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Genetics of attention deficit/hyperactivity disorder (ADHD)

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Abstract

Attention deficit hyperactivity disorder (ADHD) is a developmental disorder. ADHD is the commonly studied and diagnosed as psychiatric disorder. Here we shall see the relation between extraversion and ADHD, neuroticism, biological relation, Environmental factors and with diagnosis of ADHD. It is known that Genetics is one of the factors that may contribute to, or exacerbate ADHD. Recent research probing towards the environmental and Genetic factors causing ADHD differences is the main source for investigation.

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Introduction

ADHD is the most commonly neuropsychiatric illness studied and diagnosed psychiatric disorder in children; it is a chronic disorder with 30 to 50 percent of those individuals diagnosed in childhood continuing to have symptoms into adulthood. Standardized rating scales such as the World Health Organization's Adult ADHD Self-Report Scale can be used for ADHD screening and assessment of the disorder's symptoms' severity. Basically it was initially recognized in 1943 and was more properly acknowledged by the American Psychiatric Association in 1980 (DSMIV-TR - The Diagnostic and Statistical Manual of Mental Disorders, 4th Edition, American Psychiatric Association., 2000; Linnet *et al.*,2003; Mick *et al.,* 2002). Globally affecting about 4 to 5 percent of children and diagnosed about 3 to 15 percent of children which are under school age (Meltzer *et al.,* 2003; McCann *et al.,* 2007). ADHD is diagnosed a lot in girls than in boys.

ADHD is the common neuropsychiatric illness of childhood, it is a severe form. As per survey ADHD, affecting 3% to 7% of school age children (Lionel *et al.,* 2011) 1% of UK children are affecting by this disorder (Nigel *et al.,* 2010). In UK, after the survey of 10,438 children ages between 5 to 15 years found that 0.85% girls and 3.62% boys had ADHD Braun *et al.,* 2006). Symptoms depict difficulty in focus and thoughtful attention, difficulty in controlling of behaviour with hyperactivity. Related cognitive deficits, such as lacking in inhibitory control, detected in both children with autism spectrum disorders (ASD), ADHD and children with Tourette's syndrome (Corbett Corbett and Constantine, 2006).

It has been denoted that children with ASD (Autistic Spectrum Disorder) show ADHD characteristics (Leyfer *et al.,* 2006; Sturm *et al.,* 2004). In this case reported that the group of clinically diagnosed children with ADHD (n = 49) 65–80% showed ASD symptoms as reported by parents (Clark *et al.,* 1999). In a previous report, 26% children rigorously diagnosed with ADHD (n = 86) met criteria for ASD (Geurts *et al.,* 2004). There is an extensive common characteristic of ASD symptomatologyin children with ADHD. These three neuropsychiatric disorders are linked to deficit in fronto-striatal and front parietal circuits. Thus ASD, ADHD and TS may have partially overlapping disorders (Albin and Mink, 2006).

Level of high activity, short attention, inattentiveness and hyperactivity are found in excessive in daily functioning of ADHD children's. There are the sub types of ADHD: First, predominantly hyperactive-impulsive. Second, predominantly inattentive and third, Combined hyperactive-impulsive and inattentive, Mostly children suffers from combined type. After Effective treatments it is possible to come out from the hyperactivity, inattention, and impulsiveness ADHD and make better a person's capability to function at school, at home and surrounded environment.

ADHD and ASD have different, outcomes, trajectories and treatment protocols. For example such that of the effects of psycho stimulants in children with ASD are less consistent than in children with ADHD. But too great prominence upon ADHD could lead to awkward outlook for an overall improvement in the presenting symptoms and activities of children sensibly identified with ASD, while any dependence upon medication may hamper the concern of behavioral and educational programs within the overall intervention. Patients who are diagnosed with ASD have natural problems of hyperactivity or inattention, impulsiveness; or that another sub-sample have co morbid ADHD and ASD. Either view is armored by findings from neuroimaging studies that both situations engage some anomalies in the working of the cerebella or frontostriatal regions of the brain.

Research interest on main factors affecting ADHD

Genetics

In a recent research it's been denoted that ADHD has a direct indication that it is a genetic condition. Scientists at Cardiff University analysed that ADHD children were more likely to carry small segments of DNA duplicated or missing in normal children. There is a large overlap between the segments and it is known as copy number variants (CNVs), and genetic variants implicated in schizophrenia and autism, providing strong proof that ADHD is a neurodevelopment disorder expressing that the brains of normal children differ from those of children having ADHD (Qunitana et al., 1995). Also there is a clear genetic link between these segments and other brain disorders.

