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STUDY OF ASSOCIATION BETWEEN DRD2 POLYMORPHISM AND AGGRESSIVE BEHAVIOR IN PRISONERS

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Abstract

Aggression is defined as any act of anger or antipathy towards others. Aggressive behavior includes *inflicting physical harm or verbal humiliation to the victim. This behavior dependson attitude, emotions, values, ethics, authority, rapport, persuasion and genetics. Polymorphism in exon 7 of DRD2 gene is found to be associated with this high level of aggression among humans. Total 40 saliva samples in which 20 prisoners were selected from District Jail, Jhang (Punjab) and 20 control samples were obtained. Amplification of selected segments of exon 7 of DRD2 gene DNA was performed using Chain Termination Method. Three polymorphisms 67555 T>C, 67525 T>C and 67543 C>T within the DRD2 genewere found in the criminal samples while no SNP was found in the control sample. In Buss andPerry questionnaire, the criminal group obtained (28.2, 20.4, 27.3 and 28.1) while control groups obtained (19.31, 17.59, 23, and 23.63) marks in physical aggression, verbal aggression, anger and hostility respectively. The P-value was 0.0340 which is significant. These results provided genetic evidence regarding the involvement of DRD2 gene as a potential contributor towards aggression and violence. The present study is significant in determining the level of aggression in convicted offenders. Many anti psychotic drugs can be prepared by the pharmacists against the targeted regions to lessen the level of aggressionas well.*

Keywords: *Aggression, Behavior, Criminal, DRD2, Prisoner, SNPs*

INTRODUCTION

Human behavior includes all traits of physical and emotional behaviors. This behavior is influenced by culture, altitude, emotions, values, ethics, authority, rapport, persuasion, coercion and genetics. Aggression is defined as any act of anger or antipathy towards others. It is among those destructive behaviors that can be the result of internal frustration (1). It can be classified into direct and indirect aggression. Direct aggression may include physical and verbal abuse. Indirect aggression may include threatening someone or urging someone else to inflict harm to another individual. External and internal parameters govern such a complex trait, aggression (2).

A person with high level of aggression fails to cope with his educational, professional and social life and is not accepted by society. Human's aggressive and violent behavior correlates with different aspects i.e. aggressive behavior, violent behavior and antisocial behavior (3). Aggressive behavior includes inflicting physical harm or verbal humiliation to the victim (4). Aggressive behavior can be classified into different categories depending upon its features i.e. Intentional aggression and Unintentional aggression. In unintentional aggressive behavior there inculcates an angry feeling in a person himself while intentional aggression uses aggression intentionally. Aggression can be the consequence of many internal and external factors. Internal factors include major life happenings and external factors include the unhealthy

environment that provokes aggression. Internal factors include age, gender and personality traits that occur during the lifetime of an individual. Aggression has drastic profound effects on an individual especially if it encircles him or her in early ages of life when social, emotional, cognitive development is at its peak. Aggression is more predominant in males than in the females (5). Persons suffering from personality disorders e.g. paranoid, schizoid and histrionic and anankastic pass such traits to next generation as well. External factors suchas frustration or unpleasant situation faced by the person i.e. social rejection, use of weapons, violent media i-e violent T.V programs, child abuse, financial problems, sexual abuse and drug addiction i.e. alcohol have played an important role in promotion ofaggression (6).

All violent behaviors may be aggressive but all aggressive behaviors cannot be referred as violent. According to World Health Organization (WHO) aggressive behavior in the formof physical violence is one of the major public health problems worldwide (7). Annually 1.6 million Deaths caused by violent activity worldwide. Aggressive behavior can be of two types i.e. proactive and reactive. Proactive aggression is goal directed and is without any provocation and persons exhibiting such behavior are mostly not empathetic and are offensive in nature. The reactive aggression is defensive and is in response to some provocation (8). Many environmental and genetic factors contribute to this proactive and reactive aggression and also contribute to physical aggression [9]. Human brain is one of the most important organs that play a vital role in the regulation of neurotransmitters which control the emotional activity of an individual including aggression. Aggressive behavior in humans is under the control of two main parts of the brain i.e. amygdala and hypothalamus (10). Human impulsive behavior is controlled by the cortex which is connected to the amygdala and orbito-frontal region of the cortex (11). Reduced volume of amygdala and orbito-frontal cortex has been shown by brain imaging in persons with borderline personality disorders and behavioral disorders including aggression (12).

