

Learnings from the Genetics of ADHD



ADHD is a Disorder of the Brain

Genetic Risk for ADHD is Expressed in the Brain

The genetic data support neuroimaging data in establishing ADHD as a brain disorder rooted, in part, in one's own biology¹

History of Stigma Regarding (ADHD)²⁻⁴

1

Due to misinformation, some people still view ADHD as a disorder due to poor motivation or poor parenting.

2

This "blame the person/parent" approach creates stigma and worsens access and adherence to treatment.

3

To reduce stigma, it's important to educate individuals and their families that ADHD is a brain disorder.



ADHD has Existed for Tens of Thousands of Years⁵

! ADHD is not a new disorder, in fact the genetics of ADHD date back to Paleolithic times

- Individuals with ADHD and their caregivers need to know that data support the conclusion that **ADHD is a biological disorder which may require management** for its underlying biological differences and not just its symptoms



ADHD Runs in Families

- The **parents, siblings and children** of individuals of all ages with ADHD **are at high risk** for the disorder: they should be screened and may require management for ADHD themselves⁶
- ! **Symptoms of ADHD in parents may interfere with their ability to implement a medical and psychosocial treatment plan provided by their child's healthcare provider^{7,8}**



Genetics of ADHD are Similar in Males and Females⁹

- Genetic data suggests the biology of the disorder is similar in males and females so differential diagnosis and treatment is not warranted
- However, ADHD in girls frequently manifests differently with a predominance of inattention over hyperactivity/impulsivity
- Thus, girls with ADHD are sometimes not diagnosed or treated



Subthreshold Symptoms of ADHD are Meaningful

- Genetic studies support the idea that **ADHD diagnosis and symptoms** are correlated and **exist along a continuum** of expression¹⁰
- Substantial data indicate that **subthreshold ADHD** can be an **impairing disorder** which may require treatment, however there are several diagnostic challenges, as individuals may have:
 - Difficulty with retrospective recall¹¹
 - Less severe ADHD¹⁰
 - A history of supportive, well-structured home and school environments (e.g. psychological scaffolding)¹⁰
 - Been self-medicating¹²
 - A subthreshold case with many symptoms (e.g. 5 inattentive & 5 hyperactive-impulsive)¹⁰
- Additionally, DSM 5 may have **low sensitivity** for some cases of **adult ADHD** due to lack of criteria for **emotional dysregulation and executive dysfunction**¹³⁻¹⁴



Relationship of Genetics, Subthreshold Symptoms & Onset of ADHD

Early Onset

- Genetics support ADHD symptom severity as existing along a continuum, thus diagnosing “young for grade” youth may be appropriate¹⁵

Late Onset

- Genetic correlation between childhood and adults with persistent ADHD is 0.81, which is high but less than perfect, suggesting that different genes regulate onset and persistence of the disorder¹⁶
- When onset occurs later than the DSM 5 requirement of age 12, onset may have been delayed because the individual may have:¹⁷
 - A milder condition
 - Social and emotional scaffolding that protected them from ADHD
 - Childhood onset but cannot recall the symptoms
- Clinicians should be cautious in diagnosing late onset ADHD but also should not rule out the diagnosis due to onset after age 12¹⁷



Polygenic Risk for ADHD is Correlated with Adversity & Parental Education

! Polygenic risk is the estimated effect of many genetic variants on an individual's phenotype¹⁸

- ADHD polygenic risk correlates with adversity¹⁸
 - For children living in adverse environments, don't assume that their ADHD is “situational” unless it only occurs in one environment¹⁸
- Parental education correlates with, but does not moderate, ADHD polygenic risk¹⁹
 - Lower IQ is correlated with polygenic risk for ADHD¹⁹
 - Thus, it's important to be aware that some parents of youth with ADHD may not have sufficient intellectual resources to understand, implement and adhere to treatment regimens⁷



Somatic & Psychiatric Comorbidities are Common in ADHD

- Somatic comorbidity in ADHD is real and genetically driven²⁰
 - Individuals with ADHD should be screened for somatic comorbidities
 - Since ADHD worsens somatic outcomes, some individuals may need cognitive behavior therapy modules focused on helping them manage disease such as diabetes, asthma, and obesity
- Psychiatric comorbidity is common in ADHD²¹
 - Psychiatric disorders are correlated with one another at the level of DNA²¹
 - Many patients with mood and anxiety disorders likely have ADHD too²²
 - Multiple comorbidities are to be expected in some patients²²



ADHD Genetic Screening & Pharmacogenomics are NOT Ready for the Clinic

- DNA cannot be used to diagnose ADHD²³
 - Current polygenic risk scores are not sufficiently accurate for use in the clinic
- DNA variants are associated with drug responses but utility in the clinic has not been properly demonstrated²⁴
 - Randomized, controlled clinical trials demonstrating pharmacogenetically guided treatment as better than treatment as usual are still needed

References & Acronym List

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ADHD – Attention Deficit/Hyperactivity Disorder DNA – Deoxyribonucleic acid DSM – Diagnostic & Statistical Manual of Mental Disorders IQ – Intelligence quotient