Proc. Natl. Acad. Sci. USA
Vol. 95, pp. 7240–7244, June 1998

Perspective

Three independent lines of evidence suggest retinoids as causal to schizophrenia

Ann B. Goodman

Statistical Sciences and Epidemiology Division, Nathan S. Kline Institute for Psychiatric Research, Orangeburg, NY 10962

ABSTRACT **Retinoid dysregulation may be an important factor in the etiology of schizophrenia. This hypothesis is supported by three independent lines of evidence that triangulate on retinoid involvement in schizophrenia: (*i*) congenital anomalies similar to those caused by retinoid dysfunction are found in schizophrenics and their relatives; (*ii*) those loci that have been suggestively linked to schizophrenia are also the loci of the genes of the retinoid cascade (convergent loci); and (*iii*) the transcriptional activation of the dopamine D2 receptor and numerous schizophrenia candidate genes is regulated by retinoic acid. These findings suggest a close causal relationship between retinoids and the underlying pathophysiological defects in schizophrenia. This leads to specific strategies for linkage analyses in schizophrenia. In view of the heterodimeric nature of the retinoid nuclear receptor transcription factors, e.g., retinoid X receptor β at chromosome 6p21.3 and retinoic acid receptor β at 3p24.3, two-locus linkage models incorporating genes of the retinoid cascade and their heterodimeric partners, e.g., peroxisome proliferator-activated receptor α at chromosome 22q12-q13 or nuclear-related receptor 1 at chromosome 2q22-q23, are proposed. New treatment modalities using retinoid analogs to alter the downstream expression of the dopamine receptors and other genes that are targets of retinoid regulation, and that are thought to be involved in schizophrenia, are suggested.**

Schizophrenia is now generally considered to be a neurodevelopmental disorder with first evidence of the disorder occurring in the midgestational period *in utero* (1). This is the period when the fetal brain and its neuronal structure is actively developing (2). Vitamin A (retinoid), an essential nutrient involved in gene regulation and expression (3), is particularly active in brain neurodevelopment during this period (4–8). Previously, I have suggested that dysregulation by retinoids may be an important factor in the etiology of schizophrenia (9–12).

Retinoid-Related Anomalies in Schizophrenic Pedigrees

The first line of evidence firmly connecting retinoids to schizophrenia is that retinoid toxicity or deficit has repeatedly been shown to result in symptom presentations that, though more severe in extent, resemble the stigmata of schizophrenia, e.g., thought disorder, mental deficit, enlarged ventricles, agenesis of the corpus callosum, microcephaly, and a variety of major and minor congenital malformations, among which craniofacial and digital anomalies are prominent. Such defects have been frequently reported among schizophrenic samples (for review, see ref. 11). A recent study demonstrated significantly higher rates of these abnormalities in the extended pedigrees of schizophrenic probands, as compared with matched control pedigrees (11). Occurrence in both probands and their relatives supports the importance of genetic as well as environmental factors as a basis for the familial clustering of these retinoid-related anomalies (9, 11). Many insults, both genetic and epigenetic, and including nutritional or viral, could result in this variety of anomalies. However, as the documentation of the prominent role of retinoids in the development of the central nervous system continues to expand, the possibility of retinoid involvement in schizophrenia is strengthened.

Convergence of Retinoid Loci and Schizophrenia Loci (Convergent Loci)

Genetic linkage data now support the evidence from family history, twin, adoption (13), and epidemiologic studies (14) that schizophrenia is a complex non-Mendelian illness with a strong genetic component. A second line of evidence implicating retinoids in the genetic etiology of schizophrenia comes from studies that have identified specific replicable loci that have been suggestively linked to schizophrenia (13). The common factor among these promising schizophrenia loci is that they are known loci of genes within the retinoid signaling system or metabolic cascade. This approach of identifying overlapping disease and metabolic loci (convergent loci) provides a technique for discovering the molecular basis for a disease.

Retinoids are handled within the body by a complex genetic cascade involving metabolic pathways that transform environmental or maternal sources of beta carotene, retinyl, and retinol into the final products of the retinoid cascade, the retinoic acids. Retinoic acids are powerful morphogens, and by activating specific transcription factors various forms of retinoic acid, e.g., all-*trans*-retinoic acid and 9-*cis*-retinoic acid, regulate the expression of numerous target genes (15). The cascade is complicated by the involvement of other nuclear heterodimeric partners and their ligands. Some of these partners are liganded by environmental agents other than retinoid-containing nutrients, particularly pesticides and plasticizers, which are themselves then involved in the complex retinoid signaling pathway (16). This complicated pathway is thus susceptible to multiple epistatic interactions with environmental sources, including viruses. Many viral genomes possess DNA motifs, which in eukaryotes activate retinoid-responsive genetic transcription (17).

The enzymatic proteins in the retinoid cascade are lipoprotein lipase (LPL), involved in the reversible catalysis of retinyl ester to retinol (18); the alcohol dehydrogenases, involved in the reversible conversion of retinol to retinal, the rate-limiting step; and the aldehyde dehydrogenase (ALDH) and cyto-

The publication costs of this article were defrayed in part by page charge payment. This article must therefore be hereby marked "*advertisement*" in accordance with 18 U.S.C. §1734 solely to indicate this fact.

