

Comparative Expression Analysis of Genes Encoding Neurotransmitter Receptors Between Entrepreneurs and Non-Entrepreneurs

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ABSTRACT

Introduction and Purpose: Recent studies revealed that different behavioral and physiological processes are closely related to different receptor levels in humans. On the other hand, there weren't any studies that investigated neurotransmitter activity and entrepreneurship relationships. Little is known about how genes expressed in the blood are associated with entrepreneurship. In this study, we measured the expression of 84 genes encoding neurotransmitter receptors between the entrepreneurs and non-entrepreneurs (n=25) using RT-PCR arrays to monitor differentially expressed genes for exploring molecular mechanism behind the entrepreneurship mindset.

Materials and Methods: After determining whether participants are entrepreneurs or not, blood samples were collected. Blood samples were collected in Vacutainer® EDTA tubes as 10 ml and RNA isolation was performed at the Erzurum Technical University, Cell Culture Laboratory. Trizol® solution for RNA isolation (Thermo®, USA) was applied according to the manufacturer's instructions. Concentrations of RNA samples were measured at 260 nm using a spectrophotometer (Epoch®, Biotek). Then, total RNA was reverse transcribed into cDNA by using High-Capacity cDNA Reverse Transcription Kit (Thermo®). Total 84 genes were analyzed via RT² Profiler™ Human Neurotransmitter Receptors PCR Array (Qiagen®, USA) in Rotor-Gene Q real-time PCR cyler (Qiagen®, USA).

Findings: The gene expression results obtained from RT-PCR were compared between entrepreneurs and non-entrepreneurs, and presented as Fold Changes (FC). According to our results, positive FC values indicated an increase in the expression of the genes and negative FC values indicated decrease in gene expression levels in entrepreneurs.

Results: These 84 different genes regulate neurotransmitter biosynthesis, uptake, transport, and signaling via neurotransmitter receptors. According to gene expression analyses, gene expressions that could be related to the entrepreneur behavior might be connected to not only undesired psychological outcomes like various addictions and also neurological cases such as schizophrenia and depressive disorder. Our results firstly indicated that entrepreneurship was not only associated with neurotransmitter release but also with receptor levels.

Keywords: Entrepreneurship, Entrepreneurs, Genes, Neurotransmitter Receptors, RT-PCR Array

INTRODUCTION

While there are many definitions of entrepreneurship in the literature, the main questions have not yet been answered clearly: "Why do individuals engage in entrepreneurial activities and/or why do individuals start their businesses?"¹ There is not a consensus on entrepreneurs' psychological traits in terms of who an entrepreneur is and what an entrepreneur does. Researchers define entrepreneurs as individuals who guide others and have unique values, attitudes, and needs that distinguish them from other individuals.²

In other words, entrepreneurship is one of the most critical factors of the production process, and an entrepreneur is a part of a complex and multi-faceted new venture formation process.³

Purposes of entrepreneurs lead to an association of goals, communication, and involvement within the organization.⁴ Although entrepreneurs' purposes and precursors are a significant research field, there is still a

gap in how biological factors can affect entrepreneurial intentions as biology can play a significant role in the emergence of psychological differences. An entrepreneur affects the decision-making process directly.⁵ Thus, researchers should conduct follow-up research and obtain results if genetics affects entrepreneurial activities.⁶ⁱ As a result, to better understand individuals' desire in entrepreneurial activities, the genetic of the individuals should be considered and examined as one of the fundamental explanatory factors.⁷

Up to date, different mechanisms were suggested to elucidate the possible relations towards the genetic basis of entrepreneurship. The main findings of the conducted studies pointed out that entrepreneurship was associated with (I) up and down-regulation of genes responsible for neurotransmission (or neurotransmitter expression patterns), (II) up and down-regulation of genes affecting individual characteristics, particularly extraversion and neuroticism (III) being sensitive to environmental stimuli via genetic alterations. Literature data indicated that several

psychiatric and neurological conditions are associated with varying levels of neurotrophic factors and their receptors.⁸

To our knowledge, no study has been performed about the expression level of genes associated with entrepreneurship. Therefore, in this study, we measured the expression level of selected 84 genes encoding neurotransmitter receptors in the entrepreneurs and non-entrepreneurs (n=25). We observed that these genes regulate neurotransmitter biosynthesis, uptake, transport, and signaling via neurotransmitter receptors using real-time PCR (RT-PCR) arrays.

