Investigation of a Candidate Gene for Schizophrenia on Xq13 Previously Associated With Mental Retardation and Hypothyroidism

Lynn E. DeLisi,[1]* Angela B. Smith,[1] Kamran Razi,[1] John Stewart,[1] Zhewu Wang,[2] Harinder K. Sandhu,[2] and Robert A. Philibert[2]

[1]Department of Psychiatry, SUNY Stony Brook, Stony Brook, New York
[2]Department of Psychiatry, University of Iowa, Iowa City, Iowa

Weak support for linkage of schizophrenia to proximal Xq has previously been reported. In addition, an increased prevalence of thyroid disorder has been noted in families of individuals with schizophrenia. Recently, a gene mapped to Xq13 termed *HOPA* has been found to be associated with mental retardation, hypothyroidism, and depression and to function as a coactivator for the thyroid receptor. We therefore examined the *HOPA* gene in a group of 111 probands from a larger cohort of multiplex families with schizophrenia, several of whom (n = 53) also had a family history of hypothyroidism. Four males and two females were found with an alteration in exon 42 of the *HOPA* gene compared with 8/492 males and 18/471 females (942 X chromosomes) compared with consecutively screened newborns ($\chi^2 = 3.92$, $P < 0.05$). However, when available family members of each of the probands with an exon 42 variation were subsequently screened, the mutation did not segregate with schizophrenia in three of five families, although all 6 probands with an exon 42 variation did have hypothyroidism in either themselves (n = 3) or their mothers (n = 3) ($P < 0.008$). These findings replicate prior findings demonstrating an association between *HOPA* polymorphisms and hypothyroidism. In addition, the increased frequency of *HOPA* variants in this population may also provide a genetic basis for the familial association of thyroid disease and schizophrenia. Am. J. Med. Genet. (Neuropsychiatr. Genet.) 96:398–403, 2000. © 2000 Wiley-Liss, Inc.

KEY WORDS: X chromosome; Xq13; schizophrenia; hypothyroidism; mental retardation

INTRODUCTION

A sex chromosome locus for schizophrenia has been previously hypothesized [Crow, 1988; Crow and DeLisi, 1991; DeLisi and Crow, 1989; DeLisi et al., 1988] based on the high frequency of X chromosome anomalies (XXY and XXX) among psychiatric hospital patients with psychosis [DeLisi et al., 1994b], an excess of same sex concordance for schizophrenia within families, and sex differences in age of onset and other clinical characteristics of the disorder. Linkage studies testing this hypothesis were either negative for the entire X chromosome [Okoro et al., 1995; Pulver et al., 1995] or weakly positive pericentromeric [Dann et al., 1997; DeLisi et al., 1994b; Hovatta et al., 1998; Lichtermann et al., 1999; Paterson, 1999; Williams et al., 1998]. In two recent studies extending results to a larger cohort [DeLisi et al., 1994a; Laval et al., 1998], minimally positive peak lod scores of approximately 1.5 were found pericentromeric. In the Laval et al. study, this peak was with marker DXS8032 mapped to Xp11.2 whereas a parallel QTL analysis of asymmetric hand-skill (a presumed measure of cerebral asymmetry) peaked within the Xq21.3 region approximately 20 cM away.

In addition, there is intriguing, though unexplained evidence for a higher frequency of thyroid abnormalities among relatives of patients with schizophrenia, particularly mothers of these patients [DeLisi et al., 1991; MacSweeney et al., 1978]. This increase is not surprising because alterations in thyroid function are associated with severe mental illness. For instance, thyroid abnormalities such as blunted TSH response and hypothyroidism are significantly increased among patients with depression [reviewed in Sachar, 1974] and schizophrenia [Ryan et al., 1994]. Furthermore, hyperthyroidism has long been known to cause an

---

acute psychosis [Granet and Kalman, 1978; Greer and Parsons, 1968; Roca et al., 1990]. However, whether there is a genetic basis for this association is unclear.

