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Hebebrand, Johannes; Scherag, Andre; Schimmelmann, Benno G.; Hinney, Anke

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REVIEW

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Johannes Hebebrand · Andre Scherag · Benno G. Schimmelmann · Anke Hinney

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Abstract The current status of child and adolescent psychiatric genetics appears promising in light of the initiation of genome-wide association studies (GWAS) for diverse polygenic disorders and the molecular elucidation of monogenic Rett syndrome, for which recent functional studies provide hope for pharmacological treatment strategies. Within the last 50 years, tremendous progress has been made in linking genetic variation to behavioral phenotypes and psychiatric disorders. We summarize the major findings of the Human Genome Project and dwell on largely unsuccessful candidate gene and linkage studies. GWAS for the first time offer the possibility to detect single nucleotide polymorphisms and copy number variants without a priori hypotheses as to their molecular etiology. At the same time it is becoming increasingly clear that very large sample sizes are required in order to enable genome wide significant findings, thus necessitating further large-scaled ascertainment schemes for the successful elucidation of the molecular genetics of childhood and adolescent psychiatric disorders. We conclude by reflecting on different scenarios for future research into the molecular basis of early onset psychiatric disorders. This review represents the introductory article of this special issue of the European Child and Adolescent Psychiatry.

Keywords Candidate gene · Linkage · Rett syndrome · Gene–environment interaction · Genome-wide association study

J. Hebebrand (✉) · A. Hinney
Department of Child and Adolescent Psychiatry,
LVR-Klinikum Essen, University of Duisburg-Essen,
Virchowstr. 174, 45147 Essen, Germany
e-mail: Johannes.Hebebrand@uni-duisburg-essen.de

A. Scherag
Institute of Medical Informatics, Biometry and Epidemiology,
University of Duisburg-Essen, Essen, Germany

B. G. Schimmelmann
University Hospital Child and Adolescent Psychiatry,
University of Bern, Bern, Switzerland

Introduction

Over the past 50 years, substantial progress has been made in linking specific behavioral and psychiatric phenotypes to chromosomal aberrations or genetic variation at the DNA level. Prerequisites of this development were significant conceptual, methodological and technical advances in both molecular and statistical genetics.

Advances in cytogenetics allowed the identification of specific syndromes based on quantitative chromosomal imbalances of complete chromosomes as in trisomy 21 in 1959 [93] and later [94] of chromosomal regions as in the cri du chat syndrome due to monosomy 5p [94]. Approximately 5 Mb represents the resolution limits of banding techniques; fluorescent in situ hybridization (FISH) allows detection of deletions as small as 1.5 Mb. Micro-deletions can result in syndromes with distinct behavioral features such as the Prader-Willi syndrome (paternal 15q11), Angelman syndrome (maternal 15q11), and the velo-cardiofacial/DiGeorge syndrome (22q11). Because a single gene on average encompasses 10–15 kb, the phenotypes of micro-deletion syndromes result from the loss of a number of genes (partial monosomy). Quantitative imbalances can functionally result in overexpression (e.g., trisomy or partial trisomy) or underexpression (monosomy or partial monosomy) of those genes located on a chromosome or within a specific chromosomal region. Due to the high

proportion of genes (≈80% in mouse brain; [92]) expressed centrally, brain function is almost always perturbed in such disorders, thus entailing the cognitive and behavioral phenotypes.

Findings in Down syndrome have revealed that of the approximately 200 genes on chromosome 21 only a subset is responsible for the characteristic phenotype. One well-known example is the early onset of dementia in subjects with Down syndrome, which can partially be attributed to the over-expression of the amyloid-ß precursor protein gene (*APP*) located at 21q21-22. In addition to the quantitative imbalance, the Down syndrome phenotype is affected by allelic variation; for example, differences in length of a tetranucleotide repeat in intron 7 of the APP locus explain substantial variation in age at onset of dementia in subjects with trisomy 21 [104].

The first large scaled and systematic genotype–phenotype studies with a primary behavioral, psychological and psychiatric focus centered on sex chromosome (gonosome) disorders; due to the low frequencies of the X0 (Turner Syndrome), XXX (Triple X Syndrome), XXY (Klinefelter Syndrome) and XYY syndromes thousands of newborns had to be screened to detect low numbers of individuals with such gonosomal disorders; the long-term follow-up of their development into adulthood revealed that these disorders are characterized by subtle neuropsychiatric and neuropsychological symptoms such as an IQ distribution shifted slightly to the left and elevated rates of attention problems, speech and reading difficulties and reduced impulse-control; nevertheless, the dissection of a highly specific behavioral phenotype associated with any one of these sex chromosome disorders was not possible [62].

The ability to detect variation at the DNA level formed the basis for the successful elucidation of the molecular mechanisms underlying many monogenic disorders, which can entail more or less specific behavioral phenotypes (Table 1). Most frequently, such variation is detectable in exons of genes underlying such disorders and simplistically either entails that the respective gene product is structurally altered or not formed at all. For example, missense mutations entail the substitution of the regular amino acid at a specific position of the protein with another; this alteration of the amino acid sequence of the respective protein can have functional implications at the levels of the cell, tissue and organism. Below, we focus on the Rett syndrome (RS), because it is the only psychiatric disorder listed in DSM-IV TR which in the majority of cases results from mutations in a defined gene. Fascinatingly, within a 10-year period, the molecular analysis of this disorder is beginning to provide insight into potential future treatment venues and to contribute to our understanding of pathways involved in pervasive developmental disorders, in general.

All other DSM-IV TR psychiatric disorders are most likely complex implying that they do not at all or only

Table 1 Examples of the influence of single gene disorders on cognition and behavior

Monogenic disorder	Mode of inheritance	Gene	Cognitive phenotype	Behavioral phenotype	Reference
Lesch–Nyhan syndrome	X-chromosomal recessive	Hypoxanthine guanine phosphoribosyl transferase (*HPRT*)	Mental retardation	Self-mutilative biting of fingers and lips	[83]
Tuberous sclerosis	Autosomal dominant	Tuberous sclerosis-1 and -2 (*TSC1/-2*)	Learning difficulties, low IQ, mental retardation	Behavioral problems, autistic disorder	[97]
Fragile X syndrome	X-chromosomal, triplet repeat expansion	Fragile X mental retardation (*FMR1*)	Mental retardation, hyperactivity	Autism	[32]
Leptin deficiency	Autosomal recessive	Leptin (*LEP*)		Diminished perception of food reward, decreased response to satiety signals, hyperphagia	[39]
Chorea Huntington	Autosomal dominant, triplet repeat expansion	Huntingtin (*HTT*)	Dementia	Depression, psychosis, personality change, obsessive–compulsive behavior	[168]
Phenylketonuria	Autosomal recessive	Phenylalanine hydroxylase (*PAH*)	Mental retardation	Autism	[144]
Wilson's disease	Autosomal recessive	ATPase, Cu++ transporting, beta polypeptide (*ATP7B*)		Psychiatric symptoms (personality changes, depression, psychosis)	[30]
Neurofibromatosis	Autosomal dominant	Neurofibromin (*NF1*)	Mental retardation hyperactivity	ADHD	[3]

infrequently result from single gene mutations. Instead, it is assumed that several gene variants interact in a complex manner with environmental factors to produce the phenotype [86]. Complex disorders typically entail higher concordance rates in monozygotic than dizygotic twins; concordance rates in monozygotic twins are typically below 1 implying that environmental factors play a role in the manifestation of the disorder. Family studies have shown that complex psychiatric disorders are characterized by elevated recurrence risks in first and second degree relatives which are below those expected for classical monogenic dominant or recessive traits. Moreover, for the complex psychiatric disorders, a steep decline in recurrence risks is observable between first and second degree family members. In third degree relatives recurrence risks are usually only minimally elevated above population-based rates of the respective disorder [164].

Within child and adolescent psychiatry, the most twin, family and adoption studies have been carried out for attention deficit/hyperactivity disorder (ADHD; [46]). ADHD is also noteworthy because large population-based twin studies have analyzed quantitative dimensions of the disorder; complex gene–environment twin studies have also been performed. For many personality and behavioral traits and developmental milestones heritability estimates based on categorical or dimensional (quantitative) data indicate that overall approximately half of the variance is explained by genetic factors [124], the other half by the environment (Tables 2, 3). In their seminal review, Plomin and Daniels [125] pointed out that after controlling for genetic similarity, siblings often appear no more alike than individuals selected at random from the general population. The source of this dissimilarity is a variance component termed 'non-shared environment'. For many traits, the non-shared environment has been found to be of greater relevance than the shared environment.

For most psychiatric disorders, which are usually assessed categorically, genetic factors have also been shown to play an important role (Table 4). Heritability estimates typically exceed 0.5. ADHD has been shown to be one of the most highly heritable child and adolescent psychiatric disorders [18, 46, 64]. Knowledge of the magnitude of the genetic basis of a particular disorder is valuable for interpreting psychiatric findings within a patient's family and for probing for specific disorders in relatives of the index patient.

Until recently, candidate gene and linkage studies dominated the attempts to uncover genetic variation underlying such complex disorders. However, viewed in retrospect, it can be concluded that these large-scaled efforts were largely unsuccessful; progress in the molecular dissection of complex psychiatric phenotypes proved to be exceedingly slow for a period of over 20 years (reviewed in [19]). Candidate gene studies could only be performed for those genes for which an a priori hypothesis existed as to their relevance for the respective disorder; obviously for each disorder this represented only a very limited number in light of the totally known number of human genes. In addition, candidate gene studies in different psychiatric disorders frequently focussed on the same set of genes of a particular neurotransmitter system, such as dopamine and serotonin transporters and receptors (e.g., for ADHD, obsessive compulsive disorder, and eating disorders see [9, 141, 167]). In other words, the candidate gene studies reflected the paucity of hypotheses as to the underlying pathways involved in complex psychiatric disorders.

Until recently, molecular genetic analyses of complex psychiatric disorders were based on low numbers of cases and controls or families. It has now become evident that for many complex disorders thousands of cases and controls are required to pick up gene variants with small effect sizes. In 1996, Risch and Merikangas [130] had already calculated that thousands of sib-pairs would be required to detect linkage if the effect sizes of the relevant gene variants are small; linkage studies only infrequently included more than 500 sib-pairs.

In 2006, the first genome-wide association studies (GWAS) based on DNA chip technology were introduced (reviewed in [59]; see Table 5 for an overview of GWAS in selected neuropsychiatric disorders), whereas it is still too early to judge the total insight that this novel technology will provide into the pathogenesis of complex disorders, we can nevertheless already conclude that GWAS have entailed a paradigm shift, thus justifying the nomination as "breakthrough of the year" by Science magazine in 2007 [122]. For many complex somatic and neuropsychiatric disorders, novel genes have been detected which provide initial insights into frequently unknown pathways involved in the respective disorders. For many disorders, different groups pooled their GWAS to come up with several thousand cases and controls, such numbers had almost never been analyzed in the pre-GWAS era. A major finding has been that the effect sizes of validated trait or disease-related SNPs are modest to small; according to a recent synopsis [65], the median odds ratio was 1.33 with an interquartile range of 1.2–1.61. Despite this recent progress, the molecular genetic basis for complex disorders remains largely unknown. For each disorder, the variance explained by the single newly identified gene variants is uniformly small.

Developmental aspects represent a key feature of child and adolescent psychiatry. The unfolding of gene expression provides virtually all of the information necessary to guide the orderly succession of events underlying the development of any organism and the central nervous system, in particular [91]. A behavioral trait or the symptoms of any given mental disorder are more uniform for a specific developmental stage than across all of infancy, childhood and adolescence; in

Table 2 Selected heritability estimates of personality dimensions

	Assessments	Heritability estimates		Reference
		Female (%)	Male (%)	
Extraversion	EPQ-R	57	57	[85]
Neuroticism	EPQ-R	54	49	[85]
Lie	EPQ-R	44	35	[85]
Psychoticism	EPQ-R	39	43	[85]
Harm Avoidance	TCI	53	57	[85]
Novelty Seeking	TCI	55	55	[85]
Reward depending	TCI	56	51	[85]
Persistence	TCI	55	55	[85]
The "Big Five"				
Extraversion	NEO-PI-R	53		[82]
Neuroticism	NEO-PI-R	41		[82]
Openness	NEO-PI-R	61		[82]
Agreeableness	NEO-PI-R	41		[82]
Conscientiousness	NEO-PI-R	44		[82]

EPQ-R Eysenck Personality Questionaire [37], *TCI* Temperament and Character Inventory [26], *NEO-PI-R* NEO Personality Inventory [29]

addition, comorbidity is dependent on developmental stage [18]. Because developmental milestones, many traits and disorders must be viewed in the context of brain development, elucidation of the underlying molecular mechanisms will contribute to the identification of genes involved in normal development of the central nervous system and its function. Dyslexia genes, which are involved in global brain-development processes such as neural migration and axonal guidance represent just one such example [106, 143]. Partially heritable somatic developmental traits such as age at menarche [158] and timing of puberty [120] have successfully been subjected to GWAS.

Specific disorders run their course during specific developmental phases. Examples include enuresis nocturna which at age 7 affects approximately 10% and at 18 only 1% [54]. The frequent reduction of hyperactivity in ADHD during adolescence is another example. Both anorexia and bulimia nervosa rarely start in childhood and only infrequently persist beyond age 30; in Tourette's disorder, both comorbid disorders and the development of the tics show age-related patterns. It appears probable that alterations in expression levels of specific genes partially account for disorder-specific manifestation ages and the symptom development over time (Tables 2, 3, 4).

The Human Genome Project (HGP), other relevant international projects and interindividual variation at the DNA level

The completion of the HGP launched in the late 1980s in the USA [117] has provided the basis for a more rapid discovery of novel candidate genes for complex disorders. The first comprehensive analysis of the human draft sequence(s) was published in February 2001 by the International Human Genome Sequencing Consortium (IHGSC) in *Nature* [78] and the private enterprise Celera Genomics (CG) in *Science* [166]. Most striking was the small number of estimated human genes, which had previously been thought to range up to over 100,000. Also, it became apparent that only ~1.5% of the human genome contains coding information. About ~50% is composed of repetitive elements. Hence, human complexity is based on diversity and finely tuned interaction of gene products such as RNA and proteins rather than gene numbers. Consistent with this, ~50% of human protein coding genes exhibit alternative splicing [13, 111, 112] creating a proteome of >90,000 proteins [60]. Gene expression is regulated by the complex interaction of a wide variety of transcription factors [43, 151].

