

DRD4 exon III polymorphism and response to risperidone in Israeli adolescents with schizophrenia: a pilot pharmacogenetic study

Gil Zalsman^{a,*}, Amos Frisch^a, Shaul Lev-Ran^a, Andrés Martín^b, Elena Michaelovsky^a, Daniela Bensason^a, Doron Gothelf^a, Eitan Nahshoni^a, Samuel Tyano^a, Abraham Weizman^a

^aAdolescent Inpatient Department, Geha Mental Health Center, Rabin Medical Center, Petach Tikva, and Felsenstein Medical Research Center, Sackler Faculty of Medicine, Tel Aviv University, Tel Aviv, Israel

^bChild Study Center, Yale University School of Medicine, New Haven, CT, USA

Received 11 August 2002; accepted 9 January 2003

Abstract

This study examined the possible association between the polymorphism in the dopamine receptor DRD4 gene and response to risperidone among 24 Israeli Jewish adolescent inpatients with first-episode schizophrenia. Response was categorically determined by a change of >40% on the Brief Psychiatric Rating Scale (BPRS). No significant association was found between the DRD4 genotype and clinical response, although carriers of <7 repeat alleles demonstrated higher response rate (10/20 vs. 0/4, $P=0.11$). Studies in larger groups of adolescent schizophrenia patients are warranted to clarify the possible association between DRD4 exon III repeat alleles and the response to risperidone.

© 2003 Elsevier Science B.V./ECNP All rights reserved.

Keywords: Pharmacogenetics; Risperidone; Polymorphism; Dopamine; Adolescence

1. Introduction

Risperidone is the most widely used atypical anti-psychotic drug for adolescent schizophrenia (Schulz et al., 1998). Despite its wide spread use, it is still impossible to predict clinical response in any individual patient. Dopamine D2 receptor blockade is associated with pharmacological response among traditional antipsychotic medications (Creese et al., 1976). Dopamine receptor type 4 (DRD4) is a target site for some atypical antipsychotic drugs such as risperidone (Schulz et al., 1998). The gene for this receptor was mapped by Gelernter et al. (1992) to the short arm of chromosome 11, and includes 48 base pair (bp) repeats polymorphism in exon III, with 2–10 repeat units (Van Tol et al., 1992). Allele frequencies of this polymorphism are known to vary between populations

(Chang et al., 1996), but not between Ashkenazi and non-Ashkenazi Jews (Frisch et al., 1999). The 7 repeat allele was found to be associated with novelty seeking (Benjamin et al., 1996; Ebstein et al., 1996, 1997; Malhotra et al., 1996) and opioid dependence (Kotler et al., 1997) but not with schizophrenia (Coon et al., 1993; Petronis et al., 1995).

Pharmacogenetics provides a novel and powerful tool that attempts to predict psychotropic drugs response. The use of whole-genome single-nucleotide polymorphism (SNP) maps may soon enable us to create an SNP profile for patients who respond to psychoactive medications (Roses, 2001). However, pharmacogenetic studies in the pediatric population are still rare and sample sizes are small (Anderson and Cook, 2000). For example, in the study by Winsberg and Comings (1999), 30 children were studied. It was found that homozygosity of the 10-repeat allele of the dopamine transporter gene (DAT1) is associated with nonresponse to methylphenidate therapy in attention-deficit hyperactivity disorder.

Two pharmacogenetic studies on the relationship between

*Corresponding author. Adolescent Inpatient Department, Geha Mental Health Center, P.O. Box 102, Petach Tikva 49100, Israel. Tel.: +972-3-925-8242; fax: +972-3-924-1041.

E-mail address: zalsman@post.tau.ac.il (G. Zalsman).

DRD4 exon III 48 bp repeat polymorphism and response to clozapine in adults patients suffering from schizophrenia, were both negative (Rao et al., 1994; Kohn et al., 1997). No study on the association between DRD4 and response to risperidone in psychotic children has been published to date, although no such association was demonstrated in adult patients with schizophrenia (Hwu et al., 1998; Kaiser et al., 2000).

