Attention deficit/hyperactivity disorder (ADHD): Complex phenotype, simple genotype?

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Complex genetic traits refer to those phenotypes not fitting patterns of Mendelian segregation and/or assortment but exhibiting a preferential familial clustering that cannot be explained by cultural or environmental causes. Attention-deficit/hyperactivity disorder (ADHD) is the most common neurodevelopmental disorder of childhood and probably the most controversial. ADHD has been considered a complex genetic trait based upon the absence of a clear-cut boundary between affected and unaffected status. Furthermore, its high comorbidity with other disorders strongly suggests complex epistatic or pleiotropic effects acting in common with the environmental influences. This implies that the same gene or genes is or are associated with different and concurrently occurring phenotypes. In this study, we will review clinical and epidemiological aspects related to the ADHD phenotype, which are considered either as categorical or continuous traits. We also will discuss genetic models underlying the complexity of this behavioral phenotype and the probable role of epistatic interactions between major genes contributing to the ADHD phenotype. *Genet Med* 2004;6(1):1–15.

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Complex genetic traits exhibit a preferential familial clustering that cannot be explained by cultural or environmental causes alone,^{1,2} and do not fit patterns of Mendelian segregation or assortment. Reasons for this departure from Mendelian predictions include the presence of genetic and/or phenotypic heterogeneity with contributions from low-penetrant, common alleles, environmental factors that are often unknown or immeasurable,³ and epistasis involving an interaction among an unknown number of genes. The absence of clearly defined phenotypes also contributes to this departure.

Many psychiatric disorders have been termed complex genetic traits. Support for this notion comes from several genetic-epidemiological approaches demonstrating the significant contribution of genetics (major genes or polygenes) embedded in a complicated environmental and cultural network.⁴ This interaction among genes, environment, and cultural inheritance has been dissected by genetic-epidemiological studies using complex segregation analysis, to test the likelihood of involvement of major genes (Mendelian inheritance), environment, and cohort (randomness) effects acting alone or

as part of mixed models. This has been reported for a number of psychiatric disorders (Table 1).

ATTENTION-DEFICIT/HYPERACTIVITY DISORDER (ADHD): OVERVIEW

ADHD has been considered a complex genetic trait based upon a phenotype ranging from mildly to severely affected and familial clustering without clearly recognizable Mendelian segregation. The effect of complex epistasis or pleiotropy acting in common with the environment may explain its high comorbidity with other disorders. Thus, the same gene or genes may be associated with different and concurrent phenotypes.^{5,6}

Comorbidity of ADHD has been shown with depression, anxiety, oppositional disorder in childhood, conduct disorder, alcohol and substance abuse during adolescence, antisocial personality disorder, alcoholism, and substance dependence during early adulthood.^{7–11} Biological causes have been strongly implicated in the etiology of ADHD: (1) this disorder has been shown to follow Mendelian patterns in some families that have been used for linkage and segregation studies^{12–15}; (2) brain abnormalities that have been noted in magnetic resonance imaging (MRI) studies, single photon emission computed tomography (Table 2); and (3) neurophysiological studies (heart rate deceleration, electroencephalogram amplitude of response to stimulation, and habituation on evoked responses of ADHD patients).^{16–18} These findings, when taken together, provide increasing support for the concept of ADHD as a neuropsychiatric condition or set of conditions with biological causes.

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Table 1
Complex segregation analysis for different psychiatric conditions

Disorder or phenotype	Genetic effect	Multifactorial effects (environment plus polygenes)	Cohort effects	Ref.
Bipolar disorder	Polygenic or oligogenic	Yes		120
Bipolar disorder	Complex familial effects			121
Schizophrenia and auditory P300 latency	Major autosomal gene plus a second modifier locus	Yes		122
Schizophrenia	Major autosomal recessive gene	Yes. This model was parsimonious	Yes, 11% of the variance	123
Schizophrenia	Major autosomal gene	Yes, great environmental component (93.12%)		124
Obsessive compulsive disorder (OCD)	Major autosomal-dominant gene (with a higher penetrance for females)	No	No	125
Tourette syndrome	Major autosomal gene	No	No	126
Tourette syndrome	Major autosomal gene	Yes	No	127
ADHD	Major autosomal codominant-dominant gene	No	No	12, 13
ADHD	Major autosomal codominant gene	No	No	14
ADHD	Major autosomal gene	Yes	No	15

CLINICAL PHENOTYPE

ADHD phenotype as a categorical trait

Attention deficit and hyperactivity, respectively, has been described by the German physician, Heinrich Hoffmann, in 1845 in two boys he called “Johnny Look-in-the Air” and “Fidgety Philip.”¹⁹ In 1902, George Still, MD, delivered a series of lectures in which he described the lack of “moral control” among children without noted physical impairments.²⁰ Historically, a series of different names, including “minimal brain damage syndrome,” “minimal brain dysfunction,” and “hyperkinetic reaction of childhood” were used to describe the disorder that we know today as attention deficit/hyperactivity disorder.⁵ Early attempts to link attention deficits and behavioral disturbances to brain dysfunction were shaped by the experience of the encephalitis epidemic of 1917–1918. Children who survived the infection experienced subsequent problems including hyperactivity, personality changes, and learning difficulties. However, despite many years of research attempting to identify specific etiologic correlates of the disorder, no single cause has been identified and ADHD is currently best understood as a group of behavioral symptoms that reflect excessive impulsivity, hyperactivity, or inattention.