In April 2003, in the 50th anniversary year of the discovery of the double-helical structure of DNA [171], the human DNA sequence was virtually completely elucidated. It represented ~99% of the euchromatic portion of the human genome (2.85 Gb) with 99,999% accuracy [79]. Of main interest is the identification of all genes and a comprehensive genome annotation. Currently, 31,315 genes (including 9,899 pseudogenes, which are not transcribed) are listed in the human gene catalogue (Ensemble Database version 54.36p). The total number of protein coding genes is estimated at 20,000–25,000, which is consistent with data from cross species comparisons [115, 132]. The finished sequence also provides the basis for the identification of potentially all genes causing or predisposing to disease

Table 3 Heritability estimates of selected behaviors and developmental milestones

	Assessments	Heritability estimates (%)		Reference
Behaviors				
Dieting	EAT	42		[134]
Body dissatisfaction	EDI	52		[134]
Drive for thinness	EDI	44		[134]
Disinhibition of eating	TFEQ	40		[155]
Restrained eating	TFEQ	28		[155]
Hunger	TFEQ	28		[155]
Obsessive compulsive behav.	CBCL	45–58		[71]
Developmental milestones				
Motor development	Crawling, sitting standing, walking	90		[53]
	Crawling, sitting, walking	22–33		[123]
	Standing	0		[123]
		Heritability estimates (%)		
		Female	Male	
Expressive language "vocabulary"	MCD-I-R	8	20	[73]
"Two-word-combination-use"	MCD-I-R	28	10	[73]

EAT Eating Attitudes Test [49], *EDI* Eating Disorder Inventory [50], *MCD-I-R* MacArthur Communicative Development Inventories-short form [40], *CBCL* Child Behavior Checklist [2], *TFEQ* Three Factor Eating Questionnaire [157]

Table 4 Heritability estimates of selected psychiatric disorders

Disorder	Heritability estimates (%)	Reference
PDD	90	[139]
Enuresis	67–70	[54]
Conduct disorder	53	[51]
OCD	47	[25]
Anxiety disorders	30–40	[33]
ADHD	60–80	[64]
Anorexia nervosa	48–88	[141]
Bulimia nervosa	28–83	[141]
Schizophrenia	73–90	[160]
Bipolar disorder	60–85	[149]
Major depression	31–42	[159]

OCD Obsessive Compulsive Disorder; *PDD* Pervasive Developmental Disorders (including autistic disorder, Asperger disorder, disintegrative disorder, and PDD not otherwise specified); *ADHD* Attention Deficit/Hyperactivity Disorder

as well as genetic variations affecting individual responses to medication and environmental factors. To detect variation in a DNA region of interest (e.g., a gene repeatedly or unambiguously identified in GWAS) in individuals with a specific disorder, the respective regions are commonly re-sequenced.

Interspecies comparison is helpful to identify regulatory regions and functional motifs, and so sequencing of many prokaryotic as well as eukaryotic organisms including mammals (mouse, rat, cat, chimpanzee, cow and dog) is completed or well under way. Comparison of highly accurate genome sequences enables the study of genome evolution, i.e., lineage-specific gene birth [35, 116, 121, 135]. Chimpanzee is the closest relative to humans having DNA sequences 98% identical to each other. Of special medical interest is the high proportion of recent segmental duplications [7] and inversions [42] in the human genome. The respective chromosomal regions are prone to rearrangements and/or deletions potentially resulting in phenotypic effects and can now be reliably analyzed [24, 108].

To systematically identify all genetic variations in the human population, the international HapMap Project was initiated in 2002 [77]. Populations with African, Asian, and European ancestry are studied to identify and catalogue genetic similarities and differences in humans. Genotyping a subset of these in the three populations generates an invaluable resource for the discovery of genes related to complex disorders via GWAS.

The Human Epigenome Project [74] aims to identify, catalogue and study genome-wide DNA methylation patterns. DNA methylation is a natural modification of the nucleotide cytosine via which gene expression is controlled. It is tissue-specific and changes over time in response to environmental factors. DNA methylation thus represents a direct link between environment and an individual's state. Epigenetic differences between monozygous twins potentially account for phenotypical variation despite an identical genome at the DNA level. Although twins have been found to be epigenetically indistinguishable during the early years of life, older monozygous twins exhibited remarkable differences in their overall content and genomic distribution of 5-methylcytosine DNA and histone acetylation, affecting their gene-expression portrait [45]. These findings indicate how an appreciation of epigenetics is currently largely missing from our understanding of the origin of different phenotypes from the same genotype.

The international Human Brain Proteome Organization Project (HBPP) is concerned with the brain proteome in health, aging and neuropsychiatric disorders [109]. The Encyclopedia of DNA Elements Project (ENCODE) aims at identifying all functional elements in the human genome [36]. Together with these and future initiatives, the HGP

Table 5 Examples of single nucleotide polymorphisms (SNPs) and copy number variations (CNVs) detected in genome wide association studies (GWAS) for selected neuropsychiatric disorders

Disorder	Gene(s) or region	Marker-risk allele	*P* value	Sample (cases/controls)	Reference
Restless legs syndrome					
GWAS	*PTPRD*	rs4626664-A	6×10^{-10}	628/1,644; replication in 1,835/3,111	[142]
		rs1975197-T	6×10^{-9}		
	BTBD9	rs3923809-A	3×10^{-14}	306/15,633; replication in 311/1,895	[152]
	MEIS1	rs2300478-G	3×10^{-28}	401/1,644; replication in 1,158/1,178	[176]
	BTBD9	rs9296249-T	4×10^{-18}		
	MAP2K5, LBXCOR1	rs12593813-G	1×10^{-15}		
ADHD					
CNV	*CTNND2, GRM5, GRM7, PARK2*	Deletions	9.48×10^{-3}	335 parent–child trios/2,026	[34]
Schizophrenia					
GWAS	*ZNF804A*	rs3923809-A	1.61×10^{-7}	479/2,937; replication in 6,666/19,897	[118]
	CSF2RA, IL3RA	rs4129148-C	4×10^{-7}	178/144	[95]
	MHC/*HIST1H2BJ*	rs6913660-C	1.1×10^{-9}	2,663/13,498; follow-up in 4,999/15,555	[154]
	MHC/*PRSS16*	rs13219354-T	1.3×10^{-10}		
		rs6932590-T	1.4×10^{-12}		
	MHC/*PGBD1*	rs13211507-T	8.3×10^{-11}		
	MHC/*NOTCH4*	rs3131296-G	2.3×10^{-10}		
	NRGN	rs12807809-T	2.4×10^{-9}		
	TCF4	rs9960767-C	4.11×10^{-9}		
	MHC class 1 region	rs13194053-C	9.5×10^{-9}	3,322/3,587; meta-analysis with 8,008/19,077	[80]
	6p22.1		9.54×10^{-9}	Meta-analysis of 8,008/19,077	[147]
CNV	*1q21.1*		2.9×10^{-5}	1,433/33,250; replication in 3,285/7,951	[153]
	15q11.2		6×10^{-4}		
	15q13.3		5.3×10^{-4}		
Bipolar disorder					
GWAS	*ANK3*	rs10994336-T	9×10^{-9}	4,387/6,209	[41]
	CACNA1C	rs1006737-A	7×10^{-8}		
	DGKH	rs1012053-A	2×10^{-8}	461/563	[10]
	PALB2, NDUFAB1, DCTN5	rs420259-A	6×10^{-8}	1,868/2,938	[173]
Autism					
GWAS	*CDH10, CDH9*	rs4307059-T	2×10^{-10}	1,204/6,491; 3,101 family members; replication in 1,390 family members; 108/540	[170]
CNV	*MDGA2*	Exonic deletions	1.3×10^{-4}	912 families/1,488; replication in 859/1051	[17]
	BZRAP1	Exonic deletions and duplications	2.3×10^{-5}		
	AK123120	Duplication	3.57×10^{-6}	859/1,409; replication in 1,336/1,110 cc[1]	[52]
	PARK2, UBE3A, RFWD2, FBXO40	Duplication or deletion	3.3×10^{-3}		
	NLGN1, ASTN2	Duplication or deletion	9.5×10^{-3}		
	16p11.2	Microdeletions/microduplications		751 families/4,234; replication in 811/19,268	[172]

PTPRD protein tyrosine phosphatase, receptor type, D; *BTBD9* BTB (POZ) domain containing 9; *MEIS1* Meis homeobox 1; *MAP2K5* mitogen-activated protein kinase kinase 5; *LBXCOR1* LBXCOR1 homolog; *CTNND2* catenin delta-2; *GRM5* glutamate receptor metabotropic 5; *GRM7* glutamate receptor metabotropic 7; *ZNF804A* zinc finger protein 804A; *RELN* reelin; *CSF2RA* colony stimulating factor, receptor 2 alpha; *IL3RA* interleukin-3 receptor subunit alpha; *MHC* major histocompatibility complex; *HIST1H2BJ* histone cluster 1 H2bj; *PRSS16* thymus-specific serine protease; *HIST1H2BJ* histone H2B type 1-J; *PGBD1* PiggyBac transposable element-derived protein 1; *NOTCH4* notch homolog 4; *NRGN* neurogranin; *NLGN1* neuroligin 1; *TCF4* neurogranin, transcription factor 4; *ANK3* ankyrin 3; *CACNA1C* calcium channel, voltage-dependent, L type, alpha 1C subunit; *DGKH* diacylglycerol kinase eta; *PALB2* partner and localizer of BRCA2; *NDUFAB1* NADH dehydrogenase (ubiquinone) 1, alpha/beta subcomplex, 1; *DCTN5* dynactin subunit 5; *CDH10* Cadherin-10 precursor; *CDH9* cadherin-9 precursor; *MDGA2* MAM domain containing glycosylphosphatiddylinositol anchor 2; *BZRAP1* benzodiazapine receptor (peripheral) associated protein 1; *AK123120* cDNA; *PARK2* Parkinson disease 2; *RFWD2* ring finger and WD repeat domain 2; *UBE3A* ubiquitin-protein ligase E3A; *FBXO40* F-box protein 40; *ASTN2* astrotactin 2

demonstrates the immense power lying in coordinated efforts to provide the foundation of biological and biomedical research at a new, more global but at the same time intertwined level. More recently, the 1,000 Genomes Project was initiated to re-sequence the genomes of at least 1,000 individuals from around the world to create the most detailed and medically useful picture to date of human genetic variation [162].

The comparison of whole genome sequences between individuals has allowed the detection of substantially more variation than expected [96, 169]. It had been assumed that most variation is due to single nucleotide polymorphisms (SNPs; exchanges at the level of a single base). Any two individuals differ by only one in 1,000 DNA bases or at approximately 3 million bases out of the total of 3 billion in the human genome. However, the comparison of a single sequenced genome (that of Craig Venter) with the National Center for Biotechnology Information human reference assembly identified more than 4 million variants (almost 1.3 million were novel) encompassing more than 12 Mb; roughly 1 million variants were not due to SNPs; instead these variants encompassed block substitutions, insertion/deletion events (indels), 90 inversions, as well as numerous segmental duplications and copy number variation (CNV) regions. In total, non-SNP DNA variation accounted for 22% of all events identified in the genome of Craig Venter, which however accounted for 74% of all variant bases, suggesting an important role for non-SNP genetic alterations in defining the diploid genome structure [96]. 44% of Venter's genes were heterozygous for one or more variants.

Due to their importance in neuropsychiatric genetics [28], CNVs deserve particular notice. These are defined as segments of DNA as large as several megabases in which copy number differences due to genomic rearrangements such as inversions, deletions, duplications and translocations have been found via representational oligonucleotide microarray analysis [145] and comparison of genomes (e.g., [88, 96]); CNVs are either inherited or de novo. It is estimated that approximately 0.4% of the genomes of unrelated people typically differ with respect to copy number [88].

RS as a monogenic psychiatric disorder

Originally, Rett [128] delineated the features of this serious neuropsychiatric disorder in three females; 17 years later, Hagberg et al. [58] reported on 35 females with 'progressive autism, loss of purposeful hand movements, ataxia, and acquired microcephaly', which represent the cardinal symptoms of the disorder with an incidence of approximately 1 out of 10,000 female live births. After apparently normal development for 6–18 months, girls with RS lose acquired cognitive, social, and motor skills and develop autistic behavior accompanied by stereotypic hand movements. As the disorder progresses severe mental retardation and motor impairments, including ataxia, apraxia, and tremors ensue. Seizures, hyperventilation, apnea and feeding difficulties are also common. The disorder is sporadic in 99% of all cases [22]. The RS brain is small for age and height of the patient. Dendritic trees in pyramidal neurons of layers III and V in selected lobes are small. The RS brain has small neurons with an increased neuronal packing density; it exhibits a changing pattern of neurotransmitter receptors with an apparent reduction in many neurotransmitters [5].

In 1999, different mutations in the methyl-CpG binding protein 2 gene (*MECP2*; human genes are commonly abbreviated in italic capital letters) were detected in RS females [4]. This discovery marked a turning point in psychiatric genetics: a DSM-IV (and ICD-10) psychiatric disorder was found to be due to mutations within a single gene. About 95% of classical RS patients have one of >300 known pathogenic *MECP2* mutations, the spectrum of which includes missense, nonsense, and frameshift mutations and deletions [22], the last three entailing a more severe phenotype. The X-chromosomal location (Xq28) of *MECP2* explains why mostly only females are affected: males, who have only one copy of *MECP2*, are frequently not viable, if the gene is mutated. In those alive at birth, a much more severe clinical phenotype results; death mostly occurs prior to age 2.

Seemingly, both a reduced and an elevated expression of *MECP2* lead to a similar phenotype: duplications of Xq28 including *MECP2* were detected in males with clinical features similar to RS. Transgenic mice that express wild-type *Mecp2* (only the first letter of murine genes is capitalized) at twice the normal level also have a progressive neurological phenotype similar to that observed in human patients [27].

