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Polymorphisms in dopamine receptors: what do they tell us?

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Abstract

Many genetic studies have focussed on dopamine receptors and their relationship to neuropsychiatric disease. Schizophrenia, bipolar disorder, and substance abuse have been the most studied, but no conclusive linkage or association has been found. The possible influence of dopamine receptor variants on drug response has not received as much attention. While there is some evidence that polymorphisms and mutations in dopamine receptors can alter functional activity and pharmacological profiles, no conclusive data link these gene variants to drug response or disease. The lack of unequivocal findings may be related, in part, to the subtle changes in receptor pharmacology that these polymorphisms and mutations mediate. These subtle effects may be obscured by the influence of genes controlling drug metabolism and kinetics. Further insight into the pharmacogenetics of dopamine receptors may require not just more studies, but novel approaches to the study of complex genetic traits and diseases.

Keywords: Dopamine receptor; Pharmacogenetics; Polymorphism; Mutation; Antipsychotic; Schizophrenia

1. Introduction

The pharmacogenomics of dopamine receptors is a broad area of research that straddles the boundaries of several biological disciplines. The dopamine system is involved in motor control, endocrine function, reward and cognition. Disruption or manipulation of this system can cause symptoms and signs similar to those seen with Parkinson's disease, schizophrenia, Alzheimer's disease, and Huntington's chorea. Dopamine receptors are the target of drugs used to treat psychosis, Tourette syndrome, and attention deficit hyperactivity disorder. In addition, drugs of abuse like cocaine and amphetamine are powerful dopaminergic stimulants. Thus, understanding the pharmacogenetics of dopamine receptors may have implications for the therapeutic effects, abuse potential, and side effects of these drugs.

Polymorphisms in dopamine receptor genes also have the potential to affect susceptibility to disease, or to affect individual patients' response to a therapeutic agent. Partly because of the involvement of the dopamine system in Parkinson's disease, and in the treatment of schizophrenia with neuroleptics, much of the work has focussed on exploring possible associations between receptor polymorphisms and neuropsychiatric diseases. Comparatively little work has been devoted to the study of the pharmacological function of receptor polymorphisms. In reviewing the polymorphisms in the various dopamine receptor genes, we will discuss the mutations or polymorphisms that affect the structure or function of the receptor, and those that are merely genetic markers. We will attempt to cover the literature in all these areas in this review, recognising that the various topics may be of interest to distinct groups of readers. For clarity, each dopamine receptor gene is depicted in a diagram that illustrates the relationship of each polymorphism to the others, and the variants that are

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Table 1
Dopamine receptor polymorphisms and gene function

Author	Year	Polymorphisms	Phenotype
Dopamine D1 receptor			
Cichon et al.	1999	Polymorphisms in 5′ promoter region	Schizophrenia/bipolar disease
Liu et al.	1995	−48 A/G; 198 G/A; 1263 G/A	Schizophrenia/alcoholism
Dopamine D2 receptor			
Arinami et al.	1997	−141C Insertion/Deletion and A241G	receptor density
Barr et al.	1993	*Taq*I A	population study
Cravchik et al.	1996	$Pro^{310}Ser$ and $Ser^{311}Cys$	G-protein activation
Finckh et al.	1996	*Taq*I A1 and $Ser^{311}Cys$	Linkage/haplotypes
Gejman et al.	1994	Single stranded conformational analysis	Alcoholism
Gelernter et al.	1998	−141C Insertion/Deletion	population study
Hitzemann	1998	review of studies on functional mutations	receptor density
Itokawa et al.	1993	$Ser^{311}Cys$	Schizophrenia
Jones et al.	1998	*Taq*I A + B *Nco*I	Intragenic Evolution
Jones et al.	1998	*Taq*I A + B *Nco*I	Intragenic Evolution
Jonsson et al.	1999	−141C(INS), *Taq*I A1, STRP	receptor density
Kidd et al.	1998	*Taq*I A + B + D;STRP	Linkage/haplotypes
Laurelle et al.	1998	fails to reproduce the finding of Jonsson	receptor density
Senogles et al.	1994	D2(S) AND D2(L) isoforms	Adenylate cyclase activation
Dopamine D3 receptor			
Crocq et al.	1996	*Bal*I/*Msp*I	population study
Gelernter et al.	1998	*Bal*I	population study
Lundstrom et al.	1996	$SER^{9}GLY$ (*Bal*I)	receptor affinity for dopamine
Sivagnanasundaram et al.	2000	3 SNP's identified in 5′ flanking region	Schizophrenia
Dopamine D4 receptor			
Asghari et al.	1994	VNTR,3^{rd} cytoplasmic loop	clozapine/spiperone binding
Asghari et al.	1995	VNTR,3^{rd} cytoplasmic loop	cyclic AMP levels
Jovanovic et al.	1999	VNTR,3^{rd} cytoplasmic loop	receptor pharmacology
Van Tol et al.	1991	VNTR,3^{rd} cytoplasmic loop	clozapine binding
Watts et al.	1999	D4.4 (short) and D4.7 (long)	sensitization to cyclic AMP
Zenner et al.	1998	12 bp repeat in exon 1	receptor pharmacology
Dopamine D5 receptor			
Beischlag et al.	1996	(TC)13 in promoter	Receptor transactivation
Cravchik et al.	1999	$Asn^{351}Asp$ and $Leu^{88}Phe$	Dopamine binding affinity
Sobell et al.	1995	Nine single nucleotide polymorphisms	5 result in sequence changes

associated with functional or pharmacogenetic changes are shown in Tables 1 and 2.

2. Dopamine D1 receptor

2.1. Dopamine D1 receptor gene structure and polymorphisms

The dopamine D1 receptor gene is located at chromosome 5q35.1, and is composed of two exons separated by a small intron in the 5′ untranslated region (Grandy et al., 1990; Zhou et al., 1992). It has multiple transcription start sites between −1061 and −1040 relative to the first ATG, and its TATA-less promotor has features consistent with housekeeping and tissue-specific genes (Mouradian et al., 1993). The main activator region is between −1342 and −1102 (Minowa et al., 1993). The gene contains restriction fragment length polymorphisms recognized by *Eco*RI (Grandy et al., 1990), and *Taq*I (Litt et al., 1991). Liu et al. (1995) reported three polymorphisms: −48 A > G substitution in the 5′ untranslated region of exon 2, 198 G > A, and 1263 G > A. Six single base pair substitutions have been identified in the 5′-flanking region of the human dopamine D1 receptor gene: −2218T > C, −2102 C > A, −2030 T > C, −1992 G > A, and −1251 G > C (Cichon et al., 1996). Four restriction enzyme polymorphisms were identified by Cichon et al., two of which are the same as those published by Liu et al.: −94 G > A (*Bst*N1), −48 A > G (*Dde*I), 1263 G > A (*Pvu*I), and 1403 T > C (*Bsp*1286I) (Cichon et al., 1994a).

