New Perspectives for the Elucidation of Genetic Disorders

Hans-Hilger Ropers

For almost 15 years, genome research has focused on the search for major risk factors in common diseases, with disappointing results. Only recently, whole-genome association studies have begun to deliver because of the introduction of high-density single-nucleotide–polymorphism arrays and massive enlargement of cohort sizes, but most of the risk factors detected account for only a small proportion of the total genetic risk, and their diagnostic value is negligible. There is reason to believe that the complexity of many "multifactorial" disorders is primarily due to genetic heterogeneity, with defects of different genes causing the same disease. Moreover, de novo copy-number variation has been identified as a major cause of mental retardation and other complex disorders, suggesting that new mutations are an important, previously overlooked factor in the etiology of complex diseases. These observations support the notion that research into the previously neglected monogenic disorders should become a priority of genome research. Because of the introduction of novel high-throughput, low-cost sequencing methods, sequencing and genotyping will soon converge, with far-reaching implications for the elucidation of genetic disease and health care.

Until the early '90s, the project to sequence the human genome was driven by the expectation that it would pave the way for the elucidation of all known Mendelian disorders (e.g., see the work of Guyer and Collins[1] and references therein). Later, expectations were raised further by optimistic statements of leading genome researchers about the impact of this research for common disorders like coronary heart disease, stroke, dementia, psychiatric disorders, asthma, and cancer. For the pharmaceutical industry and for politicians alike, these prospects were extremely attractive. This was the reason why the search for genetic causes of complex diseases has received highest priority worldwide.

Genetic Risk Factors for Complex Disorders: Light at the End of the Tunnel?

On the basis of the assumption that most frequent disorders are multifactorial—that is, due to an interplay of genetic and nongenetic factors—and that hereditary risk factors for common diseases are evolutionarily old,[2–5] industry and government agencies have spent billions of dollars to search for associated DNA variants in the human genome that are more common in patients with specific complex disorders than in healthy individuals. However, genomewide association studies have often yielded contradictory results, which was generally ascribed to insufficient cohort sizes and marker densities,[6–9] and, apart from a few notable exceptions (e.g., the work of Klein et al.[10]), major risk factors for complex disorders have remained elusive.

Recent studies have shown that even mildly deleterious, evolutionarily old mutations are unlikely to have survived as common polymorphisms in the human population.[11] Thus, most of the genetic risk for common disease must be conferred by low-frequency alleles, as suggested elsewhere[12,13] and empirically confirmed—for example, for high-density lipoprotein levels in plasma.[14]

Identification of rare risk alleles, either directly or through association, requires a dense network of polymorphic markers. Closely linked genetic markers are often transmitted as evolutionarily conserved haplotype blocks.[15] To maximize the resolution of whole-genome association studies and to limit the number of markers that have to be typed, the International HapMap Project generated dense genomewide maps of SNPs and has characterized the linkage disequilibrium among them. According to recent estimates, however, comprehensive haplotype-based genomewide association studies still require typing of several hundred thousand of the ~6 million validated SNPs that are currently known (see National Center for Biotechnology Information dbSNP, build 127, March 2007). This number is much larger than originally expected but still manageable because of the availability of DNA arrays that allow typing of >500,000 SNPs in a single experiment.[16]

Array-based SNP typing and analysis of large cohorts of patients and controls have significantly enhanced the power of association studies; very recently, this has led to the identification of genetic risk factors for various complex disorders, including type 2 diabetes, myocardial infarction, prostate cancer, Crohn disease, and obesity.[17–24] Moreover, pooling strategies have been developed that drastically reduce the costs of such investigations.[25]

Most Risk Factors Are of No Diagnostic Relevance

After the long, futile search for such risk factors, these developments have been greeted with elation and relief,

From the Max Planck Institute for Molecular Genetics, Berlin

Received May 23, 2007; accepted for publication June 6, 2007; electronically published June 29, 2007.

Address for correspondence and reprints: Dr. Hans-Hilger Ropers, Max Planck Institute for Molecular Genetics, Ihnestrasse 73, D-14195 Berlin, Germany. E-mail: ropers@molgen.mpg.de

Am. J. Hum. Genet. 2007;81:199–207. 0002-9297/2007/8102-0002$15.00
DOI: 10.1086/520679

but, in view of the growing euphoria, it may be necessary to put these results into perspective. So far, the identification of these novel risk factors has not shed much light on the pathogenesis of the relevant complex diseases. Many of the associated markers were found in noncoding regions[17–22] or in genes with unknown function,[23,24] and, in other studies, the responsible sequence variants could not be precisely mapped because of limited resolution of association and linkage analysis.

Moreover, most of these factors account for only a small proportion of the total genetic risk, and their presence or absence will rarely increase or reduce the recurrence risk for the relevant disorder more than twofold. In contrast, being the sibling of a patient with a complex disorder such as schizophrenia, type 1 diabetes, or cleft lip and palate will raise the recurrence risk 10- to 40-fold above the population risk. These recently identified genetic risk factors are thus of no diagnostic and little prognostic value. This will change only if most other genetic risk factors are determined—and, even then, only if and when typing of all these factors becomes part of the diagnostic routine, which is not likely to happen in the near future.[26]

Why Association Studies May Still Fail

Insufficient sample sizes and marker densities are not the only problems complicating the search for genetic factors that are associated with complex disorders. In fact, there are more fundamental reasons why this strategy can meet with only limited success. One of these is genetic heterogeneity, which accounts for the complexity of many "multifactorial" disorders.[27] The most extreme example of this is mental retardation (MR), the complex disorder with the highest socioeconomic costs in developed societies.[28–30] Almost 300 different gene defects are known to give rise to MR,[31] but their total number may run into the thousands, and most of them are still unknown (reviewed elsewhere,[30] and see the "Large-Scale Mutation Screening in MR and Other Diseases" section). Different single-gene defects have also been identified in a wide variety of other complex disorders, such as Alzheimer and Parkinson disease, breast and colon cancer, coronary heart disease, hypertension (reviewed by Peltonen et al.[32] and Campion[33]), and atopic dermatitis,[34,35] and much of our present knowledge about the pathogenesis of complex disorders has come from the study of monogenic forms. Moreover, novel disease-causing gene defects may be much more common in these conditions than previously thought, as judged from the high number of de novo copy-number variants (CNVs) recently detected in various complex disorders (see the "CNV and Disease" section), and most of these mutations may be too short lived to be detectable by association studies.

