Abstracts

Genetics and Genomics

Given space limitations and varying reprint permission policies, not all of the influential publications the editors considered reprinting in this issue could be included. This section contains abstracts from additional articles the editors deemed well worth reviewing.

Strategies to Identify Genes for Complex Disorders: a Focus on Bipolar Disorder and Chromosome 16p
Byerley W, Badner JA
Psychiatr Genet. 2010 May 5. [Epub ahead of print]

Bipolar disorder, also termed manic-depression, is a genetically based neuropsychiatric disorder with heritability estimates of 80%. Over 25 genome-wide linkage studies have been completed for bipolar disorder and results are not all randomly distributed but appear to converge on several chromosomal regions. Recently, several genome-wide association studies have been reported using thousands of cases and controls and meta-analyses of combined studies have implicated at least two common alleles predisposing to illness. Taken together, genome-wide linkage and genome-wide association results indicate that both rare and common variants likely underlie the genetic architecture of bipolar disorder. Larger genome-wide association studies using tens of thousands of cases and controls will be required to map additional common loci that presumably have smaller effect sizes. Although genome-wide sequencing using thousands of cases and controls (at least 2000 cases and 2000 controls) will likely be needed to map the full range of rare variants predisposing to bipolar disorder, it is not currently technically or financially feasible for most groups using "third generation" technology. Advances in sequencing and annotation methods are anticipated, however, and "fourth generation" methods should make large-scale high throughput sequencing feasible for most investigators. In the meantime, however, high throughput sequencing can be used to scan tens-to-hundreds of genes mapping under linkage peaks or around association signals. We review the linkage evidence implicating the chromosome 16p region in bipolar disorder. Although linkage regions are by nature relatively large (approximately 10–20 Mb) for complex disorders it is currently possible to sequence all coding and proximal regulatory regions. Systematic re-sequencing under linkage peaks could be a valuable strategy for mapping some rare variants underlying bipolar disorder. Advantages of this approach, compared to large case–control sequencing samples, include smaller sample sizes, enrichment of certain alleles in the study group, and the ability to check for co-segregation.

Current Status on Alzheimer Disease Molecular Genetics: From Past, to Present, to Future
Bettens K, Sleegers K, Van Broeckhoven C.
Hum Mol Genet. 2010 Apr 15;19(R1):R4–R11. Epub 2010 Apr 13

Linkage studies, candidate gene and whole-genome association studies have resulted in a tremendous amount of putative risk genes for Alzheimer's disease (AD). Yet, besides the three causal genes-amyloid precursor protein and presenilin 1 and 2 genes-and one risk gene apolipoprotein E (APOE), no single functional risk variant was identified. Discussing the possible involvement of rare alleles and other types of genetic variants, this review summarizes the current knowledge on the genetic spectrum of AD and integrates different approaches and recent discoveries by genome-wide association studies.

Common Polygenic Variation Contributes to Risk of Schizophrenia and Bipolar Disorder
International Schizophrenia Consortium, Purcell SM, Wray NR, Stone JL, Visscher PM, O'Donovan MC, Sullivan PF, Sklar P.
Nature. 2009 Aug 6;460(7256):748–52. Epub 2009 Jul 1

Schizophrenia is a severe mental disorder with a lifetime risk of about 1%, characterized by hallucinations, delusions and cognitive deficits, with heritability estimated at up to 80%. We performed a genome-wide association study of 3,322 European individuals with schizophrenia and 3,587 controls. Here we show, using two analytic approaches, the extent to which common genetic variation underlies the risk of schizophrenia. First, we implicate the major histocompatibility complex. Second, we provide molecular genetic evidence for a substantial polygenic component to the risk of schizophrenia involving thousands of common alleles of very small effect. We show that this component also contributes to the risk of bipolar disorder, but not to several non-psychiatric diseases.