2.2. Dopamine D1 receptor mutations, polymorphisms and gene function

None of the mutations identified by Liu et al. (1995) are associated with a functional amino acid change. Cichon et al. (1996) screened the 5′-regulatory region of the human

Table 2
Dopamine receptor pharmacogenetics

Author	Year	Polymorphism	Phenotype	Drug/side effect	Outcome
Dopamine D2 receptor					
Mihara et al.	2000	*Taq*I A1	Schizophrenia	Hyperprolactinemia	significant
Serretti et al.	1999	$Ser^{311}Cys$	Mood disorders	Lithium prophylaxis	not significant
Suzuki et al.	2000	*Taq*I A1	Schizophrenia	Nemonapride	significant
Dopamine D3 Receptor					
Basile et al.	1999	Gly^9 allele Gly^9–Gly^9 homozygosity	Schizophrenia	Tardive dyskinesia	significant
Malhotra et al.	1998	Gly^9 allele of *Bal*I polymorphism	Schizophrenia	Clozapine response	not significant
Rietschel et al.	1993	Gly^9 allele Gly^9–Gly^9 homozygosity	Schizophrenia	Tardive dyskinesia	not significant
Scharfetter et al.	1999	Gly^9 allele of *Bal*I polymorphism	Schizophrenia	Clozapine response	significant
Shaikh et al.	1996	Gly^9 allele of *Bal*I polymorphism	Schizophrenia	Clozapine response	significant
Steen et al.	1997	Gly^9 allele Gly^9–Gly^9 homozygosity	Schizophrenia	Tardive dyskinesia	significant
Dopamine D4 Receptor					
Cohen et al.	1999	D4.7 (long allele of VNTR)	Schizophrenia	Clozapine versus Neuroleptic response	significant
Hwu et al.	1998	D4.7 (long allele of VNTR)	Schizophrenia	Neuroleptic response	significant
Kohn et al.	1997	VNTR,3^{rd} cytoplasmic loop	Schizophrenia	Clozapine response	not significant
Rao et al.	1994	12 bp repeat, exon1	Schizophrenia	Clozapine response	not significant
Rietschel et al.	1996	VNTR,3^{rd} cytoplasmic loop	Schizophrenia	Clozapine response	not significant
Serretti et al.	1999	VNTR,3^{rd} cytoplasmic loop	Mood disorders	Lithium prophylaxis	not significant
Shaikh et al.	1993	VNTR,3^{rd} cytoplasmic loop	Schizophrenia	Clozapine response	not significant
Shaikh et al.	1995	VNTR,3^{rd} cytoplasmic loop	Schizophrenia	Clozapine response	not significant

dopamine D1 receptor gene, but none of the polymorphisms were in regions that have an important influence on transcriptional activity. None of the other polymorphisms are associated with demonstrated functional changes.

2.3. Dopamine D1 receptor and disease genetics

Screening of the 5′ untranslated region polymorphisms showed that this region of the dopamine D1 receptor gene does not have a major role in risk for either schizophrenia or bipolar disorder (Cichon et al., 1996). This finding was confirmed by a study on the *Dde*I polymorphism in the 5′-untranslated region of the dopamine D1 receptor gene of 148 schizophrenia patients in Japan. When compared with controls, no significant differences in genotypic counts or allele frequencies was found (Kojima et al., 1999). A postmortem study of tissue from schizophrenic patients found several polymorphisms in the dopamine D1 receptor gene sequence, but none that would alter protein sequence (Ohara et al., 1993). Several studies have reported negative results of linkage or association with bipolar disorder (Jensen et al., 1992; Nothen et al., 1992) and a lack of single strand conformational polymorphisms in patients with the disorder (Cichon et al., 1994b; Shah et al., 1995). Genome scans for schizophrenia and bipolar disorder have identified some areas of interest on chromosome 5, but none of these contain the dopamine D1 receptor gene (Crowe and Vieland, 1999).

Studies examining the coding region have looked for association with Tourette's syndrome, alcohol dependence (Thompson et al., 1998), and attempted to identify mutations in patients with attention deficit hyperactivity disorder, autism, and alcoholism (Feng et al., 1998). In only one patient was there a mutation that was associated with an altered protein sequence, but the above studies found no evidence the dopamine D1 receptor coding region contains mutations that are associated with any of the disorders mentioned. Analysis of a large kindred excluded close linkage of the dopamine D1 receptor gene to Tourette syndrome (Gelernter et al., 1993b). Studies of the *Eco*R1 (Hietala et al., 1997), and *Bsp*I 1286 (1403 T > C) polymorphisms (Sander et al., 1995) have not shown any association with alcoholism, but others have reported that there is an association between homozygosity at the *Dde*I polymorphism and subjects with compulsive, addictive behaviours (Comings et al., 1997). Markers close to the dopamine D1 receptor gene have been reported to be associated with interindividual variation in systolic blood pressure (Krushkal et al., 1998).

2.4. Dopamine D1 receptor pharmacogenetics

From a pharmacogenetic perspective the dopamine D1 receptor is currently of limited interest since there is no established relationship between any dopaminergic drug therapy and this receptor. Because the dopamine D1 receptor may modulate aspects of cognition (Williams and Goldman-Rakic, 1995) and may influence Parkinson's disease symptoms, these areas could be explored in future research. However, such studies may be futile in the

absence of convincing evidence that polymorphisms or mutations in the dopamine D1 receptor gene alter the biological activity or pharmacological profile of the receptor.

3. Dopamine D2 receptor

3.1. Dopamine D2 receptor gene structure and polymorphisms

The human dopamine D2 receptor gene is located on chromosome 11q22–23, and consists of eight exons separated by seven introns (Grandy et al., 1989a,b). Alternative splicing of a 29 amino acid sequence in the third cytoplasmic loop results in two forms of the receptor $D2_L$ (long) and $D2_S$ (short) (Dal Toso et al., 1989; Giros et al., 1989; Grandy et al., 1989b; Monsma et al., 1989). Several polymorphisms were identified shortly after the gene was cloned, three of which are *Taq*I restriction fragment length polymorphisms. The first, termed *Taq*I A, is in the 3′ flanking region, 10 kilobases from the eighth exon, the second, *Taq*I B, is located close to the junction between the first intron and the second exon (Castiglione et al., 1995; Hauge et al., 1991), and the third, *Taq*I C, is within intron 2 (Parsian et al., 1991a). At the *Taq*I A polymorphic site, there appear to be four possible alleles referred to as *Taq*I A1–4 (Persico et al., 1993). In addition to a (CA)n dinucleotide polymorphism within intron 2 (Hauge et al., 1991), there exist single nucleotide polymorphisms: a 2057T insertion at a *Bso*F1 restriction site (Poduslo and Schwankhaus, 1995), and restriction fragment length polymorphisms *Hph*I (G > T) in intron 6, *Nco*I (313C > T) in exon 7 (Sarkar et al., 1991), and an A > G substitution 52 base pairs downstream from the stop codon in exon 8 (Finckh et al., 1997). Using the polymerase chain reaction and nondenaturing gel electrophoresis, a single strand conformational polymorphism (SSCP) has been found in exon 8 (Bolos et al., 1990).