…and Why Monogenic Disorders Should Be Studied in a Systematic Fashion

Thus, systematic resequencing of genes that have been implicated in related Mendelian disorders is a promising strategy for the identification of risk factors for complex diseases (see the *Nature Genetics* editorial[36]). However, monogenic disorders are also important in their own right. To date, only ~2,000 of the estimated 25,000 protein-coding human genes—and almost none of the many genes that do not code for protein—have been implicated in disease, and causative mutations are known for only 3,345 mapped disorders.[37] It is clear, however, that this is just the tip of the iceberg. Disorders listed in OMIM are enriched for diseases that run in families, because isolated cases are much less likely to be identified as being genetic, particularly if there is no specific, recognizable clinical phenotype. Severe autosomal disorders with early onset are mostly sporadic, because affected patients will seldom reproduce, and, in countries with small family sizes and low consanguinity rates, most patients with recessive disorders will be sporadic cases too. In the mouse, most loss-of-function mutations seem to result in phenotypic abnormalities; only 3%–4% of the knockout mutations listed on the Frontiers in Bioscience Database of Gene Knockouts were phenotypically normal (discussed by Brinkman et al.[38]), and learning or memory was affected in 75% of mice with mutations inactivating postsynaptic density proteins (S. Grant, Sanger-Wellcome Centre, personal communication; see also the work of Pocklington et al.[39]). Thus, it is likely that the vast majority of single-gene defects that give rise to disease have not been identified yet.

Still, in contrast to the mouse and other model organisms in which the effects of single-gene mutations are being explored in a systematic manner (e.g., see the Knockout Mouse Project), the elucidation of monogenic disorders in man lags behind. This is particularly puzzling because, for many disorders, even the closely related mouse is not a good model, since orthologous gene defects in the two species often fail to yield comparable phenotypes. Moreover, numerous complex traits, notably cognitive defects, are extremely difficult to study in model organisms.

Thus, there are compelling arguments for putting more effort into the elucidation of human monogenic disorders,[38,40,41] which has been greatly facilitated by the availability of the entire sequence of the human genome. At present, a variety of efficient strategies are available for the study of Mendelian disorders, as discussed below, and several of these are also suitable for large-scale, systematic studies of apparently complex diseases.

Balanced Chromosome Rearrangements

Disease-associated balanced chromosome rearrangements (DBCRs) truncating or otherwise inactivating genes form a visible bridge between human phenotypes and genotypes. Therefore, systematic breakpoint mapping and cloning in

patients with balanced chromosome rearrangements has been proposed as an efficient strategy for elucidating the molecular causes of hereditary disease.[42–44] De novo DBCRs can be identified by conventional karyotyping, and, with an incidence of 1 in 2,000, they are not rare.[45] About 6% of these are associated with clinical abnormalities such as MR with or without multiple congenital abnormalities (MCA), which is seen in almost half of these cases. In general, breakage events that give rise to DBCRs are not mediated by nonallelic homologous recombination,[46] and they seem to occur everywhere in the human genome. An advantage of this approach is that breakpoints can be precisely mapped, in contrast to wide mapping intervals, which are characteristic of association and linkage studies and which have hampered the identification of the relevant genes. The Mendelian Cytogenetic Network and its database MCNdb have been instrumental in the identification of numerous X-linked and autosomal candidate genes for MR and other disorders—for example, in the course of systematic studies conducted at the Max Planck Institute for Molecular Genetics (Berlin) and the Wilhelm Johannsen Centre for Functional Genome Research (Copenhagen). Recently, similar programs to characterize DBCRs in a systematic fashion have also been initiated elsewhere.[47–49]

CNV and Disease

Screening for submicroscopic deletions and duplications, with use of array-based comparative genomic hybridization (array CGH) and related methods, is a novel, powerful strategy for the identification of disease genes.[50] Array CGH was instrumental in finding the causative defects underlying several known malformation syndromes, including CHARGE (coloboma, heart anomaly, choanal atresia, retardation, genital, and ear anomalies),[51] Peters-Plus,[52] Pitt-Hopkins,[53,54] and thrombocytopenia-absent radius syndrome.[55] Moreover, thanks to high-resolution array-CGH screening, the catalogue of known genomic disorders is rapidly expanding,[56–58] and array CGH–based comparative analysis of overlapping chromosome rearrangements is beginning to shed light on the underlying major genes.

De novo genomic imbalances have been detected in 7% of patients with nonsyndromic MR, with use of tiling path BAC arrays,[59] and, in 10 of 100 mentally retarded patients studied with (Affymetrix 100k) high-density SNP typing arrays.[60] In a more recent study comprising 350 unselected mentally retarded patients with normal karyotypes, 16% of patients had apparently relevant deletions or duplications.[61] Three-fourths of these aberrations were single cases that had not been described before. On the basis of the duplication architecture of the human genome, E. Eichler and coworkers recently defined 130 sites that should be prone to genomic rearrangements; so far, one-third of these have been implicated in genomic disorders.[62] These data suggest that recurrent events associated with syndromic disease will be enriched in regions flanked by segmental duplications but that the majority of the genomic imbalances are not mediated by low-copy repeats (LCRs) and that their variety is virtually unlimited.

Recent studies have revealed that de novo CNVs are common not only in MR but also in autism,[63–65] syndromic[66] and nonsyndromic congenital heart defects (F. Erdogan, L. A. Larsen, H.-H. Ropers, N. Tommerup, and R. Ullmann, unpublished data), congenital brain malformations,[67,68] and other complex disorders. Many of these CNVs are small, encompassing only few genes. Thus, the systematic search for such nonpolymorphic CNVs and their molecular characterization in Mendelian and complex disorders is a new dimension in the identification of gene defects that play a role in disease.

Large-Scale Mutation Screening in MR and Other Diseases

Mutation screening of positional and functional candidate genes is another straightforward strategy for the identification of disease genes. X-linked disorders are plausible targets for such approaches, since they are easily identifiable because of their characteristic inheritance patterns and the unmasking of recessive traits in males. In this way, many disease-causing genes have been mapped to the X chromosome, which has greatly stimulated their identification. So far, ~18% of the ~900 annotated protein-coding genes on the X chromosome have been implicated in Mendelian disease, about twice as many as for autosomal genes (see OMIM). Still, it is likely that the proportion of genes causing disease if mutated is much higher. For example, the ~30 known genes for nonsyndromic X-linked MR genes account for only 50% of the patients, and there may be >100 genes that can give rise to this condition (reviewed elsewhere[30]). With the assumption that 8%–10% of moderate-to-severe forms of MR are X linked, the vast majority of the gene defects underlying MR must be autosomal, and linear extrapolation suggests that up to 1,000 different autosomal genes may be involved. Again, this estimate is conservative, since >10,000 genes are expressed in the CNS, many more or less exclusively; thus, the number of MR genes could still be much higher.