The final aim of pharmacogenetic studies is to be able to predict the response to a drug at the level of an individual patient through genotyping means (Cichon et al., 2000). In this pilot study we investigated the association between DRD4 exon III polymorphism and the clinical response to risperidone. To the best of our knowledge, this is the first pharmacogenetic study done in an adolescents' sample with first-episode schizophrenia.

2. Experimental procedures

All patients admitted to a university affiliated hospital (Geha Mental Health Center, Petach Tikva, Israel; affiliated to Sackler Faculty of Medicine, Tel Aviv University, Israel) during the year 2001, and who met DSM IV (American Psychiatric Association, 1994) criteria for schizophreniform disorder, were eligible for inclusion in the study. Diagnosis was based on the Schedule for Affective Disorders and Schizophrenia for Children-Patient Version (K-SADS-PL), a structured interview for Axis I diagnoses in children and adolescents developed originally by Chambers et al. (1985). The K-SADS-PL has been translated into Hebrew and shown good inter-rater reliability (Apter et al., 1989; Shanee et al., 1997). All patients were in the first psychotic episode, were drug naive, and retrospectively met the 6-month criteria for schizophrenia when this study was terminated. The study population included six girls (25%) and 18 boys (75%) with a mean age of 17 ± 6.7 years. All were Jews: 16 patients were Ashkenazi (67%), seven (29%) non-Ashkenazi and one of mixed ancestry.

Patients were treated with 2–4 mg risperidone monotherapy, given orally at bedtime.

Clinical response was assessed by the Brief Psychiatric Rating Scale (BPRS) (Overall and Gorham, 1962). BPRS ratings were conducted weekly for 8-week study period by a single rater (G.Z.) who was blind to the genotype of the patients. Reduction of 40% or more in the BPRS score at the end of the study (week 8) was considered a response, according to the criteria used by Lachar et al. (1999).

DNA was prepared from 10 ml venous blood and genotyping was performed as described by Frisch et al. (1999). The alleles were divided into short (<7 repeats) and long (7 and longer), as previously done by others (Benjamin et al., 1996; Ebstein et al., 1997). This division was chosen since the longer alleles ≥ 7 repeats were reported to be associated with high delusional scores in

psychotic patients (Serretti et al., 1999), a phenomenon which seems relevant to antipsychotic response.

Fisher's exact test was used to examine the null hypothesis that the distribution of long and short alleles between responders and non-responders is no different from chance.

The study was approved by the Geha Mental Health Center Review Board and all patients and their parents provided signed informed consent.

3. Results

Within the 8-week study period, 10 patients responded to risperidone while 14 did not respond to this agent. The responders did not differ from the non-responders in gender distribution (male/female: 7/3 vs. 11/3; Fisher's exact test $P=0.67$, NS) and severity of psychosis as measured by the BPRS (45.4 ± 8.7 vs. 46.6 ± 9.8 $t=0.30$, $df=22$, $P=0.77$, NS). Among the ≥ 7 group 0/4 (0%) responded to the treatment, while 10/20 (50%) responded among the <7 group ($P=0.11$). Since the frequencies of short and long alleles were similar between Ashkenazi and non-Ashkenazi subjects, they were considered as a single homogeneous group.

Table 1 shows the distribution of the long and short alleles (including both homozygous and heterozygous variants for each corresponding allele) between responders and non-responders. The population was in Hardy-Weinberg equilibrium for the various genotypes. Long alleles were more frequent among the non-responders as compared to the responders (14% vs. 0%). However the null hypothesis could not be rejected, since the difference did not reach a significant level (OR=0.13, 95% CI 0.006–2.616; $P=0.13$).

We are aware that negative studies conducted in small samples are liable to type II errors. Unfortunately, the small sample size and the multiplicity of the genotypes do not allow a proper power analysis.

