Illustration of the Pathways Involved in Association of Genetic Variation and Frame Effect

SABA MONTAZERI [a] , HAMED TAHERDOOST [a, b]
[a] Research and Development Department, Ahoora Ltd | Management Consultation Group, Malaysia
[b] Advanced Informatics School, Universiti Teknologi Malaysia (UTM), Malaysia
hamed.taherdoost@gmail.com http://www.ahooraltd.com

Abstract: - Previous studies demonstrated that the various single and multiple genetic variations are associated with intermediate or behavioral phenotypes, which lead to different emotional decision-making and subsequently different susceptibility to framing effect. Researchers in many prior literatures were focused mainly on identification of the 5-HTTLPR-variation roles and processes involve in regulation of the serotonin level in brain region, which associated with behavioral traits in human. In this paper we comprehensively illustrate the identified brain regions, which might associate with framing effect. We also explain the pathways involved from gene to individual behavior and how does the specific allelic variation leads to different behavioral phenotype through effecting various brain areas activation. Discussing the previous findings highlights that the existing knowledge in this field is not efficient and complete. Thereby, we suggested that the further studies are required on other known candidate genes. Moreover we argued that the correlation of non-genetic factors with genetic variation as well as gene-gene interactions must be study in details in future to determine the effects of frame effect in different population and specifically in distinct individuals.

Key-Words: - 5-HTTLPR Variation, Frame Effect, Decision Making, Brain Function, Marketing Management

1 Introduction

Framing effect is the phenomenon that almost every single individual experience it in everyday life. Frame effect is significantly influential in individual's decision-making in many different areas such as health, economic, marketing and politic (Tversky & Kahneman, 1981; Hanley & McNeil, 1982). Two important basis of human decision-making, which have been observed across different cultures are risks with known outcome probability and context with ambiguity or uncertainty outcome probability as a result of different context for individuals (Kahneman & Tversky, 1979; Sharp and Salter, 1997; Stoltenberg & Vandever, 2010).

It has been argued that the susceptibility of individual's to these bases varies substantially and the elimination of their affect in decision-making, even with training has been very difficult (McNeil et al, 1982).Therefore, it has been suggested that the researchers must focus on the fundamental unit of heredity (genes), which associated with personality traits of an individual, to find the reason of existence differences in susceptibility of each person to bases of decision-making and subsequently to framing effect biases.But "how does genetic influences the susceptibility of human to frame effect" is a complex behavior question, which has not been answered very well yet.

Over the past years, researchers have been tending to investigate the relationship between behavioral traits, brain system and genes as well as uncovering the behavioral phenotype which associated with variation in genes (Jonassen & Landrø, 2014). Theoretically, it has been claimed that some allelic variation within a genotype have a functional impact on the cellular and molecular pathways associated with gene, this alteration itself results in different response at the systems level (neural systems), such as brain circuits, and subsequently it leads to impact on personal behavior (Figure 1).

However, in practical studies, researchers moved backward, in order to investigate the genotypes responsible in behavioral traits. Hence, they have started with identifying the intermediate or behavioral phenotypes, which associated with frame effect. It has been demonstrated that the cognitive and emotional behaviors are a key factors in his phenomenon, thereby they have been focused mainly on the neural systems responsible for cognitive and emotional traits.

Particularly it has been found that several brain regions are involved in cognitive and emotional behavior, which lead to either increasing or decreasing the individual's susceptibility to frame

effect, such as Amygdala, (Ahmad R Hariri et al., 2005; Ahmad R Hariri et al., 2002;Ahmad R Hariri & Holmes, 2006;Labus et al., 2008;Munafò, Brown, & Hariri, 2008), Ventromedial prefrontal cortex, particularly in subregions of the anterior cingulate cortex (ACC)(Labus et al., 2008;Pezawas et al., 2005; Passamonti et al., 2008), Insular cortex (Labus et al., 2008), Hippocampus, Anterior cingulate gyrus and striatum. However, the neural mechanisms are responsible for differences in decision-making behavior in individuals remain still unclear.