Screening all X-chromosomal genes is a viable option for the elucidation of the molecular basis of X-linked conditions in a systematic way, as illustrated by the remarkable success of ongoing efforts to sequence most X-chromosomal genes for mutations in a large cohort of families with XLMR.[69–71] For other chromosomes, however, this approach is less attractive, since they are less densely populated by known disease loci. Moreover, the enormous sequencing capacity required for this "brute force" approach renders it feasible only for large genome centers, but, as next-generation sequencing technologies are becoming available (see the "Novel Sequencing Technologies" section), this may soon change.

Autosomal Recessive Disorders Deserve More Attention

The strategy of choice for the identification of genes underlying autosomal recessive disorders is homozygosity mapping in extended consanguineous families, followed by mutation screening of candidate genes.[72,73] However, compared with X-linked diseases, elucidation of such genes has lagged behind, largely because of the rarity of such families in outbred populations of developed countries. For example, no more than four genes for nonsyndromic autosomal recessive MR (ARMR) have been identified to date,[74–77] although functional considerations as well as epidemiological data suggest that ARMR is more common than X-linked and autosomal dominant forms of MR. Only recently have efforts been undertaken to elucidate recessive disorders in a systematic manner. For example, Woods et al.,[78] Hong et al.,[79] and Cox et al.[80] have shed light on the molecular causes of autosomal recessive microcephaly and other recessive disorders, by homozygosity mapping in consanguineous Pakistani and Arab families.

Nonsyndromic forms of ARMR are probably more common than are syndromic ones, as judged from the relative frequencies of syndromic and nonsyndromic X-linked MR.[81] In the first systematic effort of its kind, Najmabadi et al.[82] and Garshasbi and coworkers[83] used DNA array-based SNP typing to perform homozygosity mapping in >100 Iranian families with ARMR. These studies defined various novel loci for nonsyndromic ARMR and paved the way for the identification of these genes. However, in contrast to nonsyndromic recessive deafness, where 50% of the patients have mutations in a single gene,[84] these studies failed to identify frequent forms of ARMR, indicating that this condition is extremely heterogeneous, at least in the Iranian population. Systematic studies of this kind can be performed only in populations with a high degree of parental consanguinity and large family sizes, which are typical of Arab countries, Turkey, Iran, Pakistan, and some parts of India. The high percentage of MR and congenital anomalies seen in these countries is thought to reflect a higher burden of recessive disorders,[85] but, almost certainly, recessive disorders are also underdiagnosed in Western societies. Given their complementary resources, collaboration between developing and developed countries will be the most efficient way to elucidate recessive diseases, which have received too little attention in the past.

Selection of Candidate Genes and Recognition of Relevant Mutations

Finding causative mutations in large chromosomal intervals defined by homozygosity mapping can be extremely tedious, however, and the same holds for many of the deletion and duplication intervals identified by array CGH and related techniques. Even in patients with DBCRs, the identification of the relevant disease genes is not always trivial, since the clinical abnormality may result from position effects inactivating genes that are far remote from the respective breakpoints (e.g., see the work of Jones et al.,[86] Bovie et al.,[87] and Baala et al.[88]). Recently, several software programs have been developed to facilitate the selection of candidate genes, such as Positional Medline, Endeavour,[89] Prioritizer,[90] and others.[91] For heterogeneous disorders with few specific clinical features, such as MR and related diseases, the performance of these programs is still relatively modest, but it is likely to improve as the number of established links between genotypes and phenotypes continues to grow and we learn more about the function of genes in man and related species.

Another problem complicating the search for disease-causing mutations is the fact that not all of them are easily recognizable. Various databases exist that list previously described pathogenic mutations, including general databases such as the Human Gene Mutation Database, which comprises almost 70,000 entries, and more-focused ones (curated by the Human Genome Variation Society) that list known mutations in specific genes or disorders. In spite of these data, evaluating the clinical relevance of novel missense mutations is still fairly difficult, even though there are programs, such as SIFT[92] or PolyPhen,[93] that facilitate this task. However, the power of such programs depends in part on the availability of three-dimensional structures for the relevant protein and on knowledge about structural domains that are essential for their function. So far, this information is available only for a subset of the human proteins. Even silent mutations may be pathogenetically relevant,[94,95] and numerous genes may be larger than hitherto known.

Mutation screening is frequently confined to the coding regions, and the splice sites of genes—that is, intronic mutations that may alter the splicing pattern[96,97]—or promoter mutations influencing gene expression levels[98,99] will go mostly undetected, largely because of high costs of mutation screening or because of limited sequencing capacities.

Novel Sequencing Technologies

Recently, the introduction of novel multiplex sequencing-by-synthesis technologies has revolutionized resequencing (reviewed by Bentley[100]) and removed various obstacles impairing the systematic elucidation of genetic disorders. For the currently available next-generation sequencing systems, DNA fragmentation and massively parallel clonal amplification of these fragments is required, followed by multiplex pyrosequencing (454-Roche) or stepwise incorporation of fluorescent dye–labeled nucleotides (Solexa-Illumina) and visualization by sensitive detection systems. The pyrosequencing-based system produces superior read lengths (>100 bp, under routine conditions), which facilitates sequence alignment, but competing systems have a much larger yield of raw sequence per run (~1 Gb compared with ~20 Mb for the 454-Roche Sequencer 20), which renders this system more economical

despite its much shorter read lengths. With this technology, resequencing the entire (nonrepetitive portion of the) human genome has now become possible for little more than $100,000, >4 orders of magnitude less than the ~$3 billion needed to complete the Human Genome Project. Another commercial manufacturer (Helicos) has announced that, with the introduction of its sequencing system, which does not require clonal preamplification of DNA fragments, sequencing costs may again drop by a factor of 10, only 1 order of magnitude away from the "$1,000 genome'" that may become reality within the next 5–10 years.