Abbreviations: LPL, lipoprotein lipase; ALDH, aldehyde dehydrogenase; TTR, transthyretin; RAR, retinoic acid receptor; RXR, retinoid X receptor; NURR1, nuclear-related receptor 1; PPARs, peroxisome proliferator-activated receptors; RAREs, retinoic acid receptor response elements; DRD2, dopamine D2 receptor; GAD, glutamic acid decarboxylase.

chrome P450 enzymes, involved in the irreversible catalysis of retinal to retinoic acid, and, in the case of the cytochrome P450s, to the degradation of retinoic acid by hydroxylation (19–22). Transporter and binding proteins include the four cellular retinol-binding proteins; the two cellular retinoic acid-binding proteins; the cellular retinaldehyde-binding protein; and transthyretin (TTR), which transports bound retinol across the choroid plexus into the brain (for reviews, see ref. 3).

The major genes in the retinoid cascade are the transcription factors, which are the nuclear retinoid receptors, retinoic acid receptor (RAR)α, -β, and -γ and retinoid X receptor (RXR)α, -β, and -γ (15). These transcription factors act either alone or together with heterodimeric partners, in particular nuclear-related receptor 1 (NURR1) and the peroxisome proliferator-activated receptors (PPARs). These heterodimeric partners, using the morphogen 9-*cis*-retinoic acid, interact primarily with the RXRs (16).

The locus of *RXR*β is 6p21.3. The locus of *PPAR*α is 22q12-q13.1. Commonly occurring translocations at 22q12 involve the 9q34 locus of *RXR*α. The locus encoding LPL, a protein highly expressed in the hippocampus of newborn rats (23) is 8p22. How do these loci relate to those linked to schizophrenia?

Within the past 2 years replicated linkage of schizophrenia to three chromosomal loci, 6p22–6p21.1, the locus of *RXR*β and *PPAR*δ; 22q12-q13, the locus of *PPAR*α and *CYP2D6*; and 8q22-q23, the locus of *LPL*, has been reported (24–40). Other loci of retinoid cascade genes also have demonstrated positive, but weaker, statistical associations with schizophrenia (41–55) (Table 1). However, none of the above loci have been consistently linked to schizophrenia, because in each case negative findings have been reported (for reviews, see refs. 13, 37, 56, and 57). In most cases the statistical significance of these studies has been no more than suggestive of linkage or association (13). As a result, to achieve higher power for linkage statistics, several groups have joined into consortiums to study pooled samples using increasingly saturated linkage markers concentrated at these loci. At the most recent meeting of the World Congress on Psychiatric Genetics in October 1997, workshops addressing these three chromosomes in relation to schizophrenia were established, and the reports of these workshops are presently in preparation.

Table 1. Convergence of retinoid gene/heterodimeric partner loci and schizophrenia linkages (convergent loci)

Retinoid locus	Gene	Schizophrenia linkage ref(s).*
6p21.3	*RXR*β	24–29, 40
	CYP21	
6p21.2–p21.1	*PPAR*δ	
22q12–q13.1	*PPAR*α	30–37
	CYP2D6	
8p22	*LPL*	25, 29, 38, 39
3p24	*RAR*β	38, 54
	PPARγ	
3p24.3	*THRB*	
2q22–q23	*NURR1*	25, 41, 42
D2S142 at 2q22–q23		
1q22–q23	*RXR*γ	43
1q21	*CRABP2*	
17q12–q21	*RAR*α	25, 44
	THRα	
11q23.3	*LXR*	45, 46†, 47
DRD2 and *5HT3* at 11q23		
3q21–q22	*RBP1*	25, 48–50
DRD3 at 3q13.3		
adjacent to 3q21		
3q21	*RBP2*	25, 48–50
9q21	*ALDH1*	25, 51, 52
12q24.2	*ALDH2*	25
18q11.2–12.1	*TTR*	53,† 55

Retinoid loci not linked to schizophrenia (to date): 9q34.3 (*RXR*α); 12q13 (*RAR*g); 10q11.2 (*CRPB3*); 10q23-q24 (*CRBP4*); 15q22-qter (*CRABP1*); and 15q26 *CRLBP1.*

*Schizophrenia linkage or allelic association studies or karyotyping defects significant at locus.

†Bipolar.

However, schizophrenia is not well specified by single-locus models. Particularly in the case of retinoids, the nature of transcription requires a heterodimeric element that recognizes two different DNA motifs. Single-locus models do not fit the biological activity of the retinoid nuclear receptors (16). For this reason, additional attempts to augment single-locus models by increasing sample size or by using more markers may continue to be only marginally productive. Rather, two-locus models could be employed, pairing the genes for retinoid receptors or their flanking markers with their necessary heterodimeric partners. If retinoids are, indeed, involved in the genetics of schizophrenia, using a two-locus strategy would increase the odds of demonstrating this underlying molecular cause.