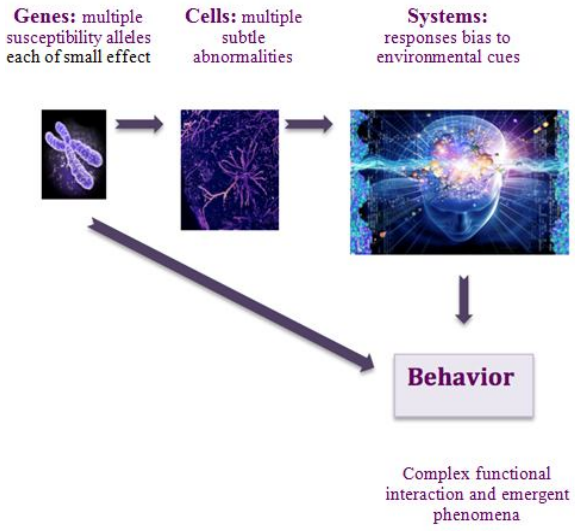

Figure 1: Illustration of the pathway from genes to behavior (A R Hariri & Weinberger, 2003).

Activation of these regions in frame effect has been found to be in association mainly with serotonin-transporter-linked polymorphic region known as (5-HTTLPR). 5-HTTLPR is one of the most well known candidate genes in frame effect studies, which has been discovered that its able to regulate the emotional circuitry and environmental reactivity in individual directly by effecting on the brain structure and function or by modulating the transcriptional activity of 5-HT transporter gene (Caspi, Hariri, Holmes, Uher, & Moffitt, 2010; Roiser, Rogers, Cook, & Sahakian, 2006; Olivier et al., 2008; T Canli, Congdon, Gutknecht, Constable, & Lesch, 2005). 5-HT transporter gene then regulates the activity of the serotonin hormone, which affects the brain regions activity that has been associated with various aspects of personality (Reif & Lesch, 2003).

Therefore many scientists have been tended to examine the effect of 5-HTTLPR by using behavioral and neuroimaging techniques on decision-making in both healthy and patient individuals such as: individuals with psychiatric disorders like depression or addiction, who are known to have deficiency in their decision making processes (Crişan et al., 2009; Olivier et al., 2008; Kuhnen & Chiao, 2009; Stoltenberg & Vandever, 2010; van den Bos, Harteveld, & Stoop, 2009; Jollant et al., 2007; Lenze et al., 2005; Trémeau et al., 2015).

In this paper, we aim to discuss about the identified brain regions, which have been in association with behavioral phenotype related to frame effect, explain the structure and function of neurotransmitters (particularly 5-HT transporter gene) and 5-HHTLPR variation, as well as explaining the processes involved in triggering the level of serotonin, which influence the activity of these brain regions and subsequently individual's behavioral traits and decision making. We will also describe the findings about how do these genes and allelic variation associated with frame effect. The reason why we focus mainly on 5-HHTLPR polymorphism is that, it has been found decades ago in middle of 1990, thus it has been extensively investigated over the past years, whereas the other polymorphism related to frame effect are haven't been studied deeply yet. We will provide the comprehensive information about the biological factors and processes involve in shaping the individual's behavior, which gives a better perspective on how the degree of susceptibility to frame effect assign in each individual.

2 Genetically Mediated Brain Regions Associated with Frame Effect

It has been proved that the frame effect is driven mostly by an emotional system, when the individuals are unable to control emotional responses and they put aside their rationality in decision-making, which lead to increased risk-seeking behavior. Thereby, researchers have been focused on the brain regions associated with logical, emotional and cognitive behavior. It has been shown that the increase or decrease in activation of some areas in brain accounts for the frame effect.

The most important of these regions in frame effect is amygdala, which is a central brain structure with serotonergic neurons and abundance of 5-HT receptors that generates both the normal and pathological emotional behavior (Azmitia & Gannon 1986; Rogan, Stäubli, & LeDoux, 1997). Thus, the activity of amygdala is uniquely sensitive to such types of neurotransmissions (serotonergic), which results in individual differences in mood, and temperament, as well as facial expression in fear

and anger situations(Davis & Whalen, 2001;Zald, 2003). It also has been implied that this subcortical region played a key role in value related prediction and learning outcomes, and increased activation in the amygdala was associated with individual's tendency to be risk averse and risk seeking in the gain frame and loss frame respectively. Researchers has been found that there is a relation between sex and amygdala activity and damages in right amygdala results in greater deficiency in decision making and social behavioral in men, whereas damages in left amygdala have a greater deficiencies in women (Gupta, Koscik, Bechara, & Tranel, 2011).