Even though there is a strong connection between genetic factors and autism, it has been recognized with no exact clearance of genetic background for autism. In ADHD Chromosome number 16 carries a large overlapping segment at a specific region. This was also seen to be identified in schizophrenia and other psychiatric related disorders and spans a number of genes including one which plays an important role in the brain development. ADHD is not only caused by a change in a single gene but it is also caused by some environmental changes. Having proved we can now state with confidence that ADHD is a genetic disease. Twin study indicates that this disorder is highly inherited and 75 % contributed genetically (Nair *et al.,* 2006). *LPHN3* is the gene which is approximate to be responsible for about 9% in ADHD, and is mainly responsive to stimulant medication (Kerstin Konrad *et al.,* 2000).

Environmental factors

Various environmental chemicals have been concerned as causative factors towards the cause for autism. The scientific report by the Collaborative Health and the Environment's Learning and Developmental Disabilities Initiative, stated that many environmental agents such as *pesticides, arsenic, polychlorinated biphenyls (PCBs), lead, manganese, mercury poly-brominated diphenyl ethers (PBDEs), polycyclic aromatic hydrocarbons (PAHs),* and solvents were recognized as contributors to learning and developmental disabilities in humans. There is not a single factor affecting autism. Environmental factors affecting other developmental systems can cause downstream defects on the brain. The individuals with enhanced vulnerability towards environmental chemicals and those with a certain genetic predispositions are more susceptible for autism (Arcos-Burgos *et al.,* 2010). It is currently not evident to explain each and every factor which contains chemicals promoting autistic disorder, while the chemicals mentioned here will highlight sources which has the strongest associative evidence. Similarly, PCBs acts as environmental pollutants from many decades and is also known for the developmental neurotoxicant. Certain PCBs disrupt the thyroid hormones, may reduce or change thyroid hormone-regulated gene expression and directs the brain development toward an autistic phenotype (Kanner *et al.,* 1943).

Symptoms

ADHD is composed of symptoms such as Hyperactivity, inattention, and impulsivity, these symptoms of ADHD are very difficult to define because it is not easy to draw the line at where normal levels of hyperactivity, inattention, and impulsivity comes to end and clinically large levels require involvement begin. Children diagnosed with ADHD, are observed in two different settings for five to six months or more and to a level that is greater than other children of the same age.

Type of measure

Peer functioning has been assessed across studies by a variety of different informants and methods. Reports from parents and teachers about peer functioning, as well as self reports, are often collected in the form of

rating scales, for example, the Social Skills Rating System (Gresham, FM *et al.,* 1989). Peer-informant methods, which is involve asking all children in a classroom or the other peer group to respond to questions about one another, are another option. These methods can be several types: nominations for positive and negative criteria, ratings of degree of liking or nominations or ratings in response to behavioral descriptors.(Parker *et al.,*1987; Hoza *et al.,* 2005).

This is an important point because although it is well established that reports from different informants are not highly correlated in the assessment of childhood behavior problems, this lack of agreement may be especially pronounced in the peer domain (Achenbach *et.al.,* 1987). More recently, authors have examined the presence of social and communicative profiles qualitatively similar to those associated with ASD in individuals with ADHD (Mulligan *et al.,* 2009; Nijmeijer *et al.,* 2009; Carpenter *et al.,* 2009).

ADHD has three subtypes

Predominantly hyperactive-impulsive

Most symptoms (six or more) are in the hyperactivity-impulsivity categories. Fewer than six symptoms of inattention are present, although inattention may still be present to some degree.

Predominantly inattentive

The majority of symptoms (six or more) are in the inattention category and fewer than six symptoms of hyperactivity-impulsivity are present, although hyperactivity-impulsivity may still be present to some degree (DSM-III-Diagnostic and statistical manual of mental disorders. 3rd ed. American Psychiatric Association; 1980).

Children with this subtype are less likely to act out or have difficulties getting along with other children. They may sit quietly, but they are not paying attention to what they are doing. Therefore, the child may be overlooked, and parents and teachers may not notice that he or she has ADHD.

Combined hyperactive-impulsive and inattentive

Six or more symptoms of inattention and six or more symptoms of hyperactivity-impulsivity are present. Most children have the combined type of ADHD.

Causes of ADHD

Scientists are not confined to the main cause for ADHD but recent studies indicate Genetics as a vital factor. Genes Inherited from parents, genes being the blueprints for life. In addition to genetics, researchers are looking at possible environmental factors, and are studying how brain injuries, nutrition, and the social environment might contribute to ADHD. Results from several international studies of twins show that ADHD often runs in pedigree familial traits. Researchers are analysing several genes that may make people more likely to develop the disorder. Studying the genes involved may one day help researchers prevent the disorder before symptoms arise (Faraone *et al.,* 2005; Khan and Faraone, 2005). Learning about specific genes could also lead to better treatments.