…and Implications for the Elucidation of Genetic Disease

Compared with the $1,000 genome and its implications for health care and research, which are the subject of a current public debate (see the *Nature Genetics* "Question of the Year"), the ongoing substitution of Sanger sequencing by much less costly and faster resequencing techniques has received little attention so far. For the elucidation of genetic disorders, the consequences of these developments are particularly obvious and far reaching. With these novel techniques at hand, direct sequencing will often replace indirect (e.g., SNP typing) approaches for the identification of disease genes and genetic risk factors; high-throughput, low-cost sequencing will greatly facilitate the search for causative mutations in large physical or genetic intervals defined by array CGH or linkage studies; for the first time, it will be economically feasible to screen entire genes, including introns, UTRs, and promoter regions, which are likely to harbor previously undetected pathogenetic variation. Even the sequencing of entire (sorted) chromosomes will become possible—for example, to shed more light on the pathogenetic relevance of genes that do not code for protein and other evolutionarily conserved, noncoding regions in the human genome.[101,102] Depending on the availability of cost-effective methods for enriching DNA sequences from specific genomic intervals, further widening of the spectrum of applications for these novel sequencing methods can be envisaged.

In principle, multiplex resequencing by synthesis should be much more accurate and reliable for mutation detection in known genes than is hybridization-based mutation screening with use of high-density oligonucleotide arrays, which is supported by our own preliminary data (L. Jensen, W. Chen, A. Kuss, and H.-H. Ropers, unpublished data). Thus, it is likely that the novel high-throughput sequencing techniques will have wide diagnostic applications, even in cytogenetics. For example, sequencing sorted derivative chromosomes is a very fast and economical strategy for characterization of chromosomal breakpoints in patients with disease-associated balanced chromosome rearrangements (W. Chen, V. Kalscheuer, R. Ullmann, and H.-H. Ropers, unpublished data). In the near future, genomic sequencing should even enable us to identify submicroscopic deletions and duplications and to characterize them with unmatched precision, thereby replacing array CGH, which has only just added a novel dimension to human genetics and genome research.

Conclusions and Outlook

High-resolution SNP-typing arrays and recently described pooling strategies have greatly facilitated the identification of major genetic risk factors underlying complex diseases, but such major genes seem to be rare. Instead, there is growing evidence that rare alleles and evolutionarily short-lived mutations play a major role in the etiology of complex disorders, which seem to be far more heterogeneous than previously assumed. This may be bad news for pharmaceutical companies searching for blockbuster drugs that will cure most if not all patients who have a specific common disease. The good news is that the dissection of complex disorders into many separate, often monogenic, entities has greatly increased the chances for understanding the underlying pathogenetic mechanisms—for example, by defining novel candidate genes that are part of the same pathway.

An illustrative example for this is Noonan syndrome, in which disease-causing mutations have been identified in *PTPN11, KRAS,* and *SOS1*[103,104] and have clarified the relationship between Noonan syndrome and related disorders that are also due to mutations in the *RAS-RAF-MEK-ERK* pathway. Novel insights into the molecular causes of schizophrenia have come from a familial t(1;11) translocation disrupting the *DISC1* gene,[105] which was found to cosegregate with schizophrenia and affective disorders. *DISC1* interacts with *NDE1* and several other genes involved in brain development and function.[106,107] Recent studies suggest that *NDE1* is also directly involved in schizophrenia,[108] and microduplications and deletions encompassing the *NDE1* gene were found to predispose to autism and MR, respectively.[109] Very recently, *NDE1* was also implicated in Asperger syndrome (L. Peltonen, personal communication). These observations argue for an important role of the *DISC1-NDE1* pathway in the pathogenesis of schizophrenia, autism, and related disorders.

In view of the existing powerful strategies for elucidating genetic defects—including whole-genome screening for CNV and high-throughput, low-cost sequencing—genotyping is no longer the bottleneck. Instead, a major challenge will be to distinguish disease-causing variants from functionally neutral ones, which will require the study of very large cohorts of patients and controls. The outcome of such studies will critically depend on the clinical characterization and on the handling and interpretation of the expected flood of new data. Thus, phenotyping, statistics, and bioinformatics but also functional verification of the results will be of central importance for systematic efforts to identify genetic variants that play a role in disease, including causative mutations, genetic risk factors, and

modifiers influencing the clinical severity. Their identification will have far-reaching consequences for health care, eventually fulfilling old promises that convinced decision makers to fund the sequencing of the human genome.

Acknowledgments

I thank Sarah Shoichet, Wei Chen, Lars Jensen, Vera Kalscheuer, Andreas Kuss, and Andreas Tzschach (all from Max Planck Institute for Molecular Genetics, Berlin), for critically reading the manuscript, and Hannelore Markert, for assisting me with its preparation.

Web Resources

The URLs for data presented herein are as follows:

Helicos, http://www.helicosbio.com/
Human Gene Mutation Database, http://www.hgmd.cf.ac.uk/ac/index.php
Human Genome Variation Society, http://www.hgvs.org/ (for the locus-specific mutation database)
International HapMap Project, http://www.hapmap.org/
Knockout Mouse Project, http://www.knockoutmouse.org/data.shtml
Max Planck Institute for Molecular Genetics, http://www.molgen.mpg.de/research/ropers/
Mendelian Cytogenetic Network, http://www.mcndb.org/index.jsp (for the MCNdb database)
Online Mendelian Inheritance in Man (OMIM), http://www.ncbi.nlm.nih.gov/Omim/
PolyPhen, http://genetics.bwh.harvard.edu/cgi-bin/pph/polyphen.cgi
Positional Medline, http://omicspace.riken.jp/PosMed/
Question of the Year, http://www.nature.com/ng/qoty/index.html
SIFT, http://blocks.fhcrc.org/sift/SIFT.html
Wilhelm Johannsen Centre for Functional Genome Research, http://www.wjc.ku.dk/publications/ (for systematic characterization of disease-associated balanced chromosome rearrangements)