However, the investigations highlighted the importance of amygdala in frame effect, but it has been reported that amygdala activity did not predict the susceptibility of subjects to frame effect. Instead the correlation between the amygdala and neural activities in the Orbital and Medial Prefrontal Cortex (OMPFC) was suggested to specify the individual's tendency to be susceptible to frame effect. Amygdala and OMPFC each have a distinct functional role in decision-making and there is a strong reciprocal relationship between them. Functional neuroimaging studies revealed that the activation of prefrontal cortex during the variety of cognitive tasks, results in inhibition of amygdala's activity (Beauregard, Lévesque, & Bourgouin, 2001; Hariri et al., 2000; Nakamura, hoshino, kodama, & yamamoto, 1999; Narumoto et al. 2000).

It has been shown that lesions of the OMPFC result in inability to adapt behavioral strategies, which leads to impulsivity and followed by that causes impairments in decision-making. Moreover, findings have been illustrated that the OMPFC uses the inputs from amygdala such as emotional and cognitive information, then signifies the motivational value of stimuli (or choices), and subsequently integrate and evaluate the value of predicted outcomes in frame effect in order to guide future behavior. This proposed model has been represented that the individuals who exhibited more rational behavior have a greater OMPFC activation and thus better ability to modify their behavior in different circumstances and resist frame effect. Thus, it has been illustrated that the higher activation in OMPFC, specifically in right orbitofrontal cortex (R-OFC) and the ventromedial prefrontal cortex (vmPFC), diminishes the susceptibility of individuals to framing effect. The ventromedial prefrontal cortex (vmPFC) encompasses the medial part of the orbitofrontal cortex, ventral sectors of the medial prefrontal cortex and anterior cingulate cortex and plays an important role in successful decision-making (Eslinger & Damasio, 1985; Damasio, 1994; Cato et al., 2004). Thus any kind of deficiencies or damages results in poor judgment, impulsivity and inappropriate behavior (Bechara, Damasio, Damasio, & Anderson, 1994;Berlin, Rolls, & Kischka, 2004).

Later, it has been discussed that striatum also influence the subject's behavior in decision-making. Findings, demonstrated that some part of striatum including: caudate nucleus, ventral striatum, and posterior putamen, receive part of information and output of cognitive computation, which has been performed by cortical area, and subsequently use them to initiate, adjust or alter behavior (Rolls, 2013).

Investigation of the extensive reciprocal connectivity between insular cortex and vmPFC, amygdala and ventral striatum, suggested that the insular cortex region in the brain also plays a critical role in emotional decision-making in individuals (Augustine, 1996; Ongur, 2000; Reynolds & Zahm, 2005). The hypothesis of activation of insular cortex in emotional decision-making was then examined by functional resonance imaging (fMRI) studies, and its activation was reported prior to risk-averse decisions, correlating with the uncertainty of monetary reward, overall risk preference and reward variance (Paulus, Rogalsky, Simmons, Feinstein, & Stein, 2003; Preuschoff, Bossaerts, & Quartz, 2006; Kuhnen & Knutson, 2005; Critchley, Mathias, & Dolan, 2001).

Memory is another factor other than emotion, which involved in the complex process of decision-making. Emotion can improve the memory and learning of the individuals, or in extreme conditions impair memory, which is required in decision-making. Thereby, it has been suggested that hippocampus, the brain region, which is essential for memory function and behavioral control can also influence the decision making in frame effect in stress conditions. Following by that, researchers described the characteristic of episodic memory emerge in the context of reward-based decision-making task to support the proposed hypothesis.

In summary, findings have been suggested that the frame biases occurs as result of additional emotional information to the decision processes, and this biases are highly significant today's modern society, where many organizations in different areas used a variety of symbolic artifacts. Conversely neglecting such information allows the individuals to make the optimal decision in various environments.

3 Serotonergic Neurotransmission Serotonin (5-hydroxytryptamine; 5-HT) and 5-HTTLPR Variation

Several theories has been proposed by researchers about the relation of serotonergic pathway deficiencies and psychological disorders, which brought up the hypothesis hat serotonin has an important function in behavioral phenotypes in individuals. Concentration level of this Serotonin (5-HT) neurotransmission due to genetic variation plays an essential role in activation of brain regions in response to different stimulus. In this section we focus on the genetically mediated process involved in production of serotonin transporter protein (5-HTT), which has been found to be significantly influential in framing effect. 5-HTT has been known as the key regulator in vulnerability to negative affect and unpleasant stimuli by removing serotonin from the synaptic cleft (Canli & Lesch, 2007; Ichise et al., 2006).