MECP2 and the RS phenotype

MECP2 is expressed in all tissues. In the adult mouse, Mecp2 (protein encoded by *Mecp2*) is high in brain, lung and spleen, lower in heart and kidney, and barely detectable in liver, stomach and small intestine. The timing of the expression of murine *Mecp2* and human *MECP2* in humans has been shown to correlate with the maturation of the central nervous system, with the ontogenetically older structures such as the spinal cord and brainstem becoming positive before newer structures such as the hippocampus and cerebral cortex. In the cortex, MeCP2 first appears in the Cajal-Retzius cells, then in the neurons of the deeper, more mature cortical layers, and finally in the neurons of the more superficial layers [146]. Both timing and

localization of *MECP2* expression should explain developmental aspects of the RS phenotype.

MECP2 is subject to alternative splicing (different processing of the mRNA results in proteins of different sizes with partially identical domains). The B isoform has the highest expression in brain, and mutations specific to the exons encoding this isoform are sufficient to cause RS. The respective protein MeCP2 includes four functional domains, one of which is the methyl-CpG binding domain (MBD). This protein domain binds to symmetrically methylated CpGs located in the upstream region of many genes; binding of MeCP2 to methylated CpGs has an influence on the transcription rate of such a gene and is thus an important epigenetic mechanism in the regulation of distinct genes. The three other functional domains include an arginine-glycine repeat RNA-binding domain, a transcriptional repression domain that interacts with a co-repressor complex involving mSin3A and histone deacetylases and a RNA splicing factor binding region [165].

MeCP2 seemingly influences the transcription of a limited number of specific genes as either a repressor or activator, which is not only due to MeCP2 binding to CpG-islands but also to periodic MeCP2 binding outside gene boundaries, entailing the organization of chromatin into functionally important domains or loops of imprinted regions [70, 178], which, in turn, modulate gene expression. If due to a non-functional (or over-expression of) MeCP2, the expression of target genes continues or is not initiated, more and more RS symptoms ensue over time [11]. Future research will potentially reveal which RS symptoms are related to activation or repression of specific genes due to the loss of function of MeCP2. For example, the frequent feeding problems in RS might be related to the persistent expression of brain-derived neurotrophic factor (BDNF), which aside from being involved in the regulation of neural survival, development, function, and plasticity in the brain also has an influence on feeding behavior and body weight regulation [61].

Transgenic and knockout mice models and comparative sequence analysis [127] have helped considerably to elucidate the function of MeCP2, to assess the effect of specific mutations on the phenotype and to enable the identification of evolutionary conserved regions. If *Mecp2* is completely knocked out in male mice, a mild RS-like phenotype ensues (female mice remain healthy into adulthood). A conditional knockout of *Mecp2* in postnatal neurons of restricted regions in the brain leads to a similar although delayed neuronal phenotype, suggesting that the gene plays a role in post-mitotic neurons. Abnormalities in social interaction and home-cage behavior were identified in mice, in which a mutation similar to common RS causing alleles had been introduced [113]. The resultant phenotype was reminiscent of the sleep/wake dysfunction and autistic features of RS patients. Interestingly, transgenic expression of *Mecp2* in *Mecp2* knockout mice largely rescues the RS phenotype [101].

Although it is thought that the primary cause of RS results from a lack of functional MeCP2 in neurons (cell autonomous), non-cell autonomous factors also contribute to the disease. Thus, loss of MeCP2 also occurs in glial cells of RS brains [8, 102]. Because mutant astrocytes from a RS mouse model, and their conditioned medium, failed to support normal dendritic morphology of either wild-type or mutant hippocampal neurons, astrocytes in the RS brain carrying *MECP2* mutations may have a non-cell autonomous effect on neuronal properties, probably as a result of aberrant secretion of a soluble factor(s) [8].

MeCP2 deficiency in astrocytes causes significant abnormalities in BDNF regulation, cytokine production, and neuronal dendritic induction, which may contribute to abnormal neurodevelopment. In addition, the MeCP2 deficiency state can progressively spread at least in part via gap junction communications between mosaic $Mecp2^{-/+}$ astrocytes in a novel non-cell-autonomous mechanism, which may lead to the pronounced loss of MeCP2 observed selectively in astrocytes in mouse $Mecp2^{-/+}$ brain, which is coincident with phenotypic regression characteristic of RS. Based on these findings, Maezawa et al. [102] suggest that astrocytes are viable therapeutic targets for RS and perhaps regressive forms of autism.

A broader role of MECP2 in neurodevelopmental disorders

Significant differences in MeCP2 expression have been detected between brain samples of individuals with related neurodevelopmental disorders, including autism, pervasive developmental disorder, Prader-Willi and Angelman syndromes and age-matched controls [136, 137]. Hence, the elucidation of the molecular mechanisms underlying RS has led to the theory that multiple pathways regulate the complex developmental expression of *MECP2* and are not only defective in RS but also in other autism spectrum disorders. The common features of human neuro-developmental disorders caused by loss or increase of MeCP2 function suggest that even modest alterations of MeCP2 levels result in neurodevelopmental problems. In support of this hypothesis, a 50% reduction of the level of wild-type MeCP2 in mice was shown to result in a spectrum of subtle abnormalities such as learning and motor deficits, decreased anxiety, altered social behavior and nest building, decreased pain recognition and disrupted breathing patterns [138]. Seemingly, the precise control of MeCP2 expression level is critical for normal behavior.

A series of studies have aimed at assessing the role of *MECP2* and related genes in autistic disorder and mental

retardation. *MECP2, MBD1, MBD2, MBD3,* and *MBD4* comprise a nuclear protein family sharing the methyl-CpG binding domain (MBD) and are related to transcriptional repression. However, mutations in *MECP2* have only infrequently been detected in patients with autistic features; mutations in the other genes have not systematically been found to play a role in the etiology of autistic disorders [98]. Future candidate gene studies in autism spectrum disorders can focus on those genes whose expression levels are regulated by MeCP2 (see, e.g., [165]). The investigation of the role of frequent *MECP2* polymorphisms in polygenic autism also merits consideration: in two family samples a three-marker SNP haplotype was associated with autism and autism spectrum disorders suggesting that one or more functional variants of *MECP2* existing at significant frequencies in the population may confer increased risk [100].

Therapeutic implications

The finding that transgenic expression of Mecp2 in *Mecp2* knockout mice largely rescues the RS phenotype [101] suggests that RS might be amenable to treatment. Because treatment would typically only be possible after the diagnosis of RS and thus after development of clinical symptoms, this rescue in the mouse model appears promising for the treatment of RS patients. As systemic treatment of MeCP2 mutant mice with an active peptide fragment of Insulin-like Growth Factor 1 (IGF-1) extends life span, improves locomotor function, ameliorates breathing patterns, and reduces irregularity in heart rate IGF-1 has been suggested as a prime candidate for pharmacological treatment of RS and other disorders caused by a deficit in synapse maturation in the brain [163]. Treatment with IGF-1 peptide was also shown to increase brain weight of the mutant mice; additionally, IGF-1 partially restored spine density and stabilized cortical plasticity to wild-type levels [163]. In Mecp2 mutants, BDNF overexpression extended the lifespan, rescued a locomotor defect, and reversed an electrophysiological deficit [23].

Histone deacetylases (HDACs) are enzymes that affect the acetylation status of histones and other cellular proteins. Pharmacological manipulations using small-molecule HDAC inhibitors, which may restore transcriptional balance to neurons, modulate cytoskeletal function, affect immune responses and enhance protein degradation pathways, have proven beneficial in various experimental models of brain diseases [84] and could thus prove beneficial in diverse neurodevelopmental disorders including RS. In other genetic disorders, it has been shown that aminoglycosides can cause a read-through of nonsense mutations with an efficiency of up to 20%. Brendel et al. [12] showed that this read-through of *MECP2* nonsense mutations can be achieved in vitro with efficiency comparable to that seen in other disorders.

Identification of predisposing alleles in complex disorders

In conclusion, within a ten year period, substantial progress has been made in elucidating the molecular mechanisms underlying RS and deducing strategies for potential treatment. The situation in polygenic disorders is obviously much more complex. In the following, we examine how gene variation can be picked up in complex disorders.

Association studies

The comparison of genetic variants between cases and controls is the most common approach taken to identify variants predisposing to the respective disorder. In association studies, a familial loading is per se not required for classification as a case. However, requirement of such a loading would be expected to increase the probability that genetic factors indeed contribute to the disorder of the index patient. Controls are frequently screened for the respective disorder; a positive screen entails exclusion of the proband as a control. Use of controls with a phenotype that quantitatively differs as much as possible from cases can theoretically enhance the probability of detecting genes. Controls should be matched to cases for well-established, strong risk factors (e.g., ethnic group, sex, socio-economic status and intelligence) to ensure that significant results are not caused by a confounding risk factor differing between the two groups other than the trait of interest [89]. Such confounders would bias the study if they interact with the considered candidate gene. Overmatching, on the other hand, e.g., for many potential, small risk factors, will lead to substantial loss of efficiency. Matching has to be accounted for in the analysis as well.

One of the most important confounders in genetic studies could be ethnicity in ethnically admixed or structured populations [90]. This will cause serious bias if the studied candidate gene differs in allele frequencies between ethnically defined sub-populations (population stratification). It has been proposed to genotype several markers that are thought to bear no relationship to the disorder of interest in both cases and controls to potentially enable adjustment for systematic genetic differences [31, 126]; this has become a standard requirement for GWAS (see below, [6]).

Another popular approach to circumvent the potential confounding population stratification effects of case–control studies are family-based association studies, which include family members of the cases to use as (ethnically)

matched controls. These can be unaffected sibs or pseudo-controls constructed from non-transmitted parental alleles. The first statistical tests for such case-parent trios were the haplotype relative risk method (HRR; [38]) and the haplotype-based haplotype relative risk method (HHRR; [161]). These tests influenced the development of the most widespread test—the transmission disequilibrium test (TDT; [150]) which is unaffected by population stratification phenomena and a valid test for both association and linkage. The TDT test statistic is based on the comparison of the number of times the allele of interest is transmitted versus non-transmitted by heterozygous parents to an affected child. The ascertainment of parents is usually readily possible in disorders with a childhood onset.

Family-based association studies have certain disadvantages; in particular, they are less efficient than case–control studies. Sibs share on average one allele identical by descent, so there is effectively only one allele that can differ instead of two for unrelated cases and controls. Also, sibs tend to be more similar in many possible risk factors which imply over-matching with its associated loss in efficiency. In the trio design, three subjects have to be genotyped to yield approximately the similar information as two subjects in the case–control design. And finally, for diseases with a later age-of-onset, it will be difficult to ascertain parents of cases. Therefore, family-based association studies are more expensive and complex than case–control studies.

Effect size

In polygenic disorders, each gene variant (subsequently also referred to as an allele) has only a minor to minimal effect. Typically the effect size of a particular allele or genotype is indicated via its relative risk or the odds ratio in case–control designs. In diploid cells, humans have two copies of every gene (with the exception of most genes located on the X and Y chromosomes in males); in this context, the term genotype refers to both gene variants; typically the genotype relative risk is given for heterozygotes (AB) and homozygotes (BB) for the predisposing allele, it is set to 1 in individuals homozygous for the wild-type allele (AA). Low relative risks imply that (1) the variant (or genotype) in itself is by no means sufficient to explain the disorder of an affected individual and (2) many individuals without the respective disorder harbor the same allele (or genotype).

Given a limited number of cases and controls (e.g., 1,000 each), detection of predisposing alleles becomes more difficult (a) the lower the population frequency of such a variant and (b) the lower its effect size. A study is underpowered if a significant difference cannot reliably be detected between cases and controls. Recent GWAS for height, weight and body mass index (BMI in kg/m^2) based on ten thousands of individuals have picked up single variants which in the heterozygous state on average entail a 3 mm increased height [57] and a 180 g heavier weight [175], respectively. Because presumably only those gene variants with the most pronounced effects have currently been detected, effect sizes of most as yet undetected alleles may well be below 2 mm or 100 g. The implications for psychiatric disorders are evident: whereas previous molecular genetic studies frequently at best included only a few hundred individuals, current studies already include thousands of cases and controls. Many more are needed to confirm initial true positive or to rule out false negative findings in independent samples.

Common variants versus private mutations

The common disease—common variant hypothesis predicts that specific common alleles or variants predispose to common disorders and that such alleles/variants will be found in all human populations, in which the respective disease occurs. Indeed, for several complex traits and disorders common variants, mostly SNPs, have been detected in coding and regulatory sequences of genes (e.g., [65, 76]); however, in many cases the localization of such a SNP does not allow any conclusions as to how this variation affects the function of the gene; it appears likely that in many cases, the respective SNP in itself merely tags a functionally relevant SNP or variant (linkage disequilibrium) in close proximity. In addition, because such SNPs can be located far from a gene it frequently is not even possible to definitely determine which gene (e.g., 3′ or 5′) is altered in its function. It appears likely that many of the functional variants influence gene expression levels.

The identification of variants with moderate effect sizes has been successful in single non-psychiatric disorders with complex inheritance such as Crohn's disease [72, 119], breast cancer [110, 177], and type 2 diabetes mellitus [56]. However, for complex psychiatric disorders, common gene variants with modest and robust effect sizes have not been detected. Even upon use of large-scaled GWAS (see below), the total number of validated common variants is rather low and their effect sizes are uniformly small.

Despite the recent advances, the explained variance of a quantitative phenotype remains low even if heritability estimates are high. Thus, even though heritability estimates exceed 0.8 for body height, less than 5% of the total variation in height has been uncovered despite the detection of over 40 validated gene variants [57, 69]. Similarly, only about 1% of the variance in BMI has currently been found to be due to about 20 common variants [67, 68, 175] despite heritability estimates of roughly 0.4–0.8.