References

1. Guyer MS, Collins FS (1993) The Human Genome Project and the future of medicine. Am J Dis Child 147:1145–1152
2. Ghosh S, Collins FS (1996) The geneticist's approach to complex disease. Annu Rev Med 47:333–353
3. Risch N, Merikangas K (1996) The future of genetic studies of complex human diseases. Science 273:1516–1517
4. Cardon LR, Bell JI (2001) Association study designs for complex diseases. Nat Rev Genet 2:91–99
5. Terwilliger JD, Weiss KM (1998) Linkage disequilibrium mapping of complex disease: fantasy or reality? Curr Opin Biotechnol 9:578–594
6. Ioannidis JP, Trikalinos TA, Ntzani EE, Contopoulos-Ioannidis DG (2003) Genetic associations in large versus small studies: an empirical assessment. Lancet 361:567–571
7. Lohmueller KE, Pearce CL, Pike M, Lander ES, Hirschhorn JN (2003) Meta-analysis of genetic association studies supports a contribution of common variants to susceptibility to common disease. Nat Genet 33:177–182
8. Gibbs RA (2005) Deeper into the genome. Nature 437:1233–1234
9. Jorgenson E, Witte JS (2006) A gene-centric approach to genome-wide association studies. Nat Rev Genet 7:885–891
10. Klein RJ, Zeiss C, Chew EY, Tsai J-Y, Sackler RS, Haynes C, Henning AK, SanGiovanni JP, Mane SM, Mayne ST, et al (2005) Complement factor H polymorphism in age-related macular degeneration. Science 308:385–389
11. Kryukov GV, Pennacchio LA, Sunyaev SR (2007) Most rare missense alleles are deleterious in humans: implications for complex disease and association studies. Am J Hum Genet 80:727–739
12. Pritchard JK (2001) Are rare variants responsible for susceptibility to complex diseases? Am J Hum Genet 69:124–137
13. Pritchard JK, Cox NJ (2002) The allelic architecture of human disease genes: common disease—common variant…or not? Hum Mol Genet 11:2417–2423
14. Cohen JC, Kiss RS, Pertsemlidis A, Marcel YL, McPherson R, Hobbs HH (2004) Multiple rare alleles contribute to low plasma levels of HDL cholesterol. Science 305:869–872
15. Gabriel SB, Schaffner SF, Nguyen H, Moore JM, Roy J, Blumenstiel B, Higgins J, DeFelice M, Lochner A, Faggart M, et al (2002) The structure of haplotype blocks in the human genome. Science 296:2225–2229
16. Zaitlen N, Kang HM, Eskin E, Halperin E (2007) Leveraging the HapMap correlation structure in association studies. Am J Hum Genet 80:683–691
17. McPherson R, Pertsemlidis A, Kavaslar N, Stewart A, Roberts R, Cox DR, Hinds DA, Pennacchio LA, Tybjaerg-Hansen A, Folsom AR, et al (2007) A common allele on chromosome 9 associated with coronary heart disease. Science 316:1488–1491
18. Helgadottir A, Thorleifsson G, Manolescu A, Gretarsdottir S, Blondal T, Jonasdottir A, Jonasdottir A, Sigurdsson A, Baker A, Palsson A, et al (2007) A common variant on chromosome 9p21 affects the risk of myocardial infarction. Science 316:1491–1493
19. Rioux JD, Xavier RJ, Taylor KD, Silverberg MS, Goyette P, Huett A, Green T, Kuballa P, Barmada MM, Datta LW, et al (2007) Genome-wide association study identifies new susceptibility loci for Crohn disease and implicates autophagy in disease pathogenesis. Nat Genet 39:596–604
20. Haiman CA, Patterson N, Freedman ML, Myers SR, Pike MC, Waliszewska A, Neubauer J, Tandon A, Schirmer C, McDonald GJ, et al (2007) Multiple regions within 8q24 independently affect risk for prostate cancer. Nat Genet 39:638–644
21. Gudmundsson J, Sulem P, Manolescu A, Amundadottir LT, Gudbjartsson D, Helgason A, Rafnar T, Bergthorsson JT, Agnarsson BA, Baker A, et al (2007) Genome-wide association study identifies a second prostate cancer susceptibility variant at 8q24. Nat Genet 39:631–637
22. Yeager M, Orr N, Hayes RB, Jacobs KB, Kraft P, Wacholder S, Minichiello MJ, Fearnhead P, Yu K, Chatterjee N, et al (2007) Genome-wide association study of prostate cancer identifies a second risk locus at 8q24. Nat Genet 39:645–649
23. Frayling TM, Timpson NJ, Weedon MN, Zeggini E, Freathy RM, Lindgren CM, Perry JRB, Elliott KS, Lango H, Rayner NW, et al (2007) A common variant in the FTO gene is associated with body mass index and predisposes to childhood and adult obesity. Science 316:889–894
24. Dina C, Meyre D, Gallina S, Durand E, Körner A, Jacobson P, Carlsson LMS, Kiess W, Vatin V, Lecoeur C, et al (2007) Variation in FTO contributes to childhood obesity and severe adult obesity. Nat Genet 39:724–726