Prior studies have demonstrated that 5-HTT is encoded by serotonin transporter gene (SLC6A4) and its expression is regulated by serotonin transporter-linked promoter region (5-HTTLPR), which is located on chromosome 17q11.1-q12 of the SLC6A4 gene (Canli & Lesch, 2007; Lesch et al., 1996;Little et al., 1998; Heils et al. 1996.)5-HTTLPR is a degenerate repeat polymorphic region, consists of variation of the repetitive sequence containing GC-rich, 20-23-bp-long repeat elements. Deletion/insertion (indel) mutations in the sequences of the promoter region results in these variations and creates a several alleles including short (S) allele with 14-repeats and long (L) allele comprising 16-repeats, which has been subdivided into two variants of LA and LGdistinguished bysingle-nucleotide polymorphism (rs25531 and rs25532), (Hu et al., 2006; Nakamura, Ueno, Sano, & Tanabe, 2000).However, neither of these SNPs was functional (Nakamura et al., 2000). It has been clarified that the polymorphism does not occur within the open reading frame of the gene, but in the 5' regulatory region (Glatz, Mössner, Heils, & Lesch, 2003), (Figure 2).In addition, three new alleles with 18-, 19- and -20 repeats have been identified by occurrence of mutation. S allele has been known to be associated with lower 5-HTT expression, function and appearance of negative mood in healthy individuals, whereas L allele has been associated with normal expression of 5-HTT (Lesch et al., 1996; Ichise et al., 2006).

Figure 2 has been illustrated that the only difference between S and L alleles are the length of 5' regulatory region, which is a transcriptional control region. Otherwise the other regions of the gene such as Transcription factor sites and translated region are completely similar.

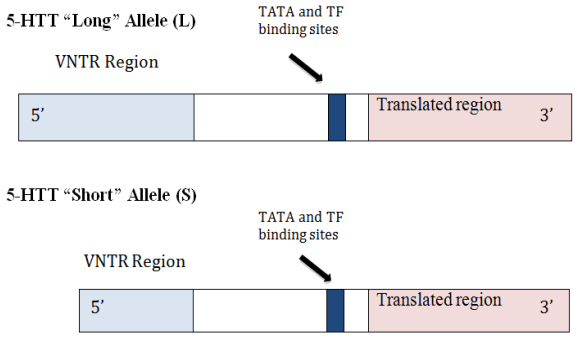

Figure 2: Diagram of 5-HTT's Short and Long alleles (Glatz et al., 2003)

Thereby, it has been suggested that the 5-HTTLPR polymorphism of SLC6A4 associated with amygdala response during negative emotion through changing the transcriptional activity of 5-HTT (Kobiella et al., 2011). To support, and in order to better understanding of this idea, researchers have been used highly specific radio ligand-specific positron emission tomography (PET), to analysis the both 5-HT synthesis and availability. It could also be utilized to determine the level of 5-HT based on 5-HTTLPR genotype (Brun et al., 2002; Szabo, 1999; Meyer et al. 2001). Figure 3 comprehensively illustrates the processes involved in triggering the level of serotonin, which influence the activity of amygdala and subsequently pathways of controlling mood, emotion, anxiety and aggression (Turhan Canli & Lesch, 2007).

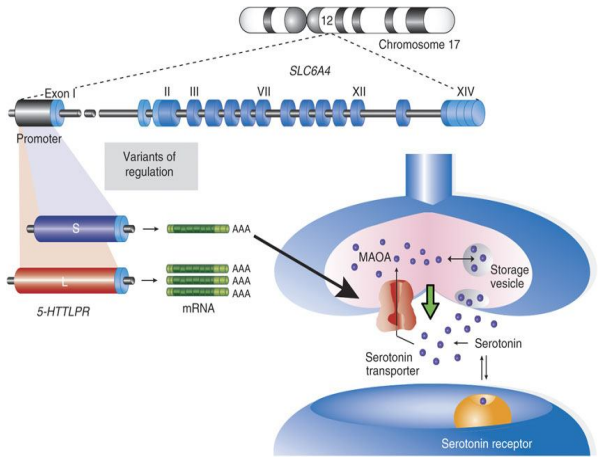

Figure 3:Processes involve in emotion regulation through allelic variation of serotonin transporter (5-HTT)

The Figure illustrated that the short (S) 5-HTTLPR variant of the SLC6A4 gene produces significantly less 5-HTT mRNA and as a result less 5-HTT protein in comparison to long (L) variant, which leads to the presence of higher concentration of serotonin in the synaptic cleft (Lesch et al., 1996;T Canli et al., 2005; Mortensen et al., 1999). The existence of higher concentration of serotonin in the cleft is because of the SLC6A4 gene abnormal function. This gene is responsible for the reuptake of serotonin from the synaptic cleftto the presynaptic cells. Thus, when the s allele carriers inhibit the activity of this gene, higher concentration will remain in the cleft, mediates greater emotional processing, by altering the duration and intensity of 5-HT communication with postsynaptic receptors and targets located in limbic structures, or in presynaptic receptors mediating inhibitory control of the 5-HT neuron itself.