MATERIAL & METHODS

Selection of Entrepreneurs and Non-Entrepreneurs:

There has been a growing interest in who an entrepreneur is and whether hereditary factors affect this identification.⁹ Entrepreneurship was frequently associated with risk and uncertainty. To date, studies investigated the reasons why some individuals can take risks or endure uncertainty. However, genetic factors have never been considered in explaining these reasons. Should qualitative or quantitative methods be used in this research?¹⁰ emphasized the equal need for qualitative and quantitative methods, and he stated that researchers should be careful when making connections between methods.

Recent research accomplished to make unmeasurable dimensions of entrepreneurship measurable. Within this context, Zhang et al.¹¹ asked three questions to participants in their study. These questions were: (a) Do you own a company currently or are you a partner in a company? (1=yes; 0=no), (b) Do you own your own business for the past three years or do you have partial ownership in a company? (1=yes; 0=no), and (c) Were you in the position of an employer for the past three years? (1=yes; 0=no). These three indications showed high correlation in the study ($r^2 > 0.91$, $p < 0.001$). The researchers used the mean scores of the three items to determine correlations between the variables. The alpha coefficient for this three-item scale is 0.87. The researchers used these three indicators for a composite measure (equals to an average score) representing a latent structure in the structural equation model. In other words, these indicators were used to reveal the entrepreneurial tendency of an individual. A similar hidden structure approach used by other researchers to study the biological foundations of entrepreneurship.¹² In our study, we identified the entrepreneurial tendency by using these three questions. We found that the alpha coefficient in our study was 0.91. Participants who received a score of 1.5 and higher were considered as active entrepreneurs while those who received a score of less than 0.33 were considered passive entrepreneurs. After determining whether participants are entrepreneurs or not, blood samples were collected.

Molecular Genetic Analysis: The experimental protocol of this study approved by the local ethical committee of Atatürk University (B.30.2.ATA.0.01.00.93). In addition, We would like to thank Erzurum Technical University BAP Unit for their financial support. Briefly, blood samples were collected in Vacutainer® EDTA tubes as 10 ml and RNA isolation was performed at the Erzurum Technical University, Cell Culture Laboratory.

Trizol® solution for RNA isolation (Thermo®, USA) was

applied according to the manufacturer's instructions. Concentrations of RNA samples were measured at 260 nm using a spectrophotometer (Epoch®, Biotek). Then, total RNA was reverse transcribed into cDNA by using High-Capacity cDNA Reverse Transcription Kit (Thermo®). Total 84 genes were analyzed via RT² Profiler™ Human Neurotransmitter Receptors PCR Array (Qiagen®, USA) in Rotor-Gene Q real-time PCR cycler (Qiagen®, USA).

The studied genes embraced to (I) adrenergic (Adra1a, Adra1d, Adra2a, Adrb2, Adrb3), (II) cholinergic (Chrm1, Chrm4, Chrm5, Chrna3, Chrna4, Chrna5, Chrna6, Chrna7, Chrne), (III) dopaminergic (Drd1, Drd2, Drd5), GABAergic (Gabra1, Gabra2, Gabra4, Gabra5, Gabra6, Gabrb1, Gabrb3, Gabrd, Gabre, Gabrg1, Gabrg2, Gabrg3, Gabrq, Gabbr1, Gabbr2), (IV) glutamate (Gria1, Gria2, Gria3, Grik1, Grik2, Grik4, Grik5, Grin1, Grin2a, Grin2b, Grin2c, Grm1, Grm3, Grm4, Grm5, Grm6, Grm7, Grm8), (V) serotonin (Htr1a, Htr1b, Htr1d, Htr1f, Htr2a, Htr2c, Htr3a, Htr4, Htr7) and (VI) other neurotransmitter receptors (Avpr1a, Avpr1b, Hrh1, Hrh4, Npy2r, Npy5r, Sstr1, Sstr2, Sstr4, Tacr1, Tacr2, Tacr3, Brs3, Cckbr, Cnr1, Gcgr, Grpr, Hcrtr2, Ntsr2, Oxtr, Prokr2, Sctr, Tspo).

RESULTS

The gene expression results obtained from RT-PCR were compared between entrepreneurs and non-entrepreneurs, and presented as Fold Changes (FC). According to our results, positive FC values indicated an increase in the expression of the genes and negative FC values indicated decrease in gene expression levels in entrepreneurs. FC values within the range of -2 to 2 accepted to be significant expression changes. We found that there are 27 genes with significant changes in entrepreneurs (Table 1). Most differentiated 14 genes in entrepreneurs as compared to non-entrepreneurs were shown in Figure 1. Also, normalization graph of gene expressions resulting from comparison between entrepreneurs and non-entrepreneurs were shown in Figure 2. Yellow dots upper side of the threshold showed up-regulated genes and blue dots down side of the threshold showed down-regulated genes.