Recently, exonic variations in exon 42 of an Xq13 gene termed *HOPA* were associated with a syndrome of mental retardation, hypothyroidism, and psychiatric symptoms [Philibert et al., 1998; Philibert et al., 1999]. The association with hypothyroidism became more interesting after another group reported that the *HOPA* gene codes for a thyroid receptor coactivator [Ito et al., 1999]. Given the evidence suggesting some linkage of schizophrenia to proximal Xq and the high prevalence of hypothyroidism in the schizophrenic population, we then hypothesized that alterations in the *HOPA* sequence may be associated with increased risk for schizophrenia or hypothyroidism. Thus, in the present study, we report the results of our initial investigation of this hypothesis and conclude that further studies are clearly merited.

METHODS AND MATERIALS
Clinical

Families with schizophrenia or schizoaffective disorder in at least 2 siblings were identified over a period of approximately 15 years, from 1985 to the present [see DeLisi et al., 1987, 1994a; Garner et al., 1996; Shaw et al., 1998]. Those from the United States and collected within the Department of Psychiatry, SUNY, Stony Brook were screened for a history of multiple medical disorders including thyroid disease in a first-degree relative. Recruitment involved several methods: catchment area screening, systematic contact with health professionals at hospital and out-patient facilities, and advertisement through local and national support organizations for families of the mentally ill [i.e., the National Alliance for Mental Illness (NAMI)].

Diagnoses were made using *DSM–III–R* [American Psychiatric Association, 1987] criteria based on a combination of structured interviews, medical records from all hospitalizations, or other relevant treatment and structured information about each individual obtained from at least one reliable family member. A modified SADS interview was used from 1985–1994 [Schedule for Affective Disorder and Schizophrenia, Spitzer and Endicott, 1978] combined with the SIDP [Structured Interview for Personality Disorders, Pfohl et al., 1990]. From 1994 to the present, these forms were replaced by the newer, comprehensive DIGS interview [Diagnostic Interview for Genetic Studies, Nurnberger et al., 1994] and many of the ill individuals in previously obtained families were reinterviewed using this method.

In stage I of this study, coded blood or DNA samples from 111 unrelated probands (82 male, 29 females) from the aforementioned families were selected for genotyping with respect to *HOPA* exon 42. Of these, 85 were diagnosed with chronic schizophrenia, 22 schizoaffective disorder, depressed or mixed type, and 4 schizoaffective, manic type. Fifty-three of these schizophrenic probands (47 males, 6 females) had either personal and/or family history (first-degree relative) of hypothyroidism (11 probands, 32 mothers of probands, 5 fathers of probands, 19 siblings of probands). The other 58 schizophrenics (37 males, 21 females) did not have personal or family histories of hypothyroidism.

In stage II, DNA sample genotyping was performed on all available DNA from family members of probands who showed an unusual allelic variation in exon 42 of the *HOPA* gene.

Laboratory

Individuals who were blind to diagnostic status conducted all laboratory procedures. When necessary, DNA from blood samples of schizophrenic probands was prepared using a QuiAmp kit (Qiagen, Santa Clarita, CA, U.S.A.). Genotyping of the proband DNA at the exon 42 dodecamer repeat was performed using standard PCR protocols and conditions for radioisotopic genotyping, ^{35}S-dATP internal labeling, 10% DMSO and the following primers: (5′ to 3′) Forward TGCTTCCTCATCCCCTGCCCTCA and Reverse GGGCTGTAGTCCAGCAGCTACCTG. Cycling parameters were as follows: 95°C × 5 min, then 45 cycles of 95°C × 1 min, 65°C × 30 sec, and 72°C for 1 min. Approximately 3 μl of each of the PCR products were denatured, then loaded on a standard 6% polyacrylamide sequencing gel and electrophoresed for 2–3 hr. The gels were exposed to standard X-ray film and the visualized PCR products sized by comparison to an internal sequencing ladder. Gels were read independently and blindly with respect to sample status by R.P. and H.S.

The frequency of the exon 42 size polymorphism was determined by the sampling consecutive bloodspots provided by the State of Iowa Birth Registry. Briefly, DNA from bloodspots provided from a newborn registry (courtesy of Dr. Jeff Murray) were prepared using a standard QiaAmp kit (Qiagen). This DNA was then genotyped and analyzed as described earlier.

The sequence of *HOPA* exon 42 was delineated by standard methods in all four hemizygous probands and the father of one of the heterozygous probands who was a carrier for the 265 bp allele. Briefly, using the primers and cycling parameters delineated earlier and standard PCR conditions, a PCR product representing exon 42 was amplified, separated on agarose gel, excised from the gel with a razor blade, and then purified using a QUIquick PCR purification kit (Qiagen). The resulting PCR product was then sequenced using standard fluorescent protocols [Philibert et al., 1995].