Furthermore it has been investigate that the 5-HTTLPR also affects the brain development and brain circuitries. It has been reported that 5-HT, in addition to shaping the neuronal activity patterns of serotonergic neuron, plays a key role in cortical development and shaping neuronal circuitries. Finding illustrated that the S allele eliminate the individual's ability to alter differentiation of glutamatergic neuron, which is a major neuron for cortico-cortical interactions. Further studies also specifically demonstrated the affect of 5-HTTLPR on interaction between amygdala and rACC. It has been showed that S allele diminishes the amygdala-rACC coupling by decreasing the volume of Amygdala and anterior cingulate cortex (ACC), which as a results reduces the functional connectivity of them and lead to deregulation amygdala responses (hyper-reactivity) and therefore induce variation in emotional behavior (Gaspar, Cases, & Maroteaux, 2003;Ansorge, Zhou, Lira, Hen, & Gingrich, 2004).

3.1 Other Identified Candidate 5-HT Synthesis Gene

Various allelic variations have been found in previous years in 5-HT genes, which influence serotonin synthesis, reuptake and metabolism. Therefore all results in alteration of serotonergic neurotransmission and following by that the brain circuit in subjects. In Table 1 we have been summarized some of these identified candidate 5-HT synthesis gene, their processes and affects in human behavioral traits (Caspi et al., 2002; Manuck, Flory, Ferrell, Mann, & Muldoon, 2000; Nielsen, Thrane, Larsen, Nielsen, & Gravesen, 1998; Nolan et al., 2000).

Table 1: Summary of candidate 5-HT synthesis gene, their functions and their associated effect on regulation of emotional behavior in human

Genetic Variation	Function	Associated effect on human phenotype
Promoter polymorphism in MAOA gene	Catabolize 5-HT to 5-HIAA	Alteration in transcriptional activity and heightening the levels of aggression and impulsivity in men
Polymorphism in human gene for Aromatic L-amino acid decarboxylase (AADC)	Convert 5-HTP to 5-HT	Bipolar disorder
SNP in the human gene for tryptophan hydroxylase (TPH)	Catalyze oxygenation of tryptophan to 5-hydroxytryptophan	Increased risk of suicide, impulsivity, aggression and alcoholism
5-HTTLPR polymorphism	Carrying serotonin from the synaptic cleft to presynaptic neuron during uptake	Susceptibility to depression, suicidality in response to stressful life events and emotional decision-making under ambiguity and risk

The effects of gene-gene interactions on behavioral phenotype have also been demonstrated by several studies. It has been identified that the multiple gene variants can also contribute to amygdala hyper-excitability associated with the 5-HTTLPR S allele.

4 5-HTTLPR Variation Associated with Frame Effect

Researchers identified serotonin role in brain development and neural plasticity, as well as 5-HTTLPRvariations, which has been associated with brain structure and function. Finding has been indicated the importance of the presence of balance 5-HT in development, differentiation and maturation of both nerve cells and networks in brain areas that control sensorial input, stimulus processing and motor response.

As mentioned in previous section, reduced transcription of 5-HTT mRNA and protein expression in S carriers lead to greater amygdala activity, as well as increase in resting-state amygdala blood flow, which has been associated with mood disturbances, depression and increase anxiety in individuals and specifically reflects

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increased sensitivity toward emotionally significant stimuli (Malison et al., 1998; Turhan Canli et al., 2006; Ahmad R Hariri et al., 2002; Bertolino et al., 2005; Munafò et al., 2008; Willeit et al., 2000). This sensitivity in individuals, results in emotionally unstable behavior. Furman et al. (2011) later highlighted the stronger and earlier activation of left amygdala in S carriers individuals (Both homozygous and heterozygous), which leads to increase sad mood state. However, recent studies based on the meta-analysis have been explored that the direct effect of serotonin transporter gene (5-HTTLPR) on amygdala activity is smaller (but statistically significant) than it thought to be (Murphy et al., 2012).

