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The association of the Catechol-O-methyl transferase (*comt*) Val 158 Met gene polymorphism with violent criminal behavior in Iraq

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Abstract : Behavioral genetic studies had examined whether the genetic basis had an influence on antisocial behaviors, they revealed that the violent criminal behavior arising from the interaction between several genetics and environmental factors .The present study reflect the role of polymorphisms in Catechol- O- methyl transferase (comt) gene on violent criminal behavior in Iraqi prisoners.

Methods: blood samples were collected from 200 prisoners (case group) who convicted with terrorism (150 sample), murder(30 sample) and drug trading (20 sample) issues selected from Al –Hila prison reformist central for men and women / Babylon city and from position and deporting division /Karbala ,this sample include (160 male and 40 female).Additionally, 100 sample were collected as control groups included (54 male and 46 female).

DNA was extracted from the peripheral blood of all participants, and the above mentioned single-nucleotide polymorphisms (SNPs) were genotyped by RFLP -PCR(Restriction Fragment Length Polymorphism). The results were confirmed by using sequencing technique.

Results: The result of the RFLP PCR and DNA sequencing methods for *comt* (Val 158 Met) polymorphism revealed that the homo-mutant genotype A/A(Met/Met) have significant higher risk of criminal behavior (p= 0.001 ;OR= 3.98 ; 95% CI= 1.7-9.3) when compared with control and the A allele (Met allele) frequency was a significant associated with case group (p=0.003; OR= 1.68; 95%CI= 1.19-2.37).

Conclusion: the presence of the Met allele of the *comt* gene results in a significant increase in the risk of the susceptibility of individual to engage in to crimes in the presence of certain environment risk factors.

Key word: Catechol- O- methyl transferase *(comt)* gene, alleles, dopaminergic system ,violent criminal behavior.

Introduction:

Genetic studies of offending and criminal behaviour are rare in spite of the wide recognition that individuals may differ in their tendency for delinquency and criminality[1].

The relationship between genes and behavior is a complex. Much of the human genome is devoted to behavior, and more genes are expressed in the brain than in any other organ .researchers have approached the investigation of genetic factors in behavior in several different ways to try and establish whether violence is more product of inherited characteristics or environmental influence .two of the main methods are twin studies and adoption studies[2].

Research in behavioral genetics provided strong evidence that genetic polymorphisms are risk factors for the development of violence and psychiatric disorder[3]. The most promising genes at least in the etiology of deviancy are those that involved in the production ,transportation and breakdown of certain neurotransmitters ,the most commonly neurotransmitter studied is a dopamine because its functionally associated to the regulation of behavior that may affect crime and offending[4]. The dopaminergic system plays critical role in mediating behavior effects by its polymorphic genes, One of these genes that has received attention is (*comt*) gene encode for Catechol - O- Methy-transferase enzyme responsible for regulation of catechol hormones such as dopamine .a common polymorphism at codon 108/158 (S- COMT/MB-COMT) resulting from a single nucleotide transition G to A (SNP- rs4680) and causing a valine to methionine substitution in the enzyme[5].

The aim of this study is to establish the association between Val 158 Met *comt* gene polymorphism frequencies with violent criminal behavior in Iraqi prisoners.

Materials and Methods :

The study subjects comprised from 200 prisoners who convicted with terrorism, murder and drug trading issues selected from Al- Hilla Prison Reformist Central For Men and Women /In Babylon city and from Position and Deporting Division /In Karbala. The samples include (160 male and 40 female),One hundred randomly collected people were taken included (54 male and 46female) were taken as control group to compare with cases group.

Blood samples (3-5ml) were collected in EDTA tubes from each subject in the study and stored frozen at -20 C˚ until analysis.

Each frozen blood specimen was thawed, genomic DNA was then extracted directly using FAVORGEN tissue genomic DNA extraction kit (Taiwan). DNA purity and concentration were determined using a spectrophotometer (Nanodrop).

Genotyping the *comt* (Val 158 Met) SNP polymorphism :

Genotyping was performed using Restriction fragment length polymorphism (RFLP - PCR) of the *comt* gene and DNA sequencing method used for polymorphism analysis. The polymorphism was detected by PCR using primers forward:5′TACTGTGGCTACTCAGCTGTGC-3′and revers:

5′GTGAACTGTGTGTGAACACC -3′ [6]

the components of PCR working solution were mentioned in table (1).

Table (1): The Master Mix components of PCR :

Component	Amount (µl)	Concentration
Master Mix	**12.5**	**1X**
DNA	**3**	**50-150 ng/µl**
***drd2* primers**	**2**	**10pomol**
DNas free water	**Up to 25µl**	**-**
Total volume	**25µl**	**-**

PCR Protocol:

PCR was performed in a thermo cycler under the following conditions adopted in table (2).