3.2. Dopamine D2 receptor mutations, polymorphisms and gene function

Changes in the function of the dopamine D2 receptor are seen with some of these polymorphisms. Three polymorphisms result in amino acid substitutions: $Val^{96}Ala$, $Pro^{310}Ser$, and a C to G substitution that results in a serine to cysteine change at amino acid 311 ($Ser^{311}Cys$) (Gejman et al., 1994; Itokawa et al., 1993; Jones and Peroutka, 1998). Two of the polymorphisms, $Pro^{310}Ser$ and $Ser^{311}Cys$, are located in the third cytoplasmic loop, and the more common Pro^{310} and Ser^{311} variants are substantially more effective in inhibiting cAMP synthesis. All variants however, are functionally active in Chinese hamster ovary cells (Cravchik et al., 1996). Two single base pair mutations −241A > G, and −141C ins/del are within the promoter region. The −141C del allele disrupts a *Bst*N1 restriction enzyme site, and produces lower expression levels of the dopamine D2 receptor in Y-79 and human embryonic kidney (HEK) 293 cells (Arinami et al., 1997). Striatal dopamine D2 receptor density is increased in individuals with the −141C del promoter variant (Jonsson et al., 1999a), and is reduced with the *Taq*I A1 allele (Pohjalainen et al., 1998; Thompson et al., 1997), but contradictory results have also been found (Laruelle et al., 1998). There is considerable variation in levels of dopamine D2 receptor expression between individuals that may not be related to polymorphisms in the gene or promoter region (Hitzemann, 1998).

There is also considerable variation in the distribution of the *Taq*I A1 allele in different ethic and racial populations (Barr and Kidd, 1993), as well as for other polymorphisms (Gelernter et al., 1998). Overall, haplotype frequencies, and linkage disequilibrium between some of these polymorphisms also varies in different geographic regions and populations. The least linkage disequilibrium is found in African populations, followed by European, and then Asian and Amerindian populations (Kidd et al., 1998). Some of these polymorphic alleles are commonly found together in a limited number of haplotypes of the dopamine D2 receptor gene (Jones and Peroutka, 1998), while others, like the *Taq*I A1 and Cys^{311} are part of different haplotype groups (Finckh et al., 1996).

3.3. Dopamine D2 receptor and disease genetics

The majority of the literature dealing with phenotypic differences related to dopamine D2 receptor gene polymorphisms is related to alcohol and other substance abuse. First noted by Blum et al. (1990), the *Taq*I A1 association with alcoholism and the severity of alcoholism has been supported by many other case-control studies (Amadeo et al., 1993; Arinami et al., 1993; Comings et al., 1991; Hietala et al., 1997; Ishiguro et al., 1998; Neiswanger et al., 1995a), a meta-analysis (Pato et al., 1993), and has been noted in early onset alcoholism (Kono et al., 1997). Other dopamine D2 receptor gene variants have also been associated with alcoholism: *Taq*I B1 (Blum et al., 1993), Cys^{311} allele (Higuchi et al., 1994), and the −141C insertion allele (Ishiguro et al., 1998). Many other case-control studies have failed to replicate these findings (Chen et al., 1996, 1997c; Cook et al., 1996; Cruz et al., 1995; Edenberg et al., 1998; Gejman et al., 1994; Gelernter and Kranzler, 1999; Gelernter et al., 1991; Lu et al., 1996; Sander et al., 1999; Suarez et al., 1994) and no family based association and linkage studies have confirmed this association (Bolos et al., 1990; Neiswanger et al., 1995a; Parsian et al., 1991b). Some of these negative studies reported associations with other clinical outcomes in alcoholic patients (Finckh et al., 1997). One group found that the *Taq*I A1 allele was associated with significantly lower

[^{3}H]naloxone binding in the caudate nucleus of post-mortem tissue from both alcoholics and non-alcoholic controls (Ritchie and Noble, 1996).

Findings with patients dependent on, or abusing other substances have been similarly inconsistent. The *Taq*I A1 allele has been found to be associated with cocaine dependence (Noble et al., 1993), substance abuse (Comings et al., 1994; Goldman et al., 1997; Noble, 1994; Smith et al., 1992; Uhl et al., 1992), psychostimulant-preferring polysubstance abusers (Persico et al., 1996), smoking in the presence of reduced P300 amplitudes (Anokhin et al., 1999) and substance abuse in white Americans (O'Hara et al., 1993). However, a population (Singleton et al., 1998), and a family study of habitual smoking and the *Taq*I A1 allele found no association (Bierut et al., 2000), nor was the finding of an association with cocaine dependence replicated in European- and African-Americans (Gelernter et al., 1999a). Negative reports in African-American populations have also been published (Berrettini and Persico, 1996; O'Hara et al., 1993). Furthermore, comorbid psychopathology in incarcerated substance abusers was not associated with *Taq*I A or *Taq*I B frequencies (Smith et al., 1993).

These opposing findings have spawned a debate about the methodology used in these studies and in psychiatric and pharmacological genetics in general. The diversity of genotypes for the dopamine D2 receptor polymorphisms both within and between populations of African, European, Asian and other racial groups has prompted some to suggest the use of haplotypes and other methods to compensate for the problem of finding appropriately matched control groups (Kidd et al., 1996). Factors that may confound the findings with respect to alcoholism and the dopamine D2 receptor gene (and are applicable to many of the findings discussed throughout this review) include population stratification (Uhl et al., 1993), and the clinical heterogeneity of alcoholism and other neuropsychiatric phenotypes (Gelernter et al., 1993a). The selection of patients and controls varies widely, with the result that diagnosis, severity, chronicity and comorbidity are not comparable between studies. Even if the findings are considered to be positive overall, they likely represent a susceptibility associated with certain alleles of the dopamine D2 receptor gene, one that is modulated by environmental (Noble, 1994) factors and possibly other genetic factors such as the genes controlling the metabolism and pharmacodynamic effects of alcohol (Li, 2000).

As with other polygenic diseases or traits, some have argued that the application of rules designed for single-gene disorders is problematic, and that the disparate findings are not necessarily in conflict (Comings, 1998). It is difficult to know what explanation can unify the various results. It may be that variation in the gene contributes only a small increase in risk to alcoholism, so that some studies do not have sufficient power to detect the effect. The selection of random vs. non-alcoholic controls may also introduce further confounding factors, in that non-alcoholic controls may exaggerate the difference between the affected and control groups (Neiswanger et al., 1995b). Meta-analyses of the grouped results offer some support to this explanation, but confirmation of a physiologic effect of the polymorphisms related to alcohol or substance dependence may be the most elegant way of resolving these issues. Despite the rationale that these disorders may be modulated by the dopaminergic reward system, no functional changes in the dopamine D2 receptor gene have been related to the pathophysiology of substance abuse.

Schizophrenia and bipolar disorder are often treated with neuroleptics, whose clinical potency is primarily related to dopamine D2 receptor affinity. Thus, the dopamine D2 receptor gene has been a candidate for population and linkage studies in these two disorders. As with the other dopamine receptor genes discussed below, no consistent findings have emerged. There are positive case-control studies showing association between schizophrenia and the Cys^{311} variant (Arinami et al., 1994; Kaneshima et al., 1997), and the promoter −141C insertion allele in Japanese (Ohara et al., 1998), Swedish (Jonsson et al., 1999b) populations. In a British population, the −141C insertion allele was associated with schizophrenia (Breen et al., 1999). No association was found between the Cys^{311} allele (Harano, 1997; Nanko et al., 1994), the −141C ins/del polymorphism (Li et al., 1998; Stober et al., 1998; Tallerico et al., 1999), and the *Taq*I A polymorphism (Sanders et al., 1993) and schizophrenia in other studies. Furthermore, a study examining the sequence of the dopamine D2 receptor gene region that couples to G-proteins found no changes that would alter the protein in schizophrenia (Seeman et al., 1993). A linkage study with two schizophrenia pedigrees has largely excluded the dopamine D2 receptor gene as a major candidate (Moises et al., 1991). Studies with bipolar disorder and the promoter polymorphism (Furlong et al., 1998), the $Ser^{311}Cys$ polymorphism (Craddock et al., 1995), and the *Taq*I A polymorphism (Kelsoe et al., 1993) have been negative.

