

Schizophrenia: what's DAO and DAOA got to do with it?

Abstract

Schizophrenia is a complex disease with a high heritability rate of about 80%. Many linkage and association analysis revealed different chromosomal regions as candidates and functional studies showed the gene expression differences for many genes. Among them there are two interacting proteins found on the candidate regions- D-amino oxidase (DAO) and D-amino oxidase activator (DAOA). DAO oxidizes D-amino acids notably D-serine in the brain. D-serine is a coagonist of the endogenous N-methyl D-aspartate receptor (NMDAR). The hypofunction of N-methyl-D-aspartate glutamatergic neurotransmission has an important effect in the pathophysiology of the disease. DAOA is shown to be activating DAO. Because of their functions these two proteins are thought to be related with schizophrenia. Association studies also showed that these two are associated with schizophrenia in some populations from different regions of the world. Although positive associations were shown in these populations, in the others researchers failed to replicate that data. It is a common concept for schizophrenia association studies to have conflicting results in many candidate genes for different populations. Here we try to summarize the studies that were targeting the effect of DAO and DAOA SNPs in schizophrenia.

Keywords: DAO, DAOA, G72, schizophrenia, SNP, population study

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Abbreviations: GWAS, genome-wide association studies; DAO, d-amino oxidase; DAOA, d-amino oxidase activator; SNP, single nucleotide polymorphism; NMDAR, n-methyl d-aspartate receptor

Introduction

Schizophrenia is a common chronic mental disorder which affects ~1% of the world's population.¹ It is a major cause of morbidity and patients need long term medical and social care. It is caused by both environmental and genetic factors. The contribution of inheritance to the disease is ~80% and family, twin, and adoption studies showed the importance of genes on the susceptibility to disease. Genome-wide association analysis (GWAS), case-control studies, and meta-analysis also demonstrate the genetic risks of the disease.² From the genetic epidemiologic studies it is known that the mode of transmission of schizophrenia is complex.

Several linkage studies were performed to point out the candidate regions for schizophrenia. These studies have found linkage for different localizations of the genome at the significant level. There are many association studies with these candidate regions.³⁻¹⁰ But the results of the positive or negative associations should be replicated by population studies with large number of individuals. One of the candidates that was found in these studies was DAOA (D-amino oxidase activator) gene. In 2002, Chumakov and colleagues published a paper about the association to a new human gene- G72.¹¹ They focused on 13q22-q34 chromosomal region and by doing single point association analysis, population analysis with different groups and gene discovery and functional studies, they figured out the interaction in between the G72 and DAO genes. Yeast two hybrid experiments performed with G72 protein identified G72 as an interacting partner with D-amino oxidase (DAO) enzyme. *In vitro* studies revealed that DAO enzyme activity was enhanced with G72. Hence it has been named D-amino

acidoxidase activator (DAOA). The interaction of these two genes points the involvement of N-methyl D- aspartate receptor regulation pathway in schizophrenia. Because of their functions in the brain and their chromosomal localizations these two interacting partners are candidates for the studies about the molecular mechanisms underlying schizophrenia. In this study we try to summarize the literature on schizophrenia relation with DAO and DAOA genes.

DAO and DAOA

DAO gene is located at chromosome 12q24, it has 11 exons and full length transcript of 1595bp. It codes 39kDa flavoenzyme D-amino oxidase with 347 amino acids. It oxidizes D-amino acids notably D-serine which is a coagonist of the endogenous N-methyl D-aspartate receptor (NMDAR). DAOA gene is located at chromosome 13q34 and the gene spans 29kb. G72 and G30 overlaps on the complementary strands of the chromosome and they are transcribed in the opposite direction.¹²

Glutamatergic neurotransmission abnormalities were shown to be involved in schizophrenia pathogenesis. The hypofunction of N-methyl-D-aspartate glutamatergic neurotransmission has an important effect in the pathophysiology of the disease.¹³ Several studies showed that D-serine facilitates the NMDAR function and DAO activity is increased in the case of schizophrenia.¹⁴ D-serine is a coagonist for NMDAR and DAO gene product -D-amino acid oxidase enzyme- degrades D-serine. On the other hand DAOA gene product D-amino acid oxidase activator-activates DAO enzyme.¹⁵ Because of their role in NMDAR signalling and by being interaction partners DAO and DAOA studies were good examples for investigating the molecular complexity of schizophrenia.

Population studies

Several association studies with schizophrenia patients from

different ethnic backgrounds were performed by different research groups. PubMed search of “schizophrenia and DAO” revealed 71 articles. These include both mechanistic work and association studies together when we narrow the search with the keywords (DAO SNPs and schizophrenia there are 22 articles are found in between 2005 and 2013. There were 112 articles for “DAOA gene and schizophrenia” 63 of which were about DAOA SNPs and schizophrenia. But the association studies with different populations displayed conflicting results. Many groups reported significant associations with DAOA gene at the allelic, genotypic and haplotypic level for the different populations and the sample size.

Chumakov's findings were the first study that showed the relation of DAOA and schizophrenia. They also showed the association between DAO SNPs and the disease. They reported the association of four SNPs with schizophrenia in Canadian samples.¹¹ Schumacher et al.¹⁶ Reported the relationship of DAO and DAOA variations in German population. Yang et al.,¹⁵ reported a significant association of DAO SNPs (DAO7-DAO8-DAO13) in Taiwan Han Chinese population.

On the other side there are reports about lack of association between polymorphisms of DAO and DAOA in different ethnic groups. As an example Bass et al.,¹⁷ couldn't find an association in their patients from UK. Like Sacchetti et al.,¹⁸ couldn't find an association with the SNPs of DAO and DAOA in their group of patients from Northern Italy. In our group of patients from Turkey we couldn't find an association as well (Acar and Kartalci, unpublished study). A study that was performed by Chung et al.,¹⁹ with Korean schizophrenia patients investigated the relationship of aggressive behaviour in schizophrenia patients and they also couldn't find an association neither with DAO nor DAOA. By looking at these and many others, it is possible to think these results as false positives or false negatives depending on the sample size or SNP numbers that are involved in these studies. But one thing should be kept in mind that there should be more mechanistic work and proteomic data to support or understand the effect of these two genes or the other schizophrenia candidate genes. Because it is known that DAO expression and enzyme activity is increased in the case of this disorder.²⁰ Besides depending on the presence of positive or negative symptoms of the disease, different candidate genes may be taking part in the pathology of the disease.

Conclusion

Schizophrenia is a mental disorder affecting about 30 million people worldwide. It should be noted that schizophrenia is a very complex disease and it is not caused by only one mutation in a particular gene. The interaction of environmental factors and genetic architecture of the individuals both contribute to the disease pathology. Genetic architecture includes sequence variations, gene function and differential protein expression. When these factors are taken into account it is reasonable to combine genomics and proteomics to understand the molecular pathology of this global health problem. Searching for candidate genes, and association studies, can go hand in hand with post mortem brain studies, cell culture, and animal models in order to enlighten the molecular mechanisms underlying schizophrenia. By this way novel therapeutic targets or effective treatment methods can be found.

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Conflict of interest

The author declares no conflict of interest.

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