Table (2): The PCR protocol for *comt* Val158Met polymorphism detection.

No.	Steps	Temperature °C	Time	cycle	Product size (bp)	Reference
1.	Initial denaturation	94	10 min.	1	237	6
2.	Denaturation	94	30 sec.	35		
3.	Annealing	56	30 min.			
4.	Extension	72	30 min.			
5.	Final extension	72	5 min.	1		
6.	Hold	4	5 min.	1		

The PCR product samples were loaded to electrophoresis with gel electrophoreses in 2 % agarose gels stained with ethidium bromide (10 mg/ml) , photographed and analyzed using gel documentation system **(**Harvard/UK**)** to check the amplification of the desire piece of gene which is approximately 237 bp A 100 bp DNA ladder (Bioneer -south Korea) were used as a size marker[6].

RFLP – PCR protocol:

The RFLP analysis of *comt* gene is accomplished according to New BioLabs England company protocol with some modifications :

Table (3) Component volume of RFLP Val 158 Met SNP digested by restriction enzyme Nlalll.

Materials	Volume µl
PCR product	10
Enzyme	0.5(10 unit)
Cut smart buffer 1X	5
dH2O	To 30
Incubation at 2-4 hour	37Cº

The digested amplified DNA fragments were polyacrylamide gel electrophoresis on 12% , and the bands visualized after staining with ethedium bromide under UV light . A 100 and 50 base-pair ladder were used as assize marker for estimation of fragment sizes.

PCR –Sequencing

The polymorphisms analysis through Sequences (Sanger test) through Korean laboratory (Macrogen company), by sending the PCR products samples by a Al Musiab Bridge Company in Aljaderia / Baghdad for technique work analysis through sequencer system.

Analysis of Data:

Data analysis were conducted in 2 ways :

Analysis of sequence results for both strand (forward and reverse)by (Bio Edit version 7.2.5 program.

Statistical analysis :

Statistical analysis was carried out using SPSS version 23.categorical variables were presented as frequencies and percentage . Chi-square test and fisher exact test were used to compare between percentages (frequencies) in this study. The odds ratios (ORs) and 95% confidence intervals (95% CIs) was used to evaluate the potential associations between genetic variants dopaminergic genes and the risk of violent criminal behaviour in this study.

P value for all tests was considered significant if <0.05

Results and Discussion :

Demographic character features of case group .

The characteristic features of case group can be demonstrated in table (4), The study show that the percentage of male were (80%), while it was (20%) in female, majority of case group according to marital status and education level were married (72.5%) and illiterate (41.5%) respectively , (77.5%) of case samples were from rural while (22.5%) from urban, this group were self- employed in (84%)more than government employee (16%).Furthermore, the case with negative family history were (91%) while the positive were (9%) only . in addition (79.5%) of case sample without previous delinquency in contrast (2.5%)were with previous delinquency .

Table (4) Character features of case group.

Variable	NO. (%)
Sex	
Male	160 (80.0)
Female	40 (20.0)
Marital status	
Single	42 (21.0)
Married	145 (72.5)
Widow	10 (5.0)
Divorced	3 (1.5)
Educational levels	
Illiterate	83 (41.5)
Primary school	70 (35.00)
Secondary school	31 (18.50)
Diploma/University	1 (5.00)
Residence	
Urban area	45 (22.5)
Rural area	155 (77.5)
Occupational status	
Governmental employed	32 (16.0)
Self-employed	168 (84.0)
Family history	
Negative	182(91)

Positive	18(9)
Previous delinquency	
Yes	5(2.5)
No	195(97.5)

The association between study groups (case Vs controls) by variables.

The study showed that there was a significant association between cases and control (P≤ 0.001) regarding the sex, marital status ,residence , education level and family history ,while there was no significant association between cases and control with regarding occupation status (p=0.39) and previous delinquency (p=0.17)as shown in table (5).

Table (5) The association of study groups by study variables .