Chi-square analyses (df = 1) were performed to compare the frequency of unusual variants in unrelated schizophrenic probands to the frequency of these variants in the newborn population.

RESULTS

Three differently sized alleles (238 bp, 253 bp, or 265 bp) for exon 42 of the *HOPA* gene were noted in the 111 probands from the Stony Brook cohort (see Table I). Three males were hemizygous for the 265 bp allele, 1 male was hemizygous for the 238 bp allele, and 2 females were heterozygous for the 265 base pair allele. The remainder of the subjects were either hemi- or homozygous for the more common 253 bp allele.

The frequency distribution of size polymorphisms was also determined in almost 1,000 consecutive new-

TABLE I. Frequency of HOPA Exon 42 Size Polymorphisms in Schizophrenic Probands

	With family history of hypothyroidism		Without family history of hypothyroidism	
	Male	Female*	Male	Female*
238 BP	1	0	0	0
253 BP	41	14	37	42
265 BP	3	2	0	0

*Denotes that the number of females have been multiplied by two giving the correct number of X-chromosomes.

borns from the state of Iowa. As Table II demonstrates, the 253 bp allele was the most common. (The X chromosomes of 484 males and 924 females carried this allele.) One female was heterozygous for the 238 bp allele, another female was heterozygous for the 256 bp allele, and 16 females were heterozygous for the 265 bp allele. We are still investigating whether 1 apparently homozygous female is truly homozygous or a partial or full Turner syndrome (X0) subject. For the purposes of this study, her data were excluded. Seven males were hemizygous for the 265 bp allele whereas 1 other male was hemizygous for the 250 bp allele. The remainder of the males and females appeared to be either hemizygous or heterozygous for the common 253 bp allele.

A chi-square analysis comparing schizophrenics to the controls (by all inherited X chromosomes; 1 from each male and 2 from each female) revealed a trend toward an excess of the 265 bp expansion in patients with schizophrenia ($\chi^2 = 2.83$, $P < 0.09$). When all anomalies were considered together (n = 6), the resulting chi square was 3.92, $P < 0.05$. However, it should be noted that all of these calculations are based on a few observations of an uncommon allele.

All 6 probands with an alteration in their sequence HOPA exon 4 had a history of hypothyroidism in themselves (n = 3) or their mother (n = 3) (6/53 vs. 0/58; $\chi^2 = 6.94$; $P < 0.008$). Because genotyping only allows alleles to be assessed on the basis of size, all 4 male hemizygotes and the father of 1 of the heterozygous female probands were sequenced with respect to HOPA exon 42. As Figure 1 shows, all four 265 bp hemizygotes possessed the same four amino acid polymorphism associated with an Xq13 mental retardation/hypothyroidism/depression syndrome reported previously. In addition, Figure 1 demonstrates that the newly discovered 238 bp variant allele is caused by the deletion of five glutamate residues in exon 42. The impact of these polymorphisms on protein function is not known.

TABLE II. Frequency of HOPA Exon 42 Six Polymorphisms in Iowa Newborns

	Male (N = 492)	Female* (N = 942)
238 BP	0	1
250 BP	1	0
253 BP	484	924
256 BP	0	1
265 BP	7	16

*Denotes that the number of females have been multiplied by two giving the correct number of X-chromosomes.

Available DNA from family members of the 5 probands with either the 265 bp expansion variant or the 238 bp deletion variant revealed a pattern of inheritance that segregated with hypothyroidism in each family, but with schizophrenia in only 2 of the 5 families. The 6th proband with an abnormality (265 bp) had hypothyroidism, but her family was not examined by genotyping. Figure 2 indicates the family pattern of inheritance of each allele, schizophrenia, and hypothyroidism.

DISCUSSION

In view of the previous observations, HOPA seemed to be a promising candidate gene for schizophrenia. The present study shows a small, but significant, excess of an allelic expansion of this gene among unrelated patients with schizophrenia (6 of 111 unrelated patients). However, when their family members were studied, HOPA variations did not significantly segregate with psychosis in the first-degree relatives. Taken together, these data suggest that although these variant polymorphisms may confer increased susceptibility to schizophrenia, they are clearly not a major risk factor for schizophrenia.

