For reprint orders, please contact: reprints@futuremedicine.com

Genetic variation and the D2 dopamine receptor: implications for the treatment of neuropsychiatric disease

“...variation in D2 receptor expression might account for individual differences in response to pharmacotherapies that engage the D2 receptor system.”

First draft submitted: 16 May 2016; Accepted for publication: 17 May 2016; Published online: 5 July 2016

Keywords: bipolar disorder • dopamine receptor • Huntington disease • major depressive disorder • molecular imaging • Parkinson disease • schizophrenia • striatum

Genetic variation & the D2 dopamine receptor: implications for the treatment of neuropsychiatric disease

The D2 dopamine receptor is a G-protein-coupled receptor that is highly expressed in the brain, particularly in the striatum. Striatal circuitry is critical to the regulation of movement and motivational states. Accordingly, D2 receptors are a key target of pharmacologic agents used to treat neurologic and psychiatric diseases. Agonists of the D2 receptor (and the closely related D3 receptor) improve disordered movements and depressed mood in Parkinson disease, and they quiet the overwhelming urge to move one's legs in restless legs syndrome. D2 receptor antagonists, on the other hand, quell the delusions and hallucinations that commonly occur in schizophrenia, bipolar disorder and major depressive disorder. D2 antagonists also suppress the involuntary movements of Huntington disease. Furthermore, because of the variety of pharmacotherapies and drugs of abuse that indirectly influence the D2 receptor, this system is relevant to a range of other conditions, from drug addictions to disorders of attention and arousal. The societal impact of these afflictions, and neuropsychiatric disorders in general, is truly astounding. It is no surprise, therefore, that the D2 receptor has been a

focus of intense research in basic science and drug development circles for decades.

In recent years, researchers have paid increasing attention to inter-individual variation of the D2 receptor system. Postmortem studies of human brain and, increasingly, *in vivo* molecular imaging (positron emission tomography and single-photon emission tomography) can reliably quantify D2/D3 receptor density at the individual level. Substantial variation in striatal D2 receptor expression has been noted in these studies, with typical coefficients of variation in the range of 20–60% [1–3]. This between-subject variation is important for at least three reasons. First, individual differences in D2 receptor expression are hypothesized to contribute to normal variability in motivated behaviors and neurocognitive abilities – basic functions of the human brain that help define who we are as individuals. Second, such differences may influence the risk of neuropsychiatric disorders. For example, studies have consistently demonstrated abnormally low striatal D2 receptor levels among individuals with addictions, although the causal direction of this association remains unclear [4]. Third, variation in D2 receptor expression might account for individual differences in response to pharmacotherapies that engage the D2 receptor system. Clinically, the most

Brian J Mickey

Department of Psychiatry, University of Utah School of Medicine, Salt Lake City, UT, USA

and
Department of Psychiatry, University of Michigan Medical School, Ann Arbor, MI, USA

Tel.: +1 801 581 7952

Fax: +1 801 581 5604

brian.mickey@utah.edu

important manifestation of these individual differences is treatment resistance, which affects roughly 30% of individuals with psychotic and mood disorders. Identification of D2 receptor system biomarkers that robustly predict pharmacological response could transform the way we treat neuropsychiatric disorders, replacing current trial-and-error practices with a more personalized ‘precision medicine’ approach. Identification of such predictors would also pave the way for clinically relevant subtyping of diseases, which could facilitate development of novel therapies targeted to those patients who need them most – in other words, those with treatment-refractory disease.

“Complementary approaches in animal models and *in vitro* systems are also needed to understand the molecular, cellular and circuit-level mechanisms through which these genetic variants act.”

Genetic factors appear to play a major role in the observed individual differences in D2 receptor expression in humans. A recent *in vivo* molecular imaging study of twins estimated that the genetic and environmental contributions to the observed variance in striatal D2 receptor levels were 67 and 33%, respectively [5]. The specific genetic loci that drive variation in D2 receptor expression are just beginning to emerge. In a recent systematic review and meta-analysis of *in vivo* imaging studies, we found that only 11 candidate genes had been examined in the published literature [6]. The most commonly studied variant was a single nucleotide polymorphism (rs1800497, Glu713Lys, also called ‘Taq1A’) in the *ANKK1*, which lies 10 kb downstream from the *DRD2*. Meta-analysis demonstrated that striatal D2 receptor levels were robustly lower among carriers of the minor allele (Lys713) relative to major allele homozygotes, with an estimated effect size of 0.57, corresponding to a variance explained of approximately 7% [6]. Interestingly, the association of rs1800497 with striatal D2 receptor levels was present only among healthy individuals, not neuropsychiatric disease groups, suggesting that such disorders disrupt and obscure the normal genetic effects.