Variable	Cases (%)	Control (%)	Sig.
Sex			
Male	160 (80.0)	54 (54.0)	**< 0.001** *
Female	40 (20.0)	46 (46.0)	
Marital status			
Single	42 (21.0)	42 (42.0)	**0.001***
Married	145 (72.5)	54 (54.0)	
Widow	10 (5.0)	2 (2.0)	
Divorced	3 (1.5)	2 (2.0)	
Residence			
Urban area	45 (22.5)	82 (82.0)	**<0.001***
Rural area	155 (77.5)	18 (18.0)	
Occupational status			
Governmental employed	32 (16.0)	20 (20.0)	0.39
Self-employed	168 (84.0)	80 (80.0)	
Educational levels			
Illiterate	83 (41.5)	10 (10.0)	**<0.001***
Primary school	70 (35.00)	55 (55.0)	
Secondary school	31 (18.50)	25 (25.0)	
Diploma/University	1 (5.00)	10 (10.0)	
Family history			
Negative	182(91)	100 (100)	**0.001***
Positive	18(9)	0	
Previous delinquency			
Yes	5(2.5)	0	0.17
No	195(97.5)	100 (100)	

*p value ≤ 0.05 was significant

Distribution of Samples according to accusation type

Figure (1) showed the distribution of 200 prisoners participated in the present study according to accusation type, the results revealed that about 75%(150 prisoners) convicted with 4-terrorist issue in comparison with murder issue 15%(30 prisoners) and drug trading issue 10%(20 prisoners).

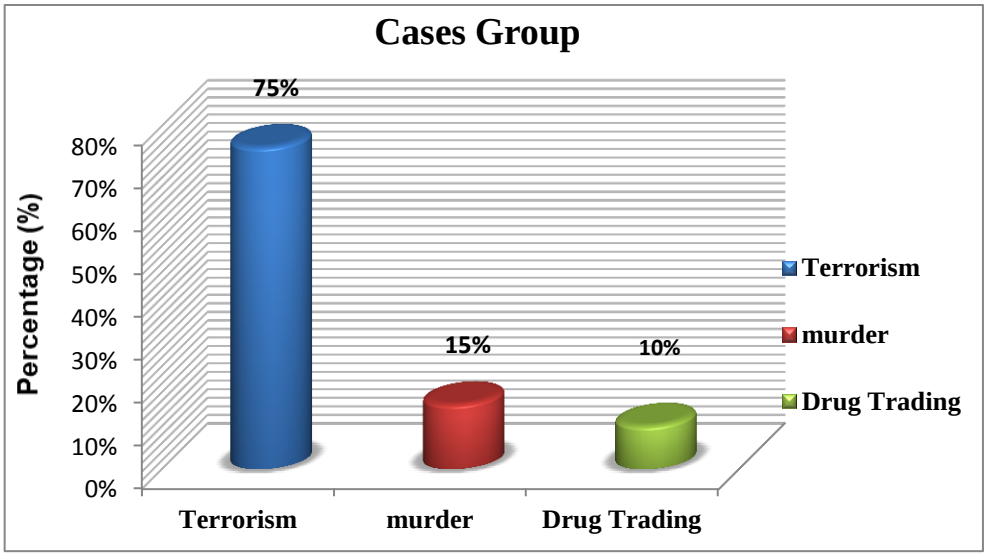


Figure (1): Distribution of study samples according to accusation type:

Distribution of study samples according to sex:

A wealth of research suggested that genes in androgen synthesis are implicated in male associated violence[7], Among the 200 prisoners , 160 (80%) were males and 40 (20.00%) were females , while the control include 46(46%) were males and 54(54%) were females. Frequency distribution of study groups according to gender is shown in figure (2).

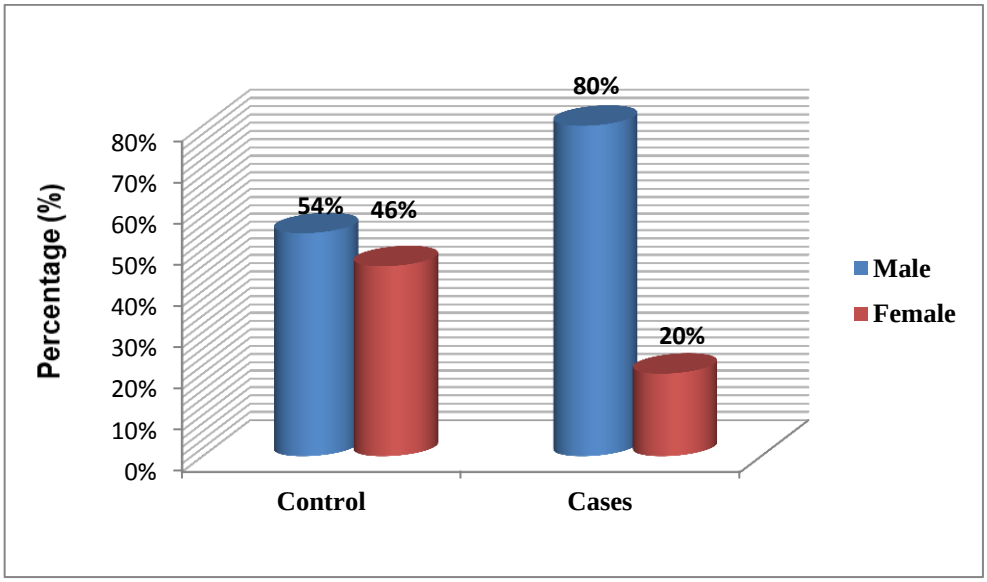


Figure (2) : Distribution of study samples according to sex.