Table 1. Gene differentiation in entrepreneurs as compared to non-entrepreneurs ($-2 \geq FR \geq 2$)

Gene Symbol	Fold Regulation
ADRA2A	14.7912
HTR2C	14.5539
PROKR2	12.4092
GABRB3	5.8971
GRIK1	4.5525
RTC	4.2772
GABRR1	3.2191
HRH4	3.0738
SSTR2	2.4737
CHRM1	2.4509
GABRB1	2.4396
GAPDH	2.0753
GRM3	-6.1617
HTR3A	-6.1760
GCGR	-6.2767
HCRT2	-6.4830
CHRNA4	-7.1107
HTR2A	-7.2434

GRIA1	-7.9081
HPRT1	-8.0930
GABBR2	-8.9177
GABRA1	-8.9590
GRM5	-9.3179
GRM8	-9.8037
GABRA6	-9.9866
CCKBR	-10.8779

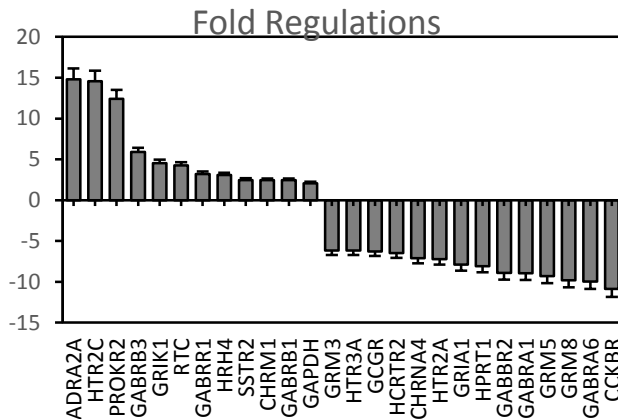


Figure 1. Most up-regulated and down-regulated 14 genes in entrepreneurs compared to non-entrepreneurs.

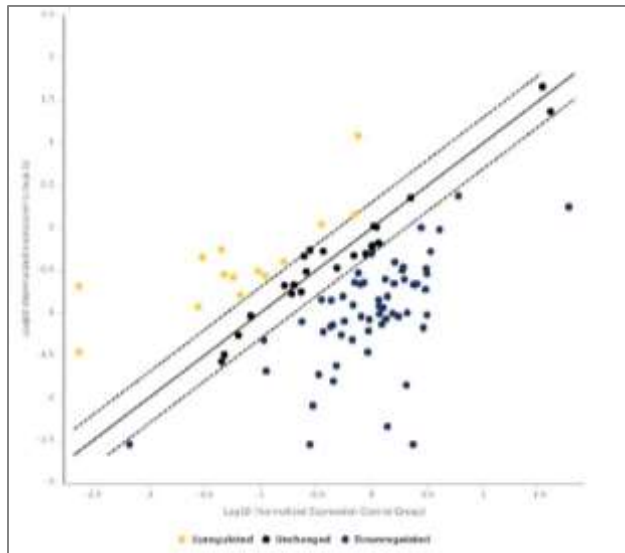


Figure 2. Normalization graph of gene expressions resulting from comparison between entrepreneur and non-entrepreneur individuals.

DISCUSSION

RT² Profiler PCR array analysis showed that total 27 of the 84 genes related to human neurotransmitter receptors were differentiated between entrepreneurs and non-entrepreneurs. Gene expression profile displayed that HTR2C gene was highly active in the enthusiastic group. According to previous studies, this gene was found to be responsible in serotonin neurotransmitter signaling pathway and any abnormalities in the gene could affect people life severely. Recent analysis exhibited suicide victims and also people who suffer from depression had some

abnormalities in RNA editing in HTR2C gene. Also, other abnormalities in this gene were investigated that behavioral disorders. Mental illness could be resulted in a statistically significant level and our analysis support the activity of this gene which could easily change behavior of a person to be a successful businessman.¹³⁻¹⁴⁻¹⁵

One of the highly active genes in our research, GABRB3 expresses ionic channel used as gate for ligand passage. It is one of the most important neurotransmitter inhibitors in mammalian nervous system. Recent investigations showed that this gene is located on the chromosome 15 long arm close to related gene family which was responsible for negative regulation of nervous system. Different types of brain disorders were associated with GABRB3 dysfunction such as Prader-Willi syndrome, Angelman syndrome, autism, non-syndromic orofacial and epilepsy. Interestingly, one of the research exposed that polymorphism on 5' regulatory region of the GABRB3 could be associated with dependence on the heroin and increased expression level of the gene could contribute heroin dependence pathogenesis¹⁶⁻¹⁷⁻¹⁸ Recent data also revealed that the GRIK1 encodes glutamate receptor, which is responsible for crucial neurophysiologic processes. One of the kainate family GRIK1 has four subunits and these subunits form ligand activated ion channels. Activity of gene was associated with the daily drink of alcohol by people and overexpression of the gene increased desire to drink alcohol.¹⁹⁻²⁰⁻²¹

These results indicated that if people are more enthusiastic in entrepreneurship, they would be more likely to have tendency to be alcohol or drug dependence.