On the other hand, these data contribute more evidence about whether the 265 bp variant allele is associated with the pathogenesis of hypothyroidism or merely a neutral polymorphism physically linked to another causative mutation. In the first report [Philibert et al., 1998], only an association of the 265 bp polymorphism and the surrounding gene region with the syndrome was established. Thus, it was unclear whether the 265 bp allele was causal or was simply a neutral polymorphism that segregated with a "causative mutation." Because prior to the current study we had not found the 241 bp variant in any of over 1,000 males that we had studied previously, the finding of another new polymorphism in exon 42 in a family and a patient with hypothyroidism tends to suggest the former possibility. Furthermore, the recent findings by Ito and colleagues [Ito et al., 1999] that HOPA functions as a thyroxine receptor coactivator also strongly supports the hypothesis that these polymorphisms can cause thyroid hormone deficiency. Nevertheless, more definitive proof will require the completion of larger linkage disequilibrium and case control studies currently in progress.

The increase in thyroid disease among relatives of patients with schizophrenia, particularly mothers [DeLisi et al., 1991; MacSweeney et al., 1978], may be an important clue to the susceptibility for schizophrenia that still requires an explanation. One possibility could be that a gene for schizophrenia is on the X chromosome, more proximal or distal, but still linked to the HOPA gene. This would be consistent with the weak, but positive linkage results previously reported near this region [Dann et al., 1997; DeLisi et al., 1994a; Laval et al., 1998; Williams et al., 1998]. Thus, thyroid disease caused by a variant in the HOPA gene would be more likely to be inherited with schizophrenia in families if both are relatively common in the population. Alternatively, the genetic mechanisms that lead to in-

```
NORMAL    CTGCTTCCTCATCCCCTGCCCTCAGCCCTTTAGTTCTGAGGCTTAGCTTCCTCCCTCTGCTCCTTCTGAAGTATCTTTTGTGTTCTTATAG
FAMILY 1  CTGCTTCCTCATCCCCTGCCCTCAGCCCTTTAGTTCTGAGGCTTAGCTTCCTCCCTCTGCTCCTTCTGAAGTATCTTTTGTGTTCTTATAG
FAMILY 2  CTGCTTCCTCATCCCCTGCCCTCAGCCCTTTAGTTCTGAGGCTTAGCTTCCTCCCTCTGCTCCTTCTGAAGTATCTTTTGTGTTCTTATAG
FAMILY 3  CTGCTTCCTCATCCCCTGCCCTCAGCCCTTTAGTTCTGAGGCTTAGCTTCCTCCCTCTGCTCCTTCTGAAGTATCTTTTGTGTTCTTATAG
FAMILY 4  CTGCTTCCTCATCCCCTGCCCTCAGCCCTTTAGTTCTGAGGCTTAGCTTCCTCCCTCTGCTCCTTCTGAAGTATCTTTTGTGTTCTTATAG
FAMILY 5  CTGCTTCCTCATCCCCTGCCCTCAGCCCTTTAGTTCTGAGGCTTAGCTTCCTCCCTCTGCTCCTTCTGAAGTATCTTTTGTGTTCTTATAG
```

Continued
```
NORMAL    CAGCAGCAGCAACAGCAACAGCAGCAGCAGCAGCAGCAGCAACAGCAACAGCAGCAGCAGCAACAGCAACAA                CAGCAA
FAMILY 1  CAGCAGCAGCAACAGCAACAGCAGCAGCAGCAGCAGCAGCAACAGCAACAGCAGCAGCAGCAACAGCAACAACAGCAACACCAGCAGCAA
FAMILY 2  CAGCAGCAGCAACAGCAACAGCAGCAGCAGCAGCAGCAGCAACAGCAACAG                CAACAA                CAGCAA
FAMILY 3  CAGCAGCAGCAACAGCAACAGCAGCAGCAGCAGCAGCAGCAACAGCAACAGCAGCAGCAGCAACAGCAACAACAGCAACACCAGCAGCAA
FAMILY 4  CAGCAGCAGCAACAGCAACAGCAGCAGCAGCAGCAGCAGCAACAGCAACAGCAGCAGCAGCAACAGCAACAACAGCAACACCAGCAGCAA
FAMILY 5  CAGCAGCAGCAACAGCAACAGCAGCAGCAGCAGCAGCAGCAACAGCAACAGCAGCAGCAGCAACAGCAACAACAGCAACACCAGCAGCAA
              Q  Q  Q  Q  Q  Q  Q  Q  Q  Q  Q  Q  Q  Q  Q  Q  Q  Q  H  Q  Q  Q
```