There is a panoply of studies dealing with other phenotypes and dopamine D2 receptor polymorphisms. Associations have been found with Parkinson's disease (Plante-Bordeneuve et al., 1997), idiopathic short stature (Miyake et al., 1999), reduced risk of levodopa-induced dyskinesias in Parkinson's disease (Oliveri et al., 1999), prolonged P300 latency in children (Noble et al., 1994) and prolonged P300 latency in a neuropsychiatric population (Blum et al., 1994). Positive results have also been published with schizoid/avoidant behaviour (Blum et al., 1997), psychological defense styles (Comings et al., 1995), obesity (Comings et al., 1993, 1996), brain regional glucose metabolism measured by positron emission tomography (Noble et al., 1997), reproductive success (Legro et al., 1994), visuospatial performance in children (Berman and Noble, 1995), tardive dyskinesia in female schizophrenics (Chen et al., 1997b), and migraine with aura (Peroutka et

al., 1998). Others have reported no association with post-traumatic stress disorder (Gelernter et al., 1999b), obsessive-compulsive disorder (Novelli et al., 1994), Tourette syndrome (Nothen et al., 1993), symptoms of attention-deficit hyperactivity disorder (Rowe et al., 1999), Parkinson's disease (Pastor et al., 1999), migraine with aura (Dichgans et al., 1998), and panic disorder (Crawford et al., 1995).

3.4. Dopamine D2 receptor pharmacogenetics

Nemonapride, a selective dopamine D2 receptor antagonist, has been reported to be associated with the *Taq* A1 allele and early response to treatment in schizophrenic patients (Suzuki et al., 2000). The same allele was also associated with higher prolactin elevation in female patients, possibly putting this group at higher risk for hyperprolactinemia-related side effects (Mihara et al., 2000). The association between the *Taq* A1 and antipsychotic drug response needs to be replicated and explored with other neuroleptics. It would be of particular relevance to pharmacogenetics to understand how this polymorphism affects the functioning of the dopamine D2 receptor. No association between the $Ser^{311}Cys$ polymorphism and response to lithium prophylaxis in mood disorders was found (Serretti et al., 1999a). Despite extensive studies on the polymorphisms in the dopamine D2 receptor gene, there is inconsistent evidence of a functional change that is related to substance abuse. Future research might include examining the polymorphisms in relation to drugs of abuse that act directly on the dopaminergic system such as cocaine and amphetamines.

4. Dopamine D3 receptor

4.1. Dopamine D3 receptor gene structure and polymorphisms

The dopamine D3 receptor gene is located on chromosome 3q13.3, and its coding sequence consists of six exons that are distributed over 40,000 base pairs. The complete transcript has three shorter variants in which the second and/or third exons are deleted. These deletions result in a frame shift that leads to a truncated protein (Griffon et al., 1996). There are several commonly studied polymorphisms. $Ser^{9}Gly$ (*Bal*I/*Msc*I) is located at amino acid position 9 of the N-terminal extracellular domain of the receptor. This mutation results in the creation of a *Bal*I restriction enzyme site and the alteration of a recognition site for *Msc*I that allows for easy detection of the polymorphism after amplification of genomic DNA with the polymerase chain reaction (Crocq et al., 1992). The Ser^{9} variant is referred to as allele 1, and the Gly^{9} variant is identified as allele 2. *Msp*I restriction nuclease digests are able to identify polymorphic sites in the fourth (Crocq et al., 1996) and fifth (Griffon et al., 1996) introns, and the third cytoplasmic loop (known as D3-208) (Sabate et al., 1994) of the dopamine D3 receptor gene. *Pvu*II digests of a portion of the 5′-untranslated region, the sequence containing the N-terminus and transmembrane domains I and II (known as D3-Hsac) yield three possible polymorphisms known as P1, P2 and P3 (Sabate et al., 1994). Three single nucleotide polymorphisms were identified in the 768 base-pair 5′-leader region. All are closely linked to each other, and to the *Bal*I polymorphism (Sivagnanasundaram et al., 2000).

4.2. Dopamine D3 receptor mutations, polymorphisms and gene function

The functional importance of polymorphic changes has not been examined by many studies, with the exception of Lundstrom et al., who report that the homozygote $Ser^{9}Gly$ dopamine D3 receptor variant has a higher affinity for dopamine than the heterozygote or the wildtype receptor. This was demonstrated using the Semliki Forest virus vector to infect Chinese hamster ovary (CHO) cells. No significant differences in receptor affinity were found for other dopamine D3 receptor ligands other than dopamine and GR99841, a dopamine D3 receptor-selective ligand (Lundstrom and Turpin, 1996). A single nucleotide polymorphism within the 5′ leader region of the D3 receptor gene encodes for a $Lys^{9}Gly$ variant in a 36 amino acid residue of an upstream open reading frame (Sivagnanasundaram et al., 2000). The significance of this small open reading frame and the associated polymorphism is not known.

4.3. Dopamine D3 receptor and disease genetics

Most studies of polymorphisms in the dopamine D3 receptor gene have explored linkage to schizophrenia, and to a lessor extent bipolar disorder or other psychotic illnesses. Linkage to other psychiatric diagnoses such as substance abuse has also been studied. No consistent findings of linkage to any psychiatric disorder have been found for any genes on chromosome 3 (Nimgaonkar, 1998). A positive association between homozygosity at the *Bal*I polymorphism and/or the 1–1 genotype and schizophrenia has been reported in case-control studies (Asherson et al., 1996; Crocq et al., 1992; Durany et al., 1996; Kennedy et al., 1995; Mant et al., 1994; Spurlock et al., 1998) and a meta-analysis of case-control studies (Williams et al., 1998). Another meta-analysis found an excess of homozygosity at the *Bal*I polymorphism and of the 1–1 genotype in schizophrenics but only in African and Caucasian groups (Dubertret et al., 1998). Some of these also found weaker evidence for association between the 1–1 genotype and schizophrenia. Discordant results from a case-control study indicated an association between homozygotes for either *Bal*I allele and schizophrenia, and an excess of allele 1 in

the schizophrenia group when compared to controls (Nimgaonkar et al., 1996). Two independent samples were studied, but results were not consistent between the two groups. One study with a relatively small number of subjects (73 with schizophrenia, and 56 matched controls), found an association between one of the genotypes, in which three of the four single nucleotide polymorphisms in the 5′-leader region differ, and schizophrenia (Sivagnanasundaram et al., 2000). In 133 schizophrenia patients, allele 1 of the *Bal*I polymorphism was reported to be more frequent than in a control group (Shaikh et al., 1996). These authors also performed a meta-analysis of previously published results and concluded that the Ser^9 allele conferred a small increase in susceptibility to schizophrenia.