Common Variants on Chromosome 6p22.1 are Associated with Schizophrenia
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.
Nature. 2009 Aug 6;460(7256):753–7. Epub 2009 Jul 1

Schizophrenia, a devastating psychiatric disorder, has a prevalence of 0.5–1%, with high heritability (80–85%) and complex transmission. Recent studies implicate rare, large, high-penetrance copy number variants in some cases, but the genes or biological mechanisms that underlie susceptibility are not known. Here we show that schizophrenia is significantly associated with single nucleotide polymorphisms (SNPs) in the extended major histocompatibility complex region on chromosome 6. We carried out a genome-wide association study of common SNPs in the Molecular Genetics of Schizophrenia (MGS) case-control sample, and then a meta-analysis of data from the MGS, International Schizophrenia Consortium and SGENE data sets. No MGS finding achieved genome-wide statistical significance. In the meta-analysis of European-ancestry subjects (8,008 cases, 19,077 controls), significant association with schizophrenia was observed in a region of linkage disequilibrium on chromosome 6p22.1 ($P = 9.54 \times 10(-9)$). This region includes a histone gene cluster and several immunity-related genes–possibly implicating aetiological mechanisms involving chromatin modification, transcriptional regulation, autoimmunity and/or infection. These results demonstrate that common schizophrenia susceptibility alleles can be detected. The characterization of these signals will suggest important directions for research on susceptibility mechanisms.

Meta-analysis of 32 Genome-wide Linkage Studies of Schizophrenia
Ng MY, Levinson DF, Faraone SV, Suarez BK, DeLisi LE, Arinami T, Riley B, Paunio T, Pulver AE, Irmansyah, Holmans PA, Escamilla M, Wildenauer DB, Williams NM, Laurent C, Mowry BJ, Brzustowicz LM, Maziade M, Sklar P, Garver DL, Abecasis GR, Lerer B, Fallin MD, Gurling HM, Gejman PV, Lindholm E, Moises HW, Byerley W, Wijsman EM, Forabosco P, Tsuang MT, Hwu HG, Okazaki Y, Kendler KS, Wormley B, Fanous A, Walsh D, O'Neill FA, Peltonen L, Nestadt G, Lasseter VK, Liang KY, Papadimitriou GM, Dikeos DG, Schwab SG, Owen MJ, O'Donovan MC, Norton N, Hare E, Raventos H, Nicolini H, Albus M, Maier W, Nimgaonkar VL, Terenius L, Mallet J, Jay M, Godard S, Nertney D, Alexander M, Crowe RR, Silverman JM, Bassett AS, Roy MA, Mérette C, Pato CN, Pato MT, Roos JL, Kohn Y, Amann-Zalcenstein D, Kalsi G, McQuillin A, Curtis D, Brynjolfson J, Sigmundsson T, Petursson H, Sanders AR, Duan J, Jazin E, Myles-Worsley M, Karayiorgou M, Lewis CM.
Mol Psychiatry. 2009 Aug;14(8):774–85. Epub 2008 Dec 30

A genome scan meta-analysis (GSMA) was carried out on 32 independent genome-wide linkage scan analyses that included 3255 pedigrees with 7413 genotyped cases affected with schizophrenia (SCZ) or

related disorders. The primary GSMA divided the autosomes into 120 bins, rank-ordered the bins within each study according to the most positive linkage result in each bin, summed these ranks (weighted for study size) for each bin across studies and determined the empirical probability of a given summed rank (P(SR)) by simulation. Suggestive evidence for linkage was observed in two single bins, on chromosomes 5q (142–168 Mb) and 2q (103–134 Mb). Genome-wide evidence for linkage was detected on chromosome 2q (119–152 Mb) when bin boundaries were shifted to the middle of the previous bins. The primary analysis met empirical criteria for "aggregate" genome-wide significance, indicating that some or all of 10 bins are likely to contain loci linked to SCZ, including regions of chromosomes 1, 2q, 3q, 4q, 5q, 8p and 10q. In a secondary analysis of 22 studies of European-ancestry samples, suggestive evidence for linkage was observed on chromosome 8p (16–33 Mb). Although the newer genome-wide association methodology has greater power to detect weak associations to single common DNA sequence variants, linkage analysis can detect diverse genetic effects that segregate in families, including multiple rare variants within one locus or several weakly associated loci in the same region. Therefore, the regions supported by this meta-analysis deserve close attention in future studies.

Interaction Between the Serotonin Transporter Gene (5-HTTLPR), Stressful Life Events, and Risk of Depression: a Meta-analysis

Risch N, Herrell R, Lehner T, Liang KY, Eaves L, Hoh J, Griem A, Kovacs M, Ott J, Merikangas KR
JAMA. 2009 Jun 17;301(23):2462–71