Continued
```
NORMAL    CACCAGCAGCAACAGCAGCAACAGGCGGCTCCTCCCCAACCCCAGCCCCAGTCCCAGCCCCAGGTAGCTGCTGGACTACAGCCC
FAMILY 1  CACCAGCAGCAACAGCAGCAACAGGCGGCTCCTCCCCAACCCCAGCCCCAGTCCCAGCCCCAGGTAGCTGCTGGACTACAGCCC
FAMILY 2  CACCAGCAGCAACAGCAGCAACAGGCGGCTCCTCCCCAACCCCAGCCCCAGTCCCAGCCCCAGGTAGCTGCTGGACTACAGCCC
FAMILY 3  CACCAGCAGCAACAGCAGCAACAGGCGGCTCCTCCCCAACCCCAGCCCCAGTCCCAGCCCCAGGTAGCTGCTGGACTACAGCCC
FAMILY 4  CACCAGCAGCAACAGCAGCAACAGGCGGCTCCTCCCCAACCCCAGCCCCAGTCCCAGCCCCAGGTAGCTGCTGGACTACAGCCC
FAMILY 5  CACCAGCAGCAACAGCAGCAACAGGCGGCTCCTCCCCAACCCCAGCCCCAGTCCCAGCCCCAGGTAGCTGCTGGACTACAGCCC
          H  Q  Q  Q  Q  Q  Q  Q  A  A  P  P  Q  P  Q  P  Q  S  Q  P  Q
```

Fig. 1. Sequence and amino acid translation of the four hemizygous variants compared with the normal sequence of exon 42 of *HOPA* in five male individuals possessing a variant *HOPA* allele compared to the normal sequence. The male from Family 1 is the father of a heterozygous female proband. The other four males are from Families 2, 3, 4, and 5. Exonic regions of the sequence are underlined. The primer sequence areas are italicized and boldfaced. The amino acid translation is given in standard single letter format below the nucleic acid sequence. Q = CAG = Glutamine, H = CAC = Histadine, A = GCG = Alanine, P = CCC = Proline, S = TCC = Serine.

creased risk for hypothyroidism through variants in the *HOPA* gene may also lead to a pleiotropic increased relative risk to mental illness, in particular, schizophrenia. This latter possibility is particularly intriguing given findings that *HOPA* may interact with a number of other RXR nuclear receptors [Naar et al., 1999; Rachez et al., 1999] including the retinoic acid and the glucocorticoid receptors, and these have been hypothesized to be important in the pathogenesis of schizophrenia [Goodman, 1998] and depression [Barden, 1999], respectively. Unfortunately, because

the *HOPA* exon 42 variation is relatively uninformative, these hypotheses require testing with more informative markers and larger numbers of subjects.

The data from our present study may also be relevant to recent findings demonstrating that maternal thyroid deficiency during pregnancy can have an adverse effect on the subsequent neuropsychological functioning of offspring. In a recent study [Haddow et al., 1999], the offspring of mothers who had undiagnosed thyroid hormone deficiency during pregnancy showed significantly lower performance in some cognitive

Fig. 2. Pedigree diagrams of the families with schizophrenia in at least two siblings and the rare variants in the *HOPA* gene.

tasks of attention and language at ages 7–9 as compared with matched controls. These findings in humans complement early experiments in rodents that show abnormal neuronal biochemistry and cell maturation with reduced thyroid hormone exposure in utero [Balazs et al., 1971; Eayrs, 1967]. Because schizophrenia susceptibility, whether determined by variable gene sequences, is likely to result from a neurodevelopmental anomaly, these observations could explain why there is an association of schizophrenia with maternal thyroid deficiency and suggest a genetic mechanism through which this effect could be accomplished.