A case in point is the recent discovery that the nuclear transcription factor, NURR1, in heterodimeric tandem with RXR, is unequivocally necessary for the expression of dopaminergic neurons in the midbrain region of NURR1-knockout mice (58). Dopamine neurons in the midbrain have been implicated by numerous studies as abnormal in schizophrenia (for reviews see refs. 59–62). NURR1 (also known as NOT) is mapped between *D2S284* and *D2S142*. *D2S142* is at chromosome 2q22-q23. A karotyping anomaly has been associated with schizophrenia near this locus (41) and the *D2S142* marker has been suggestively linked to schizophrenia in an Icelandic isolate (25), but proof of the linkage has not been convincingly demonstrated (42). ALDH1 expression is also lacking in the dopamine-expressing regions of NURR1-knockout mice. Because ALDH1 and RXR are important for retinoic acid synthesis (6, 16), Zetterstrom *et al.* (ref. 58, p. 249) suggest that "retinoids may activate RXR–NURR1 heterodimers in developing dopamine neurons." Despite weak evidence for linkage of schizophrenia to the 2q22 locus of NURR1, the finding of the lack of midbrain dopamine neurons in NURR1-knockout mice strongly implicates NURR1 and its heterodimeric partner, RXR, in the etiology of schizophrenia.

The biochemical connection between retinoic acid and schizophrenia is made via the dopamine system. The genetic connection is that the locus of *RXR*β is at 6p21.3 and *RAR*β is at 3p24.3. Both of these loci have been suggestively linked to schizophrenia (24–29, 38, 54). RXR has been termed the "master regulator" of retinoid transcription (ref. 16, p. 841). In line with the above explication that retinoid transcription requires heterodimeric partners, the linkage findings at the 6p21.3, 3p24.3, and 2q22-q23 loci may be improved if markers at the loci flanking the retinoid nuclear receptors and the NURR1 heterodimer were modeled simultaneously (i.e., *RXR*β*–RAR*β*, RXR*β*–NURR1, RAR*β*–NURR1*).

Expression of Schizophrenia Candidate Genes Is Regulated by Retinoic Acid

The third line of evidence relates the targets of retinoid regulation to numerous schizophrenia candidate genes. Retinoic acid regulates target genes by combining with RARs and RXRs, which control transcription of these targets. After activation in the presence of retinoic acid, these receptors bind to specific DNA sequences within the promoter–enhancer regions of target genes. These DNA motifs are known as retinoic acid response elements (RAREs or RXREs). Through this mechanism retinoic acid receptors and their

partners regulate the expression of multiple target genes. The regulation in the expression of these target genes results in changes in cell function that produces normal or abnormal physiological states (15).

Among the many genes and molecules shown to be the targets of retinoic acid transcriptional regulation are dopamine (63) and dopamine receptors (64, 65). In addition, serotonin (66, 67), glutamate receptors (68, 69), tyrosine hydroxylase and dopamine β-hydroxylase (70, 72), nicotine receptors (76), choline acetyltransferase (70–74, 77–79), arachidonic acid (80), and phospholipase A2 (81, 82) are retinoid targets proposed as a candidates in schizophrenia. Other schizophrenia candidate genes and molecules regulated by retinoic acid include: amyloid precursor protein (83), microtubule-associated protein 2 (tau) (83), c-*fos* (84), c-*jun* (85), ciliary neurotropic/leukemia inhibitory factor (86, 87), *N*-methyl-D-aspartate receptors 1 and 2B (88), δ opioid receptor (88), γ-aminobutyric acid type A receptor (89), growth-associated protein 43 (90), interleukin 2 receptors α and β (91), neurofilament 66 (92), neurofilament light (92), oxytocin (75, 93, 94), and protein kinase Cα and -β (95, 96).

Considering the vast capacity for retinoids to regulate numerous target genes involved in neurodevelopment (63–96), what are the possibilities for narrowing retinoid function specifically to schizophrenia? Retinoid regulation specific to schizophrenia should occur through receptor-mediated signaling involving crosstalk between the retinoid receptors and receptors involved in schizophrenia, particularly the dopamine receptors. The temporal appearance of the dopamine receptors in the developing brain at a time of high retinoid activity (6) provides the necessary window of receptivity for retinoid regulation of these schizophrenia candidates.

Recent reports from three different laboratories working on the dopamine D2 receptor (*DRD2*) promoter provide major support for the role of retinoid regulation of dopamine receptors in schizophrenia. The promoter region of the *DRD2* gene has been sequenced (97), and in a Japanese sample this region demonstrates a functional polymorphism significantly associated with schizophrenia (98). Most importantly, Chambon and coworkers (64) have demonstrated that this region contains a functional *RARE/RXRE* DNA motif sequence that regulates the expression of DRD2 in the dopaminergic cells in mesencephalic neurons. RAR–RXR double null mutants, but not RAR or RXR single mutants, display aberrant locomotive behaviors and dopamine signaling (99). These new findings clearly relate retinoid-regulated genetic transcription to control of the expression of dopamine receptors, "the most obvious candidate genes in schizophrenia" (ref. 56, p. 128).

