GENETIC POLYMORPHISM OF CATECHOL-O-METHYLTRANSFERASE AND KARYOTYPING ABNORMALITIES IN MENTALLY RETARDED CHILDREN

Thesis
Submitted for Complete Fulfillment of
The Doctorate (M.D.) degree in
Clinical and Chemical Pathology

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2012

بسم الله الرحمن الرحيم

ACKNOWLEDGEMENT

I would like to express my sincere thanks and deepest gratitude to ***Prof. Dr. Aisha Moustafa Abd El-Rahman****, Professor of Clinical and Chemical Pathology, Faculty of Medicine, Cairo University, for her encouragement and her continuous guidance and valuable advice for enriching this work.*

I am also grateful to ***Prof. Dr. Hoda Mohamed Abd-El-Ghany,*** *Professor of Clinical and Chemical Pathology, Faculty of Medicine, Cairo University, for her valuable advice, encouragement throughout the entire study, cooperative attitude and creative suggestions.*

I would like to express my sincere thanks and deep gratitude to ***Prof. Dr. Sawsen Mohamed Abd El-Hady,*** *Professor of Pediatrics, Faculty of Medicine, Cairo University, for her energetic follow-up with constructive advice, criticism and creative suggestions.*

I would like to express my sincere thanks and deep gratitude to ***Prof. Dr. Amal Mahmoud Mohamed,*** *Professor of Cytogenetics, National Research Institute, for her valuable help and continuous support. Her remarks and advice undoubtedly aided in improving this work.*

Finally, most thanks to my family especially my husband who supported me during preparation of this work.

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ABBREVIATIONS

AACAP	**:**	**American Academy of Child and Adolescent Psychiatry**
AAIDD	**:**	**American Association of Intellectual and Developmental Disabilities**
AAMR	**:**	**American Association of Mental Retardation**
ABS	**:**	**Adaptive behavior scale**
APA	**:**	**American Psychiatric Association**
ARC	**:**	**Association of Retarded Citizens**
BSID	**:**	**Bayley scales of infant development**
CI	**:**	**Confidence interval**
CM	**:**	**Clinical modifications**
CNS	**:**	**Central nervous system**
COMT	**:**	**Catechol-O-methyltransferase**
CT	**:**	**Computerized tomography**
CVS	**:**	**Cardiovascular system**
DD/MR	**:**	**Developmental delay/mental retardation**
DA	**:**	**Dopamine**
DOMA	**:**	**3,4-dihydroxymandetic acid**
DQ	**:**	**Developmental quotient**
DSM	**:**	**Diagnostic and statistical manual of mental disorders**
EEG	**:**	**Electroencephalography**
ESAC	**:**	**Extra Structurally Abnormal Chromosome**
FISH	**:**	**Fluorescence in situ hybridization**
FMR-1	**:**	**Fragile-X mental retaration-1 gene**
FRAX	**:**	**Fragile X syndrome**
GDD	**:**	**Global developmental delay**
GIT	**:**	**Gastrointestinal tract**
HCG	**:**	**Human chorionic gonadotropin**
HPLC	**:**	**High performance liquid chromatography**
ICD-10	**:**	**The tenth edition of the International Classification of Diseases and Related Health Problems**
ICD-9	**:**	**The ninth edition of the International Classification of Diseases**
ICF	**:**	**International classification of functioning disability and health**
ID	**:**	**Intellectual disability**
IEP	**:**	**Individualized education program**

IQ	**:**	**Intelligent quotient**
ISCN	**:**	**International system for cytogenetic nomenclature**
IVF	**:**	**In-vitro fertilization**
MAOIs	**:**	**Monoamine oxidase inhibitors**
MAPH	**:**	**Multiplex Amplifiable Probe Hybridization**
MB-COMT	**:**	**Membrane bound-COMT**
MCA	**:**	**Multiple congenital abnormalities**
MDI	**:**	**Mental developmental index**
MR	**:**	**Mental retardation**
MRI	**:**	**Magnetic resonance imaging**
NOS	**:**	**Not otherwise specified**
NTM	**:**	**Normal transmitting male**
OR	**:**	**Odds ratio**
PCPID	**:**	**President's Committee for People with Intellectual Disabilities**
PCR-RFLP	**:**	**Polymerase chain reaction restriction-fragment length polymorphism**
PDI	**:**	**Psychomotor development index**
PFC	**:**	**Prefrontal Cortex**
PKU	**:**	**Phenylketonuria**
RE	**:**	**Restriction enzyme**
RT	**:**	**Room temperature**
SAH	**:**	**S-adenosyl-homocysteine**
SAM	**:**	**S-adenosyl-methionine**
S-COMT	**:**	**Soluble-COMT**
SMC	**:**	**Supernumeray Marker Chromosome**
SNP	**:**	**Single Nucleotide Polymorphism**
SQ	**:**	**Social quotient**
SSRIs	**:**	**Serotonin selective reuptake inhibitors**
TORCH	**:**	**Toxoplasmosis, Rubella, CMV, Herpes simplex, Other infections**
UG	**:**	**Urogenital**
VABs	**:**	**Vineland adaptive behavior scale**
VCFS	**:**	**Velocardiofacial syndrome**
VSD		**Ventricular septal defect**
WHO	**:**	**World Health Organization**
WISC-III	**:**	**Wechsler Intelligence Scale 3rd edition**
WPA	**:**	**World Psychiatric Association**
WPPSI-R	**:**	**The Wechsler preschool and primary scale of intelligence-revised**

ABSTRACT

Mental retardation (MR) remains one of the most lifelong handicaps. Chromosomal abnormalities are important cause of MR and they are usually combined with congenital anomalies. Catechol-O-methyltransferase (COMT) plays an important role in breakdown of dopamine in the prefrontal cortex and this is functionally related to individual intellectual ability. Two co-dominant alleles (G and A) in exon 4 of the COMT gene influence the amino acid structure (Val or Met) at codon 158. Therefore, the COMT enzyme activity is genetically polymorphic with trimodal distribution (high activity in Val/Val genotype, intermediate activity in Val/Met genotype, and low activity in Met/Met genotypes).