Traumatic injury to the brain areas especially to the prefrontal cortex results in extreme aggressive behavior and violent activity (KRUESI et al. 2010). Any dys-regulation in the limbic derived response can cause aggression (13). A prefrontal cortex region gyro plays an important role in regulation of human behavior. Frustrated behavior leads to gyri atrophy. This region contains two major systems that control the level of neurotransmitters that are involved in behavioral response. Serotonergic systems and dopaminergic systems have a key role in maintenance of our behavior (14). Abnormality in the serotonergic system will lead to the malfunctioning of the dopaminergic system this will result in violentbehavior (15). These two systems are controlled by major genes of our body. Serotonergic system is under the influence of 9 genes (16). Genes that control the functioning of the dopaminergic system are *DRD2*,*DAT* and *MAOB* genes (17). Contributions of genetic factors towards aggression have always been important in mass media and have vastapplications in forensics (18). Individual's personality is greatly influenced by genetic variations. Dispositions in Multiple genes i.e. *MAOA*, *DRD2*, *DBH*, *COMT*, *TPH* and *SLC6A4* contribute to antisocial behavior including aggressive behavior in humans (19). *DRD2* gene spans 66,097 bases and is located on chromosome 11q23.2 (20). Dopamine receptor-ligand interaction leads to neurotransmission. This gene lies under the category of dopaminergic gene that controls the activity of the dopaminergic system. The DRD2 genecomprises of 7 introns and 8 exons. This gene encodes the D2 subtype of the dopamine receptors. G protein coupled receptor-ligand interaction leads to inhibition of cAMP. Mutation in this gene can cause many psychiatric disorders. Major target for antipsychotics is this gene. Polymorphism in this gene can cause severe neural disorders like schizophrenia, high level of aggression and violent behavior (21). There are 514 polymorphisms identified in this gene. *C957T* is the single nucleotide polymorphism associated with exon 7 of *DRD2* gene. *C957T* polymorphism can result in dys-regulation of dopamine. C957T polymorphism in *DRD2* gene has been shown to affect the translation of *DRD2* receptor. Behavioral misconduct is due to polymorphism in this gene which results in aggressive behavior and impulsivity (22). Cumulative effect of environmental factors(such as early childhood psychological trauma) with *DRD2* Taq1A polymorphism is found to be significant in causing violent behavior (23, 24). Aim of the study was to find the association of *DRD2* gene polymorphism in aggressive behavior in prisoners which compel them to make crime.

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Traumatic injury to the brain areas especially to the prefrontal cortex results in extreme aggressive behavior and violent activity. Any dys-regulation in the limbic derived response can cause aggression (13). A prefrontal cortex region gyro plays an important role in regulation of human behavior. Frustrated behavior leads to gyri atrophy. This region contains two major systems that control the level of neurotransmitters that are involved in behavioral response. Serotonergic systems and dopaminergic systems have a key role in maintenance of our behavior (14). Abnormality in the serotonergic system will lead to the malfunctioning of the dopaminergic system this will result in violent behavior (15). These two systems are controlled by major genes of our body. Serotonergic system is under the influence of 9 genes (16). Genes that control the functioning of the dopaminergic system are *DRD2*,*DAT* and *MAOB* genes (17). Contributions of genetic factors towards aggression have always been important in mass media and have vast applications in forensics (18). Individual's personality is greatly influenced by genetic variations. Dispositions in Multiple genes i.e. *MAOA*, *DRD2*, *DBH*, *COMT*, *TPH* and *SLC6A4* contribute to antisocial behavior including aggressive behavior in humans (19). *DRD2* gene spans 66,097 bases and is located on chromosome 11q23.2 (20). Dopamine receptor-ligand interaction leads to neurotransmission. This gene lies under the category of dopaminergic gene that controls the activity of the dopaminergic system. The DRD2 gene comprises of 7 introns and 8 exons. This gene encodes the D2 subtype of the dopamine receptors. G protein coupled receptor-ligand interaction leads to inhibition of cAMP. Mutation in this gene can cause many psychiatric disorders. Major target for antipsychotics is this gene. Polymorphism in this gene can cause severe neural disorders like schizophrenia, high level of aggression and violent behavior (21). There are 514 polymorphisms identified in this gene. *C957T* is the single nucleotide polymorphism associated with exon 7 of *DRD2* gene. *C957T* polymorphism can result in dys-regulation of dopamine. C957T polymorphism in *DRD2* gene has been shown to affect the translation of *DRD2* receptor. Behavioral misconduct is due to polymorphism in this gene which results in aggressive behavior and impulsivity (22). Cumulative effect of environmental factors (such as early childhood psychological trauma) with *DRD2* Taq1A polymorphism is found to be significant in causing violent behavior (23, 24). Aim of the study is to find the association of *DRD2* gene polymorphism in aggressive behavior in prisoners which compel them to make crime.