The first empirically based official set of diagnostic criteria for ADHD was delineated in the American Psychiatric Association’s Diagnostic and Statistical Manual of Mental Disorders (DSM III) in 1980.²¹ Early focus on hyperactivity symptoms shifted toward attention and impulsivity symptoms later reflected in the changes taking place on the Diagnostic and Statistical Manual of Mental Disorders, Revised Third Edition (DSM III-R).²¹ The current classification criteria of the Diagnostic and Statistical Manual of Mental Disorders, Fourth Edi-

tion (DSM IV)²² for ADHD allows diagnosis of subtypes as predominantly inattentive, predominantly hyperactive, or combined (Box 1). Although current diagnostic criteria including attention difficulties or distractibility are central to the disorder, the nomenclature suggests otherwise; attention is the main core deficit. These successive changes in diagnostic criteria reflect a combination of empirical research findings and expert committee consensus.

Taken as a whole, these criteria require an illness pattern that is enduring and has led to impairment. To make this diagnosis appropriately, the clinician must be familiar with normal development and behavior, gather information from several sources to evaluate the child’s symptoms in different settings, and construct and appropriate differential diagnosis for the present complaints. This helps, for example, to distinguish between children with ADHD from unaffected children whose parents or teachers are mislabeling normal behavior as pathological. The diagnostic criteria as used by appropriate examiners demonstrate high reliability on individual items and for overall diagnosis.²³

Disturbances in attention and/or activity level are part of numerous genetic conditions, some of which are listed in Table 3. Thus, the diagnosis of “primary ADHD” is made when there is no evidence from the clinical history, physical examination, laboratory findings, or clinical criteria of another condition producing the clinical picture.²⁴ Overall, ADHD is one of the best-researched disorders in medicine and the overall data on its validity are far more compelling than for many medical conditions.^{5,25–29}

ADHD phenotype as a continuous trait

Studies of children with ADHD have generally used categorical definitions derived from DSM-IV²² and/or ICD-10.³⁰ Un-

Table 2
Imaging and other studies implicating specific brain regions in ADHD

Technique	Methodology	Structures affected	Additional findings	Ref.
MRI	Volumetric measurements of brain structures; single measures and longitudinal sample (5–18 years)	Smaller total brain volume, special caudate and cerebellum, right frontal lobe	Unmedicated patients had strikingly white matter volumes compared with medicated patients. No differences by gender. Morphometric differences correlated significantly with several ratings of ADHD.	128–131
MRI	Monozygotic twins discordant for ADHD	Affected twins have significantly smaller caudate volumes than their unaffected co-twin		132
MRI	12 boys with ADHD and matched control sample	Decreased frontal lobe gray and white matter volumes	More than one subdivision of the frontal lobes appears to be reduced in volume, suggesting that the clinical picture of ADHD encompasses dysfunctions attributable to anomalous development of both premotor and prefrontal cortices.	133
MRI	Adult patients with ADHD compared with controls	Significant reduction of the volume of the left OFC in patients with ADHD	Unmedicated adults patients	134
MRI	ADHD children compared with normal control	Smaller right frontal region, smaller corpus callosum (genu-splenium)	Reverse L>R pattern of asymmetry of the head of caudate in ADHD children.	135, 136
f-MRI	go/no-go task	Frontostriatal circuits	ADHD children do not activate frontostriatal regions in the same manner as normally developing children, but rather rely on a more diffuse network of regions, including posterior and dorsolateral prefrontal regions	137
f-MRI	Go/no-go task with and without methylphenidate	ADHD children had greater frontal activation on one task and reduced striatal activation on the other task	MPH increased frontal activation to an equal extent in both groups, but it increased striatal activation in ADHD children but reduced it in healthy children.	138
QEEG (Quantitative EEG)	QEEG with eyes open during Continuous Performance Task	ADHD children showed increased slow cortical activity mainly over frontal areas and decreased fast cortical activity	These findings may indicate a different arousal level in children with ADHD	139
SPECT-99mTc-HMPAO	40 children ADHD compared with 17 control	Decreased cerebral blood flow in right lateral prefrontal cortex, right middle temporal both orbital prefrontal cortex and both cerebellar cortex	ADHD group showed increased blood flow in some parietal and occipital regions	140

der these diagnostic systems, individuals are classified as affected if they meet a specific number of criteria, which are determined with reliable and validated psychiatric instruments. However, multiple lines of evidence suggest the relationship between risk genes and the symptoms of ADHD is likely to be pleiotropic, i.e., that the same gene or genes may be associated with different and concurrent phenotypes.³¹ Similarly, several studies have suggested that ADHD represents one extreme of the quantitative manifestation of normal behavior.^{32–35} Based on these considerations, Curran and colleagues³⁵ recently concluded that “both categorical (diagnostic) and continuous (quantitative trait) approaches to phenotypic dimension are valid and may be complementary in molecular genetic studies on ADHD.”^{35(p86)}