4. Discussion

This study suggests no association between DRD4 exon III 48 bp repeat polymorphism and clinical response to risperidone among 24 adolescents with first episode of schizophrenia. This finding is in concordance with two other studies of this polymorphism and response to the

Table 1

Allele frequencies of the DRD4 exon III polymorphism in risperidone responders and non-responders among adolescents with schizophrenia

Allele length (No. of 48 bp repeats)	Responders	Non-responders
≥ 7	0 (0%)	4 (14%)
<7	20 (100%)	24 (86%)

$P=0.130$; odds ratio=0.13; 95% CI (0.006–2.616).

atypical antipsychotic clozapine in adult patients suffering from schizophrenia (Rao et al., 1994; Kohn et al., 1997). The difference in risperidone response rates between carriers and non-carriers of ≥ 7 repeat alleles at the DRD4 exon III polymorphism did not obtain significance (0/4 vs. 10/20, $P=0.11$). However, these preliminary results suggest that studies in larger groups of adolescents and young adult patients are warranted and may well demonstrate a clinically important influence of the exon III alleles in response to risperidone.

Acknowledgements

This work was supported by the The National Institute for Psychobiology in Israel—The Charles Smith Foundation. Grant No. 9b-99.

References

- American Psychiatric Association, 1994. Diagnostic and Statistical Manual of Mental Disorders (DSM), 4th Edition. American Psychiatric Association Press, Washington, DC.
- Anderson, G.M., Cook, E.H., 2000. Pharmacogenetics: promise and potential in child and adolescent psychiatry. *Child Adolesc. Psychiatry Clin. N. Am.* 9, 23–42.
- Apter, A., Orvaschel, H., Laseg, M., Moses, T., Tyano, S., 1989. Psychometric properties of the K-SADS-P in an Israeli adolescent psychiatric population. *Am. Acad. Child Adolesc. Psychiatry* 28, 61–65.
- Benjamin, J., Li, L., Patterson, C., Greenberg, B.D., Murphy, D.L., Hamer, D.H., 1996. Population and familial association between the D4 dopamine receptor gene and measures of novelty seeking. *Nat. Genet.* 12, 81–84.
- Chambers, W., Puig-Antich, J., Hirsch, M., Paez, P., Ambrosini, P.J., Tabrizi, M.A., Davies, M., 1985. The assessment of affective disorders in children and adolescents by semi-structured interview: test-retest reliability of the Schedule for Affective Disorders and Schizophrenia for School-Age Children, Present Episode version. *Arch. Gen. Psychiatry* 42, 696–702.
- Chang, F.M., Kidd, J.R., Livak, K.J., Pakstis, A.J., Kidd, K.K., 1996. The world-wide distribution of allele frequencies at the human dopamine D4 receptor locus. *Hum. Genet.* 98, 91–101.
- Cichon, S., Nothen, M.M., Rietschel, M., Propping, P., 2000. Pharmacogenetics of schizophrenia. *Am. J. Med. Genet.* 97, 98–106.
- Coon, H., Byerley, W., Holik, J., Hoff, M., Myles-Worsley, M., Lannfelt, L., Sokoloff, P., Schwartz, J.C., Waldo, M., Freedman, R., 1993. Linkage analysis of schizophrenia with five dopamine receptor genes in nine pedigrees. *Am. J. Hum. Genet.* 52, 327–334.
- Creese, I., Burt, D.R., Snyder, S.H., 1976. Dopamine receptor binding predicts clinical and pharmacological potencies of anti-schizophrenic drugs. *Science* 192, 418–483.
- Ebstein, R.P., Novick, O., Umansky, R., Priel, B., Osher, Y., Blaine, D., Bennett, E.R., Nemanov, L., Katz, M., Belmaker, R.H., 1996. D4DR exon III polymorphism associated with the personality trait of Novelty Seeking in normal human volunteers. *Nat. Genet.* 12, 78–80.
- Ebstein, R.P., Nemanov, L., Klotz, I., Gritsenko, I., Belmaker, R.H., 1997. Additional evidence for an association between the dopamine D4 receptor (D4DR) exon III repeat polymorphism and the human personality trait of Novelty Seeking. *Mol. Psychiatry* 2, 472–477.