25. Pearson JV, Huentelman MJ, Halperin RF, Tembe WD, Melquist S, Homer N, Brun M, Szelinger S, Coon KD, Zismann VL, et al (2007) Identification of the genetic basis for complex disorders by use of pooling-based genomewide single-nucleotide–polymorphism association studies. Am J Hum Genet 80:126–139
26. Cox DR (2007) Association of human DNA variation with complex traits. Plenary abstract 12 presented at the Human Genome Meeting, Montreal, May 24
27. Passarge E (1993) Wither polygenic inheritance: mapping Hirschsprung disease. Nat Genet 4:325–326
28. Roeleveld N, Zielhuis GA, Gabreels F (1997) The prevalence of mental retardation: a critical review of recent literature. Dev Med Child Neurol 39:125–132
29. Ropers HH, Hamel BC (2005) X-linked mental retardation. Nat Rev Genet 6:46–57
30. Ropers HH (2006) X-linked mental retardation: many genes for a complex disorder. Curr Opin Genet Dev 16:260–269
31. Inlow JK, Restifo LL (2004) Molecular and comparative genetics of mental retardation. Genetics 166:835–881
32. Peltonen L, Perola M, Naukkarinen J, Palotie A (2006) Lessons from studying monogenic disease for common disease. Hum Mol Genet 15:R67–R74
33. Campion D (2001) Dissection génétique des maladies à hérédité complexe. Médecine/Sciences 17:1139–1148
34. Sandilands A, Terron-Kwiatkowski A, Hull PR, O'Regan GM, Clayton TH, Watson RM, Carrick T, Evans AT, Liao H, Zhao Y, et al (2007) Comprehensive analysis of the gene encoding filaggrin uncovers prevalent and rare mutations in ichthyosis vulgaris and atopic eczema. Nat Genet 39:650–654
35. Palmer CNA, Irvine AD, Terron-Kwiatkowski A, Zhao Y, Liao H, Lee SP, Goudie DR, Sandilands A, Campbell LE, Smith FJD, et al (2006) Common loss-of-function variants of the epidermal barrier protein filaggrin are a major predisposing factor for atopic dermatitis. Nat Genet 38:441–446
36. Editorial (2007) Genomics of common diseases. Nat Genet 39:569
37. McKusick VA (2007) *Mendelian Inheritance in Man* and its online version, OMIM. Am J Hum Genet 80:588–604
38. Brinkman RR, Dubé M-P, Rouleau GA, Orr AC, Samuels ME (2006) Human monogenic disorders—a source of novel drug targets. Nat Rev Genet 7:249–260
39. Pocklington AJ, Cumiskey M, Armstrong JD, Grant SGN (2006) The proteomes of neurotransmitter receptor complexes form modular networks with distributed functionality underlying plasticity and behaviour. Mol Syst Biol 2: 2006.0023
40. Antonarakis SE, Beckmann JS (2006) Mendelian disorders deserve more attention. Nat Rev Genet 7:277–282
41. O'Connor TP, Crystal RG (2006) Genetic medicines: treatment strategies for hereditary disorders. Nat Rev Genet 7: 261–276
42. Tommerup N (1993) Mendelian cytogenetics: chromosome rearrangements associated with Mendelian disorders. J Med Genet 30:713–727
43. Wirth J, Nothwang HG, van der Maarel S, Menzel C, Borck G, Lopez-Pajares I, Brøndum-Nielsen K, Tommerup N, Bugge M, Ropers HH, et al (1999) Systematic characterisation of disease associated balanced chromosome rearrangements by FISH: cytogenetically and genetically anchored YACs identify microdeletions and candidate regions for mental retardation genes. J Med Genet 36:271–278
44. Bugge M, Bruun-Petersen G, Brøndum-Nielsen K, Friedrich U, Hansen J, Jensen G, Jensen PKA, Kristoffersson U, Lundsteen C, Niebuhr E, et al (2000) Disease associated balanced chromosome rearrangements: a resource for large scale genotype-phenotype delineation in man. J Med Genet 37:858–865
45. Warburton D (1991) De novo balanced chromosome rearrangements and extra marker chromosomes identified at prenatal diagnosis: clinical significance and distribution of breakpoints. Am J Hum Genet 49:995–1013
46. Erdogan F, Chen W, Kirchhoff M, Kalscheuer VM, Hultschig C, Müller I, Schulz R, Menzel C, Bryndorf T, Ropers HH, et al (2006) Impact of low copy repeats on the generation of balanced and unbalanced chromosomal aberrations in mental retardation. Cytogenet Genome Res 115:247–253
47. Williamson RE, Darrow KN, Michaud S, Jacobs JS, Jones MC, Eberl DF, Maas RL, Liberman MC, Morton CC (2007) Methylthioadenosine phosphorylase (*MTAP*) in hearing: gene disruption by chromosomal rearrangement in a hearing impaired individual and model organism analysis. Am J Med Genet A 143:1630–1639
48. Lu W, Quintero-Rivera F, Fan Y, Alkuraya FS, Donovan DJ, Xi Q, Turbe-Doan A, Li QG, Campbell CG, Shanske AL, et al (2007) *NFIA* haploinsufficiency is associated with a CNS malformation syndrome and urinary tract defects. PLoS Genet 3:e80
49. Alkuraya FS, Saadi I, Lund JJ, Turbe-Doan A, Morton CC, Maas RL (2006) *SUMO1* haploinsufficiency leads to cleft lip and palate. Science 313:1751
50. Vissers LELM, Veltman JA, Geurts van Kessel A, Brunner HG (2005) Identification of disease genes by whole genome CGH arrays. Hum Mol Genet 14:R215–R223
51. Vissers LE, van Ravenswaaij CM, Admiraal R, Hurst JA, de Vries BB, Janssen IM, van der Vliet WA, Huys EH, de Jong PJ, Hamel BC, et al (2004) Mutations in a new member of the chromodomain gene family cause CHARGE syndrome. Nat Genet 36:955–957
52. Lesnik Oberstein SAJ, Kriek M, White SJ, Kalf ME, Szuhai K, den Dunnen JT, Breuning MH, Hennekam RCM (2006) Peters plus syndrome is caused by mutations in *B3GALTL,* a putative glycosyltransferase. Am J Hum Genet 79:562–566 (erratum 79:985)
53. Zweier C, Peippo MM, Hoyer J, Sousa S, Bottani A, Clayton-Smith J, Reardon W, Saraiva J, Cabral A, Göhring I, et al (2007) Haploinsufficiency of *TCF4* causes syndromal mental retardation with intermittent hyperventilation (Pitt-Hopkins syndrome). Am J Hum Genet 80:994–1001
54. Amiel J, Rio M, de Pontual L, Redon R, Malan V, Boddaert N, Plouin P, Carter NP, Lyonnet S, Munnich A, et al (2007) Mutations in *TCF4,* encoding a class I basic helix-loop-helix transcription factor, are responsible for Pitt-Hopkins syndrome, a severe epileptic encephalopathy associated with autonomic dysfunction. Am J Hum Genet 80:988–993
55. Klopocki E, Schulze H, Strauß G, Ott CE, Hall J, Trotier F, Fleischhauer S, Greenhalgh L, Newbury-Ecob R, Neumann LM, et al (2007) Complex inheritance pattern resembling autosomal recessive inheritance involving a microdeletion in thrombocytopenia–absent radius (TAR) syndrome. Am J Hum Genet 80:232–240
56. Sharp AJ, Hansen S, Selzer RR, Cheng Z, Regan R, Hurst JA, Stewart H, Price SM, Blair E, Hennekam RC, et al (2006) Discovery of previously unidentified genomic disorders from