Among statistical approaches, latent class analysis, i.e., a categorical approach to ADHD applied to parent report rating

scales, has identified the presence of six to eight latent classes underlying the ADHD phenotype in contrast to the three DSM-IV ADHD categorical subtypes. These findings suggest the presence of more subtle independent groups within the ADHD phenotype than those advocated by the classical categorical classification.^{36,37}

Natural history and comorbidity of ADHD

Longer-term follow-up studies of children with ADHD as well as studies of symptomatic adults who have been retrospectively diagnosed with childhood ADHD show that there is symptomatic persistence of ADHD into adulthood in many cases. On average, symptoms diminish by about 50% every 5 years between ages 10 to 25 years. Hyperactivity itself declines more quickly than impulsivity or inattentiveness.^{38,39} On the other hand, a number of psychiatric conditions co-occur with

Box 1	
Diagnostic criteria: Behavioral findings often present in individuals with ADHD	
Inattention	Hyperactivity/Impulsivity
Careless errors, inattentive to detail	Fidgets or squirms
Sustains attention poorly	Cannot stay seated
Appears to not be listening	Restless (subjective in adolescents)
Follows through poorly on obligations	Loud, noisy
Disorganized	Always “on the go”
Avoids or dislikes sustained mental effort	Talks excessively
Looses needed objects	Blurts out
Easily distracted	Impatient
Forgetful	Intrusive
Modified from DSM IV. ²²	

ADHD. Between 10% and 20% of children with ADHD have mood disorders, 20% have conduct disorders,⁷ and 30% to 45% of patients with ADHD also have oppositional defiant disorder (ODD). Conversely, between 61% and 67%, patients with ODD have ADHD.^{40,41} Furthermore, bipolar disorder is being increasingly recognized in ADHD.^{42–49}

Only about 7% of those with ADHD have tics or Tourette syndrome, but 50% to 90% of individuals with Tourette syndrome have ADHD,^{50–54} raising questions about common etiologic mechanisms. Learning disorders (especially reading disorders) and subnormal intelligence also are increased in the total population of those with ADHD and vice versa.^{55,56} Overall, perhaps as many as 65% of children with ADHD will have one or more comorbid conditions, although their presence will not be recognized with appropriate questioning and evaluation.^{57–59} In general, when ADHD is untreated there is a gradual accumulation of adverse processes and events that increase the risk of serious psychopathology later in life.⁶⁰

The relation between substance abuse disorder and ADHD is complex. Children with ADHD who do not have comorbid conditions have a risk of substance use that is not different from children without ADHD up to the age of about 14 years.⁶¹ The risk of developing substance abuse disorder when ADHD is present increases in adolescents and the risk ratio increases further in adulthood, regardless of whether there is comorbidity.^{38,62} Persistence of ADHD symptoms and family history of both ADHD and substance use disorders are risk factors for the development of substance abuse.³⁸ Highly potent risks for substance abuse disorder are the presence of comorbid conduct disorder or bipolar disorder.^{9,63–65} One prospective study, which followed an ADHD cohort over an average of 16 years along with a matched control group found an 11-fold increase in on-going ADHD symptoms (11% vs. 1%), a 9-fold increase

in antisocial personality disorder (18% vs. 2%), and a 4-fold higher rate of drug use disorder (16% vs. 4%).⁶⁶

Finally, current clinical evidence suggests that there are two nosologically and clinically distinct categories of ADHD: one category correlates with conduct disorder, and the other one correlates with learning disabilities.^{8,67} The subset associated with conduct disorder appears to be a particularly powerful target group for molecular genetic analyses because of the extremely elevated recurrence risk in siblings.^{62,68}

EPIDEMIOLOGY OF ADHD

Epidemiological research in ADHD has been hampered by difficulties involved in the diagnosis of ADHD and the numerous definitional changes that have taken place in the past 20 years. It is clear that individuals with ADHD comprise a heterogeneous population sharing a cluster of symptoms. The frequently subjective definition as well as the lack of available biological markers makes an adequate comparison of epidemiological studies difficult. Despite these difficulties, rigorous estimates indicate that ADHD has been described almost everywhere around the world. Community studies have estimated prevalence ranging between 1.7% and 21%, depending upon the population and the diagnostic methods (Table 4).

These results suggest that across populations under diverse geographic, racial, ethnic, and socioeconomic conditions there exists a sizable percentage of school-aged children with ADHD. Furthermore, because the evolution of criteria from DSM III to DSM IV have broadened the limits of case definition, more children appear to be affected.⁶⁹ This is largely a function of the increased emphasis on attentional problems as opposed to a more narrow focus on hyperactivity in earlier diagnostic sets. As a result, girls have been diagnosed as having ADHD more frequently than they were in the past.^{70,71}

Caution must be used when comparing epidemiological data from different studies, because diverse types of instruments and questionnaires have been used in different epidemiological trials and the DSM-IV definition of impairment is operationally vague. These issues are a source of subjective knowledge to the clinical evaluator when deciding the affection status. Furthermore, random selection of the sample versus “volunteer” participation could introduce a relevant bias in the estimation of epidemiological parameters. For example, stigmatization of ADHD patients and their families may lead to an underestimation of its prevalence. On the other hand, patients already under medication will exhibit less severe symptoms at the time of the screening.