The current study was conducted on 40 mentally retarded patients with stigmata of dysmorphology and malformations to detect chromosomal abnormalities and to clarify the association between COMT gene polymorphism and intelligence quotient (IQ) level. They were classified into two groups. Group I**:** 26 patients (65%) with mild and moderate degree of MR (IQ: 35-70) and Group II: 14 patients (35%) with severe degree of MR (IQ: 20-34). All patients were subjected to full clinical examination, karyotyping by conventional GTG banding and assay of genetic polymorphism of catechol-O-methyltransferase by polymerase chain reaction-restriction fragment length polymorphism (PCR-RFLP). Association of MR with congenital anomalies was present in 70% of studied patients, 2.5% had major anomalies in the form of ventricular septal defect and minor anomalies were detected in 67.5% in the form of: eye abnormalities in 67%, mouth abnormalities in 60%, ear abnormalities in 55%, nose abnormalities in 52.5%, hand and skeletal abnormalities in 12.5%, speech delay in 20% and urogenital manifestations in 5% of the studied patients.47.5% of the studied patients had more than three minor anomalies in the craniofacial region.

The results of karyotyping by conventional GTG banding revealed that 87.5% of the studied patients had normal karyotype and 12.5% had chromosomal abnormalities. Numerical chromosomal abnormalities were detected in 5% [(47,XY, +Marker in 2.5% and 47,XX,+Marker in 2.5%)], structural chromosomal abnormalities in 5% [(46,XX,del(9)(p22p24) in 2.5% and 46,XY,dup(22)(p11) in 2.5%] and sex chromosomal abnormalities in 2.5% ((46,XY,del(Y)(p11)).

The frequency of wild COMT (HH) genotype (55%) was the highest followed by heterozygous mutant (HL) genotype (37.5%) and homozygous mutant (LL) genotype (7.5%) i.e. the mutant COMT genotypes (HL,LL) were detected in 45% of the studied patients. The results of COMT genotyping by PCR-RFLP revealed that significantly higher mean IQ score in patients with wild (HH) genotype (42.1 ± 8.9) compared to those with mutant (HL, LL) genotypes (36.2 ± 11.8) *p*-value = 0.14. It could be suggested that the association between COMT gene polymorphism and IQ level in MR is present, as the mutant COMT (HL, LL) genotypes showed an increased risk in reduction of IQ level. Odds ratio (OR) for IQ groups is 5.625, 95% confidence interval = 1.349-23.449. The results of this study need to be confirmed by subsequent studies investigating a larger number of patients in each group to avoid statistical interference and bias. More trials are needed to clearly delineate the magnitude of the role of COMT gene polymorphism in the pathogenesis of MR that might lead towards realistic therapies or preventive strategies for it.

Keywords:

Mental retardation, Chromosomal abnormalities, COMT polymorphism, Intelligence quotient

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INTRODUCTION

Mental retardation (MR) is a human mental disorder characterized by an Intelligence Quotient (IQ) score 70 or lower. Other life limitations include problems with communication, self care, social situations and school activities **(Zhang *et al.*, 2007)**.

The incidence of MR is estimated currently around 1-3% of the population. Chromosomal abnormalities are an important cause of mental retardation and its frequency increased with the severity of the disease. 5-30% of moderate to severe MR can be accounted for by chromosomal disorders and the majority have associated with malformations, growth retardation, dysmorphism and family history of similar occurrence **(Lam *et al.*, 2006)**.

The coexistence of neuropathology and cognitive deficits supports the view that MR is a result of genetic mutations in the degradation pathway and the release of neurotransmitters in the central nervous system CNS **(Zhang *et al.*, 2007)**.

Dopamine is one of the most important neurotransmitters in human CNS, its levels are mediated by catechol-O-methyltransferase (COMT), this allows for critical modulation of cognitive function, especially in the prefrontal cortex **(Matsumoto *et al.*, 2003)**.

Catechol-O-methyltransferase plays an important role in the metabolism of endogenous and drug catechols. COMT catalyzes the O-methylation of catechols by transferring the methyle group from S-adenosyl-L-methionine to one of the hydroxyl groups of the catecholmoiety. COMT substrate includes neurotransmitters such as norepinephrine, epinephrine, dopamine, catechole estrogens and catechole drugs **(Sharon and Cherie, 2009).**

COMT is encoded by a single gene localized on chromosome 22q 11.1-q11.2. Two co-dominant alleles (G and A) in exon 4 of the COMT gene influence the amino acid structure (Val or Met) at codon 158 **(Mathotra *et al.*, 2002)**.

This single nucleotide polymorphism (SNP) is broadly referred to as Val 158 Met polymorphism **(Yirmi *et al.*, 2001)**. Therefore, the COMT enzyme activity is genetically polymorphic with trimodal distribution (high activity in Val/Val genotype, intermediate activity in Val/Met genotype, and low activity in Met/Met genotypes).

COMT regulates dopamine degradation and is associated with psychosis, making it a promising candidate gene for studying MR **(Zhnag *et al.*, 2007).**