It has been suggested that this effects are highly significant in connectivity of amygdala-anterior cingulate cortex (ACC). ACC is a sub-region of prefrontal cortex (PFC), and it has been presented that this variants influences the function and structure of this brain regions (Pezawas et al., 2005; Heinz et al., 2005; Passamonti et al., 2008). Carriers of the S allele at this locus, including S/S homozygous and S/L heterozygous show greater reduction of amygdala-anterior cingulate cortex connectivity particularly in the rostral subgenual anterior cingulate (rACC), as well as greater functional amygdala and the ventromedial prefrontal cortex coupling, in compare to L carriers (L/L homozygous genotype), (Pezawas et al., 2005; Heinz et al., 2005). It has been reported that the PFC region of the brain is associated with resistance to the framing effect (De Martino, Kumaran, Seymour, & Dolan, 2006), by down regulating the emotional activity due to the prominent stimuli, particularly when PFC is connected efficiently to amygdala. It has been represented that inefficient regulation of PFR, and decreases down regulation of emotional activation thereby leads to increase sensitivity to negative emotional stimuli in S carriers.

The findings, has been illustrated the substantial association of 5-HTTLPR variation with cognitive control of emotion, which then confirms the essential role of 5-HTTLPR genotype in emotion processing circuitry and subsequently decision-making behavior in frame effect (Turhan Canli & Lesch, 2007; Roiser et al., 2006; Blair et al., 2008; Olivier et al., 2008; Jonassen & Landrø, 2014; Beevers et al., 2010b).Improved cognition in subjects carrying S allele has been demonstrated by (Roiser et al., 2006) in the context of potential emotion-evoking stimuli such as reward appraisal and incentive motivation.

Furthermore, Canli et al. (2005) studied the whole brain activation by using the Emotional Stroop Task; they have found the association of 5-HTTLPR allelic variations with differential activation of limbic, striatal, and cortical regions in response to negative, positive and neutral stimuli. They also found that individuals carrying homozygous L/L genotypes had considerably greater volume in various subdivisions of the PFC, as well as greater gray matter density in some areas, including insula, frontal lobe, right temporal lobe, anterior cingulate and cerebellum.

Further studies then investigated that L/L individuals could also lead to depression. The hypothesis was supported by Frodl et al., 2008. They have been reported that long variants were associated with reduced hippocampal volume in subjects who suffered from major depression.

5 Discussion

In this article we have highlighted that, among the candidate 5-HT synthesis genes, which all have substantial impact on brain regions such as amygdala, researchers have been mainly focus on Serotonin transporter polymorphisms (5-HTTLPR), since it has been identified as the only alleles, which was deeply studied and its polymorphism specifically influences emotional decision-making under ambiguity and risk, which is highly correlated with framing effect. Thereby, researchers could rely on (5-HTTLPR) variation to represent the degree of individual's susceptibility to frame effect.

Findings of Munafò et al., 2008 illustrated that 5-HTTLPR polymorphism accounts for only about 10% of phenotypic variances, which is a great value in biological sciences, thus, attracted even more attention from researchers to study on 5-HTTLPR genotype in various contexts such as: neural plasticity, gender differences, basal cognitive and even clinical decision making.

The importance of sex differences in serotonin neurotransmission was discovered decades ago (Fink et al., 1998), however, the issues of gender studies restricted the researchers in choosing the participants. Hence, either men or women were included in most of the previous studies (Heinz et al., 2005; Jonassen et al., 2012). Addressing the association of 5-HTTLPR variability with serotoninneuro transmission in different gender has been partially successful only in recent years and different patterns and sometimes precisely opposite patterns of susceptibility to gene-environment effect in men and women have been identified (Kendler, Kuhn, Vittum, Prescott, & Riley, 2005; Eley et al., 2004; Sjöberg et al., 2006; Brummett et al., 2008). Importance of sexual dimorphism in the same species, therefore stresses the necessity of the

studies to consider gender differences and include both men and women in their work.

In summary, in this article we illustrated that even though, there have been many studies about association of genetic variation with behavioral phenotype in human, but still there is a lack of knowledge and understanding in its processes. And several factors such as gender differences, contribution of ethics, population's culture, and gene-gene interactions have been excluded in most of the studies. Thereby we suggest that in the future studies, other than focusing on single genetic variation associated with behavioral traits, researchers must consider to detect multiple gene variation and how different polymorphism can interact and enhance the individual's susceptibility in various contexts. Researchers also require to expanding their studies on interaction of non-genetic factors on hereditary traits and identify how exactly they can influence the degree of susceptibility.

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