Numerous genes are involved in the exquisitely complicated and sensitive activation of the retinoid signaling cascade to ensure the control and fine tuning of the expression of target genes (2). These genes are situated throughout the genome (Table 1), activating target genes (see above) located on many different chromosomes. But it appears that, because the genes are highly conserved across phyla, the various loci of retinoid transcriptional regulators contain not only the transcription factors themselves, but also several of their retinoid target genes (10). Locus of control or operon-like functioning has been proposed for chromosomal regions containing retinoid-regulated genes (78, 100, 101); therefore, perturbation of the chromatin structure (102) in areas under retinoid control may disrupt the expression of many interrelated genes that are part of the retinoid signaling system and its regulated targets, absenting any mutation in the genes in question (10). Chromosomal perturbation has been suggested in relation to an expanding trinucleotide repeat identified in a large Danish schizophrenia pedigree (103). This expanding repeat is near the locus of the retinol transport protein, TTR, a crucial protein in the retinoid cascade (104). TTR represents 25% of all protein made in the cerebrospinal fluid and contained in the brain ventricles and is a major transporter of retinoid across the choroid plexus into the brain (10, 105, 106). The 18q12 locus containing TTR has very recently been linked to both bipolar illness (53) and schizophrenia (55). Determination of TTR expression, as well as the expression of other schizophrenia candidates in this pedigree, will be of interest.

Future Directions

I have suggested that retinoid dysregulation may be responsible for the altered expression of glutamic acid decarboxylase (GAD) neurons found in schizophrenic brains, because a *RARE* motif has been identified in the promoter region of a murine *GAD* (12). Human *GAD3* is at the chromosome 22q13 locus of *PPAR*α, one of the retinoid heterodimeric partners. *GAD1* is at chromosome 2q23-q24, immediately adjacent to, and perhaps overlapping, the *NURR1* locus, also a retinoid heterodimer. A similar mechanism may apply to *DRD2*, where the point mutation of the promoter associated with schizophrenia in the Japanese sample (98) may perturb the activation of the recently identified promoter RARE (64). As with *DRD2*, it is important to determine whether the promoter regions of other schizophrenia candidate genes contain functional *RARE*s and heterodimeric partner response element motifs. Such findings would indicate direct control of these schizophrenia candidate genes by retinoid.

To my knowledge no laboratories have studied sequencing of promoters and coding regions or differential expression of any of the genes of the retinoid cascade in schizophrenia samples, nor have polymorphic markers exactly flanking these genes been used in schizophrenia linkage or association studies. To date, no studies using two-locus models with epistatic interaction have been published, although the head of one of the leading schizophrenia linkage laboratories has recently recommended employing such a strategy (107).

In view of the very modest logarithm of odds scores achieved in all schizophrenia linkage studies to date, and considering the heterodimeric nature of action of the retinoid nuclear transcription factors, if retinoids are involved in schizophrenia, a two-locus model, using flanking markers for *RXR*β at 6p21.3 or *RAR*β at 3p24.3 and a heterodimeric partner, e.g., *PPAR*α at 22q12-q13 or *NURR1* at 2q22-q23, would better fit the biological activity of the genes than the single-locus and multipoint models that are now being used. An even more complex model could include allelic variants of enzymes within the retinoid cascade—e.g., *LPL*, which, as reported by Straub (Chromosome 8 Workshop of the 1997 World Congress on Psychiatric Genetics), attains the maximum logarithim of odds score for the chromosome 8 linkage studies of the Irish schizophrenia pedigrees. Other possibilities might include *ALDH1* at 9q21 or *CYP2D6* at 22q12-q13, which encode enzymes that catalyze the irreversible oxidation of retinal to retinoic acid, the final and primary morphogen of the retinoid cascade. ALDH1 is normally present in the dopaminergic areas of the brain (6), but is absent in NURR1-deficient mice (58).

Such sophisticated modeling would involve the development of new computerized linkage programs, but the technology is available to support this development (107). In each case, the models would employ the convergent loci technique, which is suggested by the convergence of retinoid loci with schizophrenia linkages. Markers for retinoid cascade genes would be selected to illuminate a suspected underlying metabolic defect in schizophrenia. This modeling would narrow the focus of more random genome scans and simultaneously, by employing such specific markers, should reveal an underlying metabolic defect in the disease.

The demonstration that retinoids are involved in the downstream transcriptional regulation of schizophrenia candidate genes reveals an entirely new strategy for the treatment of this

intractible disorder, the use of retinoid analogs. Sager observed that "dys-regulated genes are at least as important potential targets for therapy as mutated genes, and there are many more of them. Inducing reexpression of these genes by pharmacological intervention offers a promising approach" (ref. 108, p. 954). This strategy would concentrate on normalizing the aberrant expression of genes involved in schizophrenia at the RNA level, rather than on seeking mutations at the DNA level (108). For example, the acute effects of inflammation caused by the liberation of arachidonic acid from phospholipase pools have been altered by a retinoid analog, which affects the transcriptional expression of phospholipase A2 (81). In this respect, retinoid-induced cell differentiation has been shown to regulate the expression of phospholipase A2 (82). Several reports have suggested that phospholipase A2 levels are abnormal in the functional psychoses (109–111). It should also be noted that arachidonic acid is a ligand for the PPARs, which interact as heterodimeric partners with the RXRs to regulate the expression of multiple target genes. Arachidonic acid itself is a target of retinoid regulation (80). Thus, there are probably many complicated interactions involving multiple transcription factors, individual promoters, regulatory roles, cascades of regulation, and autoregulatory feedback pathways, which would be effected by the employment of analogs for the transcriptional regulators of the retinoid cascade for the treatment of schizophrenia.