The common disease—common variant hypothesis has been challenged. Based on molecular genetic findings, a recent discussion has focused on the relevance of "private" mutations defined as rare mutations found only in single families in whom a specific complex disorder occurs. Particularly for disorders with reduced fecundity, associated with severe mental disorders, a negative selection pressure conceivably acts on risk alleles, thus potentially explaining why common variants have not been readily detected in disorders such as autism, schizophrenia and mental retardation. Accordingly, rare variants may account for a larger fraction of the overall genetic risk than previously assumed. Indeed, rare CNVs have been detected in schizophrenia [153], autism (reviewed in [47]) and mental retardation [107]. For example, Stefansson et al. in a genome-wide search for CNVs associating with schizophrenia used a population-based sample to identify de novo CNVs by analyzing 9,878 transmissions from parents to offspring. The 66 de novo CNVs identified were tested for association in a sample of 1,433 schizophrenia cases and 33,250 controls. Three deletions at chromosomes 1q21.1, 15q11.2 and 15q13.3 showing a nominally significant association with schizophrenia in the first sample were followed up in a second sample of 3,285 cases and 7,951 controls. All three deletions were significantly associated with schizophrenia and related psychoses in the combined sample.

In complex disorders, different sets of gene variants are operative in different affected individuals. Assume that 100 genes each occurring as the two alleles A and B in the population in total account for all genes predisposing to a particular disorder; all of these variants would have the same effect size and would act in an additive manner. Let us also assume that at least 50 predisposing alleles must be present in an individual for the disorder to break out, if predisposing environmental factors are abundant—more predisposing alleles would be necessary if only a limited number of negative environmental factors are operative. Accordingly, an affected subject could theoretically be homozygous for the predisposing variant at 25 loci, another could be heterozygous at 50 loci. Most affected individuals would be heterozygous at some loci and homozygous at others. Clearly in this scenario, any two affected individuals would not necessarily share a single predisposing variant; there is substantial genetic heterogeneity.

In reality, the frequencies and effect sizes of such alleles differ. Despite the fact that for the two quantitative phenotypes height and BMI effect sizes of currently detected variants have been shown to be additive, non-additive effects appear likely in complex disorders. Also consider that complex interactions of specific sets of gene variants presumably occur with environmental factors. Thus, a particular (set of) environmental factor(s) might only be relevant for a subgroup of individuals characterized by specific genotypes at diverse loci. Yet in current studies, all the individuals of such subgroups are analyzed as if they were a homogeneous sample.

We briefly dwell on the different strategies to detect gene variants in complex disorders.

Candidate gene studies

For many years, the candidate gene approach formed the most frequent attempt to discover genetic variation underlying psychiatric disorders. The choice of a specific candidate gene was commonly based on pharmacological, physiological, biochemical, anatomical and/or genetic data such as chromosomal localization within a linkage region or chromosomal breakpoints in chromosome aberrations in individuals with a psychiatric phenotype. However, in light of the estimated 21,000 human genes and our poor knowledge of the molecular basis of any psychiatric disorder, the a priori probability for the involvement of a particular gene is low, unless the underlying hypothesis is well founded. Most of the respective genes were originally selected because they belong to neurotransmitter systems assumed to be involved in psychiatric disorders (e.g., dopaminergic or serotonergic system). Typically, originally positive findings were not unequivocally confirmed in subsequent independent association studies; meta-analyses have been used to assess such conflicting findings. While meta-analyses may be useful to circumvent the problem of limited statistical power due to small samples, they are no means to cope with poor study quality (e.g., [99]). The advent of GWAS has led to an almost complete halt of classical candidate gene studies; in retrospect, their contribution to the elucidation of genetic mechanisms in psychiatric disorders has been minimal. Because, as has been pointed out, case numbers were frequently low, it remains to be seen if some classical candidate genes for diverse psychiatric disorders will be picked up in large GWAS.

To illustrate the candidate gene approach we refer to a study conducted by Abelson et al. [1], who identified a patient presenting with Tourette's disorder (TD) and ADHD carrying a de novo chromosome 13 inversion. Because the Slit and Trk-like family member 1 gene (*SLITRK1*) is one of three genes located within 500 kb of the two breakpoints, this gene was considered as a candidate gene for TD. Accordingly, *SLITRK1* was screened in 174 patients with TD. One subject with TD and ADHD harbored a frameshift mutation; two unrelated patients with TD and obsessive–compulsive symptoms had an identical non-coding variant. Both this variant and the frameshift mutation were absent in 4,926 and 3,600 control chromosomes, respectively. Abelson et al. concluded that *SLITRK1* mutations underlie TD in a small subgroup of patients

affected with this tic disorder. However, caution is warranted because in contrast to the 174 TD patients, *SLITRK1* was not screened for mutations in controls; hence, it cannot be excluded that healthy controls might also harbor other infrequent mutations.

Genome-wide linkage studies

DNA sequences at specific loci are inherited together as a consequence of their physical proximity on a single chromosome. The closer the loci are to each other at the DNA level, the lower the probability that they will be separated during meiosis, and hence the greater the probability that they will be inherited together. By analyzing genetic meiotic recombination frequencies between specific loci, genetic linkage analysis can be used to localize susceptibility genes within a framework map of genetic markers with known positions in the genome. Genome scans have typically been based on 350–1,000 microsatellite markers spaced rather evenly throughout the genome with marker distances of about 10–3 cM [114]. Fine mapping with additional markers is frequently performed in an attempt to narrow in the chromosomal region which initially can span over a large region of a chromosome encompassing several genes. A priori hypotheses as to functional candidate genes that could influence the phenotype are not required. In addition, no a priori assumptions about mode of inheritance, frequency of the disease allele in the general population and penetrance are required; such analyses are also termed non-parametric or model-free. For parametric linkage analyses, the search space is usually restricted to for instance specific modes of inheritance; thus, a priori assumptions are made.

Linkage studies proved to be very successful for monogenic Mendelian disorders; nevertheless, progress usually was slow: for example, it took from 1983 to 1993 to proceed from the initial linkage finding on chromosome 4p in large pedigrees to the identification of the Huntingtin gene and the molecular mechanism underlying Huntington's disease [75]. In complex disorders, linkage studies were originally also based on large, multiply affected pedigrees based on the (potentially incorrect) assumption that a single or only a small number of disease genes segregate in each of these families. Sibling pairs and small nuclear families formed the basis of more recent linkage studies [129].

With single exceptions (e.g., see [143], for linkage findings in dyslexia leading to the detection of doublecortin domain containing 2 gene) linkage scans for psychiatric disorders have failed. Potential explanations include: (1) sample sizes typically ranged well below 500 sib-pairs and thus had (very) low power. Meta-analyses of linkage studies have been performed in an attempt to cope with the small number of sib-pairs investigated in single studies; for example, for ADHD a genome-wide significant linkage was detected on chromosome 16 [179], in contrast no significant linkage finding was detected for obesity [140]. (2) If infrequent/rare gene variants (private mutations) with large effect sizes (major genes) exist in psychiatric disorders, their detection via linkage studies is exceedingly difficult or impossible. It remains to be seen to what extent GWAS will pick up genes located within linkage peaks detected via previous linkage studies; we are aware of one such example [140].

Genome-wide association studies (GWAS)

The possibility to place hundreds of thousand oligonucleotides on small chips in combination with the advances of the Human Genome and related projects has revolutionized molecular genetic studies of complex traits and disorders. This transition to SNP-based technology has been rendered possible by the construction of a map of naturally occurring polymorphisms [81]: 1.4 million unique SNPs were built in a ~2-kb-resolution map placing ~2–4 SNPs per human gene. Currently, there are ~79 million submitted, 18 million referenced and 6.6 million validated SNPs known (latest update: 30 April 2009 [148]). Furthermore, the construction of a haplotype map of the human genome has greatly facilitated comprehensive genetic association studies of human disease [48, 55, 103].

SNP associations are currently being detected at an unprecedented pace for many neuropsychiatric disorders [65, 66, 87, 103; see also Table 5). The chips allow the determination of genotypes for the number of SNPs that are detected with the respective oligonucleotides; currently, determination of 1 million SNP genotypes in every individual tested is feasible; only very small amounts of DNA are required. If 2,000 cases and 2,000 controls are analyzed in an association study, a total of $2 \times 2{,}000 \times 1$ million genotypes are generated. Both allele and genotype frequencies for every single SNP can be compared; P values of 0.05 divided by 10^6 (simple Bonferroni correction for the 1 million tests), i.e., P values smaller than 0.00000005 (5×10^{-8}), indicate genome-wide significant differences between cases and controls for the respective SNP. However, a Bonferroni correction is too conservative because many SNPs are in linkage disequilibrium with other SNPs implying that the respective alleles are not independent. Nevertheless, in light of the hypothesized small effect sizes of variants underlying complex disorders the necessity to analyze very large samples of both cases and controls is readily evident. Thus, the absence of significant findings in ADHD GWAS most likely reflects the too low number of cases and controls or

trios (index patient and both parents) in the currently published studies (see [9]).

The future and a word of caution

What can realistically be expected for the future? Two extreme scenarios appear possible: (1) only a limited number of novel gene variants are unambiguously identified within the next 5 years. This finding would imply that the effect sizes of most predisposing alleles are so small that they cannot be picked up. The ultimate step would be to re-sequence the whole genome (or at least all known genes) in a substantial number of cases and controls in an attempt to statistically identify those loci in which variations cluster in cases [105]. Genome-wide re-sequencing is currently, however, not yet feasible in a large number of individuals. Moreover, special statistical methodology for this data is still in its infancy. The accumulating costs for the search for alleles with very small effect sizes at some time point will need to be put into perspective to the expected outcome. (2) GWAS lead to the identification of at least ten novel gene variants for each analyzed psychiatric disorder. These genetic results are robust, implying that there is a consensus that indeed the respective genes contribute to the etiology of the respective disorder; (repeated) replications of each single finding are the prerequisite for the attainment of such a consensus. This knowledge will allow us to identify (a) the molecular genetic mechanisms relevant for psychiatric disorders (e.g., variation primarily within regulatory versus coding regions), (b) novel systems and pathways relevant in specific disorders, which may or may not include pharmacological targets, (c) the extent of overlap in the genetic predisposition to different psychiatric disorders (e.g., identification of genetic variation predisposing to both ADHD and autism; see [133]), (d) gene–gene and gene–environment interactions and (e) developmental relationships between genotype and phenotype.

The crucial prerequisite for the use of sophisticated molecular technology is that several large and well-characterized samples of patients with a given disorder exist to allow repeated confirmations of a single finding and subsequent meta-analyses. By large, we imply that the respective samples should encompass well over 1,000 cases and an equal number of controls, thus providing sufficient power to detect alleles with a modest to weak effect. Undoubtedly, the need to analyze large samples and to confirm original findings will lead to extensive collaborations which need to also address ethnic aspects; the contribution of single researchers and groups to novel results will become small; thus, a total of 146 authors contributed to a recent GWAS for BMI [175]. Family-based association and linkage studies will also be helpful in specific situations such as the involvement of imprinted genes in the etiology of a given disorder.

As the field of molecular genetics of psychiatric disorders advances, we as child and adolescent psychiatrists need to stay at the forefront of these developments. To achieve our goals we depend on an interdisciplinary approach also encompassing molecular geneticists and biologists, biostatisticians, and several other specialists. We will profit by extensively integrating these disciplines into our research; a fundamental issue is to establish a sufficient amount of cross-talk to ensure that the full potential of this interdisciplinary approach can bear full profit. We as psychiatrists will also be responsible for the integration of novel molecular findings into our clinical routine. We need to be aware of ethical and societal implications of molecular genetic findings. We need to have training programs which provide us with the capability to grasp the molecular findings and to integrate them into novel research (e.g., analysis of gene–environment interactions) and even more important into our daily clinical routine if the evidence is strong enough. If a sufficiently large number of predisposing alleles for a given disorder become known, genetic analyses will most likely for the first time provide us with genetic markers useful for diagnostic purposes, prediction of the clinical course of a disorder and its treatment (personalized medicine). We will learn that the elucidation of the molecular puzzle of psychiatric disorders has the potential to alter our current phenomenological basis for the definition of neuropsychiatric disorders.

Despite these exiting potential implications of the discovery of predisposing alleles, we nevertheless should remain critical. Due to the necessity to reach a diagnosis via explicit diagnostic criteria, we as psychiatrists have become extremely critical of our own research work; with good reason we have come to expect a solid diagnostic procedure based on standard criteria. We would recommend that this critical approach is extended to the field of psychiatric genetics, where at times novel results are either extended beyond the evidence or are uncritically taken for granted.

For example, in 1993, Brunner and co-workers [15, 16] reported that a mutation in the *MAO-A* gene underlies a phenotype characterized by 'borderline mental retardation' and 'aggression'. This study is widely held to indicate that human aggression can be caused by a mutation in a single gene. However, the phenotype depicted in the respective publications is anything but straight forward: the mutation carriers were reported to have been involved in voyeurism, exhibitionism, arson and/or rape. The affected males were described as '…withdrawn and shy, being often without friends. All have shown aggressive outbursts of some sort,

usually with little or no provocation. A number of males exhibit sexually aberrant behavior… Aggressive behavior tended to cluster in periods of 1–3 days, during which the affected male would sleep very little and would experience frequent night terrors.' No attempt was made to classify the symptoms according to a psychiatric classification scheme. The common trait appears to be 'aggressive outbursts of some sort', which without further specification could well apply to a substantial minority of the general population. This criticism all the more applies because the investigators deduced the presence of borderline mental retardation in nine males of the pedigree from information compiled 30 years ago by an unaffected family member. The only information provided for those mutation carriers whom the investigators themselves were able to phenotypically assess was as follows: 'A typically affected male showed a full-scale IQ of 85'. It was not specified how many of the males were psychologically tested and what IQ test was used (for a more detailed critical evaluation of the Brunner et al. studies [15, 16], see [63], and the response of Brunner et al. [14]). Conceivably, the *MAOA* mutation entails symptoms compatible with the diagnosis of a personality disorder, which, in turn, could be associated with aggressive behavior in specific circumstances. In our opinion, there is no reason for us to be lenient when molecular geneticists uncover genetic variation underlying interindividual differences in behavioral phenotypes, particularly if they are as complex as aggression or intelligence. This is particularly important because the media frequently simplify and exploit such findings, thus conveying false or largely imprecise information to the lay public.

The delineation of the 'aggression gene' (term used by the media; see e.g., [156]) paved the way for another sensational finding, which pertains to a genotype–environment interaction, only few of which have been studied in psychiatry. *MAO-A* alleles can be classified as leading to low or high activity of its gene product; a study published in *Science* in 2003 [21], which was purportedly independently confirmed [44], showed that maltreated children with a genotype conferring low levels of MAO-A were less likely to develop conduct disorders.