Differences in perception between parents and teachers should also be considered in ADHD studies. Teacher reports may be influenced by factors such a class size, teacher training, or disciplinary aptitudes and practices. Although the DSM IV age criterion to establish the diagnosis is 7 years, new studies are reporting patients with diagnosis done after 7 years, in particular those cases exhibiting the inattentive type.⁷² Associated limitations involve the presence of comorbid and underlying conditions that mimic in part ADHD, especially in studies us-

Table 3
Selected genetic disorders associated with ADHD

Genetic Condition	Neuroanatomic alteration	Neuropsychological impairments	Gene and/or biochemistry	Ref.
Neurofibromatosis I	Aqueductal stenosis, hydrocephalus	30% learning disabilities, 10% mild mental retardation	Caused by mutations in the neurofibromin gene (NF1)	141
Varying degrees of Holoprosencephaly (HPE) associated with mild features	Microcephaly and general abnormalities involving telencephalic and diencephalic structures	Impaired executive functions, attention problems	HPE is caused most frequently by mutations in SHH, but also in SIX3, TGIF and ZIC2	142
Turner Syndrome	Unknown	Girls with Turner syndrome have significantly more problems with social relationships and school progress and were more likely to meet criteria for ADHD than control girls	Complex	143–145
Williams Syndrome	In the mice, haploinsufficiency for Cyln2 encoding CLIP-115, located in the 1.6 Mb common deletion leads to brain abnormalities, hippocampal dysfunction and particular deficits in motor coordination. Absence of CLIP-115 also leads to increased levels of CLIP-170 (a closely related cytoplasmic linker protein)	Mental retardation (average IQ 56), relative sparing of language, poor visual-motor integration (Range 41–80), hypersensitivity to sound, attention deficit disorder, cocktail party personality	Contiguous gene syndrome with haploinsufficiency, of multiple genes including Elastase (ELN), LIM kinase-1 (LIMK1), and RFC2	146, 147
Fragile X Syndrome	Cortical and sub-cortical grey matter alterations (caudate, vermis), abnormalities in dendritic arborization of the cortex, alterations in volume of caudate nucleus and in the cerebellar vermis.	Wide range of variability in mental retardation, ADHD symptoms (74%), ODD, impaired executive function, visio-spatial abilities, visuomotor coordination	Unclear, possible several neurotransmitters affected.	148
Smith-Magenis Syndrome	Ventriculomegaly, dysgenesis of the cerebellar vermis overlapping with features of Joubert Syndrome	Speech delay, mental retardation (IQ 20–78), behavioral problems, self-destructive behavior, sleep disturbance, hyperactivity, peripheral neuropathy, decreased pain sensitivity	Caused by an interstitial deletion of 17p11.2	149–153
Phenylketonuria	Prefrontal cortex dysfunction	Altered executive functions	Alterations of the Dopamine metabolic pathway as consequence of PAH alteration	154–158
Fetal alcohol syndrome	D1 receptors in mesolimbic dopamine system	Difficulties in learning, speed information, attentional, working memory and self regulation processes	Several neurotransmitters are affected including dopamine, serotonin norepinephrine, glutamate, GABA, histamine	159
Deletion 22q11.2 syndrome	Abnormal left/right pattern of caudate nucleus (also seen in ADHD)	13 of 20 children tested have ADHD, mainly inattentive or combined type and/or autism spectrum problems	Suspected the involvement of COMT, contained in the deleted region	160–162
Traumatic Brain Injury (TBI)	According with severity, lesion localization and time. Frontal lobe and basal ganglia lesions specially associated with ADHD phenotype	ADHD symptoms, depression, executive dysfunction, memory and behavioral alterations	Disruption of frontobasal ganglia pathways among other alterations	163–166

ing rating scales or structured diagnostic interviews, rather than clinician-based semistructured interviews.

GENETICS OF ADHD

Family-based and segregation studies

Over the past decade, twin, adoption, family, and association studies have shown that genetic factors contribute to the etiology of ADHD. Genetic studies in twins indicate a substantially higher genetic (additive) contribution to phenotypic

variation, reaching 0.91, even when shared environmental factors have been excluded.^{32,33} Adoption studies have also confirmed that genetics rather than shared environment cause familial clustering of ADHD.⁷³ Family studies have confirmed the observation of increased recurrence risk by comparing the ratio of the prevalence of ADHD in various kinds of relatives to the population prevalence using the λ statistic.^{62,74,75}

Complex segregation analysis of 257 nuclear families ascertained from Caucasian, non-Hispanic, male ADHD probands