In the prior study, an increased incidence of the 265 bp variant allele was reported in males from three independent mentally retarded and institutionalized cohorts [Philibert et al., 1998]. The overall incidence of the 265 bp allele in these three cohorts of males of European ethnic origin was reported to be between 5–8% whereas in this study the incidence of the allele in males from the over 98% European-derived Iowa population was 1.3%, indicating that the increased relative risk for mental retardation due to this allele is between three- and five-fold. In the current study, 4 males were observed to be hemizygous for the 265 bp allele but none of them have been diagnosed with mental retardation. The incidence of mental retardation in the general population is approximately 1% [Hodapp and Dykens, 1996]. If the calculated relative risk for this gene is approximately three- to five-fold, we would hypothesize that only 1 in 20 to 30 male hemizygotes for the 265 bp allele have mental retardation. Therefore, it is not surprising that none of the 4 probands were observed to have mental retardation in the current study. However, decreased intellectual functioning has been documented to occur in individuals who develop schizophrenia even prior to the onset of psychosis [Davidson et al., 1999]. Although cognitive testing was not performed on the probands with the 265 bp allele in the present study, we nevertheless speculate that some of the diminished intellectual functioning seen in schizophrenia could represent pleiotropic effects of *HOPA* gene variations.

False positive results in association studies can be due to population stratification differences between patients and control groups. Although this might explain our present results, both the Iowa newborn and national U.S. schizophrenia samples consisted of almost all of Caucasions and no known ethnic differences emerged between those in the schizophrenia sample with and without thyroid disorder in their families. However, future studies using parent offspring triads examining the frequency of transmitted versus nontransmitted alleles may be more reliable for avoiding this problem.

In summary, we replicate the prior association of hypothyroidism with exonic polymorphisms in the Xq13 gene *HOPA* in this subset population of schizophrenic/schizoaffective probands. Although the overall allele frequency is higher in this cohort, we do not demonstrate familial segregation of this exonic polymorphism with psychosis. We conclude that further research is needed to examine this and other X-chromosome loci involved with neurodevelopment and their role in the subsequent development of neuropsychiatric and cognitive disorders.

REFERENCES

American Psychiatric Association. 1987. Diagnostic and statistical manual of mental disorders (3rd ed., revised). Washington, DC.

Balazs R, Kovacs S, Cocks WA, Johnson AL, Eayrs JT. 1971. Effect of thyroid hormone on the biochemical maturation of rat brain: postnatal cell formation. Brain Res 25:555–570.

Barden N. 1999. Regulation of corticosteroid receptor gene expression in depression and antidepressant action. J Psychiatr Neurosci 24:25–39.

Crow TJ. 1988. Sex chromosomes and psychosis: the case for a pseudoautosomal locus. Br J Psychiatr 153:675–683.

Crow TJ, DeLisi LE. 1991. X and Y linkage in schizophrenia. Psychiatr Genet 2(1):102–103.

Dann J, DeLisi LE, Devoto M, Laval S, Nancarrow D, Shields G, SmithA, Loftus J, Peterson P, Vita A, Vita A, Comazzi, M, Invernizzi, G, Levinson, DF, Wildenauer, D, Mowry, BJ, Collier, D, Powell, J, Crowe, RR, Andreasen, NC, Silverman, JM, Mohs, RC, Murray, RM, Walters, MK, Lennon, DP, Hayward, NK, Albus, M, Lerer, B, Maier, W, Crow, TJ. 1997. A linkage study of schizophrenia to markers within Xp11 near the MAOB gene. Psychiatr Res 70:131–143.

Davidson M, Reichenberg A, Rainowitz J, Weiser M, Kaplan Z, Mordehai, M. 1999. Behavioral and intellectual markers for schizophrenia in apparently healthy male adolescents. Am J Psychiatr 156:1328–1335.

DeLisi LE, Crow TJ. 1989. Evidence for an X chromosome locus for schizophrenia. Schiz Bull 15:431–440.

DeLisi LE, Boccio AM, Riordan H, Hoff AL, Dorfman A, McClelland J, Kushner M, Van Eyl O, Oden N. 1991. Familiar thyroid disease and delayed language development in first admission patients with schizophrenia. Psychiatr Res 38:39–50.

DeLisi LE, Goldin LR, Maxwell ME, Kazuba DM, Gershon ES. 1987. Clinical features of illness in siblings with schizophrenia or schizoaffective disorder. Arch Gen Psychiatr 44:891–896.