Context: Substantial resources are being devoted to identify candidate genes for complex mental and behavioral disorders through inclusion of environmental exposures following the report of an interaction between the serotonin transporter linked polymorphic region (5-HTTLPR) and stressful life events on an increased risk of major depression. **Objective:** To conduct a meta-analysis of the interaction between the serotonin transporter gene and stressful life events on depression using both published data and individual-level original data. **Data Sources:** Search of PubMed, EMBASE, and PsycINFO databases through March 2009 yielded 26 studies of which 14 met criteria for the meta-analysis. **Study Selection:** Criteria for studies for the meta-analyses included published data on the association between 5-HTTLPR genotype (SS, SL, or LL), number of stressful life events (0, 1, 2, > or = 3) or equivalent, and a categorical measure of depression defined by the Diagnostic and Statistical Manual of Mental Disorders (Fourth Edition) or the International Statistical Classification of Diseases, 10th Revision (ICD-10) or use of a cut point to define depression from standardized rating scales. To maximize our ability to use a common framework for variable definition, we also requested original data from all studies published prior to 2008 that met inclusion criteria. Of the 14 studies included in the meta-analysis, 10 were also included in a second sex-specific meta-analysis of original individual-level data. **Data Extraction:** Logistic regression was used to estimate the effects of the number of short alleles at 5-HTTLPR, the number of stressful life events, and their interaction on depression. Odds ratios (ORs) and 95% confidence intervals (CIs) were calculated separately for each study and then weighted averages of the individual estimates were obtained using random-effects meta-analysis. Both sex-combined and sex-specific meta-analyses were conducted. Of a total of 14,250 participants, 1769 were classified as having depression; 12,481 as not having depression. **Results:** In the meta-analysis of published data, the number of stressful life events was significantly associated with depression (OR, 1.41; 95% CI, 1.25–1.57). No association was found between 5-HTTLPR genotype and depression in any of the individual studies nor in the weighted average (OR, 1.05; 95% CI, 0.98–1.13) and no interaction effect between genotype and stressful life events on depression was observed (OR, 1.01; 95% CI, 0.94–1.10). Comparable results were found in the sex-specific meta-analysis of individual-level data. **Conclusion:** This meta-analysis yielded no evidence that the serotonin transporter genotype alone or in interaction with stressful life events is associated with an elevated risk of depression in men alone, women alone, or in both sexes combined.

Genomewide Association Studies: History, Rationale, and Prospects for Psychiatric Disorders
Psychiatric GWAS Consortium Coordinating Committee, Cichon S, Craddock N, Daly M, Faraone SV, Gejman PV, Kelsoe J, Lehner T, Levinson DF, Moran A, Sklar P, Sullivan PF. Collaborators: Faraone S, Anney R, Buitelaar J, Elia J, Franke B, Gill M, Hakonarson H, Kent L, McGough J, Mick E, Nisenbaum L, Smalley S, Thapar A, Todd R, Todorov A, Devlin B, Daly M, Anney R, Arking D, Buxbaum JD, Chakravarti A, Cook E, Gill M, Peltonen L, Piven J, Rouleau G, Santangelo S, Schellenberg G, Scherer S, Sutcliffe J, Szatmari P, Vieland V, Kelsoe J, Sklar P, Andreassen OA, Blackwood D, Boehnke M, Breuer R, Burmeister M, Cichon S, Corvin A, Craddock N, Ferreira M, Flickinger M, Greenwood T, Guan W, Gurling H, Li J, Mick E, Moskvina V, Muglia P, Muir W, Noethen M, Nurnberger J, Purcell S, Rietschel M, Ruderfer D, Schork N, Schulze T, Scott L, Steffens M, Upmanyu R, Wienker T, Smoller J, Craddock N, Kendler K, Nurnberger J, Perlis R, Purcell S, Rietschel M, Santangelo S, Thapar A, Sullivan P, Blackwood D, Boomsma D, Breuer R, Cichon S, Coryell W, de Geus E, Hamilton S, Hoogendijk W, Kloiber S, Lawson WB, Levinson D, Lewis C, Lucae S, Martin N, McGrath P, McGuffin P, Muglia P, Muir W, Noethen M, Offord J, Penninx B, Potash JB, Rietschel M, Scheftner WA, Schulze T, Slager S, Tozzi F, Weissman MM, Willemsen AH, Wray N, Gejman P, Andreassen OA, Blackwood D, Cichon S, Corvin A, Daly M, Fanous A, Gill M, Gurling H, Holmans P, Hultman C, Kendler K, Kivikko S, Laurent C, Lencz T, Levinson D, Malhotra A, Mowry B, Noethen M, O'Donovan M, Ophoff R, Owen M, Peltonen L, Pulver A, Rietschel M, Riley B, Sanders A, Schulze T, Schwab S, Sklar P, St Clair D, Sullivan P, Suvisaari J, van den Oord E, Wray N, Wildenaver D, Daly M, Awadalla P, Devlin B, Dudbridge F, Frigessi A, Holliday E, Holmans P, Lencz T, Levinson D, Lewis C, Lin D, Moskvina V, Mowry B, Neale B, Pickering E, Posthuma D, Purcell S, Rice J, Ripke S, Schork N, Sebat J, Steffens M, Stone J, Tzeng JY, van den Oord E, Vieland V.
Am J Psychiatry. 2009 May; 166(5):540–56. Epub 2009 Apr 1