Why should such an exciting finding be subjected to a critical evaluation? Critical issues include (for a more detailed and general discussion of gene × environment interactions see also [174]): (1) solid molecular genetic findings in complex disorders are as yet scarce. There is no a priori evidence to indicate that a switch to gene–environment interactions will make the elucidation of predisposing alleles easier. (2) The delineation of a single specific hypothesis pertaining to a gene–environment interaction implies that just this one out of very many different possible ones is tested; both the gene (e.g., *MAO-A*) and the environmental condition (e.g., maltreatment) must be selected. If, however, different gene–environment interactions are tested, the effects of multiple testing need to be considered. (3) The quality of the underlying hypothesis needs to be assessed. The investigation of *MAO-A* in conduct disorders to a considerable extent rests on the aforementioned study of Brunner et al. [15, 16], which as delineated above was not satisfactory in defining a psychiatric phenotype. (4) Confirmatory studies in gene–environment analyses become almost impossible if the original assessment procedure for the relevant environmental factor is not employed in subsequent studies. Foley et al. [44], who used different variables to construct a maltreatment index than Caspi et al. [20], elegantly discuss this problem by speculating that their own positive molecular genetic results suggest that the measures used by the two different groups are 'intercorrelated and they may indicate an overlapping set of environmental risks'. A direct comparison of the variables assessed in the two studies is not too convincing to make this circular reasoning plausible. To the contrary, it seems probable that the two distinct sets of variables used to construct the maltreatment indices tap on different environmental and genetic factors; the extent of overlapping is subject to debate. (5) Finally, as Foley and co-workers [44] note, most of the power to detect the interaction stemmed from the extremes of the distribution. Only 15 and 5 subjects out of a total of 514 were ranked to be in the second highest and highest level of exposure to childhood adversity. The genotypes of these 20 subjects in total accounted for the significant effect of the genotype–environment interaction and thus for the confirmation of the original Caspi et al. [21] study.

In the context of such gene–environment interactions, a recent meta-analysis deserves notice: despite previous reports to the contrary, the serotonin transporter genotype alone or in interaction with stressful life events was not found to be associated with an elevated risk of depression in men alone, women alone, or in both sexes combined; the number of stressful life events was however associated with depression [131].

There are no easy solutions to these problems. The complexity of the issues at hand requires that psychiatrists apply all their knowledge to adequately conduct genetic studies and to assess novel genetic findings. We believe that the elucidation of genes involved in psychiatric disorders has a tremendous potential to advance our understanding of their aetiologies and to contribute to future therapies. At the same time we need to remain humble in light of the complexity inherent to genetic and environmental factors in psychiatric disorders.

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References

1. Abelson JF, Kwan KY, O'Roak BJ, Baek DY, Stillman AA, Morgan TM, Mathews CA, Pauls DL, Rasin MR, Gunel M, Davis NR, Ercan-Sencicek AG, Guez DH, Spertus JA, Leckman JF, Dure LS 4th, Kurlan R, Singer HS, Gilbert DL, Farhi A, Louvi A, Lifton RP, Sestan N, State MW (2005) Sequence variants in SLITRK1 are associated with Tourette's syndrome. Science 310:317–320
2. Achenbach TM (1991) Manual for the Child Behavior Checklist/4-18 and 1991 profile. Department of Psychiatry, University of Vermont, Burlington, VT
3. Acosta MT, Gioia GA, Silva AJ (2006) Neurofibromatosis type 1: new insights into neurocognitive issues. Curr Neurol Neurosci Rep. 6:136–143
4. Amir RE, Van den Veyver IB, Wan M, Tran CQ, Francke U, Zoghbi HY (1999) Rett syndrome is caused by mutations in X-linked MECP2, encoding methyl-CpG-binding protein 2. Nat Genet 23:185–188
5. Armstrong DD (2002) Neuropathology of Rett syndrome. Ment Retard Dev Disabil Res Rev 8:72–76
6. Attia J, Ioannidis JP, Thakkinstian A, McEvoy M, Scott RJ, Minelli C, Thompson J, Infante-Rivard C, Guyatt G (2009) How to use an article about genetic association. B: are the results of the study valid? JAMA 301:191–197
7. Bailey JA, Gu Z, Clark RA, Reinert K, Samonte RV, Schwartz S, Adams MD, Myers EW, Li PW, Eichler EE (2002) Recent segmental duplications in the human genome. Science 297:1003–1007
8. Ballas N, Lioy DT, Grunseich C, Mandel G (2009) Non-cell autonomous influence of MeCP2-deficient glia on neuronal dendritic morphology. Nat Neurosci 12:311–317
9. Banaschewski T, Becker K, Scherag S, Franke B, Coghill D (2010) Molecular genetics of attention-deficit/hyperactivity disorder: an overview. Eur Child Adolesc Psychiatry (this issue)
10. Baum AE, Akula N, Cabanero M, Cardona I, Corona W, Klemens B, Schulze TG, Cichon S, Rietschel M, Nöthen MM, Georgi A, Schumacher J, Schwarz M, Abou Jamra R, Höfels S, Propping P, Satagopan J, Detera-Wadleigh SD, Hardy J, McMahon FJ (2008) A genome-wide association study implicates diacylglycerol kinase eta (DGKH) and several other genes in the etiology of bipolar disorder. Mol Psychiatry 13:197–207
11. Ben-Shachar S, Chahrour M, Thaller C, Shaw CA, Zoghbi YH (2009) Mouse models of MeCP2 disorders share gene expression changes in the cerebellum and hypothalamus. Hum Mol Genet 18:2431–2442
12. Brendel C, Klahold E, Gärtner J, Huppke P (2009) Suppression of nonsense mutations in Rett Syndrome by aminoglycoside antibiotics. Pediatr Res 65:520–523
13. Brett D, Hanke J, Lehmann G, Haase S, Delbruck S, Krueger S, Reich J, Bork P (2000) EST comparison indicates 38% of human mRNAs contain possible alternative splice forms. FEBS Lett 474:83–86
14. Brunner HG, Ropers HH (1995) Specification of the phenotype required for men with monoamine oxidase type A deficiency. Reply to Hebebrand and Klug 1995. Hum Genet 96:374–375
15. Brunner HG, Nelen M, Breakefield XO, Ropers HH, van Oost BA (1993) Abnormal behavior associated with a point mutation in the structural gene for monoamine oxidase A. Science 262:578–580
16. Brunner HG, Nelen MR, van Zandvoort P, Abeling NG, van Gennip AH, Wolters EC, Kuiper MA, Ropers HH, van Oost BA (1993) X-linked borderline mental retardation with prominent behavioral disturbance: phenotype, genetic localization, and evidence for disturbed monoamine metabolism. Am J Hum Genet 52:1032–1039
17. Bucan M, Abrahams BS, Wang K, Glessner JT, Herman EI, Sonnenblick LI, Alvarez Retuerto AI, Imielinski M, Hadley D, Bradfield JP, Kim C, Gidaya NB, Lindquist I, Hutman T, Sigman M, Kustanovich V, Lajonchere CM, Singleton A, Kim J, Wassink TH, McMahon WM, Owley T, Sweeney JA, Coon H, Nurnberger JI, Li M, Cantor RM, Minshew NJ, Sutcliffe JS, Cook EH, Dawson G, Buxbaum JD, Grant SF, Schellenberg GD, Geschwind DH, Hakonarson H (2009) Genome-wide analyses of exonic copy number variants in a family-based study point to novel autism susceptibility genes. PLoS Genet 5:e1000536
18. Buitelaar JK (2005) ADHD: strategies to unravel its genetic architecture. J Neural Transm Suppl 69:1–17
19. Burmeister M, McInnis MG, Zöllner S (2008) Psychiatric genetics: progress amid controversy. Nat Rev Genet 9:527–540
20. Caspi A, McClay J, Moffitt TE, Mill J, Martin J, Craig IW, Taylor A, Poulton R (2002) Role of genotype in the cycle of violence in maltreated children. Science 297:851–854
21. Caspi A, Sugden K, Moffitt TE, Taylor A, Craig IW, Harrington H, McClay J, Mill J, Martin J, Braithwaite A, Poulton R (2003) Influence of life stress on depression: moderation by a polymorphism in the 5-HTT gene. Science 301:386–389
22. Chahrour M, Zoghbi HY (2007) The story of Rett syndrome: from neurobiology to clinic. Neuron 56:422–437
23. Chang Q, Khare G, Dani V, Nelson S, Jaenisch R (2006) The disease progression of Mecp2 mutant mice is affected by the level of BDNF expression. Neuron 49:341–348
24. Cheung J, Estivill X, Khaja R, MacDonald JR, Lau K, Tsui LC, Scherer SW (2003) Genome-wide detection of segmental duplications and potential assembly errors in the human genome sequence. Genome Biol 4:R25
25. Clifford CA, Murray RM, Fulker DW (1984) Genetic and environmental influences on obsessional traits and symptoms. Psychol Med 14:791–800
26. Cloninger CR, Przybeck TR, Svrakic DM (1991) The tridemisional personality questionnaire: U.S. normative data. Psychol Repl 69:1047–1057
27. Collins AL, Levenson JM, Vilaythong AP, Richman R, Armstrong DL, Noebels JL, David Sweatt J, Zoghbi HY (2004) Mild overexpression of MeCP2 causes a progressive neurological disorder in mice. Hum Mol Genet 13:2679–2689
28. Cook EH Jr, Scherer SW (2008) Copy-number variations associated with neuropsychiatric conditions. Nature 16:919–923
29. Costa PT, McCrae RR (1990) Personality disorders and the five-factor model of personality. J Pers Disord 4:362–371
30. DeBie P, Muller P, Wijmenga C, Klomp LW (2007) Molecular pathogenesis of Wilson and Menkes disease: correlation of mutations with molecular defects and disease phenotypes. J Med Genet 44:673–688
31. Devlin B, Roeder K, Wasserman L (2003) Analysis of multilocus models of association. Genet Epidemiol 25:36–47
32. Devys D, Lutz Y, Rouyer N, Bellocq JP, Mandel JL (1993) The FMR-1 protein is cytoplasmic, most abundant in neurons and appears normal in carriers of a fragile X premutation. Nat Genet 4:335–340
33. Eley TC, Bolton D, O'Connor TG, Perrin S, Smith P, Plomin R (2003) A twin study of anxiety-related behaviors in pre-school children. J Child Psychol Psyc 44:945–960
34. Elia J, Gai X, Xie HM, Perin JC, Geiger E, Glessner JT, D'arcy M, Deberardinis R, Frackelton E, Kim C, Lantieri F, Muganga BM, Wang L, Takeda T, Rappaport EF, Grant SF, Berrettini W,