Remarkably little is known about the functional impact of rs1800497 at the molecular or cellular level. This polymorphism is predicted to cause a missense mutation in *ANKK1* (Glu713Lys) [7]. *ANKK1* and *DRD2* mRNA are both expressed in human striatum (Allen Human Brain Atlas [8]) [9], but regulation of D2 receptors by *ANKK1* has not been shown, and no *in vitro* studies have yet examined the effects of rs1800497 on the expression or molecular function of *DRD2* or *ANKK1* proteins. A causal link between rs1800497 and D2 receptor expression or function

appears plausible, but it may be that another polymorphism in linkage disequilibrium with rs1800497 is causal. Prime candidates include the *ANKK1* missense polymorphism, rs7118900, which is predicted to create a new *ANKK1* phosphorylation site, and which appears to alter subcellular *ANKK1* expression patterns *in vitro* [10,11]. Other candidates include intronic *DRD2* variants rs1079597, rs2283265 and rs1076560. The latter two were reported to alter *DRD2* RNA splicing [12]. Further *in vitro* and *in vivo* mechanistic studies of these variants are clearly warranted.

Inter-individual variation has also been observed in activation of the D2/D3 receptor system – as distinguished from resting or baseline receptor levels. Some radiotracers utilized for *in vivo* molecular imaging, such as [¹¹C]raclopride, compete with exogenous drugs and endogenous neurotransmitters. This property allows experimenters to quantify displacement of the radiotracer from the receptor during a pharmacologic challenge or, alternatively, during a behavioral challenge that induces dopamine release. Several studies have incorporated such behavioral challenge paradigms (e.g., cigarette smoking or experimental pain) and found associations between activation of the D2 receptor system and polymorphisms in dopaminergic genes, including the dopamine transporter (*SLC6A3*) [13], and D2-family receptors [13–15]. In addition, associations have been reported for variants in genes for the serotonin 2C receptor (*HTR2C*) [16] and μ -opioid receptor (*OPRM1*) [17,18] both of which regulate dopamine release via their expression in ventral tegmental interneurons. Replication of these findings with adequately powered studies is needed, but the existing studies suggest that polymorphisms in a broad range of genes could impact the D2 receptor system.

Given our expanding knowledge of genetically-driven individual differences in the D2 receptor system, what are the implications of this knowledge for future treatment and understanding of neuropsychiatric disorders? The greatest implications may be for personalized therapeutics with drugs that act directly at the D2 receptor. If additional genetic variants are identified, it appears feasible to predict to a useful degree an individual’s therapeutic response or adverse effects with such drugs. For example, relative to rs1800497 major allele homozygotes, carriers of the minor allele (who tend to have lower D2 receptor expression, as reviewed above) showed lower sensitivity to the nonselective dopaminergic agonist apomorphine [19]. Beyond the pharmacogenetic implications, our conceptualizations of neuropsychiatric disorders may also benefit. Low apomorphine sensi-

tivity is found among many, but not all, individuals with alcoholism, suggesting that this pharmacological phenotype might be a genetically influenced characteristic of one type of alcohol addiction [19]. This example illustrates just one potential path through which a genetic variant might inform diagnosis and treatment. More than likely, polygenic predictors – possibly combined with intermediate phenotypes – will be needed to construct robust markers with utility at the level of an individual patient.

Future progress will depend on work with human participants and animal models to systematically discover other genetic determinants of D2 receptor variation. Up to this point, the great majority of post-mortem, *in vivo* molecular imaging and pharmacologic challenge studies have been underpowered to detect influential genetic variants, even those with relatively large effects like rs1800497. Larger prospective human studies are needed. But human studies are not enough. Complementary approaches in animal models and *in vitro* systems are also needed to understand

the molecular, cellular and circuit-level mechanisms through which these genetic variants act. This work will require substantial public and private investment, but given the enormous burden of neuropsychiatric diseases on society, the investment is easy to justify. The time has come to develop neuropsychiatric disease subtypes based on biomarkers that are objectively measured, genetically driven, informed by neural circuitry and clinically relevant. Only then will we be able to claim that the era of precision medicine has arrived for neuropsychiatric disorders.

Financial & competing interests disclosure

During the 1-year period prior to publication, BJ Mickey was a paid consultant to Alkermes, Inc., on a topic unrelated to this work. The author has no other relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript apart from those disclosed.

No writing assistance was utilized in the production of this manuscript.