On the other hand, cholecystokinin 2 receptor (CCKBR) gene expression level was seemed to be decrease in the entrepreneurship active group. Studies reported that over expression of CCKBR gene was highly related to different cancer types such as lung, liver, stomach, thyroid, colorectal and ovarian carcinomas. Also, some research used the gastrointestinal peptides CCK as a pancreatic cancer target. Various techniques as RT-PCR and western blotting were used to treatment and diagnosis in exocrine pancreatic cancer.²²⁻²³ GRM8, which was down-regulated in active group was shown to be one of the most important receptors having a role in L-glutamate neurotransmitter transfer in the central nervous system. Glutamatergic neurotransmitters were shown to be vital components of normal brain functions. However, GRM8 up-regulation is associated with schizophrenia. This studies claimed that overexpression of the GRM8 gene might be used as indicator in schizophrenia pathogenesis.²⁴⁻²⁵ Another down-regulated gene in active group was HTR2A that was shown to express serotonin receptor with various important roles. If there were abnormalities in the HTR2A, some pathogenesis could take place for instance obsessive-compulsive disorder, susceptibility to schizophrenia and major depressive disorder. Interestingly, several studies claimed that HTR2A polymorphism could be an effector on susceptibility occurrence of suicide against loss events and stressful life.²⁶⁻²⁷ Furthermore, CHRNA4 gene expression which produces a nicotinic acetylcholine receptor decreased in our investigations. CHRNA4 was shown to be a member of the ligand gated ion channel superfamily and responsible for rapid signal

transmission through synapses. Researches were analyzed this gene polymorphisms provide protection against addiction to nicotine dependence.²⁸⁻²⁹

To sum up, two groups of people were compared to understand effects of various genes on human nature in aspect of entrepreneurship with this study. To conduct better understanding for this concept, genes responsible for neurotransmitter expression and transfer systems were analyzed. Total of 84 genes were evaluated with RT² Profiler PCR Array Gene Expression system. In the light of the findings, we found that some genes may directly affect intellectual ability of a person and HTR2C may change the behavior of an individual from being a successful businessman to suicide victim. Most striking outcome of this research might be that over expressed genes (GABRB3 and GRIK1) in active group were shown to be associated with heroin and alcohol addiction. These results could give some insight about that entrepreneur people might have high prone to addictions. Besides, some of the down-regulated genes were related to different pathologies as carcinogenesis, schizophrenia and depressive disorder.

Factors affecting entrepreneurship can be categorized as demographics, personal and sociocultural factors in the literature. Demographical factors include age, marital status, gender, income level and education.

While the need for success, focus of control, tendency to take risks, undertaking uncertainty, self-confidence and innovativeness are considered as the personal factors determining entrepreneurship, culture and society, family and religious values constitute the socio-cultural factors. Social processes of reciprocal interactions of children with the immediate circle consisting of family, school, friends and teachers, not only determine the quality but also the level of entrepreneurship.³⁰

Many studies showed that entrepreneurship is affected by psychological and behavioral factors. Particularly in individuals who are envisioned to be entrepreneurs, the dominant factor that determines the success or failure of a venture is the personality type that is dynamic and can take risks. Within this framework, many of the empirical studies focus on relationships between entrepreneurs' motivation, personal characters and behavioral traits and work performance.³¹

CONCLUSION

Our study revealed the effects of genetic factors on entrepreneurship. In this study, gene differences and certain receptor levels that were not identified in few other studies on genetic factors, were identified. Departing from the fact that entrepreneurship affected by genes and receptor levels, this study is significant, as it will contribute to private sector strategies and state policies. It is suggested particularly for researchers in the education field to participate in research conducted in this field. States can identify entrepreneurial individuals who will engage in future entrepreneurial activities and provide them special education opportunities. Thus, individuals who have entrepreneurship in their genes will be supported psychologically under the light of scientific knowledge. This study may shed light to future research. This study provides an idea for future research particularly on how entrepreneurial traits can be increased. Additionally, it

would be beneficial to study psychological, sociological and genetic factors that affect entrepreneurship altogether.

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