Objective: The authors conducted a review of the history and empirical basis of genomewide association studies (GWAS), the rationale for GWAS of psychiatric disorders, results to date, limitations, and plans for GWAS meta-analyses. **Method:** A literature review was carried out, power and other issues discussed, and planned studies assessed. **Results:** Most of the genomic DNA sequence differences between any two people are common (frequency >5%) single nucleotide polymorphisms (SNPs). Because of localized patterns of correlation (linkage disequilibrium), 500,000 to 1,000,000 of these SNPs can test the hypothesis that one or more common variants explain part of the genetic risk for a disease. GWAS technologies can also detect some of the copy number variants (deletions and duplications) in the genome. Systematic study of rare variants will require large-scale resequencing analyses. GWAS methods have detected a remarkable number of robust genetic associations for dozens of common diseases and traits, leading to new pathophysiological hypotheses, although only small proportions of genetic variance have been explained thus far and therapeutic applications will require substantial further effort. Study design issues, power, and limitations are discussed. For psychiatric disorders, there are initial significant findings for common SNPs and for rare copy number variants, and many other studies are in progress. **Conclusions:** GWAS of large samples have detected associations of common SNPs and of rare copy number variants with psychiatric disorders. More findings are likely, since larger GWAS samples detect larger numbers of common susceptibility variants, with smaller effects. The Psychiatric GWAS Consortium is conducting GWAS meta-analyses for schizophrenia, bipolar disorder, major depressive disorder, autism, and attention deficit hyperactivity disorder. Based on results for other diseases, larger samples will be required. The contribution of GWAS will depend on the true genetic architecture of each disorder.

Genetics of Clinical Features and Subtypes of Schizophrenia: a Review of the Recent Literature
Fanous AH, Kendler KS
Cuff Psychiatry Rep. 2008 Apr;10(2):164–70

Since its earliest descriptions, schizophrenia has been thought to be clinically heterogeneous. Symptomatic features and subtypes tend to aggregate in families, suggesting that genetic factors contribute to individual differences in illness presentation. Over the past 5 years, evidence from genetic linkage and association studies has mounted to suggest that some susceptibility genes are etiologic factors for more or less

specific illness subtypes. Furthermore, modifier genes may affect clinical features dimensionally only after a given patient is already affected with the illness. In this paper, we review recent findings supporting the existence of such "modifier" genes. To date, DTNBP1 has provided the greatest evidence of illness modification, as associations with negative and cognitive symptoms and worse outcome have been published in independent samples. Future directions include using whole-genome association studies to search for genetic modifiers of schizophrenia.

Association Between Microdeletion and Microduplication at 16p11.2 and Autism
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; Autism Consortium
N Engl J Med. 2008 Feb 14;358(7):667–75. Epub 2008 Jan 9

Background: Autism spectrum disorder is a heritable developmental disorder in which chromosomal abnormalities are thought to play a role. **Methods:** As a first component of a genomewide association study of families from the Autism Genetic Resource Exchange (AGRE), we used two novel algorithms to search for recurrent copy-number variations in genotype data from 751 multiplex families with autism. Specific recurrent de novo events were further evaluated in clinical-testing data from Children's Hospital Boston and in a large population study in Iceland. **Results:** Among the AGRE families, we observed five instances of a de novo deletion of 593 kb on chromosome 16p11.2. Using comparative genomic hybridization, we observed the identical deletion in 5 of 512 children referred to Children's Hospital Boston for developmental delay, mental retardation, or suspected autism spectrum disorder, as well as in 3 of 299 persons with autism in an Icelandic population; the deletion was also carried by 2 of 18,834 unscreened Icelandic control subjects. The reciprocal duplication of this region occurred in 7 affected persons in AGRE families and 4 of the 512 children from Children's Hospital Boston. The duplication also appeared to be a high-penetrance risk factor. **Conclusions:** We have identified a novel, recurrent microdeletion and a reciprocal microduplication that carry substantial susceptibility to autism and appear to account for approximately 1% of cases. We did not identify other regions with similar aggregations of large de novo mutations.