MATERIALS AND METHODS

The research work was performed in the Molecular Biology & Genomics Laboratory in the Institute of Biochemistry and Veterinary Diagnostic Laboratory, Johar Town, Lahore. Total 20 prisoners were selected from District Jail, Jhang, Pakistan who were convicted of physical violence, homicidal cases, domestic violence and sexual assaults. We followed the strategy of control samples and convicted prisoners while collecting the samples. Consent letters, personnel data and history of their self-reported aggression was taken from convicted prisoners. The consent letter and personal information were taken from all subjects which contained name, age, gender, criminal record, jail ID, biological sample as well as project

information sheet. There were 29 questions to estimate the level of aggression. The questionnaire was based on four categories of aggression, as physical aggression, verbal aggression, hostility and anger. The minimum and maximum aggression scoring was done for all aggression factors and analyzed for control samples to mark the difference of aggressive behavior between controls and convicted samples. Aggression and violent behavior scoring was done by using Buss and Perry Questionnaire with which aggression was correlated with the suspected SNP.

DNA EXTRACTION

DNA was extracted from the buccal sample collection sticks by the following method: Cotton plugs attached with the sticks which were rubbed inside the inner checks and removed with the help of sterile blades were transferred into the labeled eppendorf tubes. Then 700 micro liters of lysis buffer, 10 micro liters proteinase K, 100 micro liters of 3 M sodium acetate was added in it followed by gentle spinning. The mixture was incubated in water bath at 56 °C for overnight. Centrifugation was performed for 2 minutes at 14500rpm and condensation was collected at the bottom. The cotton plugs were then collected with the sterile tweezers following the addition of 500 micro liters of phenol: chloroform :isoamyl alcohol (PCI) and then vortexed it until the solution turned milky and centrifuged it for 10 minutes at 14500 rpm. Three layers were formed. The upper aqueous layer was collected with the help of pipette and shifted to another labeled eppendorf tube. Then in the upper separated supernatant 500 microliters of chilled absolute ethanol was added and mixed gently. Samples were incubated at -20 °C for 15 minutes and centrifuged again for 15 minutes at 14500 rpm. The supernatant was removed carefully and discarded. The pellet was washed with 500 microliters of 70 % ethanol and centrifuged for 10 minutes at 14500 rpm. The obtained pellet was dried for overnight to evaporate the ethanol. Then 30 micro liters of distilled water was added andheat shock was given at 70°C for 40 minutes. DNA was quantified using agarose gel electrophoresis. DNA was quantified by comparing sample bands with the providedstandard. DRD2 gene in homo-sapiens was located on chromosome 11 having 8 exons and 7 introns. It had a total length of 66,097 bp.

PRIMER DESIGNING AND PCR AMPLIFICATION

Primer set was designed for exon 7 of the DRD2 gene. Primers were designed by using primer 3 Software. Forward primer 5GGAGTCTTCAGAGGGGGAAA- 3 and reverse primer 5-GGAATGGGACCTTTCACAGA -3 were designed against NCBI Reference SequenceNC-000011.10 by using primer 3 software. A GRADIENT PCR was performed for primer optimization. PCR products were then sequenced by using the Sanger method.

SEQUENCE ANALYSIS

Results of sequences were visualized by using CHROMAS software. CLUSTAL W software was used for alignment of the various sequences. This alignment helped in the detection of SNP (Single Nucleotide Polymorphism) in the interested gene region. The ANOVA software was utilized to determine whether the chosen marker has significant value for violence or not.

RESULTS

SEQUENCING OF AMPLICONS OF DRD2 GENE

The desired exon of DRD2 gene was sequenced and aligned by using BLASTsequence software. Sequencing of purified amplicons was performed using Sanger Sequencing. Data analysis was performed using NCBI BLAST. Analysis of data showed three polymorphisms 67555 T>C, 67525 T>C and 67543 C>T in the criminal samples while no SNP was found in control sample (Table I).

Table I. List of identified polymorphisms in criminal samples

Serial No	Nucleotide position*	Reference*	Criminal samples
1	67555	T	C
2	67525	T	C
3	67543	C	T

T= Thyamine and C= Cytosine

BUSS AND PERRY AGGRESSION SCORING

Aggression scoring was performed using Buss and Perry aggression questionnaire between the criminal and the control groups. Criminal group exhibited a greater level of aggression as compared to the control group on the basis of four scales of aggression .i.e. physical aggression, verbal aggression, hostility and anger. Every scale had maximum 30 numbers with a total of 120 marks. In this questionnaire, the criminal group (28.2, 20.4, 27.3 and 28.1) control groups obtained (19.31, 17.59, 23, and 23.63) marks in physical aggression, verbal aggression, anger and hostility respectively. The P-value was 0.0340 which is significant. The Physical aggression was the common type of aggression in criminal group while hostility was common in control group.