Children with ADHD who carry a particular version of a certain gene have thinner brain tissue in the areas of the brain associated with directing attention. This NIMH research showed that the difference was not permanent, however, and as children with this gene grew up, the brain developed to a normal level of thickness. Their ADHD symptoms also improved (Shaw *et al.,* 2007). Studies on Environmental factors suggest a potential link between cigarette smoking and alcohol use during pregnancy and ADHD in children (Linnet *et al.,* 2003; Mick *et al.,* 2002).

In addition, preschoolers who are exposed to high levels of lead, which can sometimes be found in plumbing fixtures or paint in old buildings, may have a higher risk of developing ADHD (Braun et al., 2006). Lead which is used in old paint and in parts of plumbing and also social difficulties are often reported in children with ADHD but these difficulties are typically interpreted as resulting from ADHD

symptoms rather than reflecting the qualitative impairments in social-communicative functioning characteristic of ASD (Bagwell *et al.,* 2001; McQuade *et al.,* 2008).

Brain injury

Children who have suffered a brain injury may show some behavioural patterns to those of ADHD. However, only a small percentage of children with ADHD have suffered a traumatic brain injury and the mechanisms involved are not yet clear, but it is speculated that a sub-sample of those people who are diagnosed with ASD have inherent problems of inattention or impulsiveness or hyperactivity; or that anther sub-sample have comorbid ASD and ADHD. Either view is reinforced by findings from neuro-imaging studies that both conditions involve some anomalies in the functioning of the frontostriatal or cerebellar regions of the brain (Fombonne *et al.,* 2001).

Sugar

The idea that refined sugar causes ADHD or makes symptoms worse is popular, but more research discounts this theory than supports it. In a study, researchers gave children sweet food containing either sugar or a sugar substitute every other day. The children who received sugar showed no different in their behaviour or learning capabilities than those who received the sugar substitute (Wolraich *et al.,* 1985). another study in which children were given higher than average amounts of sugar or sugar substitutes showed similar results (Wolraich *et al.,* 1994).

In another study, children who were considered sugar-sensitive by their mothers were given the sugar substitute aspartame, also known as NutraSweet. Although all the children got aspartame, half their mothers were told their children were given sugar, and the other half were told their children were given aspartame. The mothers who thought their children had gotten sugar rated them as more hyperactive than the other children and were more critical of their behaviour, compared to mothers who thought their children received aspartame (Hoover and Milich, 1994).

Food additives

Recent British research indicates a possible link between consumption of certain food additives like artificial colours or preservatives, and an increase in activity (McCann *et al.,* 2007) Research is under way to confirm the findings and to learn more about how food additives may affect hyperactivity.

ADHD candidate genes

Many candidate gene studies have used association methods to see if gene variants affect the susceptibility of ADHD by comparing the variants in cases and controls or by family-based studies showing greater transmission of one variant from affected parents to ADHD offspring (Bobb *et al.,* 2004). There have been over 215 reports of association of various candidate genes and ADHD. The candidate genes and their ADHD association studies have been recently and extensively reviewed.

The CHRNA4 is a member of a super family of ligand-gated ion channels with a high affinity for nicotine that upon stimulation promotes the release of dopamine. Several studies have found an association between ADHD and CHRNA (Comings *et al.,* 2000; Guan *et al.,* 2008). In the dopamine transporter gene, DAT1, mediates the active reuptake of dopamine from the synapse and is a principal regulator of dopaminergic neurotransmission. Interestingly, many individuals with ADHD respond well to medications such as methylphenidate that block DAT1 leading to increased amount and duration of dopamine in the synapse (Amara *et al.,* 1993) and the dopamine D4 receptor gene, DRD4, is the most replicated gene in the field with over 20 studies examining an association between DRD4 and ADHD (Faraone *et al.,* 2001).

5-HTT has a polymorphism leading to short and long variants where the short variant results in reduced transcription and lower levels of protein. The long variant is associated with ADHD because serotonin is cleared more rapidly from the synapse resulting in reduced serotonin availability. Many studies indicate a positive association with 5-HTT and ADHD (Grevet *et al.,* 2007; Seeger *et al.,* 2001) and the serotonin 2A receptor (5-HT2A) is also a good candidate gene because decreases in hyperlocomotion in mice given selective 5-HT2A agonists are observe (O'Neill *et al.,* 1999). And also several groups have demonstrated association of SNAP25 and ADHD (Barr *et al.,* 2000; Kim *et al.,* 2007). And also several studies have linked COMT variants with ADHD. COMT catalyzes the transfer of a methyl group from S-adenosylmethionine to catecholamines, including the neurotransmitters dopamine, epinephrine, and norepinephrine (Eisenberg *et al.,* 1999).