Age Distribution :

The overall mean age of case and control were (36.51±9.41) and (32.78±9.02) years old, respectively.

Age is confound in regard to changing response and actual levels of hormones, In this study, the maximum age was 58 years within age group 50-59, as listed in Table (6).The maximum number of Cases was found within age group 20-29 and 30-39 years (34.5%).

The Federal Bureau of Investigation's (FBIs) Uniform Crime Report (UCR) arrest data revealed that 50% of all arrest occurring among younger persons was younger than 30 year for most crimes[8].

Table (6). Age distribution of studied individuals

Age group	Control(no=100)	Cases(no=200)
<20	5(5%)	21%
20-29	57(57%)	69(34.5%)
30-39	23(23%)	69(34.5%)
40-49	10(10%)	48(24%)
50-59	5(5%)	12(6%)
mean±SD	**32.78±9.02**	**36.51±9.41**

Concentration and purity of DNA:

The genomic DNA was successfully extracted from all blood samples **.** The concentration and purity of DNA range from 20 to 190 µg/ml and 1.5 to 2.3 respectively.

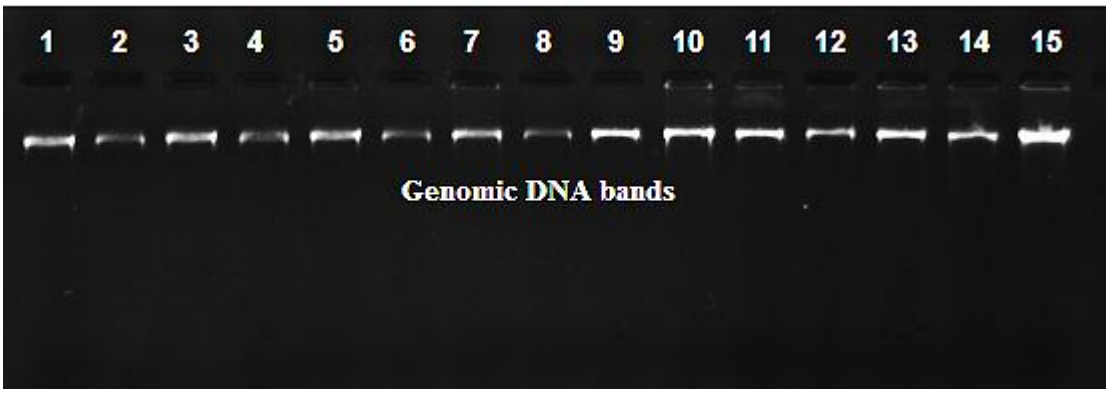


Figure 3: The electrophoresis pattern of DNA extracted from blood samples ,1% agarose gel , 5 volt/cm for 1 hour.(5 µl in each well) .

Genotypes and allele frequencies for *comt* (Val 158 Met) polymorphism :

1- Analysis of *comt* (Val 158 Met) polymorphism by RFLP-PCR :

The *comt* gene has functional polymorphism arise from rs4680 SNP **(**G1947A) resulted in amino acid substitution (valine to methionine) at codon 108/158 for S-COMT and MB-COMT, respectively[9].

The process of amplification of *comt* gene by using specific primers , the PCR resulted in a product with molecular size of approximately 237 bp as demonstrated in figure (4-10).

To detect the *comt* gene polymorphism , PCR-RFLP was applied by using a specific restriction enzyme (NlaIII) was used for digestion of PCR product of *comt* gene , the restriction enzyme digestion pattern is revealed in figure (4).