Table 4
Prevalence of ADHD in different populations using different diagnostic instruments

Instruments	Sample	Ethnicity-population characteristics	Additional comments	Prevalence	Ref.
DSMIV parents and teachers	School population; Not randomly selected	White 80%	Special screening was done to children already on medication.	12%	72
DISC module for ADHD		Afro-Americans 15%	Concordance between parents and teachers was required to be included.		
		Hispanic 5%			
DSMIV checklist parents and teachers. Confirmation of cases by individual evaluation	Randomized sample from schools; High and low socioeconomic classes (Colombia, South America)	Boys 21.8%, Girls 10.9%		17.1%	167
		Colombians of Hispanic origin			
DSMIV checklist parents and teachers. Confirmation of cases by individual evaluation	One public elementary school, all children from grade 1–5	Brazil		17.1%	168
Clinical interview, IQ scales	Randomized sample from schools in one city (4–17 years) (Manizales, Colombia)	Clean cases prevalence. Inattentive type 4.8%, combined type 6.4%, hyperactivity type 0.3%	No specific for ADHD, symptoms. It included borderline and mild mental retardation as well as developmental coordination disorder	11.5% for “clean ADHD”	169
Raven’s progressive matrices test for estimation of intellectual function. Conners scales. Positive cases with Conners, were evaluated with DSMIV checklist	433 children from 1–6 grades in one school. At the end 85% children participated in the study	Bangkok, Thailand		6.5%	170
DSMIII-R for parents, child and teacher (6–11 y) and parents, and child (12–14)	2400 representative sample from throughout Quebec		The Quebec Child Mental Health Survey	19.9% according with parents 15.8% according to the child	171
DSMIII-R DSMIV for teachers	8258 children from kindergarten to fifth grade in middle Tennessee county	6.9% population is African-American	Anxiety behavioral, academics problems and depression as well as treatment with stimulant medication was included in questionnaires	DSMIII-R 11.4%, increment of 57% of children diagnosed with ADHD with DSMIV checklist	172
		17.2% population below poverty level			
DSMIII	1077 students in 5 rural and 5 urban public schools from 44 classroom teachers in Regensburg, Germany	Most of them primary German-speaking. One teacher from each grade level 1–4 was volunteered	ODD and CD were also included in evaluation in this study	DSMIII prevalence 9.6%	173
DSMIII-R, DSMIV for teachers				DSMIV prevalence 17.8%	
DSMIII-R for teachers (included in a Conners like questionnaire)	931 nationwide sample kinder–8th grade			18.2% if they score the second highest and the highest stem in the checklist or 4% if they scored only the highest stem	174

ages 6 to 17 using the mixed model and a logistic regression model demonstrated that the best fitting model was that of a major codominant gene¹⁵ (Table 1). These results were confirmed in a complex segregation analysis by fitting class A and class D regres-

sive models on 495 nuclear families that were ascertained from fathers who were probands in a longitudinal family/high-risk study of substance abuse.¹⁴ From these 495 nuclear families, a subgroup of 130 nuclear families was selected in which at least one

Table 5

Simulation study to determine the number of ADHD affected sibpairs needed to detect linkage assuming than 40% of families are linked to the same locus, 80% power, and the marker informativeness is 1.0

λ_S	% of linked families	# of sibpairs
2.5	40	1110
3.7	40	712
5.0	40	575

of the members of the nuclear family met the DSM-III-R diagnostic criteria for ADHD. The model fitting the data best was that of a sex-dependent Mendelian codominant model.

In the third complex segregation analysis under the unified model applied to 53 nuclear families from a genetic isolate (the Paisa community in Colombia, South America), the following models were rejected: cohort effect (noninheritance), multifactorial inheritance, recessive major gene, nonmajor gene component, and nontransmission of a major gene.¹³ In contrast, dominant and codominant major gene models and a nonmultifactorial component could not be rejected. Taken together, the model fitting these data best was that of a major dominant gene without the existence of multifactorial effects. This putative major gene explained more than 99.993% of ADHD phenotypic variance, which suggests a low contribution of environmental factors to the ADHD phenotype.

Although these three studies were performed in different populations, using different schemes of ascertainment, and with various methods to test models of inheritance, they converge in explaining the predisposition to ADHD as the consequence of a major gene or genes. These major genes exhibiting Mendelian segregation have an estimated penetrance of about

50% and differential sex liability. Purely environmental or cultural causes were largely excluded in all cases.