Portions of this paper were presented at the 1997 World Congress on Psychiatric Genetics, Santa Fe, NM, on October 21, 1997. My gratitude goes to Arthur B. Pardee for the knowledgeable comments and organizational skills he generously offered in his readings of this paper. I also thank Karen Swisshelm for bringing NURR1 to my attention, Ralph Nixon, and the helpful staff of the library at The Nathan S. Kline Institute for Psychiatric Research.

1. Bullmore, E. T., Frangou, S. & Murray, R. M. (1997) *Schizophr. Res.* **28,** 147–156.
2. Eichele, G. (1997) *Trends Genet.* **13,** 343–345.
3. Sporn, M. B., Roberts, A. B. & Goodman, D. S., eds. (1994) *The Retinoids: Biology, Chemistry, and Medicine* (Raven, New York), 2nd Ed.
4. Satre, M. A., Ugen, K. D. & Kochbar, D. M. (1992) *Biol. Reprod.* **46,** 802–810.
5. Nau, H., Chahoud, I., Dencker, L., Lammer, E. J. & Scott, W. J. (1994) in *Vitamin A in Health and Disease*, ed. Blomhoff, R. (Dekker, New York), pp. 615–663.
6. McCaffery, P. & Drager, U. C. (1994) *Proc. Natl. Acad. Sci. USA* **91,** 7772–7776.
7. Lumsden, A. & Krumlauf, R. (1996) *Science* **274,** 1109–1115.
8. Forrester, L. M., Nagy, A., Sam, A., Stevenson, L., Bernstein, A., Joyner, A. L. & Wurst, W. (1996) *Proc. Natl. Acad. Sci. USA* **93,** 1677–1682.
9. Goodman, A. B. (1994) *Am. J. Psychiatry* **151,** 452–453.
10. Goodman, A. B. (1995) *Am. J. Med. Genet.* **60,** 335–348.
11. Goodman, A. B. (1996) *Schizophr. Res.* **19,** 163–170.
12. Goodman, A. B. (1996) *Arch. Gen. Psychiatry* **53,** 653.
13. Moldin, S. O. & Gottesman, I. I. (1997) *Schizophr. Bull.* **23,** 547–561.
14. Rahav, M., Goodman, A. B., Popper, M. & Lin, S. P. (1986) *Am. J. Psychiatry* **143,** 1249–1254.
15. Mangelsdorf, D. J., Umesono, K. & Evans, R. M. (1994) in *The Retinoids: Biology, Chemistry, and Medicine,* eds. Sporn, M. B., Roberts, A. & Goodman, D. S. (Raven, New York), 2nd Ed., pp. 319–349.
16. Mangelsdorf, D. J. & Evans, R. M. (1995) *Cell* **83,** 841–850.
17. Goodman, A. B. (1996) *J. NeuroVirol.* **2,** 204.
18. Blaner, W. S., Obunike, J. C., Kurlandsky, S. B., Al-Haideri, M., Piantedosi, R. P., Deckelbaum, R. J. & Goldberg, I. J. (1994) *J. Biol. Chem.* **269,** 16559–16565.
19. Duester, G. (1996) *Biochemistry* **35,** 12221–12227.
20. Westin, S., Sonneveld, E., van der Leede, B. M., van der Saag, P. T., Gustafsson, J. A. & Mode, A. (1997) *Mol. Cell. Endocrinol.* **129,** 169–179.
21. White, J. A., Guo, Y. D., Baetz, K., Beckett-Jones, B., Bonasoro, J., Hsu, K. E., Dilworth, J. F., Hones, G. & Petkovich, M. (1996) *J. Biol. Chem.* **271,** 29922–29927.
22. Raner, G. M., Vaz, A. D. & Coon, M. J. (1996) *Mol. Pharmacol.* **49,** 515–522.
23. Goldberg, I. J., Soprano, D. R., Wyatt, M. L., Vanni, T. M., Kirchgessner, T. G. & Schotz, M. C. (1989) *J. Lipid Res.* **30,** 1569–1577.
24. Antonarakis, S. E,, Blouin, J. L., Pulver, A. E., Wolyniec, P., Lasseter, V. K., Nestadt, G., Kasch, L., Babb, R., Kazazian, H. H., Dombroski, B., *et al.* (1995) *Nat. Genet.* **11,** 235–236.
25. Moises, H. W., Yang, L., Kristbjarnarson, H., Wiese, C., Byerley, W., Macciardi, F., Arolt, V., Blackwood, D., Liu, X., Sjogren, B., *et al.* (1995) *Nat. Genet.* **11,** 321–324.
26. Straub, R. E., MacLean, C. J., O'Neill, F. A., Burke, J., Murphy, B., Duke, F., Shinkwin, R., Webb, B. T., Zhang, J., Walsh, D., *et al.* (1995) *Nat. Genet.* **11,** 287–293.