In contrast to the above studies, many more have reported negative results of associations studies between schizophrenia and the *Bal*I polymorphism or homozygosity at this locus of the dopamine D3 receptor gene in case-control studies (Chen et al., 1997a; Di Bella et al., 1994; Gaitonde et al., 1996; Hawi et al., 1998; Inada et al., 1995; Jonsson et al., 1993; Malhotra et al., 1998; Nanko et al., 1993b; Nothen et al., 1993; Saha et al., 1994; Tanaka et al., 1996; Yang et al., 1993). Negative results in linkage analysis of pedigrees (Wiese et al., 1993), and in sib-pairs using the transmission disequilibrium test (Rothschild et al., 1996) have also been reported. Negative results of linkage have also been reported for the D3-208 and the D3-Hsac polymorphisms (Sabate et al., 1994).

A possible association between bipolar disorder and allele I of the *Bal*I polymorphism has been published (Parsian et al., 1995), but several studies have not replicated this finding (Piccardi et al., 1997; Rietschel et al., 1993; Shaikh et al., 1993a). Two groups have examined the relationship of alcoholism to the *Bal*I polymorphism and found no association (Gorwood et al., 1995; Higuchi et al., 1996), while another reports an association with allele 1 (Thome et al., 1999). A small study of 36 patients and 38 controls reported an association between unipolar depression and allele 2 of the *Bal*I polymorphism (Dikeos et al., 1999). A lack of association between the *Bal*I and intron 5 *Msp*I polymorphisms and attention deficit hyperactivity disorder has been reported (Barr et al., 2000). There are negative reports of association between the *Bal*I polymorphism and polycystic ovarian syndrome (Kahsar-Miller et al., 1999), anorexia nervosa (Bruins-Slot et al., 1998), Tourette's syndrome (Devor et al., 1998), heroin dependence (Kotler et al., 1999), and obsessive-compulsive disorder (Catalano et al., 1994). There are isolated reports of an association of the *Bal*I polymorphism with novelty seeking in bipolar patients (Staner et al., 1998), of the heterozygous 1–2 genotype with novelty seeking in alcohol dependence (Thome et al., 1999), of homozygosity with substance abuse in schizophrenia (Krebs et al., 1998), and of homozygosity with opiate dependence (Duaux et al., 1998). Taken together, these disparate findings do not present a convincing case that polymorphisms in the dopamine D3 receptor are related to neuropsychiatric disease.

4.4. Dopamine D3 receptor pharmacogenetics

Several studies have looked at clozapine response and the *Bal*I Ser^9Gly mutation. Although two groups (Scharfetter et al., 1999; Shaikh et al., 1996) find that the Gly^9 allele is associated with significantly greater odds for treatment response than the Ser^9 allele, others (Malhotra et al., 1998) do not confirm this. There may be some association of the glycine allele (Basile et al., 1999), or the homozygous 2–2 genotype with neuroleptic-induced tardive dyskinesia (Steen et al., 1997), although other studies have not been able to replicate this (Rietschel et al., 1993). These findings suggest that vulnerability to tardive dyskinesia may be partially influenced by dopamine D3 receptor polymorphisms. The next step could be to determine if the potential of different antipsychotic drugs to cause tardive symptoms is influenced by certain polymorphisms. This could then be clinically useful in selecting a treatment that would be least likely to give certain patients these long-term side effects.

5. Dopamine D4 receptor

5.1. Dopamine D4 receptor gene structure and polymorphisms

The dopamine D4 receptor gene is located on chromosome 11p15.5 (Gelernter et al., 1992; Petronis et al., 1993), and contains a remarkable number of polymorphic regions. The promoter is located almost immediately upstream from the initiation codon, with the region between −591 and −123 relative to the initiation codon mediating transcription. A negative modulator is located between −770 and −679 (Kamakura et al., 1997). There is a hypervariable region in the third cytoplasmic loop of the dopamine D4 receptor gene consisting of 2–10 imperfect 48 base pair repeats (Van Tol et al., 1992). By studying 178 different chromosomes, 19 different repeats were found in 25 different haplotypes that code for 18 different predicted amino acid sequences (Lichter et al., 1993). Two other variants have also been identified (Asghari et al., 1994; Van Tol et al., 1992), for a total of 27. Variants in this polymorphism are usually written as the dopamine D4.*x* receptor, where *x* represents the number of repeats. The dopamine D4.2, D4.4 and D4.7 receptor alleles occur the most frequently, but there is considerable variation in the distribution of alleles depending on ethnicity (Chang et al., 1996; Lichter et al., 1993).

A tandem duplication polymorphism 120 base pairs long can be found 1.2 kilobases upstream of the initiation codon. The duplication sequence contains transcription

factor binding sites, and the frequency of the duplication allele varies from 0.40 to 0.81 in the 11 populations studied (Seaman et al., 1999). Further downstream, there are 11 single nucleotide polymorphisms: −1217G > del (Okuyama et al., 2000), −809G > A, −768G > A, −616C > G, −603T > del, −602G > del, −600G > C, −376C > T, −291C > T, −128G > T (Mitsuyasu et al., 1999), −521C > T (Okuyama et al., 1999), and −11G > C (Cichon et al., 1995). There is also a *Sma*I (Petronis et al., 1994) and a *Pst*I (Paterson et al., 1996) restriction fragment length polymorphism in the 5′ untranslated region. There are a variable number of repeated G nucleotides in the first intron (Barr et al., 1993), with alleles containing 6–10 repeats. Exon 1 contains a 12 base-pair insertion–deletion mutation that codes for a four amino-acid sequence in the N-terminal, extra-cellular region (Catalano et al., 1993). Exon 1 also contains a 13 base pair frameshift mutation (Nothen et al., 1994). The first transmembrane region contains a 21 base pair deletion affecting codons 36 to 42 (Cichon et al., 1995). Exon 3 contains a single T–G base-pair substitution (an amino acid change $Val^{194}Gly$), that is found only in Africans (Seeman et al., 1994).

5.2. Dopamine D4 receptor mutations, polymorphisms and gene function

There does not seem to be a simple relationship between the length of the third cytoplasmic loop polymorphism and pharmacological or functional activity (Asghari et al., 1994; Jovanovic et al., 1999). However, the number of repeats can affect the pharmacological profile of this receptor. The dopamine D4.10 receptor is 2- to 3-fold more potent in dopamine-mediated coupling to adenylyl cyclase than the dopamine D4.2 receptor (Jovanovic et al., 1999), and the dopamine D4.4 and D4.2 receptor variants are 2- to 3-fold more potent than the dopamine D4.7 receptor (Asghari et al., 1995). Differences of the same magnitude are found in the affinity of some dopamine D2 receptor antagonists when comparing the dopamine D4.2 receptor and dopamine D4.10 receptor variants (Jovanovic et al., 1999). The dopamine D4 receptor variants also show differences in the sodium sensitivity of clozapine binding (Asghari et al., 1994; Van Tol et al., 1991). Some genetic studies have pooled subjects on the basis of more or less repeats in the third cytoplasmic loop polymorphism. This approach is questionable in light of the above findings, since there does not appear to be a linear relationship between the number of repeat sequences, and the functional activity. Furthermore, there are sequence variations in alleles of the same length, which are also overlooked by these pooling strategies. Therefore, simply pooling subjects as having a high or low number of dopamine D4.*x* receptor repeats is likely to confound results if there is indeed a functional effect of the polymorphism that influences the phenotype.