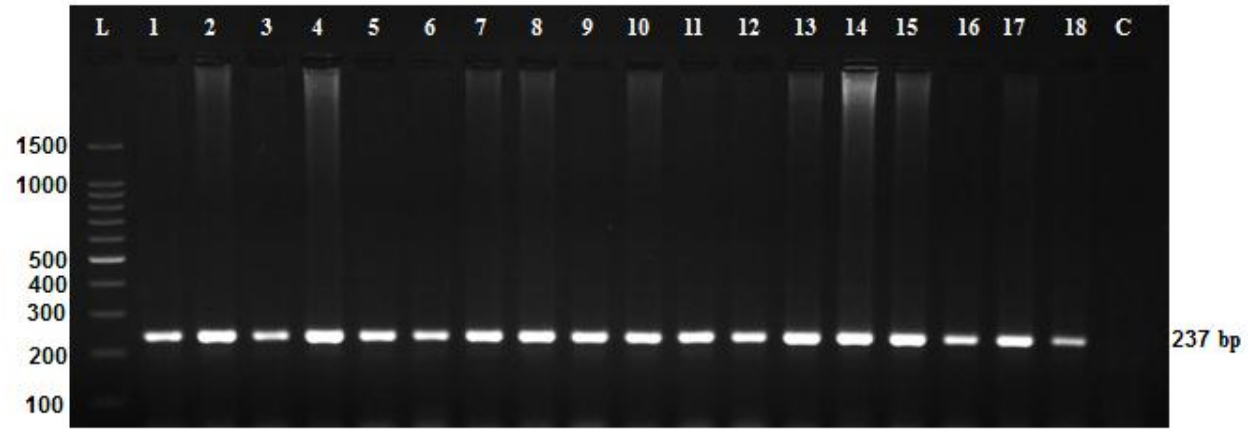


Figure (4): the electrophoresis pattern of PCR product for *COMT* gene this amplification product was 237bp , 2% agarose , 5 volt/cm , for 2 h(7 µl of PCR product loaded in each well). Lane L: DNA ladder (bp), lane 1-18 :PCR product , lane C- : negative control.

According genotypes of the studied subject were divided in to three groups based on the presence or absence the rs4680 SNP : G/G homozygous , demonstrated 114, 54, 42 & 27 bp fragments ; A/A homozygous , presents the expected 96 , 54,42 &18 bp fragment and G/A heterozygous state exhibited 114, 96,42,27 &18 fragments. Restriction fragments of 27, 42 and 54 bp were present in every digested sample . In the presence of a G at position 1947, an additional 114 bp fragment was present, which was cut by Nla III into 96 and 18 bp fragments when position 1947 contained an A (Figure 5)[10].