DeLisi LE, Reiss AL, White BJ, Gershon ES. 1988. Cytogenetic studies of males with schizophrenia. Screening for the fragile X chromosome and other chromosome abnormalities. Schiz Res 1:277–281.

DeLisi LE, Devoto M, Lofthouse R, Poulter M, Smith A, Shields G, Bass N, Chen G, Vita A, Morganti C, Ott J, Crow TJ. 1994a. Search for linkage to schizophrenia on the X and Y chromosomes. Am J Med Genet (Neuropsychiatr Genet) 54:113–121.

DeLisi LE, Freidrich U, Wahlstrom J, Boccio A, Crow TJ. 1994b. Psychosis and sex chromosome anomalies. Schiz Bull 20:495–505.

DeLisi LE, Shaw S, Sherrington R, Nanthakumar B, Shields G, Smith AB, Wellman N, Larach VW, Loftus J, Razi K, Kushner M, Stewart J, Comazzi M, Vita A, Crow TJ. 2000. Failure to establish linkage on the X chromosome in 301 families with schizophrenia or schizo-affective disorder. Am J Med Genet (Neuropsychiatr Genet) 96:330–336.

Eayrs JT. 1967. [Influence of the thyroid hormone on the development of the nervous system.] Rev Neuropsiquiatr 30:117–136.

Garner C, Kelly M, Cardon L, Joslyn G, Carey A, LeDuc C, Lichter J, Harris T, Loftus J, Shields G, Comazzi M, Vita A, Smith AM, Dann J, Crow TJ, DeLisi LE. 1996. Linkage analyses of schizophrenia to chromosome 6p24-p22: an attempt to replicate. Am J Med Genet (Neuropsychiatr Genet) 67:595–610.

Goodman AB. 1998. Three independent lines of evidence suggest retinoids as causal to schizophrenia. Proc Natl Acad Sci USA 95:7240–7244.

Granet RB, Kalman TP. 1978. Hypothyroidism and psychosis: a case illustration of the diagnostic dilemma in psychiatry. J Clin Psychiatr 39: 260–263.

Greer S, Parsons V. 1968. Schizophrenia-like psychosis in thyroid crisis. Br J Psychiatr 114:1357–1362.

Haddow JE, Palomaki GE, Allan WC, Williams JR, Knight GJ, Gagnon J, O'Heir CE, Mitchell ML, Hermos RJ, Waisbren SE, Faix JD, Klein RZ. 1999. Maternal thyroid deficiency during pregnancy and subsequent neuropsychological development of the child. N Engl J Med 341(8):549–555.

Hodapp RM, Dykens EM. 1996. Mental retardation. In: Mash EJ, Barkley RA. Editors. Child psychopathology. NewYork: Guilford. p 363–389.

Hovatta I, Varilo T, Suvisaari J, Terwilliger JD, Ollikainen V, Arajarvi R, Juvonen H, Kokko-Sahin M-L, Vaisanen L, Mannila H, Lonnqvist J, Peltonen L. 1998. A genome-wide search for schizophrenia genes in an internal isolate of Finland suggesting multiple susceptibility loci. Am J Med Genet (Neuropsychiatr Genet) 81:453–454.

Ito M, Yuan C-X, Malik S, Gu W, Fondell JD, Yamamura S, Fu S-Y, Shang S, Qin J, Roeder RG. 1999. Identity between TRAP and SMCC complexes indicates novel pathways for the function of nuclear receptors and diverse mammalian activators. Mol Cell 3:361–370.

Laval S, Dann J, Butler RJ, Loftus J, Rue J, Leask SJ, Bass N, Comazzi M, Vita A, Nanko S, Shaw S, Peterson P, Shields G, Smith AB, Stewart J, DeLisi LE, Crow TJ. 1998. Evidence for linkage to psychosis and cerebral asymmetry (relative hand skill) on the X chromosome. Am J Med Genet (Neuropsychiatr Genet) 81:420–427.

Lichtermann D, Albus M, Schwab S, Maier W, Lerer B, Wildenauer D. 1999. An X chromosomal linkage study in schizophrenia. Abstracts of the XIth World Congress on Psychiatry, Hamburg, Vol. 2: Posters and Free Presentations, Excerpta Medica Medical Communications.

