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Transcriptomic And Exomic Approaches For Decoding ADHD: A Current Social Stigma

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Abstract

Attention Deficit Hyperactivity Disorder (ADHD) is a psychiatric disorder mainly associated with children. This disorder is very common all over the globe and its prevalence is increasing rapidly because of parents' busy schedule and hectic lifestyle of both the parents and the children. It is a neurodevelopmental disorder which is diagnosed by inattentiveness, hyperactivity and impulsivity in children as well as adults. ADHD can have other significant effects on the quality of life of a person such as increase in the risk of other psychiatric disorders and failure in the major parts of life such as educational failure, occupational failure and most commonly addictions. Transcriptomics is the study of all the expressed DNA in the form of mRNA produced after transcription at a time while exomics is the study of all the functional mRNA in a cell in the form of exomes after post-transcriptional changes occurred in the transcribed mRNA at a given time. By analysing the data derived from transcriptome and exome datasets we can try and understand the disorder on a level where the genes are expressed in the form of messenger RNA. This review explores the scope of transcriptomics and exomics in analysing and understanding ADHD.

Key words: ADHD, neurodevelopmental disorder, psychiatric, transcriptomics, exomics.

INTRODUCTION

Attention Deficit Hyperactivity Disorder is a neurodevelopmental disorder and mainly affects behaviour patterns in children as well as adults. With a worldwide prevalence of 5% among children and adolescents and about 2.5% adults it is a common disorder, and its occurrence is increasing rapidly due to today's lifestyle patterns. ADHD is a multifactorial psychiatric disorder, and due to its multifactorial nature, the disease runs heterogeneous among patients. The symptoms and behaviour of patients depend on the age group of that patient and stage of the disease they are in.[1] ADHD is a predominant heritable neurological

disorder that manifests itself in early childhood and affects the quality of life significantly.[16] Its persistence in adulthood is in about 40-50% of the cases. Recent studies have proven that ADHD has a very dominant genetic predisposition which are starting to unravel through the integration of genomics and gene expression data. Twin and family studies have shown a great heritable factor of about 76% in cases related to ADHD.[2] Despite of this high heritability rate, it is difficult to identify key genes responsible for development of ADHD and the reason for this is most probably the genetic complexity and multifactorial nature of this disorder.[7] Transcriptomics and exomics data comprise of gene expression data and provide a greater understanding of genes involved in manifestation of the disorder. The Etiology of ADHD is complex as it is derived from various factors including genetic and environmental factors. All these factors combine in small amounts to produce a synergistic effect and act as a unit to increase an individual's susceptibility to the condition.[2]

The studies related to ADHD are difficult because of its nature being a psychiatric disorder. All the conclusive research can only be carried out by conducting behaviour studies and carrying out interviews of the patients.[28]

All the individuals at some point of time show some symptoms of ADHD but the patients associated with this disease have more symptoms at a point where it interferes with the day-to-day function in their lives.[3] Transcriptome studies are performed to study ADHD to understand the expression of genes that are only expressed in case of ADHD.

Symptoms of ADHD

1) Inattention: Individuals suffering from ADHD have difficulty maintaining attention span, staying organised and keeping focus only on one task.
2) Hyperactivity: The patients show hyperactivity such as excessive movement, restlessness and too much talking.
3) Impulsivity: The patients show impulsivity in their behaviour like having trouble waiting, interrupting others or acting without thinking.

Having ADHD can cause poor self-esteem in both adults and in children. It can cause people to have self-doubts, increased self-criticism and sensitivity to criticism. It can cause interference in schoolwork, and poor social relationships in children.[4]

Types of ADHD

ADHD is of three types

1) Inattention: The patient suffering from this type of ADHD has inattention symptoms more than those for hyperactivity and impulsivity. More girls are diagnosed with inattention type ADHD than boys.
2) Hyperactive-impulsive type: The most common symptoms of this type of ADHD are associated with hyperactivity and impulse control rather than inattention. More boys are diagnosed with inattention type ADHD than girls.
3) Combination: The symptoms don't fall exclusively within the signs of either of the above type, but a combination of those symptoms is observed.