Linkage studies in ADHD

One group looked at 308 sib-pairs from the US and reported linkage to markers on the chromosome 5p13, 6q12, 16p13, and 17p11 (Ogdie *et al.,* 2003; 2004; Bakker *et al.,* 2003). A second assessed 126 Dutch sib-pairs and reported linkage to the chromosome 7p13, 9q33, 13q33, and 15q15 (13). Linkage analysis in these families points to regions on chromosomes 4q13, 5q33, 11q22, and 17p11 (Arcos-Burgos *et al.,* 2004). A fourth study looked at 229 German sib-pairs and found linkage at chromosomes 5p13, 6q, 7p, 9q, 11q, 12q, and 17p (Hebebrand *et al.,* 2006). It is important to note that several regions overlap: 5p13, 6q, 9q, 11q, and 17p11. It is interesting to note that in the first ADHD linkage genome scan published that only 7 of 36 possible known candidate genes were not discounted (Ogdie *et al.,* 2003).

Diagnosis of ADHD

At this time, it is described somewhat differently in the Diagnostic and Statistical Manual of Mental Disorders-IV and in the International Statistical Classification of Diseases and Related Health Problems. Diagnosis can vary from one non-structured interview with one caregiver all the way to a battery including a semi-structured interview and rating forms with the caregiver(s), rating forms with the teacher(s) or co-worker(s); and brain imaging, rating forms, an interview, and a psychoeducational screen with the identified patient (Deeann Wallis *et al.,* 2008).

Medications and treatment

ADHD generally have a different behavioral pattern than normal, They are easily disturbed, hyperactive, bored, short memory, indecisive. So, scientist has found many medicines which can cure this ADHD disorder by which individuals would be able to concentrate and focus Such that as; *Methylphenidate* like OROS or Concerta extended release *methylphenidate*, *Ritalin LA, Focal in XR, or Metadata CD and amphetamine Adder all, Adder all XR, Dextrostat, Dexedrine, and Dexedrine Spansules* (Gilbert *et al.,* 2010; Daniels *et al.,* 2006) Methylphenidate is increases the level of neurotransmitters in the brain and is also called as nor-epinephrine and dopamine. Amphetamine is twice as powerful and it has a longer period of sustained result, and it releases nor-epinephrine and serotonin with a better degree than methylphenidate.

Importantly, it is not yet established that a reduction in ADHD symptoms necessarily leads to the hoped for improvements in academic achievement (Loe *et al.,* 2007) Medication can produce acute, short-term improvements in on-task behavior, compliance with teacher requests, classroom disruptiveness, and parent and teacher ratings of ADHD symptoms (Pelham *et al.,* 2007). No one is quite sure why a reduction in ADHD symptoms does not translate into the long-term improved academic achievement. Clearly, more research is needed on the long-term effects of stimulants on the developing brains of the ever-younger children who receive them (Erik Parens *et al.,* 2009).

ADHD is a multifactorial disorder that is usually treated with stimulants and other medications plus behavioral/educational therapy (Daley *et al.,* 2006; steer *et al.,* 2005; Campbell-Daley *et al.,* 2004). A recent review says that wide range of treatments for ADHD found that many, but not all, studies reported that combinations of both psychosocial interventions and medications produced superior results than either intervention alone. (Daly *et al.,* 2007) Current ADHD treatments usually produce only partial benefits, and development of better multidimensional treatment protocols are clearly needed (Voeller *et al.,* 2004; Kidd *et al.,* 2000).

Conclusion

ADHD and autism have shown many relevant factors like genetic, social, nutritional, developmental and environmental conditions and yet no direct correlation for a single cause found for both disorder (DSMIV-TR-The Diagnostic and Statistical Manual of Mental Disorders, 4th Edition, American Psychiatric Association., 2000; Kidd *et al.,* 2000; Happe *et al.,* 2006). The future study of ADHD should be targeted on environmental and genetic factors. There are several studies which are going on to understand the possessions of pre and post-natal exposures of environment ADHD genetics autism development (Hertz-Picciotto *et al.,* 2006). Upcoming treatment of autism will most likely need many different interventions for each patient. Hence, to develop a better protocol large well-controlled studies of diverse interventions for autism (nutrition, social and behavioral therapy, drugs, environmental control) are required with extra studies employing multidimensional ADHD treatment (Steer *et al.,* 2005). Research determined to guide physicians on the involvement and direct implication of the cases and study of the patients report would be benefited.

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