MacSweeney D, Timms P, Johnson A. 1978. Thyro–endocrine pathology, obstetric morbidity, and schizophrenia: survey of a hundred families with a schizophrenic proband. Psychol Med 8:151–155.

Naar AM, Beaurang PA, Zhou S, Abraham S, Solomon W, Tjian R. 1999. Composite co-activator ARC mediates chromatin-directed transcriptional activation. Nature 398:828–832.

Nurnberger JI, Blehar MC, Kaufman CA, York-Cooler C, Simpson SG, Harkavy-Friedman J, Severe JB, Malaspina D, Reich T. 1994. Diagnostic interview for genetic studies: rationale, unique features, and training. Arch Gen Psychiatr 51:849–862.

Okoro C, Bell R, Sham P, Nanko S, Asherson P, Owen M, Gill M, McGuffin P, Murray RM, Collier D. 1995. No evidence for linkage between the X-chromosome marker DXS7 and schizophrenia. Am J Med Genet (Neuropsychiatr Genet) 60(5):461–464.

Paterson AD. 1999. Sixth World Congress of Psychiatric Genetics: X chromosome workshop. Am J Med Genet 88:279–286.

Pfohl B, Blum M, Zimmerman M, Stangl D. 1990. Structured interview for DSM–III–R personality disorders–revised (SIDP–R). Iowa City: University of Iowa.

Philibert RA, King BH, Winfield S, Cook EH, Lee YH, Stubblefield B, Damschroder-Williams P, Dea C, Palotie A, Tengstrom C, Martin BM, Ginns EI. 1998. Association of an X-chromosome dodecamer insertional variant allele with mental retardation. Mol Psychiatry 3:303–309.

Philibert RA, Hawkins GA, Damschroder-Williams P, Stubblefield BK, Martin BM, Ginns EI. 1995. Direct sequencing of trinucleotide repeats from cosmid genomic DNA template. Anal Biochem 225(2):372–374.

Philibert RA, Winfield SL, Damschroder-Williams P, Tengstrom C, Martin BM, Ginns EI. 1999. The genomic structure and developmental expression patterns of the human OPA-containing gene (HOPA). Hum Genet 105(1–2):174–178.

Pulver AE, Lasseter VK, Kasch L, Wolyniec P, Nestadt G, Blouin JL, Kimberland M, Babb R, Vourlis S, Chen H. 1995. Schizophrenia: a genome scan targets chromosomes 3p and 8p as potential sites of susceptibility genes. Am J Med Genet 60(3):252–260.

Rachez C, Lemon BD, Suldan Z, Bromleigh V, Gamble M, Naar AM, Erdjument-Bromage H, Tempst P, Freedman LP. 1999. Ligand-dependent transcription activation by nuclear receptors requires the DRIP complex. Nature 398:824–828.

Roca RP, Blackman MR, Ackerley MB, Harman SM, Gregerman RI. 1990. Thyroid hormone elevations during acute psychiatric illness: relationship to severity and distinction from hyperthyroidism. Endocr Res 16: 415–447.

Ryan WG, Roddam RF, Grizzle WE. 1994. Thyroid function screening in newly admitted psychiatric inpatients. Ann Clin Psychiatry 6:7–12.

Sachar EJ. 1974. Psychiatric disturbance in endocrine disease: some issues for research. Res Publ Assoc Res Nerv Ment Dis 53:239–251.

Shaw SH, Kelly M, Smith AB, Shields G, Hopkins PJ, Loftus J, Laval SH, Vita A, De Hert M, Cardon LR, Crow TJ, Sherrington R, DeLisi LE. 1998. A genome-wide screen for linkage to schizophrenia. Am J Med Genet (Neuropsychiatr Genet) 81:364–376.

Spitzer RL, Endicott J. 1978. Schedule for affective disorders and schizophrenia (SADS). New York: New York State Psychiatric Institute.

Williams NM, Rees MI, Norton N, Holmans P, Fenton I, Cardno AG, Murphy KC, Jones LA, McCarthy G, Saunders R, McGuffin P, Owen MJ. 1998. A two stage sib-pair genome scan for schizophrenia susceptibility genes. Am J Med Genet (Neuropsychiatr Genet) 81:453.