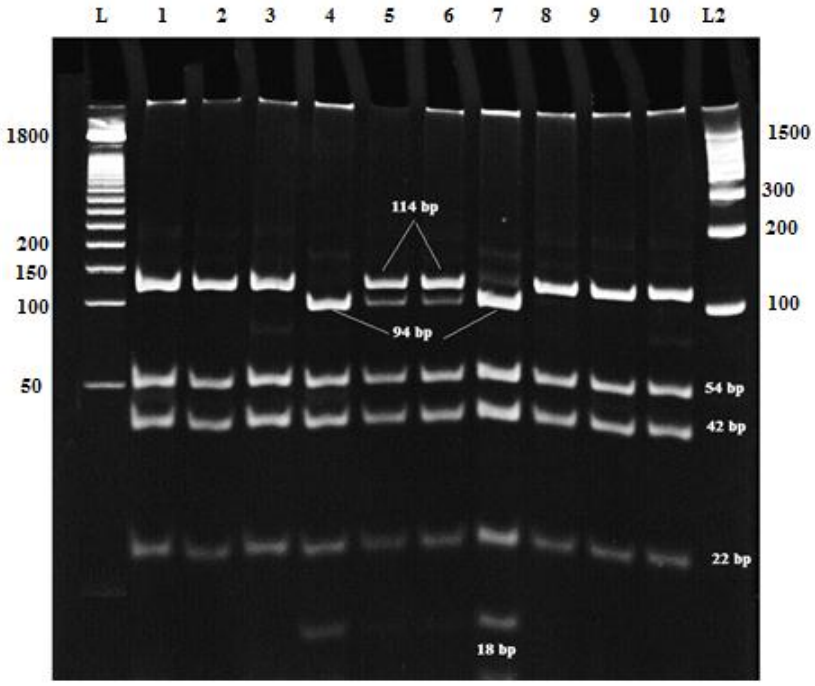


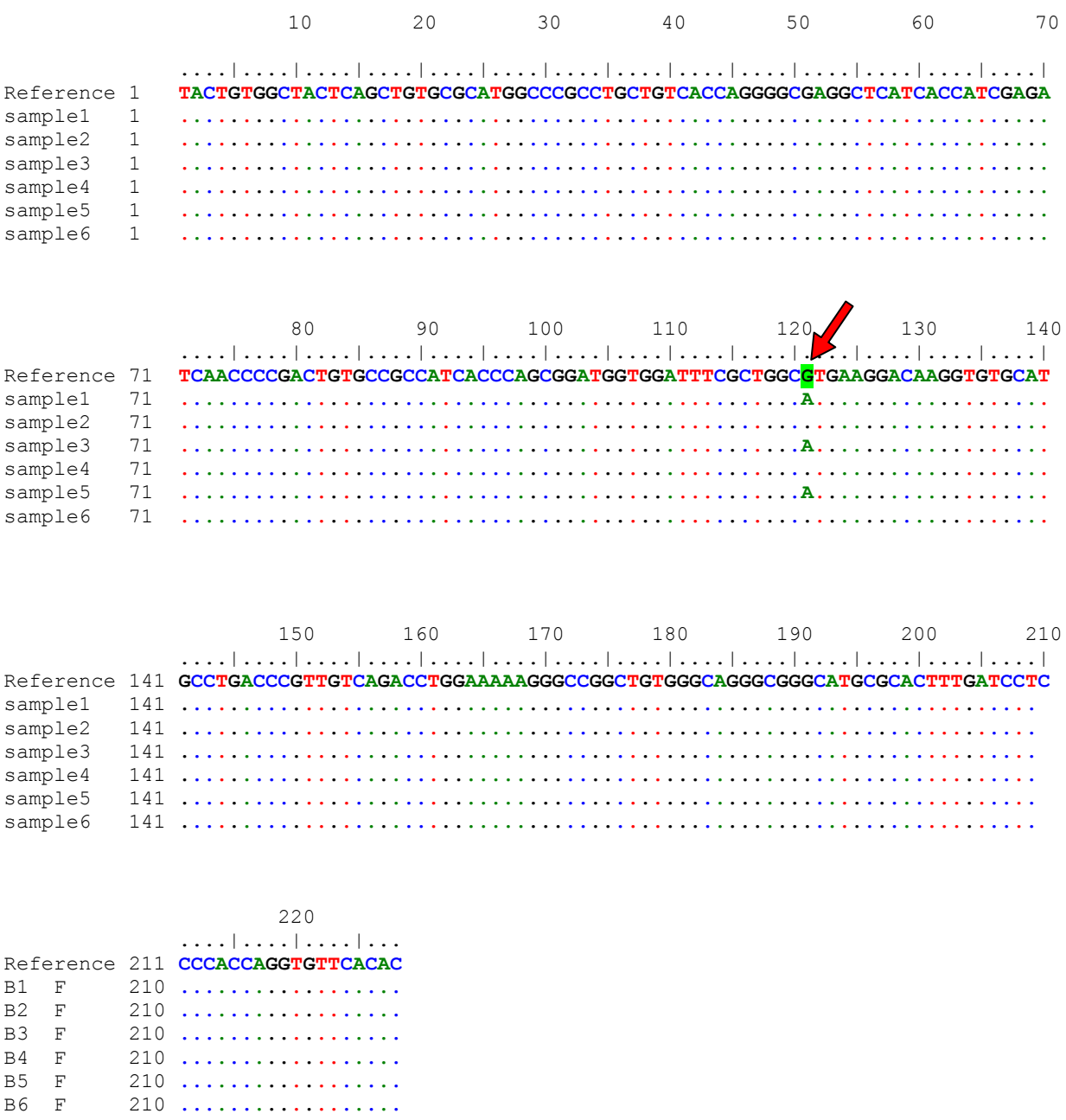
Figure (5) The electrophoresis pattern of RFLP- PCR for PCR product (237bp) with restriction enzyme (NlaIII) , 12% Polyacrylamide gel, 100 Volt for 3hours, (10 µl in each well).

Lane L1 ,L2 : DNA ladder 50 and 100 bp respectively.
Lane 1,2,3,8,9and 10 :showing bands 114 , 54,42 and 22 bp, (G/G) genotype (homozygotes wild type).
Lane 4 and 7: showing band 94,54,42 ,22 and 18 bp ,(A/A) genotype (homozygotes mutant type)
Lane 5 and 6 :showing bands 114,94,54,42,22 and 18 bp ,(G/A) Genotype (heterozygotes).

Sequence Analysis of *comt* (Val 158 Met) Polymorphism

The presence of G1947A polymorphism was established by PCR- Sequences to confirm the nucleotide changes responsible for antisocial behavior by Company Macrogen / Korea (figure 6 & 7).

The results were compared with data obtained from Gene Bank published (accession no. NG_011526.1) which is available at the NCBI and aligned by using Bio Edit program.