Searching for ADHD genes

Like all major psychiatric disorders, ADHD is considered genetically complex, in that transmission does not follow classical Mendelian models. Based on influential mathematical simulations,^{74,76} the recommended strategy for mapping genes that convey susceptibility to ADHD and other psychiatric disorders has consisted of collecting large samples of affected sibling pairs, family-based parent-proband "trios," and large samples of cases and controls.^{62,77} This recommendation follows estimations of lambda (λ) or magnitude of the risk ratios computed by dividing the affection rate among each relative type to the rate of affection in the population.^{74,76} Lower λ values may be due to a variety of factors such as oligogenic transmission, genetic heterogeneity, phenocopies, and low penetrance.⁶² In the case of ADHD, λ values from ADHD family studies are consistently low, ranging from two to three for the risk of siblings and two to eight for the risk to parents.⁶² Assuming different values for λ , our simulation study estimates that approximately 1000 ADHD affected sibpairs are necessary to detect linkage for a trait as heterogeneous as ADHD (Table 5). In families with individuals who have ADHD that persists into adulthood, or ADHD with comorbid conditions such as conduct and/or bipolar disorders, λ could reach values > 20 . Thus, a smaller number of sibpairs could be used to detect linkage.⁶²

We have initiated sibpair studies in the US population. Two other groups have published data from their own sibpair studies, reviewed later.^{78–80} In addition, however, we have analyzed data from large families from a genetic isolate (the Paisa community in Colombia, South America). Extensive descriptions

Fig. 1 Different approaches to study the genetic etiology of ADHD. Advantages (green) and disadvantages (red) of individual experimental designs are outlined. A combination of different study designs (orange and blue) is predicted to be most successful in identifying genes that contribute to ADHD.

Table 6
Candidate gene association/linkage studies in ADHD

Tested gene	Case alleles	Control alleles	Diagnostic system	Methods of assessment	Ethnic component/country	Results of the trial	Ref.
DRD4	78	79	DSM-IV	DISC	/USA	(+) In ADHD children the 7-fold repeat form of DRD4 occurred significantly more frequently than in the control sample	95
DRD4	220	220	DSM-III-R and DSM-IV	KSADS	/USA	(+) Using the TDT in the total sample (-) For the IBD mean test	175
DRD4	130	128	DSM-IV	DICA IV, CIDI, among other instruments	Caucasian/Colombia/ genetics isolated	(+) Significant association/linkage of the 7R-240 bp haplotype ($P = 0.0467$) with ADHD. The method used for the association/linkage test was the pedigree disequilibrium test (PDT)	91
DRD4					Caucasian	(+) Significant association for the haplotype of markers in the 5' promoter region of the gene (240bp-C-C). TDT for haplotypes using TRANSMIT	92
DRD4	112	82	DSM-III-R	DICA-R	White (mostly), African-American Asian- American and Hispanic/USA	(-)	176
DRD4	104	104	DSM-IV and ICD-10	DISC and SNAP	/Canada	(+) In ADHD children the 7-fold repeat form of DRD4 occurred significantly more frequently than in the control sample. Corroborated by HRR analysis	177
DRD4	214	114	DSM-IV	Emory diagnostic Rating Scale	/USA	(+) For association	178
DRD4	104	1474	DSM-III-R DSM-IV	Human Behavioral Questionnaire (DIS)	/USA	(-) For TDT and Discordant Sib-Pair analysis (+) For a classical χ^2 test of associations.	179
DRD4	110	110	DSM-IV	KSADS	/USA	(-) For the differential test of proportions with the Bonferroni correction	180
DRD4	98	98	DSM-IV	KSADS Conners Teacher Rating Scale	/Israel	(+) For TDT and prediction of the phenotype (-) For Association	181
DRD4	177	177	DSM-IV	Conners Teacher Rating Scale Child Behavior Checklist	/Ireland	(-) For HRR (-) For TDT	182
DRD4	258	884	ICD-10, DSM-III-R, or DSM-IV	CAPA	/UK	(+) For association	183
DRD4	98	98	DSM-IV	Conners Teacher Rating Scale Child Behavior Checklist	/Israel	(-) For TDT (-) For the HRR for the long allele in the ADHD group.	184
DRD4	132	132	DSM-IV	SCID WURS, BADDS and CAARS	/UK	(+) For association (-) For TDT	185, 186
						(+) For TDT by using cases-controls together to the nuclear families.	

—Continued

Table 6
Continued

Tested gene	Case alleles	Control alleles	Diagnostic system	Methods of assessment	Ethnic component/country	Results of the trial	Ref.
DRD4	144	144	DSM-IV	KSADS Conners Teacher Rating Scale	/Turkish	(+) For TDT and increasing effect with those individuals responding to Methylphenidate	187
DRD4	40	40	DSM-IV	CAPA Conners Teacher Rating Scale	/Canada	(+) For TDT at $P = 0.05$ and significance increasing when where included the Irvine sample cited in Replication Study	177, 188
COMT	96	96	DSM-IV	Conners Teacher Rating Scale, Continuous Performance Test False Alarm scale	/Israel	(+) HRR high enzyme activity COMT val allele.	105
COMT	174	174	DSM-IV	Conners Teacher Rating Scale Child Behavior Checklist	/Ireland	(+) For association in comparing gene frequencies (-) For HRR	189
COMT	144	144	DSM-IV	KSADS Conners Teacher Rating Scale	/Turkish	(-) For TDT	103
COMT	140	140	DSM-IV	Conners Teacher Rating Scale, Continuous Performance Test False Alarm scale	/Israel	(-) For HRR. Replication study of the work	105, 190
HTR2A	119	119	DSM-IV	PICS-IV TTI	/Canada	(+) Preferential transmission of the 452Tyr allele to the affected offspring by using TDT	191
DAT1	114	114			/USA	(+) For HRR on 480 bp repeat	192
DAT1	80	80			/Ireland	(+) For HRR on 480 bp repeat	193
DAT1	244	244	DSM-IV	Emory diagnostic Rating Scale	/USA	(+) For TDT	89
DAT1	258	884	ICD-10, DSM-III-R, or DSM-IV	CAPA	/UK	(-) For association	183
DAT1	204	204	DSM-IV	PICS-IV TTI	Canada	(-) For TDT (+) For TDT when is taking into account the Haplotype of the three typed regions for DAT-1	194
SNAP-25			DSM-IV		Caucasian 83%	(+) Using the transmission disequilibrium test (TDT), it was found a trend consistent with biased transmission of the TC haplotype of SNAP-25 in all transmissions and detected a significant distortion ($P = 0.027$) when paternal transmissions were evaluated.	106, 107, 195
5HTT						(+) It was found a trend for the long allele of the promoter polymorphism to influence susceptibility to ADHD using TDT. (65 transmissions vs 49 non-transmissions, $\chi^2(2) = 22.5$, $P = 0.13$)	111