Despite some minor differences in affinity for quinpirole and clozapine, no functional differences in receptor activation were found with dopamine, epinepherine or norepinepherine with variants of the exon 1, single-copy 12 base-pair repeat (Zenner et al., 1998). The 13 base pair frameshift mutation in exon 1 is predicted to result in a truncated, non-functional protein. A homozygous individual for this mutation has acousticus neurinoma, obesity and disturbances of the autonomic nervous system (Nothen et al., 1994). The exon 3, $Val^{194}Gly$ receptor variant affects transmembrane region 5, and is two orders of magnitude less sensitive to dopamine, clozapine, and olanzepine. This variant is also insensitive to guanine nucleotide, which the authors conclude, indicates the absence of a high-affinity state or functional state (Liu et al., 1996). An N-terminal trancated receptor can be generated through the use of a cryptic initiation site in transmembrane region 1. The modified receptor is termed the dopamine D4.4ΔNH_2 receptor, and has a reduced functional potency, but it is not clear if the variant is found in vivo (Schoots et al., 1996).

5.3. Dopamine D4 receptor and disease genetics

Variations in the dopamine D4 receptor sequence have been studied in relation to a variety of neuropsychiatric diseases and phenotypes. Following a report of linkage between the exon 1, single-copy 12 base-pair repeat (allele 2), and delusional disorder (Catalano et al., 1993), other psychotic illnesses were studied. Studies examining the possibility that the dopamine D4 receptor gene is associated with schizophrenia have yielded a number of negative or weak results (Barr et al., 1993; Hong et al., 1997, 1998; Kohn et al., 1997; Nanko et al., 1993a; Okuyama et al., 1999; Petronis et al., 1995; Shaikh et al., 1994; Sommer et al., 1993; Tanaka et al., 1995; Tani et al., 1997), and have largely excluded this gene as a major candidate for susceptibility to schizophrenia (Macciardi et al., 1994). One study that found results suggestive of linkage between the 48 base-pair polymorphism and schizophrenia, found no sequence differences in the main ligand binding region (Weiss et al., 1996). Furthermore, there was no genetic interaction found between the dopamine D4 receptor exon 3, and the $GABA_A$ receptor α-1 subunit in the symptoms of major psychoses (Serretti et al., 1999b). A study examining polymorphisms at dopamine D1 receptor, dopamine D2 receptor, dopamine D3 receptor, and dopamine D4 receptor genes in schizophrenia defined by different diagnostic systems failed to find an association (Dollfus et al., 1996). Association studies in bipolar disorder have also been negative (Lim et al., 1994; Oruc et al., 1997).

One controversial area in the search for a functional effect of the third cytoplasmic loop polymorphism has been the putative association with novelty seeking and other personality/temperament traits. Initial reports by

Ebstein et al. (1996) and Benjamin et al. (1996) showed an association between the dopamine D4.7 receptor variant and novelty seeking as part of a multidimensional personality questionnaire. Subsequent research confirmed these findings (Benjamin et al., 2000; Ebstein et al., 1997; Strobel et al., 1999; Tomitaka et al., 1999), but this was countered by a large number of negative findings (Bau et al., 1999; Gelernter et al., 1997; Jonsson et al., 1997, 1998; Kuhn et al., 1999; Malhotra et al., 1996; Pogue-Geile et al., 1998; Poston et al., 1998; Sander et al., 1997; Sullivan et al., 1998). Other polymorphisms were also reported to be associated with novelty seeking (Okuyama et al., 2000), and other authors found an association between the gene and the trait, but found that more repeats did not correlate with more novelty seeking, unlike the majority of the above positive studies (Ekelund et al., 1999). Related studies in neonates found a relationship between the 48 base pair polymorphism and novelty seeking (Ebstein et al., 1998) and other aspects of temperament (Auerbach et al., 1999). Dopamine D4 receptor knock-out mice exhibited reduced exploration of novel stimuli (Dulawa et al., 1999), in an intriguing parallel with humans in the positive studies. The original findings were controversial for a number of reasons, not least of which was the racial distribution of the novelty seeking-associated repeats. Speculation about the racial propensity for new experiences, and consequent development of cultural norms, was easily extrapolated from the findings. Despite the initial attractiveness of examining single personality dimensions as opposed to complex neuropsychiatric diseases in relation to dopamine D4 receptor polymorphisms, the conflicting results remain inconclusive, and have been criticized on methodological grounds (Baron, 1998; Jovanovic et al., 1999; Paterson et al., 1999).

Because of the clinical relationship of novelty seeking with substance abuse and other impulse control disorders, novelty seeking in substance abusers, as well as the relationship of the 48 base pair polymorphism to substance abuse itself was also explored. Some authors reported an association with cigarette smoking in African-Americans (Shields et al., 1998), with female pathological gamblers (Perez de Castro et al., 1997), and with alcoholism (George et al., 1993). No association was found in a Scandinavian sample of alcoholics (Adamson et al., 1995; Geijer et al., 1997), and other polymorphisms were not associated with alcoholism in Taiwanese populations (Chang et al., 1997). A case-control study of heroin dependence did not find an association with the exon 3 polymorphism (Franke et al., 2000), nor was there an association found with suicide attempts (Persson et al., 1999).

Other disorders that have an element of impaired impulse control that have been studied in relation to polymorphisms in the dopamine D4 receptor gene include obsessive-compulsive disorder, Tourette syndrome, and attention-deficit hyperactivity disorder. Cruz et al. reported suggestive findings that the dopamine D4.7 receptor variant was associated with tics in patients with obsessive-compulsive disorder (Cruz et al., 1997), but others have found that variants in the dopamine D4 receptor gene are not associated with susceptibility to either Tourette syndrome (Barr et al., 1996), or obsessive-compulsive disorder (Di Bella et al., 1996). One report, that greater than 6 repeats in the exon 3 polymorphism confers susceptibility to Parkinson's disease (Ricketts et al., 1998), has been contradicted by another study (Kronenberg et al., 1999). Results with attention deficit hyperactivity disorder are similarly inconclusive, with two papers showing an association with the D4.7 allele (Faraone et al., 1999; LaHoste et al., 1996), and two contradicting reports (Castellanos et al., 1998; Rowe et al., 1998).

5.4. Dopamine D4 receptor pharmacogenetics

Because of the relatively high affinity of clozapine for the dopamine D4 receptor (Van Tol et al., 1991), the relationship between polymorphisms in this gene and response to clozapine treatment have been investigated. Negative reports of the association with clozapine response have included the 48 base-pair repeat, exon 1, and exon 3 polymorphism (Kohn et al., 1997; Rao et al., 1994; Rietschel et al., 1996; Shaikh et al., 1993b, 1995). One group reported that the dopamine D4.7 receptor variant was associated with clozapine response when compared to response to typical neuroleptics (Cohen et al., 1999). Hwu et al. (1998), however, found an association between homozygotes for the dopamine D4.7 receptor variant and all types of neuroleptic response in schizophrenic patients. The exon 3 polymorphism does not appear to be associated with response to lithium prophylaxis in mood disorders (Serretti et al., 1999a). Despite the differences in pharmacological profile of the dopamine D4.*x* receptor variants, the clinical impact of these variants on neuroleptic response are unlikely to be the major factor determining neuroleptic response vs. non-response, considering the large range of doses that are commonly used (Marder et al., 1991).