Devoto M, Shaikh TH, Hakonarson H, White PS (2009) Rare structural variants found in attention-deficit hyperactivity disorder are preferentially associated with neurodevelopmental genes. Mol Psychiatry (Epub ahead of print)
35. Emes RD, Riley MC, Laukaitis CM, Goodstadt L, Karn RC, Ponting CP (2004) Comparative evolutionary genomics of androgen-binding protein genes. Genome Res 14:1516–1529
36. The ENCODE Project: ENCyclopedia Of DNA Elements. http://www.genome.gov/10005107. Accessed 2 Nov 2009
37. Eysenck HJ, Eysenck SBG, Barret P (1985) A revised version of the Psychoticism Scale. Pers Individ Dif 76:21–29
38. Falk CT, Rubinstein P (1987) Haplotype relative risks: an easy reliable way to construct a proper control sample for risk calculations. Ann Hum Genet 51:227–233
39. Farooqi IS, Bullmore E, Keogh J, Gillard J, O'Rahilly S, Fletcher PC (2007) Leptin regulates striatal regions and human eating behavior. Science 317:1355
40. Fenson L, Dale PS, Reznick JS (1993) MacArthur Communicative Development Inventories. Singular Publishing Group, San Diego, CA
41. Ferreira MA, O'Donovan MC, Meng YA, Jones IR, Ruderfer DM, Jones L, Fan J, Kirov G, Perlis RH, Green EK, Smoller JW, Grozeva D, Stone J, Nikolov I, Chambert K, Hamshere ML, Nimgaonkar VL, Moskvina V, Thase ME, Caesar S, Sachs GS, Franklin J, Gordon-Smith K, Ardlie KG, Gabriel SB, Fraser C, Blumenstiel B, Defelice M, Breen G, Gill M, Morris DW, Elkin A, Muir WJ, McGhee KA, Williamson R, MacIntyre DJ, MacLean AW, St CD, Robinson M, Van Beck M, Pereira AC, Kandaswamy R, McQuillin A, Collier DA, Bass NJ, Young AH, Lawrence J, Ferrier IN, Anjorin A, Farmer A, Curtis D, Scolnick EM, McGuffin P, Daly MJ, Corvin AP, Holmans PA, Blackwood DH, Gurling HM, Owen MJ, Purcell SM, Sklar P, Craddock N, Wellcome Trust Case Control Consortium (2008) Collaborative genome-wide association analysis supports a role for ANK3 and CACNA1C in bipolar disorder. Nat Genet 40:1056–1958
42. Feuk L, Macdonald JR, Tang T, Carson AR, Li M, Rao G, Khaja R, Scherer SW (2005) Discovery of human inversion polymorphisms by comparative analysis of human and chimpanzee DNA sequence assemblies. PLoS Genet 1:e56
43. Fickett JW, Wasserman WW (2000) Discovery and modeling of transcriptional regulatory regions. Curr Opin Biotechnol 11:19–24
44. Foley DL, Eaves LJ, Wormley B, Silberg JL, Maes HH, Kuhn J, Riley B (2004) Childhood adversity, monoamine oxidase a genotype, and risk for conduct disorder. Arch Gen Psychiatry 61:738–744
45. Fraga MF, Ballestar E, Paz MF, Ropero S, Setien F, Ballestar ML, Heine-Suner D, Cigudosa JC, Urioste M, Benitez J, Boix-Chornet M, Sanchez-Aguilera A, Ling C, Carlsson E, Poulsen P, Vaag A, Stephan Z, Spector TD, Wu YZ, Plass C, Esteller M (2005) Epigenetic differences arise during the lifetime of monozygotic twins. Proc Natl Acad Sci USA 102:10604–10609
46. Freitag CM, Rhode, LA, Lempp T, Romanos M (2010) Phenotypic and measurement influences on heritability estimates in childhood ADHD. Eur Child Adolesc Psychiatry (this issue)
47. Freitag CM, Staal W, Klauck SM, Duketis E, Waltes R (2010) Genetics of autistic disorders: review and clinical implications. Eur Child Adolesc Psychiaty (this issue)
48. Gabriel SB, Schaffner SF, Nguyen H, Moore JM, Roy J, Blumenstiel B, Higgins J, DeFelice M, Lochner A, Faggart M, Liu-Cordero SN, Rotimi C, Adeyemo A, Cooper R, Ward R, Lander ES, Daly MJ, Altshuler D (2002) The structure of haplotype blocks in the human genome. Science 296:2225–2229
49. Garner DM, Olmsted MP, Bohr Y, Garfinkel PE (1982) The eating attitudes test: psychometric features and clinical correlates. Psychol Med 12:871–878
50. Garner DM, Olmsted MP, Polivy J (1983) Development and validation of a multidimensional eating disorder inventory for anorexia nervosa and bulimia. Int J Eat Disord 2:15–34
51. Gelhorn HL, Stallings MC, Young SE, Corley RP, Rhee SH, Hewitt JK (2005) Genetic and environmental influences of conduct disorder: symptom, domain and full-scale analyses. J Child Psychol Psy 46:580–591
52. Glessner JT, Wang K, Cai G, Korvatska O, Kim CE, Wood S, Zhang H, Estes A, Brune CW, Bradfield JP, Imielinski M, Frackelton EC, Reichert J, Crawford EL, Munson J, Sleiman PM, Chiavacci R, Annaiah K, Thomas K, Hou C, Glaberson W, Flory J, Otieno F, Garris M, Soorya L, Klei L, Piven J, Meyer KJ, Anagnostou E, Sakurai T, Game RM, Rudd DS, Zurawiecki D, McDougle CJ, Davis LK, Miller J, Posey DJ, Michaels S, Kolevzon A, Silverman JM, Bernier R, Levy SE, Schultz RT, Dawson G, Owley T, McMahon WM, Wassink TH, Sweeney JA, Nurnberger JI, Coon H, Sutcliffe JS, Minshew NJ, Grant SF, Bucan M, Cook EH, Buxbaum JD, Devlin B, Schellenberg GD, Hakonarson H (2009) Autism genome-wide copy number variation reveals ubiquitin and neuronal genes. Nature 459:569–573
53. Goetghebuer T, Ota MO, Kebbeh B, John M, Jackson-Sillah D, Vekemans J, Marchant A, Newport M, Weiss HA (2003) Delay in motor development of twins in Africa: a prospective cohort study. Twin Res 6:279–284
54. Von Gontard A, Schaumburg H, Hollmann E, Eiberg H, Rittig S (2001) The genetics of enuresis: a review. J Urol 166:2438–2443
55. Goodstadt L, Ponting CP (2001) Sequence variation and disease in the wake of the draft human genome. Hum Mol Genet 10:2209–2214
56. Grant SF (2006) Variant of transcription factor 7-like 2 (TCF7L2) gene confers risk of type 2 diabetes. Nat Genet 38:320–323
57. Gudbjartsson DF, Walters GB, Thorleifsson G, Stefansson H, Halldorsson BV, Zusmanovich P, Sulem P, Thorlacius S, Gylfason A, Steinberg S, Helgadottir A, Ingason A, Steinthorsdottir V, Olafsdottir EJ, Olafsdottir GH, Jonsson T, Borch-Johnsen K, Hansen T, Andersen G, Jorgensen T, Pedersen O, Aben KK, Witjes JA, Swinkels DW, den Heijer M, Franke B, Verbeek AL, Becker DM, Yanek LR, Becker LC, Tryggvadottir L, Rafnar T, Gulcher J, Kiemeney LA, Kong A, Thorsteinsdottir U, Stefansson K (2008) Many sequence variants affecting diversity of adult human height. Nat Genet 40:609–615
58. Hagberg B, Aicardi J, Dias K, Ramos O (1983) A progressive syndrome of autism, dementia, ataxia, and loss of purposeful hand use in girls: Rett's syndrome: report of 35 cases. Ann Neurol 14:471–479
59. Hardy J, Singleton A (2009) Genomewide association studies and human disease. New Engl J Med 360:1759–1768
60. Harrison PM, Kumar A, Lang N, Snyder M, Gerstein M (2002) A question of size: the eukaryotic proteome and the problems in defining it. Nucleic Acids Res 30:1083–1090
61. Hashimoto K, Koizumi H, Nakazato M, Shimizu E, Iyo M (2005) Role of brain-derived neurotrophic factor in eating disorders: recent findings and its pathophysiological implications. Prog Neuropsychopharmacol Biol Psychiatry 29:499–504
62. Hebebrand J, Propping P (1990) Genetic aspects of brain maturation and behavior. In: Rothenberger A (ed) Brain and behavior in child psychiatry. Springer, Berlin, pp 79–105
63. Hebebrand J, Klug B (1995) Specification of the phenotype required for men with monoamine oxidase type A deficiency. Hum Genet 96:372–376
64. Heiser P, Friedel S, Dempfle A, Konrad K, Smidt J, Grabarkiewicz J, Herpertz-Dahlmann B, Remschmidt H, Hebebrand J (2004) Molecular genetic aspects of attention-deficit/hyperactivity disorder. Neurosci Biobehav R 28:625–641

65. Hindorff LA, Sethupathy P, Junkins HA, Ramos EM, Mehta JP, Collins FS, Manolio TA (2009) Potential etiologic and functional implications of genome-wide association loci for human diseases and traits. Proc Natl Acad Sci USA 106(23):9362–9367
66. Hindorff LA, Junkins HA, Mehta JP, Manolio TA. A catalog of published genome-wide association studies. http://www.genome.gov/26525384. Accessed 2 Nov 2009
67. Hinney A, Hebebrand J (2008) Polygenic obesity in humans. Obes Facts 1:35–42
68. Hinney A, Vogel CI, Hebebrand J (2010) From monogenic to polygenic obesity: recent advances. Eur Child Adolesc Psychiatry (this issue)
69. Hirschhorn JN, Lettre G (2009) Progress in genome-wide association studies of human height. Horm Res 71(S2):5–131
70. Hite KC, Adams VH, Hansen JC (2009) Recent advances in MeCP2 structure and function. Biochem Cell Biol 87:219–227
71. Hudziak JJ, Van Beijsterveldt CE, Althoff RR, Stanger C, Rettew DC, Nelson EC, Todd RD, Bartels M, Boomsma DI (2004) Genetic and environmental contributions to the child behavior checklist obsessive–compulsive scale: a cross-cultural twin study. Arch Gen Psychiatry 61:608–616
72. Hugot JP, Chamaillard M, Zouali H, Lesage S, Cézard JP, Belaiche J, Almer S, Tysk C, O'Morain CA, Gassull M, Binder V, Finkel Y, Cortot A, Modigliani R, Laurent-Puig P, Gower-Rousseau C, Macry J, Colombel JF, Sahbatou M, Thomas G (2001) Association of NOD2 leucine-rich repeat variants with susceptibility to Crohn's disease. Nature 411:599–603
73. Van Hulle CA, Goldsmith HH, Lemery KS (2004) Genetic, environmental, and gender effects on individual differences in toddler expressive language. J Speech Lang Hear Res 47:904–912
74. Human Epigenome Project. http://www.epigenome.org/. Accessed 2 Nov 2009
75. Huntington's Disease Collaborative Research Group (1993) A novel gene containing a trinucleotide repeat that is expanded and unstable on Huntington's disease chromosomes. Cell 72:971–983
76. Iles MM (2008) What can genome-wide association studies tell us about the genetics of common disease? PLoS Genet 4:e33
77. International HapMap Project. http://www.hapmap.org/index.html.en. Accessed 2 Nov 2009
78. International Human Genome Sequencing Consortium (2001) Initial sequencing and analysis of the human genome. Nature 409:860–921
79. International Human Genome Sequencing Consortium (2004) Finishing the euchromatic sequence of the human genome. Nature 431:931–945
80. International Schizophrenia Consortium, Purcell SM, Wray NR, Stone JL, Visscher PM, O'Donovan MC, Sullivan PF, Sklar P (2009) Common polygenic variation contributes to risk of schizophrenia and bipolar disorder. Nature 460:748–752
81. International SNP Map Working Group (2001) A map of human genome sequence variation containing 1.42 million single nucleotide polymorphisms. Nature 409:928–933
82. Jang KL, Livesley WJ, Vernon PA (1996) Heritability of the big five personality dimensions and their facets: a twin study. J Pers 64:577–591
83. Jinnah HA (2009) Lesch-Nyhan disease: from mechanism to model and back again. Dis Models Mech 2:116–121
84. Kazantsev AG, Thompson LM (2008) Therapeutic application of histone deacetylase inhibitors for central nervous system disorders. Nat Rev Drug Discov 7:854–868
85. Keller MC, Coventry WL, Heath AC, Martin NG (2005) Widespread evidence for non-additive genetic variation in Cloninger's and Eysenck's personality dimensions using a twin plus sibling design. Behav Genet 35:707–721
86. Kendler KS (2005) "A gene for": the nature of gene action in psychiatric disorders. Am J Psychiat 162:1243–1252
87. Khoury MJ, Bertram L, Boffetta P, Butterworth AS, Chanock SJ, Dolan SM, Fortier I, Garcia-Closas M, Gwinn M, Higgins JP, Janssens AC, Ostell J, Owen RP, Pagon RA, Rebbeck TR, Rothman N, Bernstein JL, Burton PR, Campbell H, Chockalingam A, Furberg H, Little J, O'Brien TR, Seminara D, Vineis P, Winn DM, Yu W, Ioannidis JP (2009) Genome-wide association studies, field synopses, and the development of the knowledge base on genetic variation and human diseases. Am J Epidemiol 170:269–279
88. Kidd JM, Cooper GM, Donahue WF, Hayden HS, Sampas N, Graves T, Hansen N, Teague B, Alkan C, Antonacci F, Haugen E, Zerr T, Yamada NA, Tsang P, Newman TL, Tüzün E, Cheng Z, Ebling HM, Tusneem N, David R, Gillett W, Phelps KA, Weaver M, Saranga D, Brand A, Tao W, Gustafson E, McKernan K, Chen L, Malig M, Smith JD, Korn JM, McCarroll SA, Altshuler DA, Peiffer DA, Dorschner M, Stamatoyannopoulos J, Schwartz D, Nickerson DA, Mullikin JC, Wilson RK, Bruhn L, Olson MV, Kaul R, Smith DR, Eichler EE (2008) Mapping and sequencing of structural variation from eight human genomes. Nature 453:56–64
89. Kupper LL, Palmer LJ (2002) Matching. In: Elston RC, Olson J, Palmer LJ (eds) Biostatistical genetics and genetic epidemiology. Wiley, Chichester, pp 518–523
90. Lander E, Schork N (1994) Genetic dissection of complex traits. Science 265:2037–2048
91. Leckman JF, Vaccarino FM, Lambroso PJ (2007) From genes to brain: developmental neurobiology. In: Martin A, Volkmar FR (eds) Lewis's child and adolescent psychiatry. Lippincott Williams & Wilkins, Philadelphia, pp 177–188
92. Lein ES, Hawrylycz MJ, Ao N, Ayres M, Bensinger A, Bernard A, Boe AF, Boguski MS, Brockway KS, Byrnes EJ, Chen L, Chen L, Chen TM, Chin MC, Chong J, Crook BE, Czaplinska A, Dang CN, Datta S, Dee NR, Desaki AL, Desta T, Diep E, Dolbeare TA, Donelan MJ, Dong HW, Dougherty JG, Duncan BJ, Ebbert AJ, Eichele G, Estin LK, Faber C, Facer BA, Fields R, Fischer SR, Fliss TP, Frensley C, Gates SN, Glattfelder KJ, Halverson KR, Hart MR, Hohmann JG, Howell MP, Jeung DP, Johnson RA, Karr PT, Kawal R, Kidney JM, Knapik RH, Kuan CL, Lake JH, Laramee AR, Larsen KD, Lau C, Lemon TA, Liang AJ, Liu Y, Luong LT, Michaels J, Morgan JJ, Morgan RJ, Mortrud MT, Mosqueda NF, Ng LL, Ng R, Orta GJ, Overly CC, Pak TH, Parry SE, Pathak SD, Pearson OC, Puchalski RB, Riley ZL, Rockett HR, Rowland SA, Royall JJ, Ruiz MJ, Sarno NR, Schaffnit K, Shapovalova NV, Sivisay T, Slaughterbeck CR, Smith SC, Smith KA, Smith BI, Sodt AJ, Stewart NN, Stumpf KR, Sunkin SM, Sutram M, Tam A, Teemer CD, Thaller C, Thompson CL, Varnam LR, Visel A, Whitlock RM, Wohnoutka PE, Wolkey CK, Wong VY, Wood M, Yaylaoglu MB, Young RC, Youngstrom BL, Yuan XF, Zhang B, Zwingman TA, Jones AR (2007) Genome-wide atlas of gene expression in the adult mouse brain. Nature 445:168–176
93. Lejeune J, Gautier M, Turpin R (1959) Étude des chromosomes somatiques de neuf enfants mongoliens. C R Hebd Seances Acad Sci 248:1721–1722
94. Lejeune J, Lafourcade J, Berger R, Vialatte J, Boeswillwald M, Seringe P, Tuppin R (1963) 3 cases of partial deletion of the short arm of a 5 chromosome. C R Hebd Seances Acad Sci 257:3098–3102
95. Lencz T, Morgan TV, Athanasiou M, Dain B, Reed CR, Kane JM, Kucherlapati R, Malhotra AK (2007) Converging evidence for a pseudoautosomal cytokine receptor gene locus in Schizophrenia. Mol Psychiatry 12:572–580
96. Levy S, Sutton G, Ng PC, Feuk L, Halpern AL, Walenz BP, Axelrod N, Huang J, Kirkness EF, Denisov G, Lin Y,