The Genetic Deconstruction of Psychosis
Owen MJ, Craddock N, Jablensky A.
Schizophr Bull. 2007 Jul;33(4):905–11. Epub 2007 Jun 5

Psychiatric research, including the search for predisposing genes, has tended to proceed under the assumptions that schizophrenia and bipolar disorder, as defined in Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition, and International Statistical Classification of Diseases, 10th Revision, are discrete disease entities with distinct etiology and pathogenesis and that these disease entities can be identified by current "operational" diagnostic conventions. However, recent findings emerging from genetic studies show increasing evidence for an overlap in genetic susceptibility across the traditional binary classification of psychosis. Moreover, the emerging evidence suggests the possibility of relatively specific relationships between genotype and psychopathology. For example, variation in Disrupted in Schizophrenia 1 (DISC1) and Neuregulin 1 (NRG1) may confer susceptibility to a form of illness with mixed features of schizophrenia and mania. The elucidation of genotype-phenotype relationships is at an early stage, but current findings highlight the need to consider alternative approaches to classification and conceptualization for psychiatric research rather than continuing to rely heavily on the traditional categorical approach. We can expect that, over the coming years, molecular genetics will catalyze a reappraisal of psychiatric nosology as well as contribute in a major way to our understanding of pathophysiology and to the development of improved treatments. However, our understanding of the brain mechanisms that link specific gene actions and products to the subjective experience of psychopathological symptoms is likely to be bridged by employing intermediate (or endo-) phenotypes in the domains such as cognition, neurophysiology, or neuroanatomy rather than relying upon clinical measures alone.

The Genetics of Autism
Muhle R, Trentacoste SV, Rapin I.
Pediatrics. 2004 May;113(5):e472–86

Autism is a complex, behaviorally defined, static disorder of the immature brain that is of great concern to the practicing pediatrician because of an astonishing 556% reported increase in pediatric prevalence between 1991 and 1997, to a prevalence higher than that of spina bifida, cancer, or Down syndrome. This jump is probably attributable to heightened awareness and changing diagnostic criteria rather than to new environmental influences. Autism is not a disease but a syndrome with multiple nongenetic and genetic causes. By autism (the autistic spectrum disorders [ASDs]), we mean the wide spectrum of developmental disorders characterized by impairments in 3 behavioral domains: 1) social interaction; 2) language, communication, and imaginative play; and 3) range of interests and activities. Autism corresponds in this article to pervasive developmental disorder (PDD) of the Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition and International Classification of Diseases, Tenth Revision. Except for Rett syndrome–attributable in most affected individuals to mutations of the methyl-CpG-binding protein 2 (MeCP2) gene–the other PDD subtypes (autistic disorder, Asperger disorder, disintegrative disorder, and PDD Not Otherwise Specified [PDD-NOS]) are not linked to any particular genetic or nongenetic cause. Review of 2 major textbooks on autism and of papers published between 1961 and 2003 yields convincing evidence for multiple interacting genetic factors as the main causative determinants of autism. Epidemiologic studies indicate that environmental factors such as toxic exposures, teratogens, perinatal insults, and prenatal infections such as rubella and cytomegalovirus account for few cases. These studies fail to confirm that immunizations with the measles-mumps-rubella vaccine are responsible for the surge in autism. Epilepsy, the medical condition most highly associated with autism, has equally complex genetic/nongenetic (but mostly unknown) causes. Autism is frequent in tuberous sclerosis complex and fragile X syndrome, but these 2 disorders account for but a small minority of cases. Currently, diagnosable medical conditions, cytogenetic abnormalities, and single-gene defects (eg, tuberous sclerosis complex, fragile X syndrome, and other rare diseases) together account for $<10\%$ of cases. There is convincing evidence that "idiopathic" autism is a heritable disorder. Epidemiologic studies report an ASD prevalence of approximately 3 to 6/1000, with a male to female ratio of 3:1. This skewed ratio remains unexplained: despite the contribution of a few well characterized X-linked disorders, male-to-male transmission in a number of families rules out X-linkage as the prevailing mode of inheritance. The recurrence rate in siblings of affected children is approximately 2% to 8%, much higher than the prevalence rate in the general population but much lower than in single-gene diseases. Twin studies reported 60% concordance for classic autism in monozygotic (MZ) twins versus 0 in dizygotic (DZ) twins, the higher MZ concordance attesting to genetic inheritance as the predominant causative agent. Reevaluation for a broader autistic phenotype that included communication and social disorders increased concordance remarkably from 60% to 92% in MZ twins and from 0% to 10% in DZ pairs. This suggests that interactions between multiple genes cause "idiopathic" autism but that epigenetic factors and exposure to environmental modifiers may contribute to variable expression of autism-related traits. The identity and number of genes involved remain unknown. The wide phenotypic variability of the ASDs likely reflects the interaction of multiple genes within an individual's genome and the existence of distinct genes and gene combinations among those affected. There are 3 main approaches to identifying genetic loci, chromosomal regions likely to contain relevant genes: 1) whole genome screens, searching for linkage of autism to shared genetic markers in populations of multiplex families (families with >1 affected family member; 2) cytogenetic studies that may guide molecular studies by pointing to relevant inherited or de novo chromosomal abnormalities in affected individuals and their families; and 3) evaluation of candidate genes known to affect brain development in these significantly linked regions or, alternatively, linkage of candidate genes selected a priori because of their presumptive contribution to the pathogenesis of autism. Data from whole-genome screens in multiplex families suggest interactions of at least 10 genes in the causation of autism. Thus far, a putative speech and language region at 7q31-q33 seems most strongly linked to autism, with linkages to multiple other loci under investigation. Cytogenetic abnormalities at the 15q11-q13 locus are fairly frequent in people with autism, and a "chromosome 15 phenotype"was described in individuals with chromosome 15 duplications. Among other candidate genes are the FOXP2, RAY1/ST7, IMMP2L, and RELN genes at 7q22-q33 and the GABA(A) receptor subunit and UBE3A genes on chromosome 15q11-q13. Variant alleles of the serotonin transporter gene (5-HTT) on 17q11-q12 are more frequent in individuals with autism than in nonautistic populations.

