtaining informed consent and fulfilling the inclusion exclusion criteria patients were given the self administered questionnaire in their language and divided into well controlled and poorly controlled group. Blood sample was collected from all the patients and their genetic analysis was done.

SAMPLE SIZE

Sample size of 160 patients were recruited comprising of 80 patients in each group

TOOL USED

Asthma control test

-a validated self administered questionnaire used to assess control of asthma in patients.

Score >19 – well controlled Score < 19 – poorly controlled

INCLUSION CRITERIA

All patients diagnosed to have asthma according to the accepted guidelines and on treatment at least for past one year. Ability and willingness to provide informed consent and Age >12 years

EXCLUSION CRITERIA

Nil

GENETIC ANALYSIS: Steps involved in genotype analysis were;

DNA extraction, PCR to amplify GRK 5 gene, RFLP using BsrI restriction enzyme and PAG electrophoresis of the digested product

RESULT S

The total number of patients recruited in the study was 160, and there were 37% males

and 63% females. Among them, 53 % of males and 52 % females were poorly controlled. Previous community based studies have shown female sex as a risk factor for developing asthma. This was also observed in our study as the male: female ratio was 1: 1.7 In our study we found that age did not seem to influence control of asthma as well. Noteworthy was that 65 % of patients were of age group >40 years.

Curiously, family history of asthma appeared to be negatively correlated with poorly controlled asthma yielding a statistical significance of $p=0.035$, and an OR of 0.502 (95 % CI 0.264 to 0.958). Most of prior literature on family history of asthma seems to be prevalence studies rather than examining association between family history of asthma and its control. From our study, patients with positive family history are found to have better control compared to those without a positive family history. This could have been due to increased awareness in the family about the disease, its outcome and treatment modalities and the need for therapeutic compliance. Thus, the patients in our study with a positive family history may have achieved a good control of asthma.

Our data for compliance of treatment and poor control shows a sturdy association ($p < 0.001$) with OR 0.206 and Confidence interval falling between 0.087 and 0.489. This implies that patients with regular treatment history are well controlled. This is understandable from the fact that in asthma, compliance improves outcome. A recently published population based cohort study in Canada showed that people adherent to treatment had less exacerbation, less hospitalizations, lower health care utilizations and need for less rescue medications⁷. It was also found that patients who had history of hospitalizations ($p<0.001$) OR 8.143 (CI 2.7-24.7) and casualty visits ($p<0.001$) with OR 4 (CI 2.2 – 9.9) in past one year fell under the poorly

controlled arm. This is an expected statistical association because these are used as diagnostic criteria for poorly controlled asthma.

In our study population about 14% were smokers and 24% had history of passive smoking. Passive smoking recipients included co workers and those who had husbands who smoke. The features associated with smokers and asthma are increased symptoms and disability coupled with accelerated decline in FEV₁, therapeutically reduced response to corticosteroids and pathological alteration in airways with inflammation and increased bronchial secretion⁸. Our results revealed statistically significant association between active smoking and poor control but not significant for passive smokers.

Known allergy or atopy to dust, smoke, seasonal variation, allergic to food and harsh smell (which included perfumes, smell during sautéing food, paint fumes, onions) were considered. Some of these like dust, season and harsh smell showed statistically significant positive association for poorly controlled asthma, whereas smoke and food allergy did not show significant association. Patients with coexisting GERD showed statistically significant correlation ($p=0.017$) OR of 2.170 (95% CI 1.146-4.107) for poorly controlled asthma. Multiple studies have stated this positive association between GERD and difficult to treat asthma. Nearly one third asthma patients have silent reflux⁹. Also history of upper respiratory tract infection and history of sinusitis were found to have statistically significant ($p < 0.001$) relationship to poorly controlled asthma. This could be due to the grounds that these may not be causally related to control in asthma rather the result of poor control.

DISCUSSION

Beside all these factors, our central hypothesis was to examine if there would be a positive association between GRK 5 SNP and poor control, because of a demonstrated endogenous beta blockade by the SNP. Hence we suspected that if this polymorphism were present in an asthmatic individual, he/she may have a decreased activity of the drug due to a pre-existing beta blockade.

A polymorphism in the GRK5 isoform was discovered at codon 41 in which a wild type glutamine (Gln) 41 is replaced by leucine(Leu). In transfected cells GRK5-Leu 41 evoked a greater degree of agonist promoted desensitization of adenylyl cyclase compared to GRK5-Gln41. Consistent with this functional effect, agonist promoted beta2-AR phosphorylation was greater in cells expressing GRK5-Leu41, similar to the rate of agonist promoted receptor internalization. So GRK5-Leu 41 represents a gain of function polymorphism that evokes enhanced loss of function of Beta2-AR during persistent agonist exposure, and thus contributing to beta agonist variability in asthma treatment. This GRK5-Leu 41 variant is approximately 10 fold more common in African-Americans¹⁰. It was found that the prevalence of this polymorphism is variable between different populations depending on the ethnicity. In some races the SNP was seen in around 2 % of the population while in the African Americans it was as high as 40 %¹⁰⁸. Our study population had 14 % of GRK5-Leu41 variant.

A prior study has demonstrated a higher prevalence of this SNP among African Americans compared to Caucasian⁵. Another study showed that African Americans exhibit a poorer control of asthma as well as potentially greater adverse effects during chronic treatment when compared with Caucasians¹⁰. Though a prospective study has not yet been

conducted to demonstrate a link between the SNP and poorer control of asthma in this population, the authors of the SMART study suggest that among other things, a genetic factor may well be the underlying reason for the same.

So we were interested in looking at how GRK5 polymorphism affected asthma control among the Indian population. However, the frequency of this variant was equal among those with well controlled and poorly controlled asthma. Thus the difference in frequency distribution of this polymorphism did not show any statistical significance ($p=0.822$). The reason for such an inference could be due to the small sample size of our study. Other plausible explanation could be because of the influence of the same SNP on muscarinic receptors resulting in bronchodilatation that could be exhibiting a possible functional antagonism on the effects of this SNP on beta 2 adrenoreceptors.

Additionally one study has demonstrated that M₂ muscarinic receptor mediated opposition of airway smooth muscle relaxation is regulated by GRK5 which is important in beta 2 receptor desensitization. In addition that study concluded GRK 5 regulates pulmonary response in a tissue specific and receptor specific manner¹¹. Chronic use of beta adrenergic agonists is known to lead to desensitization of the receptor¹². This desensitization could by itself result in poor control of asthma. Therefore, duration of treatment is a potential confounding factor, and this needs to be taken into account while interpreting the genetic effects.

CONCLUSION

This is the first study in Indian population done to assess the genotype phenotype correlation of GRK5 gene polymorphism

and poor control of asthma. The prevalence of this polymorphism was found to be 14% in our population.

The current study did not demonstrate a significant association between GRK5-Leu41 polymorphism and poor control of asthma. Risk factors like known allergic history to dust, smoking history, climatic variation, history of GERD, regularity of treatment were all found to have statistical significance for poor control of asthma. In our study risk factors like progressing age, female sex, environmental hazard exposure, and exposure to pets were not statistically significant for poor controlled asthma.

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- **Competing interests**- Nil

- **Ethics approval statement** - Approved by Institutional Human Ethics Committee of PSGIMSR (proposal number 12/277)

- **Contributorship Statement** - Dr. S. Ramalingam (late) – He was the well wisher who guided me throughout my planning conduct and data analysis

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