Journal of Down Syndrome & Chromosome Abnormalities

Ramakrishnan and Husain, J Down Syndr Chr Abnorm 2017, 3:1
DOI: 10.4172/2472-1115.1000120

Short Commentary Open Access

MAOA Gene Associated with Aggressive Behavior in Humans

Ramakrishnan V* and Akram Husain RS

Chettinad Academy of Research and Education, Kelambakkam, Chennai, India

Abstract

The focus on behavioral genetics is primarily associated with destructive and anti-social behavioral activity and its findings are dispersed to the human beings. Behavioral genetics is multi-disciplinary, involving academic areas such as biology, genetics, psychology, social science and humanities. Monoamine oxidase is a mitochondrial enzyme involved in metabolism of various biological amines which are important neurotransmitters in the pathogenesis of major psychiatric disorders. In this review, the inheritance pattern and clinically significant polymorphisms of MAOA gene has been described. The results of abnormal behavior among human beings have stimulated research in understanding the relationship between metabolomic, genetic makeup which is surrounding with the environmental factors. The findings from behavioral research have ability to change the individual's characters. Recent, research studies have documented that genetics may contribute for violent and anti-social behavior.

Genes play a vital role in the development and pathogenesis of several diseases such as cancer, cardiac diseases, metabolic disorders, neurological and also in psychiatric disorders. In this review, the genes which are concerned with neurotransmitter metabolism pathways have been focused. Monoamine oxidase A *(MAOA)* gene located in Xp11.3 spanning 15 exons containing 527 amino acids and codes for MAOA protein. X-linked genes theoretically have increased possibility of sex-specific functions [1]. The function of MAOA enzyme is to degrade monoaminergic neurotransmitters (Adrenaline, Noradrenaline, Serotonin and Dopamine) in the brain and has been area of interest for investigators working in psychiatric disorders like Schizophrenia (SCZ), Bipolar disorder (BPD) and Major depressive disorder (MDD). These neurotransmitters play an important role in arousal, emotions, mood and even affecting impulse control [2]. Further, MAOA gene in men has been associated with several aspects such as social anxiety, erectile dysfunction, abnormal sexual maturations, depression, substance abuse, attention deficit disorder and many other psychiatric disorders [3].

Monoamine oxidase A was the first candidate gene which was found to be associated with anti-social behavior, identified in a large Dutch family in the year 1993. Hence, this gene is commonly known as "Warrior Gene". There are few versions of *MAOA* gene that produces MAO-A: 2R, 3R, 4R. Especially, 2R and 3R were related with the increased aggressiveness and violence [4]. The genetic effects observed on psychiatric phenotypes are hard to identify and it may be possibly due to the inter-individual heterogeneity among the phenotypes. The mutations observed in MAOA gene lead to Brunner syndrome, which is characterized by slight mental retardation, lower IQ, hyper sexuality, violence, mood swings and sleep disorders. These mutations affect only males and females carrying the wild type function normally without any symptoms [5]. The transmission pattern of Brunner syndrome in the families was consistent with X-linked recessive inheritance [6]. The *MAOA* gene involved in various metabolic pathways such as Citalopram Metabolism, Dopamine beta-hydroxylase deficiency, Dopaminergic synapse, Serotonergic synapse, Tryptophan, Tyrosine, Tyrosinemia Type I and also in Cocaine addiction. They catalyze oxidative deamination of biogenic amines, xenobiotics and function in the metabolism of neuroactive and vasoactive amines in the peripheral tissues and also in central nervous system [7].

Nearly, there are more than 3000 Single Nucleotide Polymorphisms (SNPs) observed in the nucleotide sequences of *MAOA* gene (Figure 1). In which some of the variants are pathogenic and clinically significant, the polymorphisms with their characteristics explained in (Table 1). The variant rs6323 (Arginine297Arginine) located in the exonic region, 'G' allele (homozygous dominant) indicates higher levels of the enzyme, while 'T' allele (homozygous recessive) indicates lower levels of enzyme production. When comparing in females, 'G' allele was associated with higher anger (p value=0.002) and it seems like 'G' allele might cause aggression in males. Likewise, 'T' allele was overrepresented in patients suffering from anxiety disorders [8]. Visual-spatial working memory can be explained as the skills involved in the ability to recall shapes, colors and as well as their locations and movements. They are assessed in measures such as Spatial Span Backwards test of the WISC-IV Integrated and Spatial Recall Test of the AWMA [9]. The SNP rs6609257 is a genetic biomarker has not been associated with Visuospatial WM (VSWM) brain activity. However, it tags with the functional MAOA gene VNTR 30-bp repeat region. The higher activity of VNTR variant has found to be associated with higher enzyme expression and increased prefrontal brain activity [10]. The 3R allele is most common allele observed in humans, approximately 1/3 of men from "Western" countries carry this form of the gene. This allele is found in 58% of Black males, 36% of Caucasian males and 54% of Asian males [11]. The gene-environmental interactions also affect behavior and research should continue to find the correlations between specific forms of behavior [12-14]. By these previous findings of MAOA gene, we can confirm that this gene has been associated with aggressive and anti-social behavior. We conclude that biological, social and environmental factors are involved in anti-social behavior. Abnormal MAOA gene functions have been well-known from several studies to positively associate with destructive behavior and by other factors. Currently, behavioral genetic research is evolving and its dissemination is required not only in academics but also in public and social forums. The knowledge acquired on behavioral