In addition, animal models and linkage data from genome screens implicate the oxytocin receptor at 3p25-p26. Most pediatricians will have 1 or more children with this disorder in their practices. They must diagnose ASD expeditiously because early intervention increases its effectiveness. Children with dysmorphic features, congenital anomalies, mental retardation, or family members with developmental disorders are those most likely to benefit from extensive medical testing and genetic consultation. The yield of testing is much less in high-functioning children with a normal appearance and IQ and moderate social and language impairments. Genetic counseling justifies testing, but until autism genes are identified and their functions are understood, prenatal diagnosis will exist only for the rare cases ascribable to single-gene defects or overt chromosomal abnormalities. Parents who wish to have more children must be told of their increased statistical risk. It is crucial for pediatricians to try to involve families with multiple affected members in formal research projects, as family studies are key to unraveling the causes and pathogenesis of autism. Parents need to understand that they and their affected children are the only available sources for identifying and studying the elusive genes responsible for autism. Future clinically useful insights and potential medications depend on identifying these genes and elucidating the influences of their products on brain development and physiology.

Apolipoprotein E: High-avidity Binding to Beta-amyloid and Increased Frequency of Type 4 Allele in Late-onset Familial Alzheimer Disease
Strittmatter WJ, Saunders AM, Schmechel D, Pericak-Vance M, Enghild J, Salvesen GS, Roses AD.
Proc Natl Acad Sci U S A. 1993 Mar 1;90(5):1977–81

Apolipoprotein E is immunochemically localized to the senile plaques, vascular amyloid, and neurofibrillary tangles of Alzheimer disease. In vitro, apolipoprotein E in cerebrospinal fluid binds to synthetic beta A4 peptide (the primary constituent of the senile plaque) with high avidity. Amino acids 12–28 of the beta A4 peptide are required. The gene for apolipoprotein E is located on chromosome 19q13.2, within the region previously associated with linkage of late-onset familial Alzheimer disease. Analysis of apolipoprotein E alleles in Alzheimer disease and controls demonstrated that there was a highly significant association of apolipoprotein E type 4 allele (APOE-epsilon 4) and late-onset familial Alzheimer disease. The allele frequency of the APOE-epsilon 4 in 30 random affected patients, each from a different Alzheimer disease family, was 0.50 ± 0.06; the allele frequency of APOE-epsilon 4 in 91 age-matched unrelated controls was 0.16 ± 0.03 ($Z = 2.44$, $P = 0.014$). A functional role of the apolipoprotein E-E4 isoform in the pathogenesis of late-onset familial Alzheimer disease is suggested.

NOTES