the duplication architecture of the human genome. Nat Genet 38:1038–1042
57. Sharp AJ, Locke DP, McGrath SD, Cheng Z, Bailey JA, Vallente RU, Pertz LM, Clark RA, Schwartz S, Segraves R, et al (2005) Segmental duplications and copy-number variation in the human genome. Am J Hum Genet 77:78–88
58. Lupski JR, Stankiewicz P (2005) Genomic disorders: molecular mechanisms for rearrangements and conveyed phenotypes. PLoS Genet 1:e49
59. de Vries BB, Pfundt R, Leisink M, Koolen DA, Vissers LELM, Janssen IM, van Reijmersdal S, Nillesen WM, Huys EHLPG, de Leeuw N, et al (2005) Diagnostic genome profiling in mental retardation. Am J Hum Genet 77:606–616
60. Friedman JM, Baross Á, Delaney AD, Ally A, Arbour L, Asano J, Bailey DK, Barber S, Birch P, Brown-John M, et al (2006) Oligonucleotide microarray analysis of genomic imbalance in children with mental retardation. Am J Hum Genet 79: 500–513
61. de Vries BB (2007) Novel microdeletion syndromes. Presented at the 3rd International Meeting on Cryptic Chromosomal Rearrangements in Mental Retardation and Autism, Troina, Sicily, April 13
62. Mefford H (2007) Segmental duplications and genomic disorders: a targeted approach for disease. Presented at the 3rd International Meeting on Cryptic Chromosomal Rearrangements in Mental Retardation and Autism, Troina, Sicily, April 13
63. Jacquemont M-L, Sanlaville D, Redon R, Raoul O, Cormier-Daire V, Lyonnet S, Amiel J, Le Merrer M, Heron D, de Blois M-C, et al (2006) Array-based comparative genomic hybridisation identifies high frequency of cryptic chromosomal rearrangements in patients with syndromic autism spectrum disorders. J Med Genet 43:843–849
64. Consortium TAGP (2007) Mapping autism risk loci using genetic linkage and chromosomal rearrangements. Nat Genet 39:319–328
65. Sebat J, Lakshmi B, Malhotra D, Troge J, Lese-Martin C, Walsh T, Yamrom B, Yoon S, Krasnitz A, Kendall J, et al (2007) Strong association of de novo copy number mutations with autism. Science 316:445–449
66. Thienpont B, Mertens L, de Ravel T, Eyskens B, Boshoff D, Maas N, Fryns J-P, Gewillig M, Vermeesch JR, Devriendt K (2007) Submicroscopic chromosomal imbalances detected by array-CGH are a frequent cause for congenital heart defects in selected patients. Eur Heart J (http://eurheartj.oxfordjournals.org/cgi/content/full/ehl560v1) (electronically published March 23, 2007; accessed June 25, 2007)
67. Zuffardi O (2007) Pathogenic and benign genomic variation. Plenary abstract 8 presented at the Human Genome Meeting, Montreal, May 23
68. Moeller RM (2007) Whole genome array CGH of epilepsy patients with congenital brain malformations. Workshop abstract 25 presented at the Human Genome Meeting, Montreal, May 22
69. Raymond FL, Tarpey PS, Edkins S, Tofts C, O'Meara S, Teague J, Butler A, Stevens C, Barthorpe S, Buck G, et al (2007) Mutations in *ZDHHC9,* which encodes a palmitoyltransferase of NRAS and HRAS, cause X-linked mental retardation associated with a marfanoid habitus. Am J Hum Genet 80: 982–987
70. Tarpey PS, Raymond FL, O'Meara S, Edkins S, Teague J, Butler A, Dicks E, Stevens C, Tofts C, Avis T, et al (2007) Mutations in *CUL4B,* which encodes a ubiquitin E3 ligase subunit, cause an X-linked mental retardation syndrome associated with aggressive outbursts, seizures, relative macrocephaly, central obesity, hypogonadism, pes cavus, and tremor. Am J Hum Genet 80:345–352
71. Tarpey PS, Stevens C, Teague J, Edkins S, O'Meara S, Avis T, Barthorpe S, Buck G, Butler A, Cole J, et al (2006) Mutations in the gene encoding the Sigma 2 subunit of the adaptor protein 1 complex, *AP1S2,* cause X-linked mental retardation. Am J Hum Genet 79:1119–1124
72. Houwen RHJ, Baharloo S, Blankenship K, Raeymaekers P, Juyn J, Sandkuijl LA, Freimer NB (1994) Genome screening by searching for shared segments: mapping a gene for benign recurrent intrahepatic cholestasis. Nat Genet 8:380–386
73. Bull LN, van Eijk MJT, Pawlikowska L, DeYoung JA, Juijn JA, Liao M, Klomp LWJ, Lomri N, Berger R, Scharschmidt BR, et al (1998) A gene encoding a P-type ATPase mutated in two forms of hereditary cholestasis. Nat Genet 18:219–224
74. Molinari F, Rio M, Meskenaite V, Encha-Razavi F, Auge J, Bacq D, Briault S, Vekemans M, Munnich A, Attie-Bitach T, et al (2002) Truncating neurotrypsin mutation in autosomal recessive nonsyndromic mental retardation. Science 298: 1779–1781
75. Higgins JJ, Pucilowska J, Lombardi RQ, Rooney JP (2004) A mutation in a novel ATP-dependent Lon protease gene in a kindred with mild mental retardation. Neurology 63:1927–1931
76. Basel-Vanagaite L, Attia R, Yahav M, Ferland RJ, Anteki L, Walsh CA, Olender T, Straussberg R, Magal N, Taub E, et al (2006) The *CC2d1A,* a member of a new gene family with C2 domains, is involved in autosomal recessive nonsyndromic mental retardation. J Med Genet 43:203–210
77. Motazacker MM, Rost BR, Hucho T, Garshasbi M, Kahrizi K, Ullmann R, Abedini SS, Esmaeeli Nieh S, Hosseini Amini S, Goswami C, et al (2007) A defect in the ionotropic glutamate receptor 6 gene (*GRIK2*) is associated with autosomal recessive mental retardation. Am J Hum Genet (in press)
78. Woods CG, Cox J, Springell K, Hampshire DJ, Mohamed MD, McKibbin M, Stern R, Raymond FL, Sandford R, Sharif SM, et al (2006) Quantification of homozygosity in consanguineous individuals with autosomal recessive disease. Am J Hum Genet 78:889–896
79. Hong SE, Shugart YY, Huang DT, Shahwan SA, Grant PE, Hourihane JO, Martin ND, Walsh CA (2000) Autosomal recessive lissencephaly with cerebellar hypoplasia is associated with human RELN mutations. Nat Genet 26:93–96 (erratum 27:225)
80. Cox J, Jackson AP, Bond J, Woods CG (2006) What primary microcephaly can tell us about brain growth. Trends Mol Med 12:358–366
81. Fishburn J, Turner G, Daniel A, Brookwell R (1983) The diagnosis and frequency of X-linked conditions in a cohort of moderately retarded males with affected brothers. Am J Med Genet 14:713–724
82. Najmabadi H, Motazacker MM, Garshasbi M, Kahrizi K, Tzschach A, Chen W, Behjati F, Hadavi V, Esmaeeli Nieh S, Abedini SS, et al (2007) Homozygosity mapping in consanguineous families reveals extreme heterogeneity of non-syndromic autosomal recessive mental retardation and identifies 8 novel gene loci. Hum Genet 121:43–48
83. Garshasbi M, Motazacker MM, Kahrizi K, Behjati F, Abedini