of the Paisas have been published elsewhere.^{81–83} Briefly, the Paisa community, which contained over 4,000,000 inhabitants in 1998, is located between the Central and Western branches of the Andes Mountains and was geographically isolated from the 16th until the latter half of the 20th century.

The Paisas are historically descended largely from Spaniards, Sephardic Jews, and Basques.^{81–84} Taking advantage of the particularly large families that have generally been the norm in the Paisa community until recently, we have recruited multigenerational extended pedigrees. Based on simulations, we found that these extended families provide extraordinarily high estimates of statistical power for locating major susceptibility genes.¹² Simulations of statistical power in these large, multigenerational, densely affected families have also demonstrated exceptionally good power to detect linkage with expected LOD (logarithm of the odds) scores > 14 for recombination fractions of 0.1 or less, and expected LOD scores > 5.87 even if genetic heterogeneity were present in 50% of the families.¹² Thus, based on both the psychiatric characteristics of the participants, as well as structural genetic factors, we believe that these families will be highly informative regarding major susceptibility genes for ADHD, possibly in association with conduct disorder. We predict that studying a combination of sibpairs, cases and controls, in addition to extended, multigenerational families from a genetic isolate, will be most successful in eventually identifying ADHD susceptibility genes: advantages (in green) and disadvantages (in red) of these different approaches are shown in Figure 1.

Candidate gene approaches

Because of the cumulative evidence supporting the presence of major genes conveying susceptibility to ADHD, different genetic approaches involving family-based and case-control studies have been performed with the goal of detecting association and/or linkage to genomic regions or candidate genes. Based on theoretical considerations, animal models, and the remarkable effectiveness of stimulant treatment, many candidate genes have been selected from the dopaminergic and other pathways, some of which show real associations, but with small genetic effect^{85,86} (Table 6).

Tested genes with significant allelic association and linkage to ADHD include the dopamine transporter (DAT), which codes for the main molecular target of stimulant medications such as methylphenidate,^{87–90} and the dopamine receptor D4 (DRD4).^{90–95} In general, genes involved in the metabolic pathway of monoamines have shown positive as well as negative results of association/linkage to ADHD. These genes/proteins include dopamine-beta-hydroxylase (DBH) that catalyze the conversion of dopamine to norepinephrine,^{96–99} the monoamine oxidase A (MAOA),^{100,101} and the catecholamine-methyl transferase (COMT).^{102–105}

Another neurotransmitter tested by the candidate gene approach is SNAP-25, a gene encoding a synaptic vesicle docking protein known to play a role in the hyperactivity observed in the Coloboma mouse strain.^{106–110} The results have been consistent with biased transmission of a specific haplotype of

SNAP-25 in all transmissions and detected a significant distortion when paternal transmissions were evaluated.¹⁰⁶

Because reduced central serotonergic activity has been implicated in poor impulse regulation and aggressive behavior in animals, adults, and also young children, polymorphisms of serotonergic related genes, such as the serotonin transporter promoter SLC6A4 polymorphism, have been reported associated/linked with ADHD by several groups.^{111,112} Polymorphisms in the 5-hydroxytryptamine 2A receptor (5-HT2A) and the 5-hydroxytryptamine 1B (5-HT1B) receptor genes have been similarly associated with ADHD.⁹⁰

Genome-wide searches

In order to facilitate the search for potential major susceptibility genes, two independent groups have assembled sizable samples of affected siblings and have conducted genome-wide screens aimed at uncovering major risk genes for ADHD.^{78–80} The preliminary results from these genome-wide surveys resulted in LOD scores (put in numbers) and suggested several regions that may harbor one or more major risk genes for ADHD, particularly on chromosomes 7, 11, 12, 15, 16, and 17. The findings from these two studies do not overlap, indicating that genetic heterogeneity may represent a substantial obstacle to replication across samples, and to definitive gene mapping.