- Frisch, A., Postilnick, D., Rockah, R., Michaelovsky, E., Postilnick, S., Birman, E., Laor, N., Rauchverger, B., Kreinin, A., Poyurovsky, M., Schneidman, M., Modai, I., Weizman, R., 1999. Association of unipolar major depressive disorder with genes of the serotonergic and dopaminergic pathways. *Mol. Psychiatry* 4, 389–392.
- Gelernter, J., Kennedy, J., Van Tol, H.H.M., Civelli, O., Kidd, K.K., 1992. The D4 dopamine receptor (DRD4) maps to distal 11p close to HRAS. *Genomics* 13, 208–210.
- Hwu, H.G., Hong, C.J., Lee, Y.L., Lee, P.C., Lee, S.F., 1998. Dopamine D4 receptor gene polymorphisms and neuroleptic response in schizophrenia. *Biol. Psychiatry* 44, 483–487.
- Kaiser, R., Konneker, M., Henneken, M., Dettling, M., Muller-Oerlinghausen, B., Roots, I., Brockmoller, J., 2000. Dopamine D4 receptor 48-bp repeat polymorphism: no association with response to antipsychotic treatment, but association with catatonic schizophrenia. *Mol. Psychiatry* 5, 418–424.
- Kohn, Y., Ebstein, R.P., Levi, U., Shapira, B., Nemanov, L., Gritsenko, I., Avnon, M., Lerer, B., 1997. Dopamine D4 receptor gene polymorphisms: relation to ethnicity, no association with schizophrenia and response to clozapine in Israeli subjects. *Eur. Neuropsychopharmacol.* 7, 39–43.
- Kotler, M., Cohen, H., Segman, R., Gritsenko, I., Nemanov, L., Lerer, B., Kramer, I., Zer-Zion, M., Klotz, I., Ebstein, R.P., 1997. Excess dopamine D4 receptor (D4DR) exon III seven-repeat allele in opioid-dependent subjects. *Mol. Psychiatry* 2, 251–254.
- Lachar, D., Bailey, S.E., Rhoades, H.M., Varner, R.V., 1999. Use of BPRS-A percent change scores to identify significant clinical improvement: accuracy of treatment response classification in acute psychiatric patients. *Psychiatry Res.* 89, 259–268.
- Malhotra, A.K., Virkunen, M., Rooney, W., Eggert, M., Linnoila, M., Goldman, D., 1996. The association between the dopamine D4 receptor (D4DR) 16 amino acid repeat polymorphism and Novelty Seeking. *Mol. Psychiatry* 1, 388–391.
- Overall, J.E., Gorham, D.R., 1962. The brief psychiatric rating scale. *Psychol. Rep.* 10, 799–812.
- Petronis, A., Macciardi, F., Athanassiades, A., Paterson, A.D., Verga, M., Meltzer, H.Y., Cola, P., Buchanan, J.A., Van Tol, H.H., Kennedy, J.L., 1995. Association study between the dopamine D4 receptor gene and schizophrenia. *Am. J. Med. Genet.* 60, 452–455.
- Rao, P.A., Pickar, D., Gejman, P.V., Ram, A., Gershon, E.S., Gelernter, J., 1994. Allelic variation in the D4 dopamine receptor (DRD4) gene does not predict response to clozapine. *Arch. Gen. Psychiatry* 51, 912–918.
- Roses, A.D., 2001. Pharmacogenetics. *Hum. Mol. Genet.* 10, 2261–2267.
- Schulz, S.C., Findling, R.L., Wise, A., Friedman, L., Kenny, J., 1998. Child and adolescent schizophrenia. *Psychiatry Clin. North Am.* 21, 43–56.
- Serretti, A., Macciardi, F., Catalano, M., Bellodi, L., Smeraldi, E., 1999. Genetic variants of dopamine receptor D4 and psychopathology. *Schizophr. Bull.* 25, 609–618.
- Shanee, N., Apter, A., Weizman, A., 1997. Psychometric properties of the K-SADS-PL in an Israeli adolescent clinical population. *Isr. J. Psychiatry Relat. Sci.* 34, 179–186.
- Winsberg, B.G., Comings, D.E., 1999. Association of the dopamine transporter gene (DAT1) with poor methylphenidate response. *J. Am. Acad. Child Adolesc. Psychiatry* 38, 1474–1477.
- Van Tol, H.H.M., Caren, M.W., Guan, H.C., Ohara, K., Bunzow, J., Civelli, O., Kennedy, J., Seeman, P., Niznik, H.B., Jovanovic, V., 1992. Multiple dopamine D4 variants in the human population. *Nature* 358, 149–152.