Figure(6) : **Sequences alignment results for *Homo sapiens comt* gene fragment by Bio Edit program version 7.2.5 revealed the substitution of a guanine to adenine G>A in sample 1 ,3 and 5 in position 121 , by comparing with reference sequence from GenBank (Accession number NG_011526.1).**

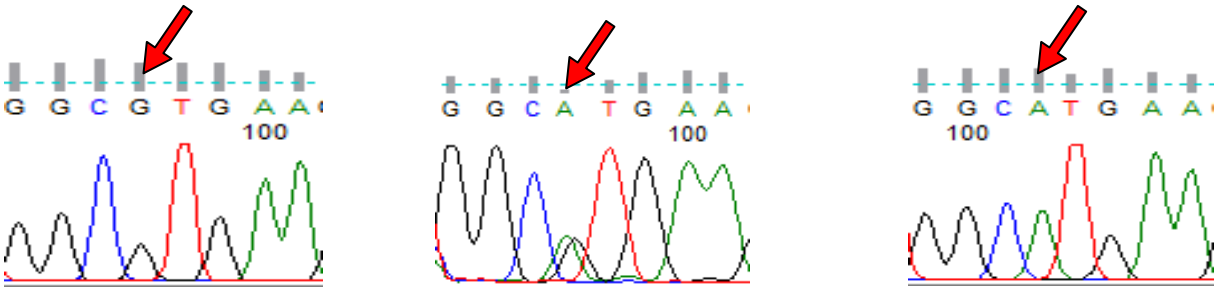


Figure (7) : **Sequence of three genotype of *comt* (rs4680) polymorphism . A. Sequence of the G/G homozygotes genotype; B. Sequence of the G/A heterozygotes genotype; C. Sequence of the A/A homozygotes genotype.**

To design the structure of the protein, the sequence of *comt* gene was retrieved from NCBI GenBank (accession no. NC_000022), the translation to amino acid had been done by ExPASY server on line at (http://web.expasy.org/translate/) further, the primary sequence was pairwise sequence alignment with catechol O-methyltransferase protein (original product of *comt* gene) has entry ID(P21964) that retrieved from UniProt KB website, alignment assay recorded that Valine (V) amino acid at position 158 of primary sequence had been shifted to Methionine (M) amino acid and the shifted amino acid is clearly appeared when *comt* gene enzyme had been homology modelled to created 3D structure model by utilized Swiss Modell server (source) (http://swissmodel.expasy.org) as showed in figure (8 & 9).

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                 ..|....|....|....|....|....|....|....|....|..
Reference        YCGYSAVRMARLLSPGARLITIEINPDCAAITQRMVDFAGVKDKV
sample 1         ..........................................M....
sample 2         ........................................................
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Figure (8) pair sequence alignment of amino acid sequence with entry ID (P21964) , drawn based on the sequence alignment BioEdit software version 7.2 revealed the substitution of Val.to Met in sample 1at position 158 .

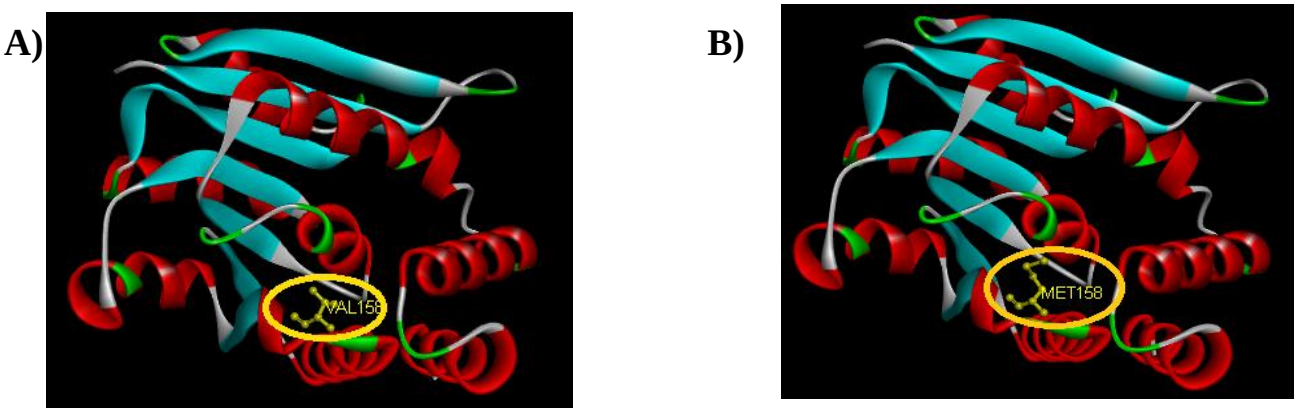

Figure (9): shifting of amino acid at position 158 of *comt* gene enzyme. (A: Normal 3D Secondary structure model, B-Abnormal 3D secondary structure model of enzyme with base substitution (G to A) at position 158 results in Methionine amino acid.