Our group has performed a genome-wide scan using the 16 extended and multigenerational families from the Paisa isolate.⁸⁴ Two-point LOD score analyses were estimated using FASTLINK¹¹³ as implemented in LINKAGE.¹¹⁴ SIMWALK2 was used to obtain multipoint location scores, nonparametric linkage statistics and to reconstruct haplotypes.¹¹⁵ Two point analysis using a parametric model revealed LOD scores higher than 1.5 in individual families at chromosomes 8q12 (D8S1110, LOD score = 3.227), 11q23.3 (D11S1998, LOD score = 2.62), 4q13.2 (D4S2367, LOD score = 2.56), 17p11.2 (D17S799, LOD score = 1.98), 12q23.2 (PAH, LOD score = 1.71), and 8p23.1 (D8S1130, LOD score = 1.66). The nonparametric analysis confirmed the parametric results.⁸⁴ In the previous genome-wide scan,^{78,79} 17p11 and 11q25 were also implicated as suggestive regions containing genes conveying susceptibility to develop ADHD but our suggested regions on chromosomes 8 and 4 are novel. Observing LODs this high in individual families by chance is highly improbable based on the eLOD scores obtained when a nonlinked marker is simulated in these pedigrees. Furthermore, the empiric family-specific pattern of LODs throughout the genome scan for families 8, 9, 11, and 14, suggest that these high LODs are not likely to be caused by chance because of the strong negative LODs observed throughout the genome. Taking these data together with other previous reports, it is reasonable to conclude that some of these regions may harbor risk genes contributing to susceptibility to ADHD.⁸⁴

CLINICAL APPLICATIONS

Family history

Family history of ADHD has important implications not only for genetic studies, but also for the assessment and treat-

ment of family members affected with this disorder. As mentioned previously, if a parent or sibling had ADHD, then the risk to a sibling is 25% to 30% based on Mendelian segregation and an estimated penetrance of 50% to 60%. This needs to be taken into account when treatment plans are designed for children with ADHD. Furthermore, there is a high risk of other psychiatric comorbidities associated with ADHD, such as conduct disorder, alcohol, and/or drug abuse among others (see earlier). ADHD and its associated comorbidities can have a significant impact on family functioning. The family dynamic can be further influenced by a parent's psychiatric status. Minde and colleagues¹¹⁶ found that children with an ADHD parent had higher rates of psychopathology and higher risk of comorbidities. Family and marital functioning are impaired by the presence of an affected parent regardless the gender. In addition, a child's diagnosis of ADHD by itself has been shown to have an impact on family styles. For example, a higher frequency of disorganization and lack of cohesion is more frequently found in families of children with ADHD and emotional disorders.¹¹⁷

Gene testing

Although several genome-wide searches have identified chromosomal regions that are predicted to contain genes that contribute to ADHD susceptibility, to date no single gene with a major contribution to ADHD has been identified. Even though a number of genes have been associated with ADHD, these genes are at present more of academic interest than helpful for patient care. Thus, gene testing for ADHD is not available at this point in time. Similarly, MRI, EEG, evoked potentials, SPECT, and f-MRI are currently used only in research settings and are not recommended for routine evaluation of ADHD. However, occasional use of these diagnostic tools may be considered to rule out other neurological diagnosis that can mimic ADHD symptoms.

Medication by ADHD subtypes

Stimulant medications are widely recognized as the first line of treatment for ADHD. After substantial debate the superiority of these medications has been established over other interventions, such as antidepressants and behavioral techniques. In general, the successful rate of treatment for stimulant medications is between 70% and 90%. However, important differences have been observed in response to medication according to ADHD subtype and associated comorbidity. For example, patients with the predominantly hyperactive-impulsive subtype as well as patients with comorbid conditions such as conduct disorder or oppositional defiant disorder have a higher rate of successful treatment than patients with the inattentive type or comorbid anxiety. In fact, over 80% of nonanxious children with ADHD responded to stimulants, whereas only 30% of the children with ADHD and anxiety benefited from the drug.¹¹⁸ In addition, patients with ADHD and anxiety had more adverse side effects than patients with ADHD alone. For children with ADHD and anxiety, psychological treatment in

combination with stimulants has been shown to be the optimal treatment.¹¹⁹

Counseling

Although stimulant medication remains the most effective treatment, family counseling is an important part of successful treatment. Behavioral intervention and academic accommodations are necessary to ameliorate the significant impairment that can be associated with ADHD. Periodic review of the treatment plan is necessary to address developmental changes across the lifespan of an individual with ADHD.

SUMMARY

ADHD represents a phenotype for which prevalence, comorbidity, and outcome have been replicated in numerous analyses around the world. Neurobiological studies using MRI show specific abnormal structural patterns of cerebral structures. Furthermore, recently independent genetic studies have replicated results of association and linkage to different candidate genes and genomic regions that overlap with mental disorders such as autism and schizophrenia. All of these data together support a model that major genes exhibit epistasis and act on cerebral ontogeny and thus contribute to the genesis of ADHD, the most common behavioral disorder of childhood.

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