DISCUSSION

Alternative characteristics of aggression are an inherent inability to control emotions and impulses (25). Genetic factors contribute 50% towards the development of aggression. Many environmental factors in combination with genetic factors contribute to aggressive behavior in humans. Contributions of genetic factors towards aggression have always been important in mass media and have vast applications in forensics (18). Individuals' personality is greatly influenced by genetic variations. Dispositions in Multiple genes i.e. MAOA, DRD2, DBH, COMT, TPH and SLC6A4 contribute to the antisocial behavior including aggressive behavior in humans (19). Candidate genes responsible are DRD2, DRD4, DAT1- 5- HT`TLPR and COMT gene. High level of aggression, violence and misconduct has been found to be linked with mutations in these genes in the children (26). Polymorphism in these above-mentioned genes together with financial stress can provoke an individual to inflict verbal, emotional, social or physical abuse on the intimate partner. A strong association was found between financial stressors and *DRD2* mutants (27). C957T polymorphism in exon 7 of *DRD2* gene is found to be associated with this high level of aggression among humans. A study conducted in the microbiology and molecular genetics Punjab university Lahore Pakistan in which they reported the association of *DAT1* (9R-allele) with the aggressive behavior (28). A study reported that Dopaminergic variants DRD2, Taq1A and DAT 40bp and COMT Val 158Met gene are associated with severe violent criminal activity and imparts their influence on many cognitive functions. These studies confirmed that DRD2 and DAT have partial roles for aggression and drug dependence. Family base case control study of DRD2, DAT, 5HTT, COMT suggested that aggressive behavior is caused by the missense mutation in these genes (29). Another study reported that Taq1 polymorphism of DRD2 gene was found to be associated with the aggressive behavior in which homozygote (*DRD2* A1/A1 and A2/A2) scored lower of association (p=0.0016) than the heterozygote (30). In the Chinese population Taq1 also reported to be associated with antisocial behavior. That study was conducted among Chinese people who were in Taiwan (31). In the study of antisocial behavior in which they reported that two genes in combination (*COMT* and *DRD2*) polymorphisms were found to be associated with antisocial behavior this could be a reason of criminal approach (32). DRD2 gene acts as a modifying gene. Taq1 A and C957T of DRD2 are linked with many psychiatric disorders like autism, Tourette Syndrome and Post Traumatic Stress Disorder (33). As the dopamine is involved in behavioral responses such as antisocial behaviors, cognition and neurological behaviors dopamine D2 receptor have been genetically studied in which number of polymorphisms are associated with the aggressive behaviors which lead to the criminal activities. In the Iraqi population *DRD2/ANKK1* Taq1 A polymorphism have been studied among alcoholic and drug addicted people, which is also involved in aggressive behaviors by criminals. A1 allele is 1.9 fold more involved in addiction than A2 allele (34). In the reported study, criminology, behavior is associated with the dopamine transporter (*DAT1*) polymorphisms (35). In a study dopaminergic system genes are observed to be involved in aggressive behavior. In this study one "G" allele of gene *DRD2 (A-241G)* polymorphism with genotypic association of p=0.002 and allelic association p=0.001 correlated with the aggressive behavior. Another polymorphism in gene *DRD2* (Taq /AT allele) has also been reported with association (p=0.001) in aggressive children (5). In our study, novelty of work is polymorphisms (67555 T>C, 67525 T>C and 67543 C>T) in the DRD2 gene which was found to be associated with the criminal attitude of prisoners (Figure 1).