27. Schwab, S. G., Albus, M., Hallmayer, J., Honig, S., Borrmann, M., Lichtermann, D., Ebstein, R. P., Ackenheil, M., Lerer, B., Risch, N., *et al.* (1995) *Nat. Genet.* **11,** 325–327.
28. Wright, P., Donaldson, P. T., Underhill, J. A., Choudhuri, K., Doherty, D. G. & Murray, R. M. (1996) *Am. J. Psychiatry* **153,** 1530–1533.
29. Schizophrenia Linkage Collaborative Group for Chromosomes 3, 6, and 8 (1996) *Am. J. Med. Genet.* **67,** 580–594.
30. Pulver, A. E., Karayiorgou, M., Wolyniec, P. S., Lasseter, V. K., Kasch, L., Nestadt, G., Antonarakis, S., Housman, D., Kazazian, H. H., Meyers, D., *et al.* (1994) *Am. J. Med. Genet.* **54,** 36–43.
31. Moises, H. W., Yang, L., Li, T., Havsteen, B., Fimmers, R., Baur, M. P., Liu, X. & Gottesman, I. I. (1995) *Am. J. Med. Genet.* **60,** 465–467.
32. Gill, M., Vallada, H. P., Collier, D., Sham, P., Holmans, P., Murray, R., McGuffin, P., Nanko, S., Owen, M., Antonarakis, S., *et al.* (1996) *Am. J. Med. Genet.* **67,** 40–45.
33. Vallada, H. P., Gill, M., Sham, P., Lim, L. C., Nanko, S., Asherson, P., Murray, R. M., McGuffin, P., Owen, M. & Collier, D. (1995) *Am. J. Med. Genet.* **60,** 139–146.
34. Zill, P., Schwab, S. G., Eckstein, G. N., Albus, M., Hallmayer, J., Lerer, B., Maier, W. & Wildenauer, D. B. (1997) *Am. J. Med. Genet.* **74,** 678.
35. Schwab, S. G., Lerer, B., Albus, M., Maier, W., Hallmayer, J., Fimmers, R., Lichtermann, D., Minges, J., Bondy, B., Ackenheil, M., *et al.* (1995) *Am. J. Med. Genet.* **60,** 436–443.
36. Coon, H., Holik, J., Hoff, M., Reimherr, F., Wender, P., Myles-Worsley, M., Waldo, M., Freedman, R. & Byerley, W. (1994) *Am. J. Med. Genet.* **54,** 72–79.
37. De Lisi, L. E. (1997) *Schizophr. Res.* **28,** 163–175.
38. Pulver, A. E., Lasseter, V. K., Kasch, L., Wolyniec, P., Nestadt, G., Blouin, J. L., Kimberland, M., Babb, R., Vourlis, S., Chen, H., *et al.* (1995) *Am. J. Med. Genet.* **60,** 252–260.
39. Kendler, K. D., MacLean, C. J., O'Neill, F. A., Burke, J., Murphy, B., Duke, F., Shinkwin, R., Easter, S. M., Webb, B. T., *et al.* (1996) *Am. J. Psychiatry.* **153,** 1534–1540.
40. Wang, S., Sun, C.-E., Walczak, C. A., Ziegle, J. S., Kipps, B. R., Goldin, L. R. & Diehl, S. R. (1995) *Nat. Genet.* **10,** 41–46.
41. Genest, P., Dumas, I. & Genest, F. B. (1976) *Union Med. Can.* **105,** 1676–1681.
42. Aschauer, H. N., Fischer, G., Isenberg, K. E., Meszaros, K., Willinger, U., Todd, R. D., Beran, H., Strobl, R., Lang, M., Fuchs, K., *et al.* (1993) *Eur. Arch. Psychiatry. Clin. Neurosci.* **243,** 193–198.
43. Kosower, N. S., Gerad, L., Goldstein, M., Parasol, N., Zipser, Y., Ragolsky, M., Rozencwaig, S., Elkabetz, E., Abramovitch Y., Lerer, B., *et al.* (1995) *Am. J. Med. Genet.* **60,** 133–138.
44. Wilhelmsen, K. C., Lynch, T., Pavlou, E., Higgins, M. & Nygaard, T. G. (1994) *Am. J. Hum. Genet.* **55,** 1159–1165.
45. St. Clair, D., Blackwood, D., Muir, W., Carothers, A., Walker, M., Spowart, G., Gosden, C. & Evans, H. J. (1990) *Lancet* **336,** 13–16.
46. Maziade, M., Raymond, V., Cliche, D., Fournier, J. P., Caron, C., Garneau, Y., Nicole, L., Marcotte, P., Couture, C., Simard, C., *et al.* (1995) *Am. J. Med. Genet.* **60,** 522–528.
47. Arinami, T., Itokawa, M., Enguchi, H., Tagaya, H., Yano, S., Shimizu, H., Hamaguchi, H. & Toru, M. (1994) *Lancet* **343,** 703–704.