MacDonald JR, Pang AW, Shago M, Stockwell TB, Tsiamouri A, Bafna V, Bansal V, Kravitz SA, Busam DA, Beeson KY, McIntosh TC, Remington KA, Abril JF, Gill J, Borman J, Rogers YH, Frazier ME, Scherer SW, Strausberg RL, Venter JC (2007) The diploid genome sequence of an individual human. PLoS Biol 5:e254

97. Lewis JC, Thomas HV, Murphy KC, Sampson JR (2004) Genotype and psychological phenotype in tuberous sclerosis. J Med Genet 41:203–207
98. Li H, Yamagata T, Mori M, Yasuhara A, Momoi MY (2005) Mutation analysis of methyl-CpG binding protein family genes in autistic patients. Brain Dev 27:321–325
99. Little J, Higgins JP, Ioannidis JP, Moher D, Gagnon F, von Elm E, Khoury MJ, Cohen B, Davey-Smith G, Grimshaw J, Scheet P, Gwinn M, Williamson RE, Zou GY, Hutchings K, Johnson CY, Tait V, Wiens M, Golding J, van Duijn C, McLaughlin J, Paterson A, Wells G, Fortier I, Freedman M, Zecevic M, King R, Infante-Rivard C, Stewart A, Birkett N (2009) Strengthening the reporting of genetic association studies (STREGA): an extension of the STROBE statement. Eur J Epidemiol 24:37–55
100. Loat CS, Curran S, Lewis CM, Duvall J, Geschwind D, Bolton P, Craig IW (2008) Methyl-CpG-binding protein 2 polymorphisms and vulnerability to autism. Genes Brain Behav 7:754–760
101. Luikenhuis S, Giacometti E, Beard CF, Jaenisch R (2004) Expression of MeCP2 in postmitotic neurons rescues Rett syndrome in mice. Proc Natl Acad Sci USA 101:6033–6038
102. Maezawa I, Swanberg SD, Harvey D, LaSalle JM, Jin LW (2009) Rett syndrome astrocytes are abnormal and spread MeCP2 deficiency through gap junctions. J Neurosci 29:505150–505161
103. Manolio TA, Brooks LD, Collins FS (2008) A HapMap harvest of insights into the genetics of common disease. J Clin Invest 118:1590–1605
104. Margallo-Lana M, Morris CM, Gibson AM, Tan AL, Kay DW, Tyrer SP, Moore BP, Ballard CG (2004) Influence of the amyloid precursor protein locus on dementia in Down syndrome. Neurology 62:1996–1998
105. Margulies M, Egholm M, Altman WE, Attiya S, Bader JS, Bemben LA, Berka J, MS, Chen YJ, Chen Z, Dewell SB, Du L, Fierro JM, Gomes XV, Godwin BC, He W, Helgesen S, Ho CH, Irzyk GP, Jando SC, Alenquer ML, Jarvie TP, Jirage KB, Kim JB, Knight JR, Lanza JR, Leamon JH, Lefkowitz SM, Lei M, Li J, Lohman KL, Lu H, Makhijani VB, McDade KE, McKenna MP, Myers EW, Nickerson E, Nobile JR, Plant R, Puc BP, Ronan MT, Roth GT, Sarkis GJ, Simons JF, Simpson JW, Srinivasan M, Tartaro KR, Tomasz A, Vogt KA, Volkmer GA, Wang SH, Wang Y, Weiner MP, Yu P, Begley RF, Rothberg JM (2005) Genome sequencing in microfabricated high-density picolitre reactors. Nature 437:376–380
106. McGrath LM, Smith SD, Pennington BF (2006) Breakthroughs in the search for dyslexia candidate genes. Trends Mol Med 12:333–1341
107. McMullan DJ, Bonin M, Hehir-Kwa JY, de Vries BB, Dufke A, Rattenberry E, Steehouwer M, Moruz L, Pfundt R, de Leeuw N, Riess A, Altug-Teber O, Enders H, Singer S, Grasshoff U, Walter M, Walker JM, Lamb CV, Davison EV, Brueton L, Riess O, Veltman JA (2009) Molecular karyotyping of patients with unexplained mental retardation by SNP arrays: a multicenter study. Hum Mutat 30:1082–1092
108. Mehan MR, Freimer NB, Ophoff RA (2004) A genome-wide survey of segmental duplications that mediate common human genetic variation of chromosomal architecture. Hum Genomics 1:335–344
109. Meyer HE (2009) HUPO Brain Proteome Project. http://www.hbpp.org/5602.html. Accessed 2 Nov 2009
110. Miki Y, Swensen J, Shattuck-Eidens D, Futreal PA, Harshman K, Tavtigian S, Liu Q, Cochran C, Bennett LM, Ding W (1994) A strong candidate for the breast and ovarian cancer susceptibility gene BRCA1. Science 266:66–71
111. Mironov AA, Fickett JW, Gelfand MS (1999) Frequent alternative splicing of human genes. Genome Res 9:1288–1293
112. Modrek B, Lee C (2002) A genomic view of alternative splicing. Nat Genet 30:13–19
113. Moretti P, Bouwknecht JA, Teague R, Paylor R, Zoghbi HY (2005) Abnormalities of social interactions and home-cage behavior in a mouse model of Rett syndrome. Hum Mol Genet 14:205–220
114. Morton NE (1998) Significance levels in complex inheritance. Am J Hum Genet 62:690–697
115. Mouse Genome Sequencing Consortium (2002) Initial sequencing and comparative analysis of the mouse genome. Nature 420:520–562
116. Nahon JL (2003) Birth of 'human-specific' genes during primate evolution. Genetica 118:193–208
117. National Research Council (1988) Mapping and sequencing the human genome. National Academy Press, Washington, DC. http://www.hugo-international.org/
118. O'Donovan MC, Craddock N, Norton N, Williams H, Peirce T, Moskvina V, Nikolov I, Hamshere M, Carroll L, Georgieva L, Dwyer S, Holmans P, Marchini JL, Spencer CC, Howie B, Leung HT, Hartmann AM, Möller HJ, Morris DW, Shi Y, Feng G, Hoffmann P, Propping P, Vasilescu C, Maier W, Rietschel M, Zammit S, Schumacher J, Quinn EM, Schulze TG, Williams NM, Giegling I, Iwata N, Ikeda M, Darvasi A, Shifman S, He L, Duan J, Sanders AR, Levinson DF, Gejman PV, Cichon S, Nöthen MM, Gill M, Corvin A, Rujescu D, Kirov G, Owen MJ, Buccola NG, Mowry BJ, Freedman R, Amin F, Black DW, Silverman JM, Byerley WF, Cloninger CR, Molecular Genetics of Schizophrenia Collaboration (2008) Identification of loci associated with schizophrenia by genome-wide association and follow-up. Nat Genet 40:1053–1055
119. Ogura Y, Bonen DK, Inohara N, Nicolae DL, Chen FF, Ramos R, Britton H, Moran T, Karaliuskas R, Duerr RH, Achkar JP, Brant SR, Bayless TM, Kirschner BS, Hanauer SB, Nuñez G, Cho JH (2001) A frameshift mutation in NOD2 associated with susceptibility to Crohn's disease. Nature 411:603–606
120. Ong KK, Elks CE, Li S, Zhao JH, Luan J, Andersen LB, Bingham SA, Brage S, Smith GD, Ekelund U, Gillson CJ, Glaser B, Golding J, Hardy R, Khaw KT, Kuh D, Luben R, Marcus M, McGeehin MA, Ness AR, Northstone K, Ring SM, Rubin C, Sims MA, Song K, Strachan DP, Vollenweider P, Waeber G, Waterworth DM, Wong A, Deloukas P, Barroso I, Mooser V, Loos RJ, Wareham NJ (2009) Genetic variation in LIN28B is associated with the timing of puberty. Nat Genet May 17 [Epub ahead of print]
121. Pavlicek A, Noskov VN, Kouprina N, Barrett JC, Jurka J, Larionov V (2004) Evolution of the tumor suppressor BRCA1 locus in primates: implications for cancer predisposition. Hum Mol Genet 13:2737–2751
122. Pennisi E (2007) Breakthrough of the year. Human genetic variation. Science 318:1842–1843
123. Peter I, Vainder M, Livshits G (1999) Genetic analysis of motor milestones attainment in early childhood. Twin Res 2:1–9
124. Plomin R (2005) Finding genes in child psychology and psychiatry: when are we going to be there? J Child Psychol Psychiatry 46:1030–1038
125. Plomin R, Daniels D (1987) Why are children in the same family so different from each other? Behav Brain Sci 10:1–16
126. Pritchard JK, Rosenberg NA (1999) Use of unlinked genetic markers to detect population stratification in association studies. Am J Hum Genet 65:220–228

127. Reichwald K, Thiesen J, Wiehe T, Weitzel J, Stratling WH, Kioschis P, Poustka A, Rosenthal A, Platzer M (2000) Comparative sequence analysis of the MECP2-locus in human and mouse reveals new transcribed regions. Mamm Genome 11:182–190
128. Rett A (1966) On a unusual brain atrophy syndrome in hyperammonemia in childhood. Wien Med Wochenschr 116:723–726
129. Risch NJ (2000) Searching for genetic determinants in the new millennium. Nature 405:847–856
130. Risch N, Merikangas K (1996) The future of genetic studies of complex human diseases. Science 273:1516–1517
131. Risch N, Herrell R, Lehner T, Liang KY, Eaves L, Hoh J, Griem A, Kovacs M, Ott J, Merikangas KR (2009) Interaction between the serotonin transporter gene (5-HTTLPR), stressful life events, and risk of depression: a meta-analysis. JAMA 301:2462–2471
132. Roest Crollius H, Jaillon O, Bernot A, Dasilva C, Bouneau L, Fischer C, Fizames C, Wincker P, Brottier P, Quetier F, Saurin W, Weissenbach J (2000) Estimate of human gene number provided by genome-wide analysis using Tetraodon nigroviridis DNA sequence. Nat Genet 25:235–238
133. Rommelse N, Franke B, Geurts HM, Hartman CS, Buitelaar JK (2010) Shared heritability of attention-deficit/hyperactivity disorder and autism spectrum disorder: a review. Eur Child Adolesc Psychiatry (this issue)
134. Rutherford J, McGuffin P, Katz RJ, Murray RM (1993) Genetic influences on eating attitudes in a normal female twin pair population. Psychol Med 23:425–436
135. Sabeti PC, Reich DE, Higgins JM, Levine HZ, Richter DJ, Schaffner SF, Gabriel SB, Platko JV, Patterson NJ, McDonald GJ, Ackerman HC, Campbell SJ, Altshuler D, Cooper R, Kwiatkowski D, Ward R, Lander ES (2002) Detecting recent positive selection in the human genome from haplotype structure. Nature 419:832–827
136. Samaco RC, Nagarajan RP, Braunschweig D, LaSalle JM (2004) Multiple pathways regulate MeCP2 expression in normal brain development and exhibit defects in autism-spectrum disorders. Hum Mol Genet 13:629–639
137. Samaco RC, Hogart A, LaSalle JM (2005) Epigenetic overlap in autism-spectrum neurodevelopmental disorders: MECP2 deficiency causes reduced expression of UBE3A and GABRB3. Hum Mol Genet 14:483–492
138. Samaco RC, Fryer JD, Ren J, Fyffe S, Chao HT, Sun Y, Greer JJ, Zoghbi HY, Neul JL (2008) A partial loss of function allele of methyl-CpG-binding protein 2 predicts a human neurodevelopmental syndrome. Hum Mol Genet 17:1718–1727
139. Santangelo SL, Tsatsanis K (2005) What is known about autism: genes, brain, and behaviour. Am J Pharmacogenomics 5:71–92
140. Saunders CL, Chiodini BD, Sham P, Lewis CM, Abkevich V, Adeyemo AA, de Andrade M, Arya R, Berenson GS, Blangero J, Boehnke M, Borecki IB, Chagnon YC, Chen W, Comuzzie AG, Deng HW, Duggirala R, Feitosa MF, Froguel P, Hanson RL, Hebebrand J, Huezo-Dias P, Kissebah AH, Li W, Luke A, Martin LJ, Nash M, Ohman M, Palmer LJ, Peltonen L, Perola M, Price RA, Redline S, Srinivasan SR, Stern MP, Stone S, Stringham H, Turner S, Wijmenga C, Collier DA (2007) Meta-analysis of genome-wide linkage studies in BMI and obesity. Obesity 15:2263–2275
141. Scherag S, Hebebrand J, Hinney A (2010) Eating disorders: the current status of molecular genetic research. Eur Child Adolesc Psychiatry (this issue)
142. Schormair B, Kemlink D, Roeske D, Eckstein G, Xiong L, Lichtner P, Ripke S, Trenkwalder C, Zimprich A, Stiasny-Kolster K, Oertel W, Bachmann CG, Paulus W, Högl B, Frauscher B, Gschliesser V, Poewe W, Peglau I, Vodicka P, Vávrová J, Sonka K, Nevsimalova S, Montplaisir J, Turecki G, Rouleau G, Gieger C, Illig T, Wichmann HE, Holsboer F, Müller-Myhsok B, Meitinger T, Winkelmann J (2008) PTPRD (protein tyrosine phosphatase receptor type delta) is associated with restless legs syndrome. Nat Genet 40:946–948
143. Schulte-Körne G, Scerri TS (2010) Genetics of developmental dyslexia. Eur Child Adolesc Psychiatry (this issue)
144. Scriver CR (2007) The PAH gene, phenylketonuria, and a paradigm shift. Hum Mutat 28:831–845
145. Sebat J, Lakshmi B, Troge J, Alexander J, Young J, Lundin P, Månér S, Massa H, Walker M, Chi M, Navin N, Lucito R, Healy J, Hicks J, Ye K, Reiner A, Gilliam TC, Trask B, Patterson N, Zetterberg A, Wigler M (2004) Large-scale copy number polymorphism in the human genome. Science 305:525–528
146. Shahbazian MD, Antalffy B, Armstrong DL, Zoghbi HY (2002) Insight into Rett syndrome: MeCP2 levels display tissue- and cell-specific differences and correlate with neuronal maturation. Hum Mol Genet 11:115–124
147. Shi J, Levinson DF, Duan J, Sanders AR, Zheng Y, Pe'er I, Dudbridge F, Holmans PA, Whittemore AS, Mowry BJ, Olincy A, Amin F, Cloninger CR, Silverman JM, Buccola NG, Byerley WF, Black DW, Crowe RR, Oksenberg JR, Mirel DB, Kendler KS, Freedman R, Gejman PV (2009) Common variants on chromosome 6p22.1 are associated with schizophrenia. Nature 460:753–757
148. Single Nucleotide Polymorphism. RELEASE: NCBI dbSNP Build 130. http://www.ncbi.nlm.nih.gov/projects/SNP/snp_summary.cgi. Accessed 2 Nov 2009
149. Smoller JW, Finn CT (2003) Family, twin, and adoption studies of bipolar disorder. Am J Med Genet C Semin Med Genet 123C:48–58
150. Spielman RS, McGinnis RE, Ewens WJ (1993) Transmission test for linkage disequilibrium: the insulin gene region and insulin-dependent diabetes mellitus (IDDM). Am J Hum Genet 52:506–516
151. Stamm S (2002) Signals and their transduction pathways regulating alternative splicing: a new dimension of the human genome. Hum Mol Genet 11:2409–2416
152. Stefansson H, Rye DB, Hicks A, Petursson H, Ingason A, Thorgeirsson TE, Palsson S, Sigmundsson T, Sigurdsson AP, Eiriksdottir I, Soebech E, Bliwise D, Beck JM, Rosen A, Waddy S, Trotti LM, Iranzo A, Thambisetty M, Hardarson GA, Kristjansson K, Gudmundsson LJ, Thorsteinsdottir U, Kong A, Gulcher JR, Gudbjartsson D, Stefansson K (2007) A genetic risk factor for periodic limb movements in sleep. New Engl J Med 357:639–647
153. Stefansson H, Rujescu D, Cichon S, Pietiläinen OP, Ingason A, Steinberg S, Fossdal R, Sigurdsson E, Sigmundsson T, Buizer-Voskamp JE, Hansen T, Jakobsen KD, Muglia P, Francks C, Matthews PM, Gylfason A, Halldorsson BV, Gudbjartsson D, Thorgeirsson TE, Sigurdsson A, Jonasdottir A, Jonasdottir A, Bjornsson A, Mattiasdottir S, Blondal T, Haraldsson M, Magnusdottir BB, Giegling I, Möller HJ, Hartmann A, Shianna KV, Ge D, Need AC, Crombie C, Fraser G, Walker N, Lonnqvist J, Suvisaari J, Tuulio-Henriksson A, Paunio T, Toulopoulou T, Bramon E, Di Forti M, Murray R, Ruggeri M, Vassos E, Tosato S, Walshe M, Li T, Vasilescu C, Mühleisen TW, Wang AG, Ullum H, Djurovic S, Melle I, Olesen J, Kiemeney LA, Franke B, GROUP, Sabatti C, Freimer NB, Gulcher JR, Thorsteinsdottir U, Kong A, Andreassen OA, Ophoff RA, Georgi A, Rietschel M, Werge T, Petursson H, Goldstein DB, Nöthen MM, Peltonen L, Collier DA, St Clair D, Stefansson K (2008) Large recurrent microdeletions associated with schizophrenia. Nature 455:232–236
154. Stefansson H, Ophoff RA, Steinberg S, Andreassen OA, Cichon S, Rujescu D, Werge T, Pietiläinen OP, Mors O, Mortensen PB, Sigurdsson E, Gustafsson O, Nyegaard M, Tuulio-Henriksson A, Ingason A, Hansen T, Suvisaari J, Lonnqvist J, Paunio T,