***Corresponding author:** Ramakrishnan V, Faculty of Allied Health Sciences, Chettinad Academy of Research and Education Chettinad Health City, Kelambakkam, Tamil Nadu, India, Tel: 044 47429041; E-mail: rkgenes@gmail.com

Received May 08, 2017; **Accepted** May 22, 2017; **Published** May 29, 2017

Citation: Ramakrishnan V, Husain RSA (2017) MAOA Gene Associated with Aggressive Behavior in Humans. J Down Syndr Chr Abnorm 3: 120. doi:10.4172/2472-1115.1000120

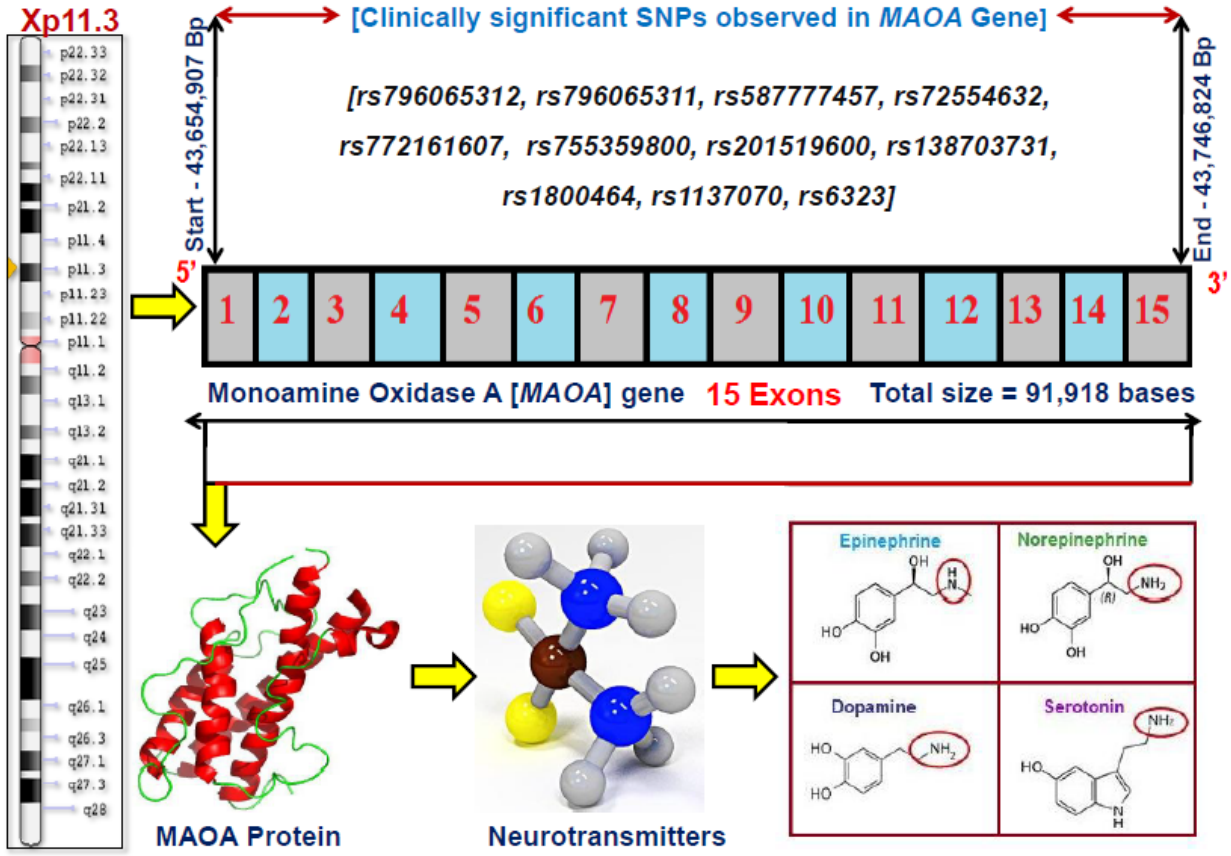

Figure 1: Cytogenetic location, exonic structure of MAOA gene and its protein function.

SNP-ID	Chromosomal location	Function	Clinical significance	Global MAF
rs796065312 [C>T]	X:43683572	Missense, UTR variant 5'	Pathogenic	NA
rs796065311 [->T]	X:43731344	Frame shift variant	Pathogenic	NA
rs587777457 [G>T]	X:43731695	Missense	Pathogenic	NA
rs72554632 [C>T]	X:43731784	Stop gained	Pathogenic	NA
rs772161607 [A>G]	X:43742033	Missense	Uncertain significance	A=0.0005/2
rs755359800 [A>G]	X:43736253	Missense	Uncertain significance	NA
rs201519600 [A>G]	X:43683576	Missense, UTR variant 5'	Uncertain significance	NA
rs138703731 [A>G]	X:43731723	Synonymous codon	other	A=0.0011/4
rs1800464 [A>C]	X:43711950	Synonymous codon, UTR variant 5'	other	C=0.1571/593
rs1137070 [C>T]	X:43744144	Synonymous codon	other	T=0.4482/1692
rs6323 [G>T]	X:43731789	Synonymous codon	other	G=0.3751/1416

MAF: Minor Allele Frequency; UTR: Untranslated Region, NA: Not Available [13,14]

Table 1: Clinically significant polymorphisms observed in the MAOA gene.

genetics can change the way by which the individuals feel about their own behavior. The use of behavioral research and its novel findings may lead to significant impact on the society.

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