48. Nimgaonkar, V. L., Sanders, A. R., Ganguli, R., Zhang, X. R., Brar, J., Hogge, W., Fann, W. E., Patel, P. I. & Chakravarti, A. (1996) *Am. J. Med. Genet.* **67,** 505–514.
49. Shaikh, S., Collier, D. A., Sham, P. C., Ball, D., Aitchison, K., Vallada, H., Smith, I., Gill, M. & Kerwin, R. W. (1996) *Hum. Genet.* **97,** 714–719.
50. Griffon, N., Crocq, M. A., Pilon, C., Martres, M. P., Mayerova, A., Uyanik, G., Burgert, E., Duval, F., Macher, J. P., Javoy-Agid, F., *et al.* (1996) *Am. J. Med. Genet.* **67,** 63–70.
51. Nanko, S., Kunugi, H., Sasaki, T., Fukuda, R., Kawate, T. & Kazamatsuri, H. (1993) *Biol. Psychiatry* **33,** 655–658.
52. Garofalo, G., Ragusa, R. M., Argiolas, A., Scavuzzo, C., Spina, E. & Bartletta, C. (1993) *Ann. Genet.* **36,** 132–135.
53. Ewald, H., Mors, O., Koed, K., Eiberg, H. & Kruse T. A. (1997) *Psychiat. Genet.* **7,** 1–12.
54. Bennett, P., Coon, H., Hoff, M., Rosenthal, J. & Byerley, W. (1997) *Am. J. Med. Genet.* **74,** 662.
55. Merette, C., Bissonnette, L., Rouillard, E., Roy, M. A. & Maziade, M. (1997) *Am. J. Med. Genet.* **74,** 674.
56. McGuffin, P. & Owen, M. J. (1996) *Cold Spring Harbor Symp. Quant. Biol.* **61,** 815–822.
57. Kirov, G. & Murray, R. (1997) *Mol. Med. Today,* no. 3, 124–130.
58. Zetterstrom, R. H., Solomin, L., Jansson, L., Hoffer, B. J., Olson, L. & Perlmann, T. (1997) *Science* **276,** 248–250.
59. Kapur, S. & Remington, G. (1996) *Am. J. Psychiatry* **153,** 466–476.
60. Horger, B. A. & Roth, R. H. (1996) *Crit. Rev. Neurobiol.* **10,** 395–418.
61. Garcia-Rill, R., Biedermann, J. A., Chambers, T., Skinner, R. D., Mark, R. E., Husain, M. & Karson, C. N. (1995) *Neuroscience* **66,** 321–325.
62. Haber, S. N. & Fudge, J. L. (1997) *Schizophr. Bull.* **23,** 471–482.
63. Mena, M. A., Casarejos, M. J., Bonin, A., Ramos, J. A. & Garcia Yebenes, J. (1995) *J. Neurochem.* **65,** 2612–2620.
64. Samad, T. A., Krezel, W., Chambon, P. & Borrelli, E. (1997) *Proc. Natl. Acad. Sci. USA* **94,** 14349–14354.
65. Farouqui, S. M. (1994) *Life Sci.* **55,** 1897–1893.
66. Ruiz i Altaba, A. & Jessell, T. M. (1991) *Development (Cambridge, U.K.)* **112,** 945–958.
67. Ito, K. & Morita, T. (1995) *Dev. Dyn.* **204,** 211–218.
68. Ray, W. J. & Gottlieb, D. I. (1993) *Biochem. Biophys. Res. Commun.* **197,** 1475–1482.
69. Hardy, M., Younkin, D., Tang, C. M., Pleasure, J., Shi, Q. Y., Williams, M. & Pleasure, D. (1994) *J. Neurochem.* **63,** 482–489.
70. Berrard, S., Faucon Biguet, N., Houhou, L., Lamouroux, A. & Mallet, J. (1993) *J. Neurosci. Res.* **35,** 382–389.
71. Pedersen, W. A., Berse, B., Schuler, U., Wainer, B. H. & Blusztajn, J. K. (1995) *J. Neurochem.* **65,** 50–58.
72. Kobayashi, M., Matsuoka, I. & Kurihara, K. (1994) *FEBS Lett.* **337,** 259–264.
73. Cervini, R., Berrard, S., Bejanin, S. & Mallet, J. (1994) *Neuroreport* **5,** 1345–1348.
74. Berse, B. & Blusztajn, J. K. (1997) *FEBS Lett.* **410,** 175–179.
75. Adan, R. A., Cox, J. J., Beischlag, T. V. & Burbach, J. P. (1993) *Mol. Endocrinol.* **7,** 47–57.
76. Cauley, K., Marks, M., Gahring, L. C. & Rogers, S. W. (1996) *J. Neurobiol.* **30,** 303–314.
77. Zeller, M. & Straus, W. L. (1995) *Int. J. Dev. Neurosci.* **13,** 437–445.
78. Berse, B. & Blusztajn, J. K. (1995) *J. Biol. Chem.* **270,** 22101–22104.