Børglum AD, Hartmann A, Fink-Jensen A, Nordentoft M, Hougaard D, Norgaard-Pedersen B, Böttcher Y, Olesen J, Breuer R, Möller HJ, Giegling I, Rasmussen HB, Timm S, Mattheisen M, Bitter I, Réthelyi JM, Magnusdottir BB, Sigmundsson T, Olason P, Masson G, Gulcher JR, Haraldsson M, Fossdal R, Thorgeirsson TE, Thorsteinsdottir U, Ruggeri M, Tosato S, Franke B, Strengman E, Kiemeney LA, Genetic Risk Outcome in Psychosis (GROUP), Melle I, Djurovic S, Abramova L, Kaleda V, Sanjuan J, de Frutos R, Bramon E, Vassos E, Fraser G, Ettinger U, Picchioni M, Walker N, Toulopoulou T, Need AC, Ge D, Yoon JL, Shianna KV, Freimer NB, Cantor RM, Murray R, Kong A, Golimbet V, Carracedo A, Arango C, Costas J, Jönsson EG, Terenius L, Agartz I, Petursson H, Nöthen MM, Rietschel M, Matthews PM, Muglia P, Peltonen L, St Clair D, Goldstein DB, Stefansson K, Collier DA (2009) Common variants conferring risk of schizophrenia. Nature 460:744–747

155. Steinle NI, Hsueh WC, Snitker S, Pollin TI, Sakul H, StJean PL, Bell CJ, Mitchell BD, Shuldiner AR (2002) Eating behavior in the old order Amish: heritability analysis and a genome-wide linkage analysis. Am J Clin Nutr 75:1098–1106
156. Stolberg S (1993) Scientists discover gene linked to aggressive behavior in humans. The Tech 113. http://tech.mit.edu/V113/N51/agression.51w.html. Accessed 2 Nov 2009
157. Stunkard AJ, Messick S (1985) The three-factor eating questionnaire to measure dietary restraint, disinhibition and hunger. J Psychosom Res 29:71–83
158. Sulem P, Gudbjartsson DF, Rafnar T, Holm H, Olafsdottir EJ, Olafsdottir GH, Jonsson T, Alexandersen P, Feenstra B, Boyd HA, Aben KK, Verbeek AL, Roeleveld N, Jonasdottir A, Styrkarsdottir U, Steinthorsdottir V, Karason A, Stacey SN, Gudmundsson J, Jakobsdottir M, Thorleifsson G, Hardarson G, Gulcher J, Kong A, Kiemeney LA, Melbye M, Christiansen C, Tryggvadottir L, Thorsteinsdottir U, Stefansson K (2009) Genome-wide association study identifies sequence variants on 6q21 associated with age at menarche. Nat Genet May 17 [Epub ahead of print]
159. Sullivan PF, Neale MC, Kendler KS (2000) Genetic epidemiology of major depression: review and meta-analysis. Am J Psychiatry 157:1552–1562
160. Sullivan PF, Kendler KS, Neale MC (2003) Schizophrenia as a complex trait: evidence from a meta-analysis of twin studies. Arch Gen Psychiatry 60:1187–1192
161. Terwilliger J, Ott J (1992) A haplotype-based 'haplotype relative risk' approach to detecting allelic associations. Hum Hered 42:337–346
162. 1000 Genomes Project Data Release. http://www.1000genomes.org/page.php. Accessed 2 Nov 2009
163. Tropea D, Giacometti E, Wilson NR, Beard C, McCurry C, Fu DD, Flannery R, Jaenisch R, Sur M (2009) Partial reversal of Rett syndrome-like symptoms in MeCP2 mutant mice. Proc Natl Acad Sci USA. 106(6):2029–2034
164. Tsuang DW, Faraone SV (2001) Tsuang MT genetic counseling for psychiatric disorders. Curr Psychiatry Rep 3:138–143
165. Urdinguio RG, Lopez-Serra L, Lopez-Nieva P, Alaminos M, Diaz-Uriarte R, Fernandez AF, Esteller M (2008) Mecp2-null mice provide new neuronal targets for Rett syndrome. PLoS One 3:e3669
166. Venter JC, Adams MD, Myers EW, Li PW, Mural RJ, Sutton GG, Smith HO, Yandell M, Evans CA, Holt RA, Gocayne JD, Amanatides P, Ballew RM, Huson DH, Wortman JR, Zhang Q, Kodira CD, Zheng XH, Chen L, Skupski M, Subramanian G, Thomas PD, Zhang J et al (2001) The sequence of the human genome. Science 291:1304–1351
167. Walitza S, Wendland JR, Gruenblatt E, Warnke A, Sontag TA, Tucha O, Lange KW (2010) Genetics of early-onset obsessive-compulsive disorder. Eur Child Adolesc Psychiatry (this issue)
168. Walker FO (2007) Huntington's disease. Lancet 369:218–228
169. Wang J, Wang W, Li R, Li Y, Tian G, Goodman L, Fan W, Zhang J, Li J, Zhang J, Guo Y, Feng B, Li H, Lu Y, Fang X, Liang H, Du Z, Li D, Zhao Y, Hu Y, Yang Z, Zheng H, Hellmann I, Inouye M, Pool J, Yi X, Zhao J, Duan J, Zhou Y, Qin J, Ma L, Li G, Yang Z, Zhang G, Yang B, Yu C, Liang F et al (2008) The diploid genome sequence of an Asian individual. Nature 456:60–65
170. Wang K, Zhang H, Ma D, Bucan M, Glessner JT, Abrahams BS, Salyakina D, Imielinski M, Bradfield JP, Sleiman PM, Kim CE, Hou C, Frackelton E, Chiavacci R, Takahashi N, Sakurai T, Rappaport E, Lajonchere CM, Munson J, Estes A, Korvatska O, Piven J, Sonnenblick LI, Alvarez Retuerto AI, Herman EI, Dong H, Hutman T, Sigman M, Ozonoff S, Klin A, Owley T, Sweeney JA, Brune CW, Cantor RM, Bernier R, Gilbert JR, Cuccaro ML, McMahon WM, Miller J, State MW, Wassink TH, Coon H, Levy SE, Schultz RT, Nurnberger JI, Haines JL, Sutcliffe JS, Cook EH, Minshew NJ, Buxbaum JD, Dawson G, Grant SF, Geschwind DH, Pericak-Vance MA, Schellenberg GD, Hakonarson H (2009) Common genetic variants on 5p14.1 associate with autism spectrum disorders. Nature 459:528–533
171. Watson JD, Crick FH (1953) Molecular structure of nucleic acids; a structure for deoxyribose nucleic acid. Nature 171:737–738
172. Weiss LA, Shen Y, Korn JM, Arking DE, Miller DT, Fossdal R, Saemundsen E, Stefansson H, Ferreira MA, Green T, Platt OS, Ruderfer DM, Walsh CA, Altshuler D, Chakravarti A, Tanzi RE, Stefansson K, Santangelo SL, Gusella JF, Sklar P, Wu BL, Daly MJ (2008) Autism consortium. Association between microdeletion and microduplication at 16p11.2 and autism. New Engl J Med 358:667–675
173. Wellcome Trust Case Control Consortium (2007) Genome-wide association study of 14,000 cases of seven common diseases and 3,000 shared controls. Nature 447:661–678
174. Wermter AK, Laucht M, Schimmelmann B, Banaschewski T, Sonuga-Barke E, Rietschel M, Becker K (2010) From nature versus nurture to nature and nurture: gene × environment interactions in mental disorder—a selective review. Eur Child Adolesc Psychiatry (this issue)
175. Willer CJ, Speliotes EK, Loos RJ, Li S, Lindgren CM, Heid IM, Berndt SI, Elliott AL, Jackson AU, Lamina C, Lettre G, Lim N, Lyon HN, McCarroll SA, Papadakis K, Qi L, Randall JC, Roccasecca RM, Sanna S, Scheet P, Weedon MN, Wheeler E, Zhao JH, Jacobs LC, Prokopenko I, Soranzo N, Tanaka T, Timpson NJ, Almgren P, Bennett A, Bergman RN, Bingham SA, Bonnycastle LL, Brown M, Burtt NP, Chines P, Coin L, Collins FS, Connell JM, Cooper C, Smith GD, Dennison EM, Deodhar P, Elliott P, Erdos MR, Estrada K, Evans DM, Gianniny L, Gieger C, Gillson CJ, Guiducci C, Hackett R, Hadley D, Hall AS, Havulinna AS, Hebebrand J, Hofman A, Isomaa B, Jacobs KB, Johnson T, Jousilahti P, Jovanovic Z, Khaw KT, Kraft P et al (2009) Six new loci associated with body mass index highlight a neuronal influence on body weight regulation. Nat Genet 41:25–34
176. Winkelmann J, Schormair B, Lichtner P, Ripke S, Xiong L, Jalilzadeh S, Fulda S, Pütz B, Eckstein G, Hauk S, Trenkwalder C, Zimprich A, Stiasny-Kolster K, Oertel W, Bachmann CG, Paulus W, Peglau I, Eisensehr I, Montplaisir J, Turecki G, Rouleau G, Gieger C, Illig T, Wichmann HE, Holsboer F, Müller-Myhsok B, Meitinger T (2007) Genome-wide association study of restless legs syndrome identifies common variants in three genomic regions. Nat Genet 39:1000–1006
177. Wooster R, Bignell G, Lancaster J, Swift S, Seal S, Mangion J, Collins N, Gregory S, Gumbs C, Micklem G (1995) Identification of the breast cancer susceptibility gene BRCA2. Nature 378:789–792

178. Yasui DH, Peddada S, Bieda MC, Vallero RO, Hogart A, Nagarajan RP, Thatcher KN, Farnham PJ, Lasalle JM (2007) Integrated epigenomic analyses of neuronal MeCP2 reveal a role for long-range interaction with active genes. Proc Natl Acad Sci USA 104:19416–19421
179. Zhou K, Dempfle A, Arcos-Burgos M, Bakker SC, Banaschewski T, Biederman J, Buitelaar J, Castellanos FX, Doyle A, Ebstein RP, Ekholm J, Forabosco P, Franke B, Freitag C, Friedel S, Gill M, Hebebrand J, Hinney A, Jacob C, Lesch KP, Loo SK, Lopera F, McCracken JT, McGough JJ, Meyer J, Mick E, Miranda A, Muenke M, Mulas F, Nelson SF, Nguyen TT, Oades RD, Ogdie MN, Palacio JD, Pineda D, Reif A, Renner TJ, Roeyers H, Romanos M, Rothenberger A, Schäfer H, Sergeant J, Sinke RJ, Smalley SL, Sonuga-Barke E, Steinhausen HC, van der Meulen E, Walitza S, Warnke A, Lewis CM, Faraone SV, Asherson P (2008) Meta-analysis of genome-wide linkage scans of attention deficit hyperactivity disorder. Am J Med Genet B Neuropsychiatr Genet 147B:1392–1398