The genotypeś distribution of *comt* gene polymorphism with allele frequency and their association in control and case groups..

The distribution of the observed *comt* genotypes and allele frequencies in the control and cases groups are shown in table (7). The highest genotype in the control group was G/A heterozygous genotype (59%),followed by G/G homozygous (32%) and (9%) for mutant homozygous A/A genotype .

In whole case group ,the highest genotype was G/A heterozygous 55.5%, The genotype distribution is pointed out that mutant homozygous A/A was more than the normal homozygous G/G , which reached 23.5% and 21.5 % respectively.

The alleles frequency of A was more than the G which reached 51.25% and 48.75% respectively in case groups , whereas the alleles frequency of G was more than A in control group that reached 61.5 % and 38.5% respectively (figure 10). The results showed there is significant association (p= 0.001; OR=3.98 ;95%CI =1.7-2.5) for A/A genotype polymorphisms with violence crime ,also there is significant association (p=0.003; OR=1.68; 95%CI=1.19-2.37) for G alleles between control and case .

Table 7 : The genotypeś distribution of *comt* gene polymorphism with allele frequency and their association in control and case groups.

***comt* polymorphism**	**Control Group NO.(%)**	**Case group NO.(%)**	**Sig**	**OR (95% CI)**
Genotype				
G/G (Val/Val)	32 (32)	42 (21.0)		
G/A (Val/Met)	59 (59)	111 (55.5)	0.21	1.43(0.82-2.50)
A/A (	9(9)	47 (23.5)	**0.001***	3.98(1.7-9.3)
Total number	**100**	**200**		
Allele				
G (Val)	123(61.5)	195(48.75)		
A(Met)	77(38.5)	205(51.25)	**0.003***	1.68 (1.19-2.37)

*P value is significant ≤ 0 .05 level
[a] reference

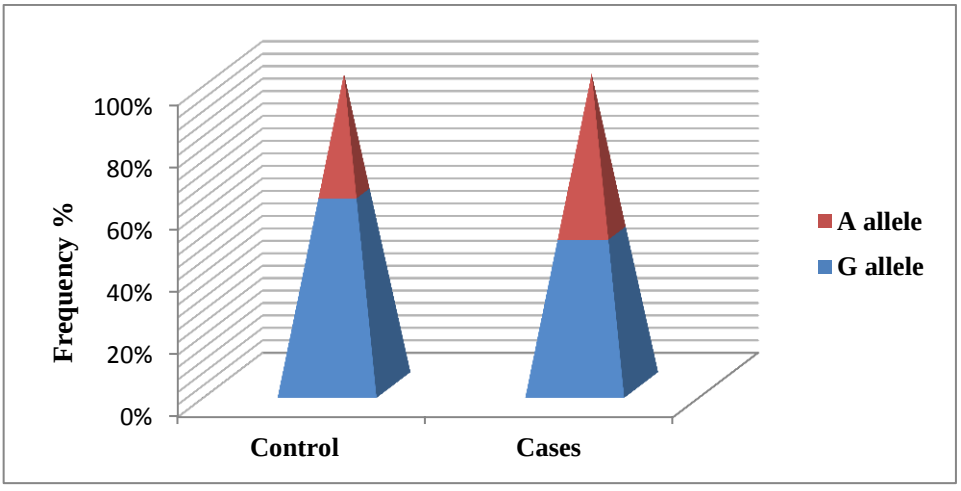

Figure (10) :The distribution of the *comt* allele frequencies in the control and cases.

Because COMT enzyme metabolizes neurotransmitters that are thought to be positively related to violence, the lower COMT activity associated with the Met allele points to the likelihood that the Met allele is the risk allele for antisocial behaviors[11].

The available research strongly suggests that carriers of the Met allele display more signs of violence and aggression, in one study to examine the effect of *comt* polymorphism on violence in sample of schizophrenic, their analysis revealed that patients who carry low activity Met alleles were at a modestly elevated risk of violence[12].

Mandelli and his colleagues found *comt* was risk factor for depression and bipolar disorder with (p=0.0015)in sample was composed from 686 italian subject[13].

The studies have mainly concentrated on the functional SNP (Val 108/158Met) I the coding region ,the enzyme containing Met is unstable at 37°C and has ¼ of the activity of the enzyme containing Val (7).

Other study show contrary results in examining the effect of SNP in sample with physical aggression ,they observed the met/met homozygotes are least aggressive, whilst wild type homozygotes (val/val) exhibited maximum aggression ($p < 0.01$)[14-23].

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