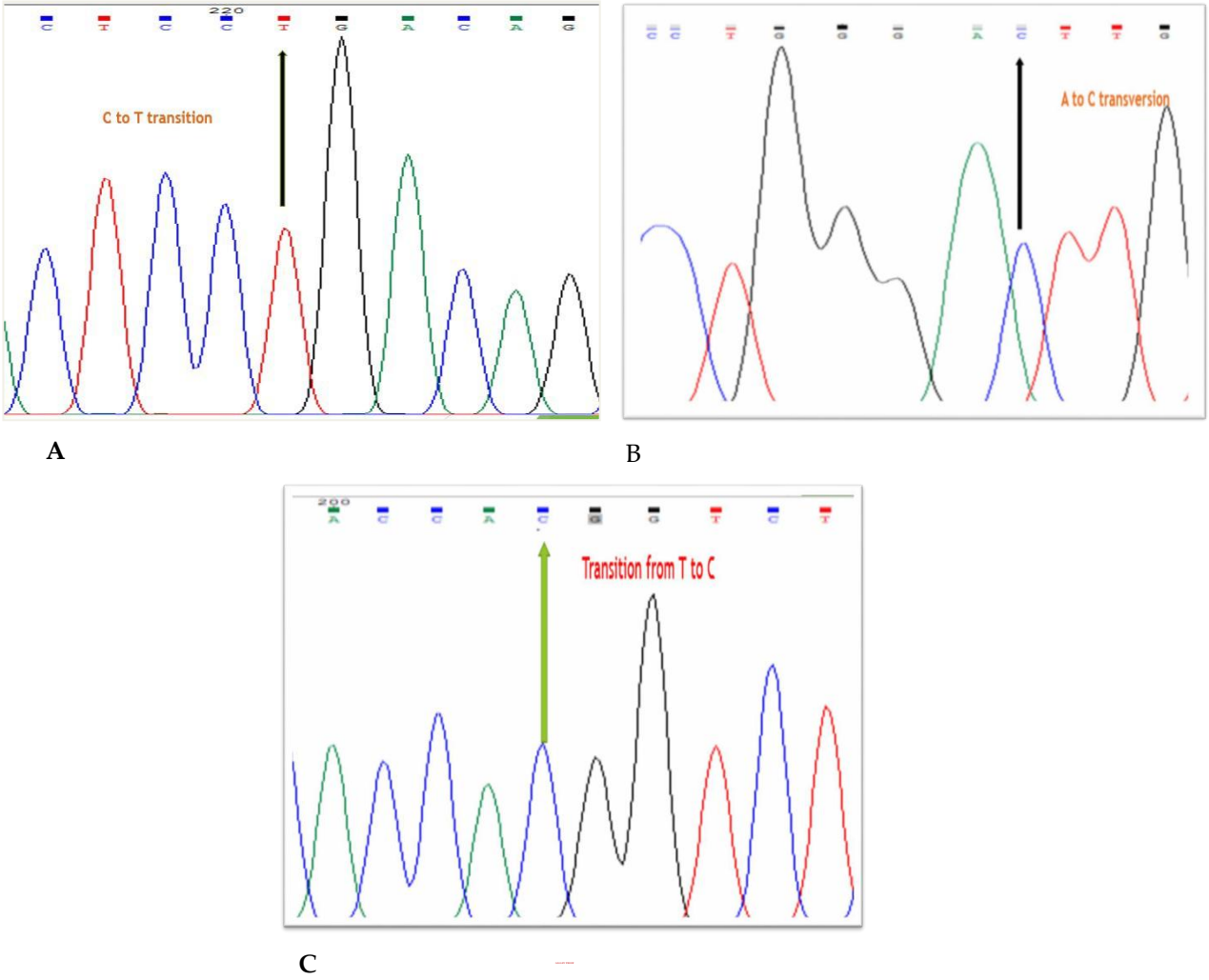

Fig. 1. Sequencing of amplicons of DRD2 gene, (A) Chromatogram of polymorphism in DRD2 gene of criminal sample at position 67543 **(B)** Chromatograph of polymorphism in DRD2 gene of criminal sample at position 67555 **(C):** Chromatographof polymorphism in criminal sample at position 67525

Our findings are not previously reported. The present study will be beneficial in determining the level of aggression in convicted offenders by scanning the genetic polymorphism in DRD2 gene among Pakistani convicted offenders which are involved in homicide, sexual and physical abuse. Bess and Perry aggression analysis is just the indicator of the criminal behavior and it does not rule out the behavior of the criminals in the near future and also does not suggest that control groups will not become aggressive. The findings of the study should be used in correlation with other observations and findings. And of course, further studies should be conducted to deeply observe the aggressive behavior and the stimulating events that bring forth that kind of responses.

CONCLUSION

There is an association between polymorphism in the DRD2 gene and aggressive behavior which results in antisocial behavioral trait, which is characterized by impulsive or unethical behavior. Patients become schizoid and express his/her aggression by inflicting harm to others. Genetic scanning of the polymorphism in the DRD2 gene can be a useful factor in the development of the tendency to criminal activity. Pakistani convicted offenders which are involved in homicide, sexual and physical abuse. Many antipsychotic drugs can be prepared by the pharmacists against the targeted regions. The study will be helpful to identify single nucleotide polymorphism (SNP) in the coding region (exon 7) of Dopamine receptor gene (DRD2) among convicted criminals and to associate the identified polymorphism with aggressive behavior and violence.

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Conflict of interest:

There is no conflict of interest.

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