6. Dopamine D5 receptor

6.1. Dopamine D5 receptor gene structure and polymorphisms

The dopamine D5 receptor gene has not been the subject of many genetic studies. It is located on chromosome 4p15.1–p15.3, and contains a highly polymorphic dinucleotide repeat region (Sherrington et al., 1993). The microsatellite (D5(CT/GT/GA)n) has 12 possible alleles. The major transactivation domain is 119–182 base pairs upstream of the transcription start site, with a negative

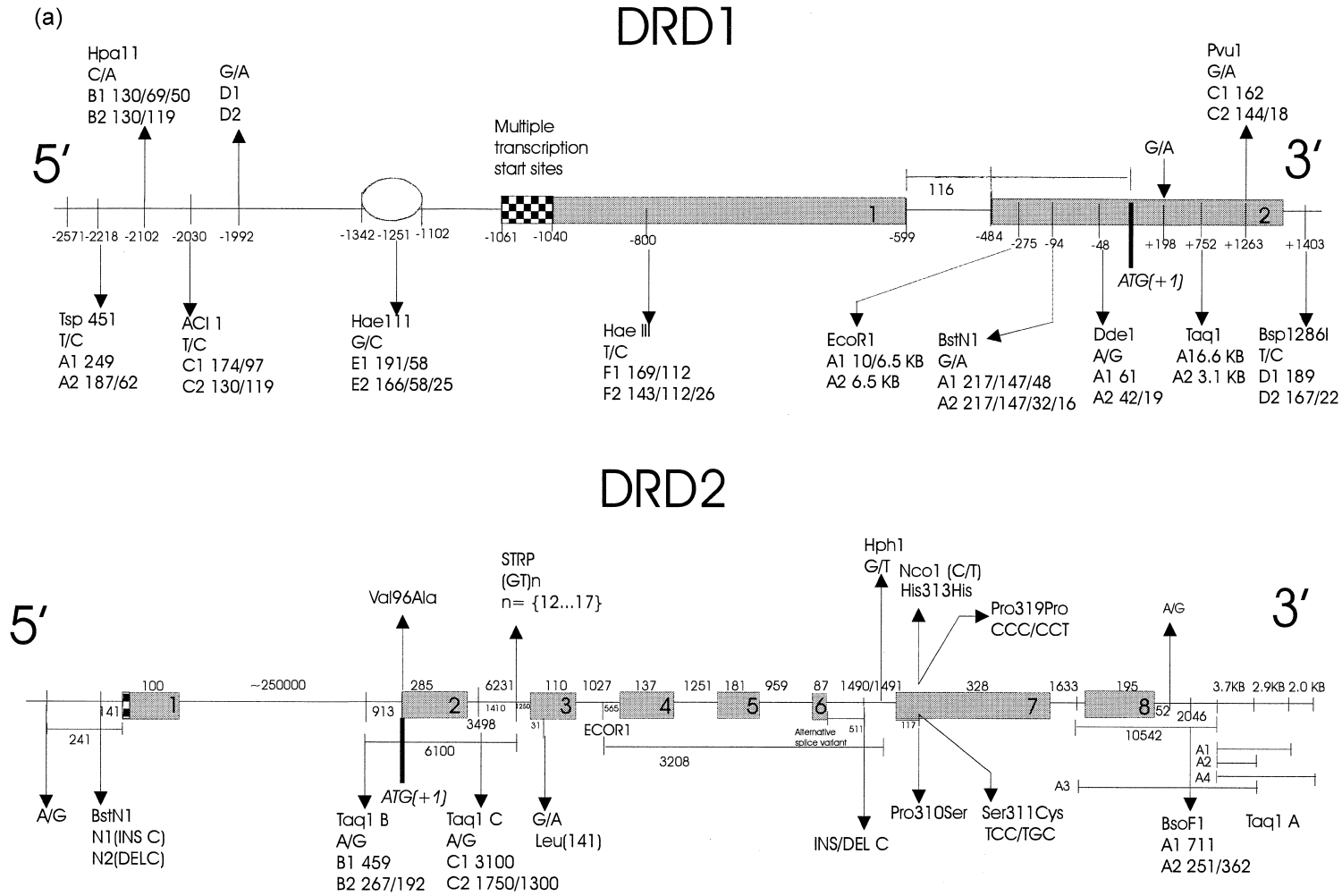

Fig. 1. Schematic representation of the sense strand for each of the five dopamine receptor genes. Both intronic and extronic polymorphisms are given, and are located relative to the ATG start codon, and assigned a value of 1. Where applicable, restriction enzymes are noted for each polymorphism, along with the size of the fragments generated with and without the cut sites present. Introns are represented by a straight line connecting the shaded grey boxes, which represent exons. Distances (in bp) are given above each intron/exon element, while the exons are sequentially numbered. Distances in small font are from one polymorphism to another or from a polymorphism to the start of the closest exon. Legend: (shaded oblong) Activator; (shaded rectangle) Exon; (shaded pentagon) Negative Modulator; (rectangle with four diagonal lines) Transcription start site; (oblong) Promotor (only shown if it extends beyond transcription start site); ▭ Transactivator domain. Maps are not to scale.