SS, Esmaeeli Nieh S, Firouzabadi SG, Becker C, Ruschendorf F, Nurnberg P, et al (2006) SNP array-based homozygosity mapping reveals *MCPH1* deletion in family with autosomal recessive mental retardation and mild microcephaly. Hum Genet 118:708–715
84. Willems PJ (2000) Genetic causes of hearing loss. N Engl J Med 342:1101–1109
85. Bittles AH (2001) Consanguinity and its relevance to clinical genetics. Clin Genet 60:89–98
86. Jones C, Booth C, Rita D, Jazmines L, Brandt B, Newlan A, Horsthemke B (1997) Bilateral retinoblastoma in a male patient with an X;13 translocation: evidence for silencing of the RB1 gene by the spreading of X inactivation. Am J Hum Genet 60:1558–1562
87. Bovie C, Holden ST, Schroer A, Smith E, Trump D, Raymond FL (2003) Neurofibromatosis 2 in a patient with a de novo balanced reciprocal translocation 46,X,t(X;22)(p11.2; q11.2). J Med Genet 40:682–684
88. Baala L, Briault S, Etchevers HC, Laumonnier F, Natiq A, Amiel J, Boddaert N, Picard C, Sbiti A, Asermouh A, et al (2007) Homozygous silencing of T-box transcription factor EOMES leads to microcephaly with polymicrogyria and corpus callosum agenesis. Nat Genet 39:454–456
89. Aerts S, Lambrechts D, Maity S, Van Loo P, Coessens B, De Smet F, Tranchevent LC, De Moor B, Marynen P, Hassan B, et al (2006) Gene prioritization through genomic data fusion. Nat Biotechnol 24:537–544
90. Franke L, van Bakel H, Fokkens L, de Jong ED, Egmont-Petersen M, Wijmenga C (2006) Reconstruction of a functional Human Gene Network, with an application for prioritizing positional candidate genes. Am J Hum Genet 78: 1011–1025
91. Lage K, Karlberg EO, Størling ZM, Ólason PI, Pedersen AG, Rigina O, Hinsby AM, Tuemer Z, Pociot F, Tommerup N, et al (2007) A human phenome-interactome network of protein complexes implicated in genetic disorders. Nat Biotechnol 25:309–316
92. Ng PC, Henikoff S (2006) Predicting the effects of amino acid substitutions on protein function. Annu Rev Genomics Hum Genet 7:61–80
93. Ramensky V, Bork P, Sunyaev S (2002) Human non-synonymous SNPs: server and survey. Nucl Acids Res 30:3894–3900
94. Kimchi-Sarfaty C, Oh JM, Kim IW, Sauna ZE, Calcagno AM, Ambudkar SV, Gottesman MM (2006) A "silent" polymorphism in the MDR1 gene changes substrate specificity. Science 315:525–528
95. Pagani F, Raponi M, Baralle FE (2005) Synonymous mutations in CFTR exon 12 affect splicing and are not neutral in evolution. Proc Natl Acad Sci USA 102:6368–6372
96. Richards AJ, Laidlaw M, Meredith SP, P. S, Poulson AV, Scott JD, Snead MP (2007) Missense and silent mutations in COL2A1 result in Stickler syndrome but via different molecular mechanisms. Hum Mutat 28:639
97. Lenski C, Kooy RF, Reyniers E, Loessner D, Wanders RJA, Winnepenninckx B, Hellebrand H, Engert S, Schwartz CE, Meindl A, et al (2007) The reduced expression of the HADH2 protein causes X-linked mental retardation, choreoathetosis, and abnormal behavior. Am J Hum Genet 80:372–377
98. Borck G, Zarhrate M, Cluzeau C, Bal E, Bonnefont JP, Munnich A, Cormier-Daire V, Colleaux L (2006) Father-to-daughter transmission of Cornelia de Lange syndrome caused by a mutation in the 5′ untranslated region of the *NIPBL* gene. Hum Mutat 27:731–735
99. Almeida AM, Murakami Y, Layton DM, Hillmen P, Sellick GS, Maeda Y, Richards S, Patterson S, Kotsianidis I, Mollica L, et al (2006) Hypomorphic promoter mutation in *PIGM* causes inherited glycosylphosphatidylinositol deficiency. Nat Med 12:846–851
100. Bentley DR (2006) Whole-genome re-sequencing. Curr Opin Genet Dev 16:545–552
101. Lunter G, Ponting CP, Hein J (2006) Genome-wide identification of human functional DNA using a neutral indel model. PLoS Comput Biol 2:e5
102. Ponjavic J, Ponting CP, Lunter G (2007) Functionality or transcriptional noise? Evidence for selection within long noncoding RNAs. Genome Res 17:556–565
103. Schubbert S, Zenker M, Rowe SL, Böll S, Klein C, Bollag G, van der Burgt I, Musante L, Kalscheuer V, Wehner L-E, et al (2006) Germline *KRAS* mutations cause Noonan syndrome. Nat Genet 38:331–336
104. Roberts AE, Araki T, Swanson KD, Montgomery KT, Schiripo TA, Joshi VA, Li L, Yassin Y, Tamburino AM, Neel BG, et al (2007) Germline gain-of-function mutations in *SOS1* cause Noonan syndrome. Nat Genet 39:70–74
105. Millar JK, Wilson-Annan JC, Anderson S, Christie S, Taylor MS, Semple CA, Devon RS, Clair DM, Muir WJ, Blackwood DH, et al (2000) Disruption of two novel genes by a translocation co-segregating with schizophrenia. Hum Mol Genet 9:1415–1423
106. Millar JK, Christie S, Porteous DJ (2003) Yeast two-hybrid screens implicate DISC1 in brain development and function. Biochem Biophys Res Commun 311:1019–1025
107. Brandon NJ, Handford EJ, Schurov I, Rain JC, Pelling M, Duran-Jimeniz B, Camargo LM, Oliver KR, Beher D, Shearman MS, et al (2004) Disrupted in Schizophrenia 1 and Nudel form a neurodevelopmentally regulated protein complex: implications for schizophrenia and other major neurological disorders. Mol Cell Neurosci 25:42–55
108. Hennah W, Tomppo L, Hiekkalinna T, Palo OM, Kilpinen H, Ekelund J, Tuulio-Henriksson A, Silander K, Partonen T, Paunio T, et al (2007) Families with the risk allele of DISC1 reveal a link between schizophrenia and another component of the same molecular pathway, NDE1. Hum Mol Genet 16:453–462
109. Ullmann R, Turner G, Kirchhoff M, Chen W, Tonge B, Rosenberg C, Field M, Vianna-Morgante AM, Christie L, Krepischi-Santos AC, et al (2007) Array CGH identifies reciprocal 16p13.1 duplications and deletions that predispose to autism and/or mental retardation. Hum Mutat 28:674–682