79. Berrard, S., Varoqui, H., Cervini, R., Mallet, J. M. & Diebler, M. R. (1995) *J. Neurochem.* **65,** 939–942.
80. Petroni, A., Blasevich, M., Papini, M., La Spada, P. & Galli, C. (1996) *J. Neurochem.* **67,** 549–556.
81. Burke, J. K., Gregor, K. R. & Tramposch, K. M. (1995) *J. Biol. Chem.* **270,** 274–280.
82. Hill, E. M., Bader, T., Nettesheim, P. & Eling, T. (1996) *Am. J. Physiol.* **270,** L854–L862.
83. Fukuchi, K., Deeb, S. S., Kamino, K., Ogburn, C. E., Snow, A. D., Sekiguchi, R. T., Wight, T. N., Puissan, H. & Martin G. M. (1992) *J. Neurochem.* **58,** 1863–1873.
84. Desai, S. H. & Niles, R. M. (1997) *J. Biol. Chem.* **272,** 2809–2815.
85. Barrett, T. J., Vig, E. & Vedeckis, W. V. (1996) *Biochemistry* **35,** 9746–9753.
86. Nakanishi, T., Ishii, K., Kukushima, N., Asanuma, M., Iwata, E. & Ogawa, N. (1996) *Biochem. Mol. Biol. Int.* **38,** 763–772.
87. Malek, R. L. & Halvorsen, S. W. (1997) *J. Neurobiol.* **32,** 81–94.
88. Beczkowska, I. W., Buck, J. & Inturrisi, C. E. (1996) *Brain Res. Bull.* **39,** 193–199.
89. Reynolds, J. N., Prasad, A., Gillespie, L. & Paterno, G. D. (1996) *Brain Res. Mol. Brain Res.* **35,** 11–18.
90. Neuman, K., Soosaar, A., Nornes, H. O. & Neuman, T. (1995) *J. Neurosci. Res.* **41,** 39–48.
91. Sidell, N., Chang, B. & Bhatti, L. (1993) *Cell. Immunol.* **146,** 28–37.
92. Chiu, F. C., Feng, L., Chan, S. O., Pakin, C. & Federoff, J. H. (1995) *Brain Res. Mol. Brain Res.* **30,** 77–86.
93. Richard, S. & Zingg, H. H. (1991) *J. Biol. Chem.* **266,** 21428–21433.
94. Larcher, A., Neculcea, J., Chu, K. & Zingg, H. H. (1995) *Mol. Cell. Endocrinol.* **114,** 69–76.
95. Khuri, F. R., Cho, Y. & Talmage, D. A. (1996) *Cell Growth Differ.* **7,** 595–602.
96. Gruber, J. R., Desai, S., Blusztajn, J. K. & Niles, R. M. (1995) *Exp. Cell Res.* **221,** 377–384.
97. Minowa, T., Minowa, M. T. & Mouradian, M. M. (1994) *J. Biol. Chem.* **269,** 11656–11662.
98. Arinami, T., Gao, M., Hamaguchi, H. & Toru, M. (1997) *Hum. Mol. Genet.* **6,** 577–582.
99. Krezel, W., Ghyselinck, N., Samad, T. A., Dupe, V., Kastner, P., Borrelli, E. & Chambon, P. (1998) *Science* **279,** 863–867.
100. Langston, A. W. & Gudas, L. J. (1992) *Mech. Dev.* **38,** 217–228.
101. Usdin, T. B., Eiden, L. E., Bonner, T. I. & Erickson, J. D. (1995) *Trends Neurosci.* **18,** 218–224.
102. Simonic, I. & Ott, J. (1996) *Schizophr. Res.* **20,** 235–237.
103. Sirugo, G., Pakstis, A. J., Kidd, K. K., Matthysse, S., Levy, D. L., Holzman, P. S., Parnas, J., McInnis, M., Breschel, T. & Ross, C. A. (1997) *Am. J. Med. Genet.* **74,** 546–548.
104. Goodman, A. B. (1998) *Am. J. Med. Genet.*, in press.
105. Herbert, J., Wilcox, J. N., Pham, K.-T. C., Fremeau, R. T., Jr., Zeviani, M., Dwork, A., Soprano, D. R., Makover, A., Goodman, D. S., Zimmerman, E. A., *et al.* (1986) *Neurology* **36,** 900–911.
106. Goodman, A. B. (1994b) *Am. J. Med. Genet.* **54,** 271–278.
107. Kidd, K. K. (1997) *Am. J. Med. Genet.* **74,** 104–111.
108. Sager, R. (1997) *Proc. Natl. Acad. Sci. USA* **94,** 952–955.
109. Gattaz, W. F., Schmitt, A. & Maras, A. (1995) *Schizophr. Res.* **16,** 1–6.
110. Hudson, C. J. (1996) *Schizophr. Res.* **21,** 111–116.
111. Ross, B. M., Hudson, C. J., Erlich, J., Warsh, J. J. & Kish, S. F. (1997) *Arch. Gen. Psychiatry* **54,** 487–494.