Transcriptomics and its significance

Transcriptomics is the study of total gene expression in a system (cell, a tissue or an organ) at any given time. Decoding the transcriptome is essential for understanding functional genomics and understanding the molecular constituents of a cells and tissues. Understanding the transcriptome of a disease can help in deciphering the development and effect of that disease in an organism. The species included in a transcriptome mRNA, non-coding RNAs and small RNAs. The main objective of transcriptomics is to list all the moieties related to the transcriptome to decode the transcriptional structure of genes. The transcriptional structure of a gene comprises of their start sites, 5' or 3' ends and post transcriptional changes like splicing. It aims to quantify the change in expression levels of different genes in different conditions.[5] Transcriptomics can help in deciphering the development of a disease by understanding the transcriptional structure of the gene at different time and during different conditions. The main objective of transcriptomic studies is to identify and analyse differentially expressed genes or DEGs. [27]

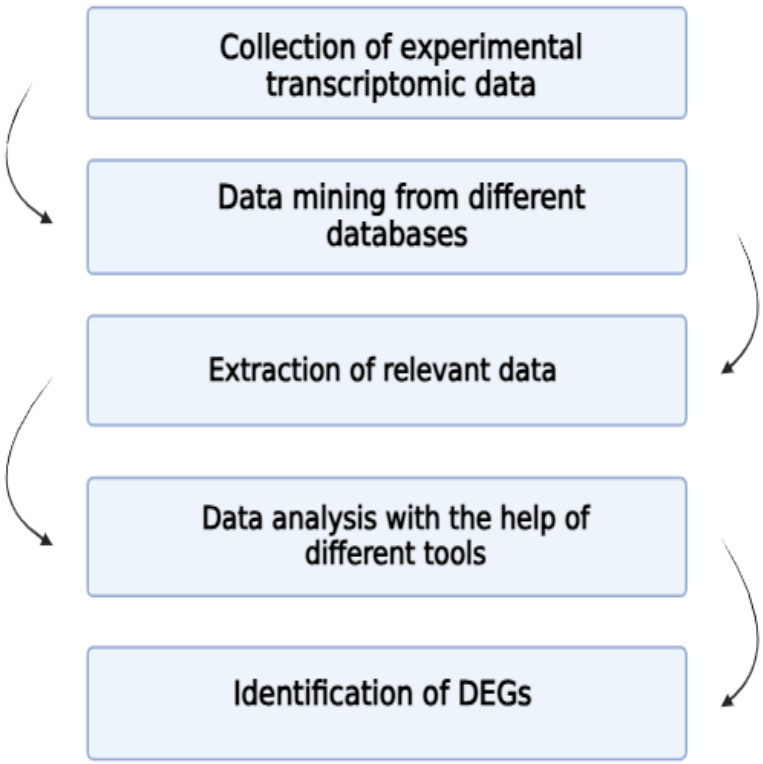

Fig. 1: - Steps in Transcriptome data analysis of ADHD

Identification and analysis of DEGs

Differentially expressed genes are those genes which show different levels of expression in different conditions.

The identification and analysis of differentially expressed genes is a very crucial part of transcriptomics which helps to identify and analyse the genes that only show expression in a certain condition.[18] This approach is important to understand the transcriptomic makeup of a disease and helps to decode the functional properties of the genes in specific pathways related to that condition. The genes that are identified and selected in transcriptomic studies as differentially expressed genes or DEG are functionally annotated using different tools to understand their significance in various pathways.[6] DEGs can help in understanding the mechanisms of a disorder and help to identify an aim for its treatment. It can also help to identify biomarkers in a disease which can be helpful in diagnostic purposes. DEGs are identified using various transcriptomic tools like GEO2R which show the significance of different in the form of a table based on their pvalue.[25]

Exomics and its significance

Exomics is the study of a complete set of post transcriptional m-RNA present in a biological system called as exome.[17] An exome is a collection of all the exons present in a genome. After transcription, m-RNA is spliced by a proficient system containing enzymes to remove the non-coding part of a gene known as introns. All that is left after splicing is an RNA sequence that only contains the coding part which is expressed in the form of proteins known as exons. By studying the exome of an organism against a control