References

- Noble EP, Blum K, Ritchie T, Montgomery A, Sheridan PJ. Allelic association of the D2 dopamine receptor gene with receptor-binding characteristics in alcoholism. *Arch. Gen. Psychiatry* 48(7), 648–654 (1991).
- Thompson J, Thomas N, Singleton A *et al.* D2 dopamine receptor gene (*DRD2*) Taq1 A polymorphism: reduced dopamine D2 receptor binding in the human striatum associated with the A1 allele. *Pharmacogenetics* 7(6), 479–484 (1997).
- Farde L, Hall H, Pauli S, Halldin C. Variability in D2-dopamine receptor density and affinity: a PET study with [¹¹C]raclopride in man. *Synapse* 20(3), 200–208 (1995).
- Volkow ND, Wang GJ, Fowler JS, Tomasi D. Addiction circuitry in the human brain. *Annu. Rev. Pharmacol. Toxicol.* 52, 321–336 (2012).
- Borg J, Cervenka S, Kuja-Halkola R *et al.* Contribution of non-genetic factors to dopamine and serotonin receptor availability in the adult human brain. *Mol. Psychiatry* doi:10.1038/mp.2015.147 (2015) (Epub ahead of print).
- Gluskin BS, Mickey BJ. Genetic variation and dopamine D2 receptor availability: a systematic review and meta-analysis of human *in vivo* molecular imaging studies. *Transl. Psychiatry* 6, e747 (2016).
- Neville MJ, Johnstone EC, Walton RT. Identification and characterization of ANKK1: a novel kinase gene closely linked to *DRD2* on chromosome band 11q23.1. *Hum. Mutat* 23(6), 540–545 (2004).
- Allen Brain Atlas. <http://human.brain-map.org>
- Hawrylycz MJ, Lein ES, Guillozet-Bongaarts AL *et al.* An anatomically comprehensive atlas of the adult human brain transcriptome. *Nature* 489(7416), 391–399 (2012).
- Garrido E, Palomo T, Ponce G, Garcia-Consuegra I, Jimenez-Arriero MA, Hoenicka J. The ANKK1 protein associated with addictions has nuclear and cytoplasmic localization and shows a differential response of Ala239Thr to apomorphine. *Neurotox. Res.* 20(1), 32–39 (2011).
- Hoenicka J, Quinones-Lombrana A, Espana-Serrano L *et al.* The ANKK1 gene associated with addictions is expressed in astroglial cells and upregulated by apomorphine. *Biological Psychiatry* 67(1), 3–11 (2010).
- Zhang Y, Bertolino A, Fazio L *et al.* Polymorphisms in human dopamine D2 receptor gene affect gene expression, splicing, and neuronal activity during working memory. *Proc. Natl Acad. Sci. USA* 104(51), 20552–20557 (2007).
- Brody AL, Mandelkern MA, Olmstead RE *et al.* Gene variants of brain dopamine pathways and smoking-induced dopamine release in the ventral caudate/nucleus accumbens. *Arch. Gen. Psychiatry* 63(7), 808–816 (2006).
- Pecina M, Mickey BJ, Love T *et al.* *DRD2* polymorphisms modulate reward and emotion processing, dopamine neurotransmission and openness to experience. *Cortex* 49(3), 877–890 (2013).
- Savitz J, Hodgkinson CA, Martin-Soelch C *et al.* The functional *DRD3* Ser9Gly polymorphism (rs6280) is pleiotropic, affecting reward as well as movement. *PLoS ONE* 8(1), e54108 (2013).
- Mickey BJ, Sanford BJ, Love TM *et al.* Striatal dopamine release and genetic variation of the serotonin 2C receptor in humans. *J. Neurosci.* 32(27), 9344–9350 (2012).
- Domino EF, Evans CL, Ni L, Guthrie SK, Koeppe RA, Zubieta JK. Tobacco smoking produces greater striatal dopamine release in G-allele carriers with mu opioid receptor A118G polymorphism. *Prog. Neuropsychopharmacol. Biol. Psychiatry* 38(2), 236–240 (2012).

- 18 Pecina M, Love T, Stohler CS, Goldman D, Zubieta JK. Effects of the Mu opioid receptor polymorphism (*OPRM1* A118G) on pain regulation, placebo effects and associated personality trait measures. *Neuropsychopharmacology* 40(4), 957–965 (2015).
- 19 Schellekens AF, Franke B, Ellenbroek B *et al.* Reduced dopamine receptor sensitivity as an intermediate phenotype in alcohol dependence and the role of the *COMT* Val158Met and *DRD2* Taq1A genotypes. *Arch. Gen. Psychiatry* 69(4), 339–348 (2012).