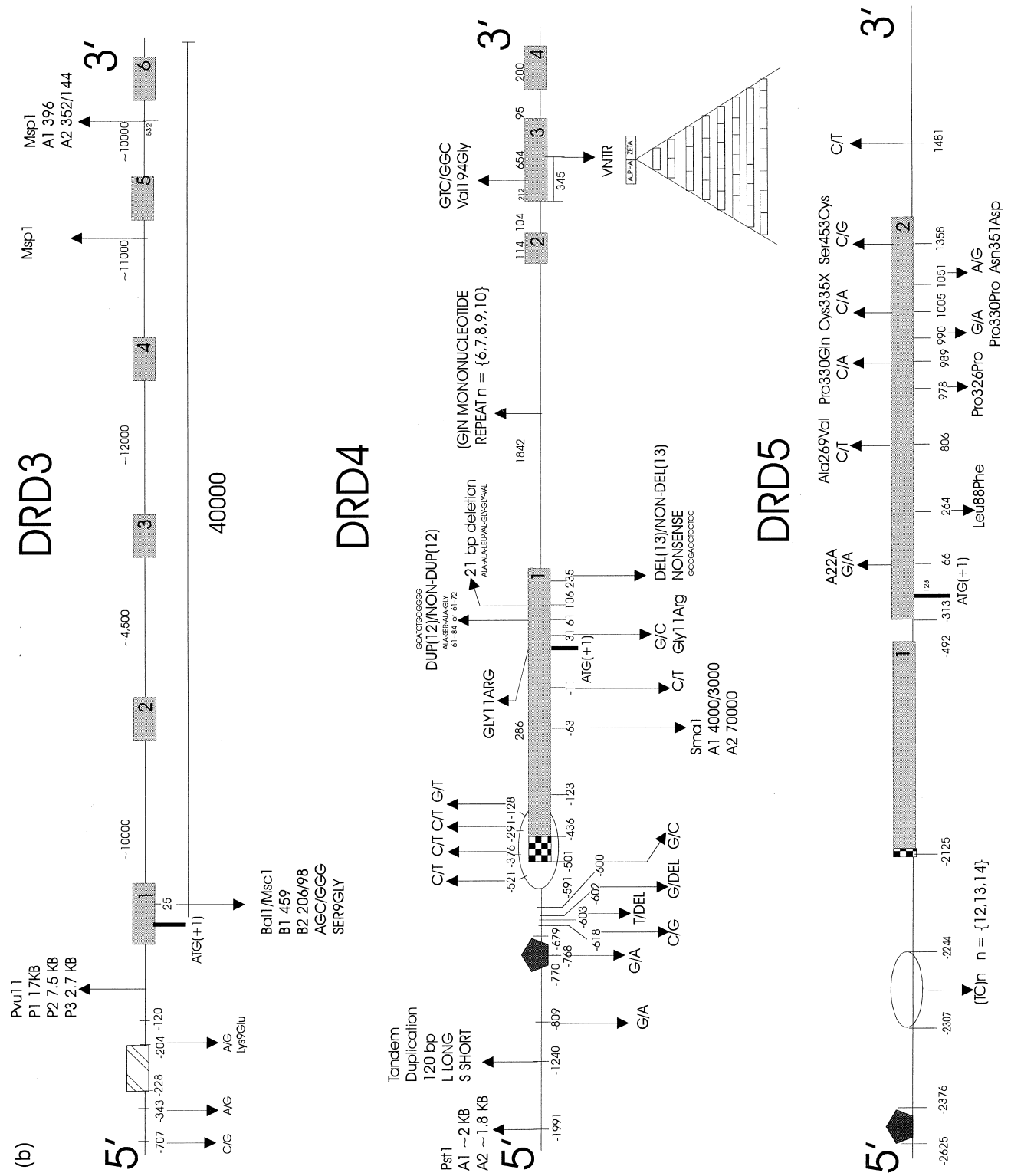

Fig. 1 (*continued*).

modulator at −500 to −251 (Beischlag et al., 1995). A dinucleotide repeat called (TC)13, is located within the promoter region (Beischlag et al., 1996). There are two dopamine receptor pseudogenes D5ψ1 and D5ψ2 that do not direct the synthesis of a functional receptor (Grandy et al., 1991). There is a silent polymorphism at base pair 978 ($Pro^{326}Pro$) and a missense change, $Leu^{88}Phe$, in transmembrane domain II (Feng et al., 1998). Nine mutations were identified using single stand conformational polymorphisms (Sobell et al., 1995).

6.2. Dopamine D5 receptor mutations, polymorphisms and gene function

Five of the nine polymorphisms identified by Sobell et al. result in protein sequence changes: $Ala^{269}Val$ in the third intracellular loop, $Pro^{330}Gln$ in the third cytoplasmic loop, $Asn^{351}Asp$ in the seventh transmembrane region, and $Ser^{453}Cys$ in the C-terminus. A nonsense mutation in the third extracellular loop at Cys^{335} results in termination (Cravchik and Gejman, 1999; Sobell et al., 1995). The $Asn^{351}Asp$ polymorphism increases dopamine and decreases *R*(+)-SKF-38393 binding affinity. The $Leu^{88}Phe$ slightly increases dopamine binding affinity, and decreases risperidone and SCH-23390 affinity (Cravchik and Gejman, 1999). Analysis of the (TC)13 mutations in the promoter region did not show any differences in dopamine D5 receptor gene activation (Beischlag et al., 1996).

6.3. Dopamine D5 receptor and disease genetics

One group reported an overrepresentation of the most common allele of the microsatellite polymorphism and substance abuse in a sample of 148 male and female subjects when compared to a control group (Vanyukov et al., 1998). Others have found a novel missense change at a highly conserved amino acid (L88F), in a patient with autism after screening 171 patient samples (Feng et al., 1998). No association with schizophrenia or bipolar disorder was found in a family linkage study (Asherson et al., 1998), or with schizophrenia in multiplex pedigrees (Kalsi et al., 1996; Ravindranathan et al., 1994). No association with schizophrenia was found in a case-control study (Sobell et al., 1995). An association of the microsatellite repeat region in the dopamine D5 receptor gene with attention deficit hyperactivity disorder was reported but has not been replicated (Daly et al., 1999). This group applied a haplotype relative-risk strategy in a sample of 118 subjects and 200 of their parents. The dopamine D5 receptor gene is located within the 4p14–16 region where suggestive linkage findings for bipolar disorder have been noted (Kennedy et al., 1999), but no clear results linking the actual gene to bipolar disorder exist (Asherson et al., 1998).

6.4. Dopamine D5 receptor pharmacogenetics

As with the dopamine D1 receptor, there are no therapeutic drugs that specifically target the D5 receptor, and so it is of relatively minor pharmacogenetic importance. However, recent observations of a functional interaction between the dopamine D5 and γ amino-butyric acid (A), ($GABA_A$) receptors (Liu et al., 2000), may form the basis to study the genetic interaction of these receptors in disease and drug response (Fig. 1).

7. Conclusions

The myriad, conflicting results of association and family linkage studies cannot be easily summarized. There is essentially no clear-cut case in which polymorphisms in any of the dopamine receptor genes are related to neuropsychiatric disorders, or even to a specific phenotype. While some receptor variants are associated with changes in receptor signaling, the significance of these findings for brain function remain to be elucidated. This uncertain picture is not unique to the pharmacogenetics of dopamine receptors, as a similarly confusing scenario is found in many complex genetic diseases, including some that have been discussed in this review such as schizophrenia and bipolar disorder.

The fundamental issue may be that dopamine receptors are only one component of the array of neurotransmitter receptor systems that influence behaviour in concert with genes that control neurodevelopment, connectivity, neuronal signaling, and synaptic plasticity. In attempting to find a trait that can be specified at the level of the organism, it may be exceedingly difficult or impossible to isolate the effect of only one gene or polymorphism. Complex genetic diseases account for most of the diseases currently subject to research, but success in understanding most has been limited. Novel strategies involving multiple genes and their interactions may be needed to gain useful insights into receptor variation and disease.

There are preliminary results that suggest a relationship between dopamine receptor polymorphisms and neuroleptic treatment. The dopamine D3 receptor may play a role in modulating susceptibility to tardive dyskinesia. Dopamine D2 and D4 receptor polymorphisms may influence response to clozapine and other neuroleptics, although the findings are inconsistent. Many polymorphisms and mutations that alter the pharmacological profile of the various dopamine receptors have been described. Few of these receptor variants have been clearly associated with therapeutic efficacy of dopamine system drugs. With respect to neuroleptic treatment of schizophrenia, many genetic studies have examined the extremes of response vs. non-response, where the effects of polymorphisms or mutations may be subtle, modulating interindividual differences in minimally effective doses. Under such circumstances, genetic variability in drug metabolism becomes an

important factor in these genetic analyses, and supports the use of more complex genetic studies that incorporate multiple genes, in the study of dopamine receptor pharmacogenetics. More research is needed to determine if clinically important differences in the efficacy or side effects of neuroleptics can be predicted by variation in dopamine receptor gene sequences.

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