(a normal sequence of a healthy person) we can derive all the gene expression that is different in case and control. Exome studies can be done by the development of sequencing techniques.[12] Exome sequencing is an advanced and effective method that utilizes next-generation sequencing technology to analyse genomic DNA. This technique selectively captures and sequences the protein-coding regions of the genome by targeting predefined exonic regions, enabling a focused and comprehensive examination of genetic variations.[26]

Other Omics Approaches in decoding ADHD

The multifactorial nature of ADHD is the reason to apply various approaches to understand and decode the mechanism behind ADHD. These approaches are used mostly to understand specific molecular markers associated with ADHD. [22]

Due to the advancement in DNA sequencing techniques, it is now possible to study and detect genetic markers responsible for a disease in any kind of a nucleotide sequence. The sequence can either be a whole genome sequence, a transcriptome sequence or an exome sequence. [23] The data containing these sequences is extracted from a database and these sequences are analysed using different tools to detect different markers for the presence of a disorders. These markers can be overactivation of a certain pathway, upregulation or downregulation of a gene or the expression of specific known as differentially expressed genes which can now be detected using different tools and software. One can apply multi-omics approach to analyse and assess this data and obtain conclusive results.

The most common approaches used are listed below: -

1. Genomics

   ADHD is studied by genomics through GWAS, and WGS. There have been seven individual genomic studies related to ADHD that are published till date. These studies have helped in mapping the exact genetic loci that are risk factors for ADHD.[7]

   - GWAS or Genome Wide Association studies helps to identify molecular markers throughout the genome of a set of different individuals. These studies are performed in twin studies, family studies etc.
   - WGS stands for Whole Genome Sequencing, WGS studies help understand whole genome of an organism. [2,8]

These studies help in deciphering the key causes responsible for ADHD by identifying the genetic markers present throughout the genome.[2] Genomic studies concluded the involvement of a region on the distal part of chromosome 16q. [7] The gene CDH13 has been repeatedly found in top GWAS studies. [9]

2. Systems biology approach

Systems biology approach is taken to identify top DEGs in ADHD. Several genes having significant p values (<1) are selected to construct a network, and several hub genes are identified. These hub genes are functionally annotated to find out their roles in different pathways in our body.[24] According to the

studies conducted by Victoria Hayman and Thomas V. Fernandez 14 genes were identified that form a cluster in the gene network with an abundance of nitric oxide synthase and alpha-1 adrenergic pathways.10 System biology approaches are essential for gene discovery in ADHD that holds a great potential for determining all the underlying genetic predispositions related to ADHD. [10,11]

All the omics studies can be performed in an integration to work towards decoding ADHD. Transcriptomics and exomics hold a greater significance in the process as they are directly related to the identification of genes that are responsible in the development of this disorder.[21] The transcriptome or exome data of an individual with the disease is run against a normal sequence to identify the specific genes with their p-value by using different tools such as GEO2R (transcriptomic and exomic approaches). These genes are then utilized to construct a network using cytoscape. Out of this network top genes are identified known as hub genes which are the most important genes out of the significant gene pool (system biology approach). [20]

Fig 2: - Integration of multi omics approaches for decoding ADHD

Future Directions and Challenges

The use of transcriptomics and exomics holds a great application in deciphering multifactorial diseases like ADHD as they are very complex in nature.[2] Transcriptomics and exomics are directly related to gene expression of an individual at a given time so it is easy to factor out the genes responsible for the development of a disease.[19] By carrying out transcriptomic studies on diseased individuals, specific genes can be targeted for better understanding and better therapeutic management. These studies have proven to be very conclusive in targeting specific genes.[28]

The challenges with these studies in mainly the availability of data on a public domain. The data in these studies is directly related to patients so the data is confidential and can not be shared without informed consent. Another challenge faced by individuals in these studies can be the unavailability of adequate statistical tools to analyse the data from transcriptomic and exomic studies.[14]

Conclusion

Transcriptomic and exomic studies are a recent development in gene expression studies. These studies provide conclusive data with an integration of various computational studies. By using transcriptomics RNA sequencing data can be analysed to study the difference between a reference (control) and a diseased (case) individual. In case of ADHD one can study the available transcriptomic datasets available to identify various DEGs and from those genes most significant or hub genes can be identified by using systems biology approaches.

This hub gene can then be annotated through software to know their exact function in different pathways in our body.[5]

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