ORIGINAL ARTICLE

Impulsive alcohol-related risk-behavior and emotional dysregulation among individuals with a serotonin 2B receptor stop codon

R Tikkanen1,2, J Tiihonen3,4,5, MR Rautiainen3, T Paunio1,5,6, L Bevilacqua7, R Panarsky8, D Goldman8 and M Virkkunen1,6

A relatively common stop codon (Q20*) was identified in the serotonin 2B receptor gene (HTR2B) in a Finnish founder population in 2010 and it was associated with impulsivity. Here we examine the phenotype of HTR2B Q20* carriers in a setting comprising 14 heterozygous HTR2B Q20* carriers and 156 healthy controls without the HTR2B Q20*. The tridimensional personality questionnaire, Brown–Goodwin lifetime aggression scale, the Michigan alcoholism screening test and lifetime drinking history were used to measure personality traits, impulsive and aggressive behavior, both while sober and under the influence of alcohol, and alcohol consumption. Regression analyses showed that among the HTR2B Q20* carriers, temperamental traits resembled a passive-dependent personality profile, and the presence of the HTR2B Q20* predicted impulsive and aggressive behaviors particularly under the influence of alcohol. Results present examples of how one gene may contribute to personality structure and behaviors in a founder population and how personality may translate into behavior.

Translational Psychiatry (2015) 5, e681; doi:10.1038/tp.2015.170; published online 17 November 2015

INTRODUCTION

Cognitive impulsivity and actual impulsive behaviors show wide inter-individual differences. Impulsivity may enhance performance in some areas of life, but it can also be a trait diagnostic of neuropsychiatric disorders. Several distinct neural pathways contribute to the complex construct of impulsivity.

Bevilacqua et al.1 discovered a stop codon mutation in the gene encoding for the serotonin 2B receptor (HTR2B Q20*), located at 2q36.3–q37.1, in a Finnish founder population. They observed that the stop codon leads to an interruption in the expression of the serotonin 2B (5-HT2B) receptor in lymphoblastoid cells, implying a 50% decrease of the receptor protein survival in humans. Conversely, only 50% of Htr2b knockout mice survive their first postnatal week, since the 5-HT2B receptor plays a key role in the differentiation of cranial neural crest cells and heart development.6 The 5-HT2B receptor has also been shown to be required to form experimental tumors in nude mice,7 and for the development of pulmonary hypertension through bone-marrow contribution,8 which suggest a potential preventive role of the HTR2B Q20* in some somatic diseases.

The primary focus of interest in our study was on impulsivity, as it is a key feature in many neuropsychiatric disorders.9 Intermediate phenotypes, such as impulsivity, may reveal shared biological constructs of diseases that are presently perceived as distinct disorders, as shown for five major psychiatric disorders (schizophrenia, bipolar disorder, major depressive disorder, autism spectrum disorders and attention-deficit/hyperactivity disorder) by the Psychiatric Genomics Consortium.10

In addition to the HTR2B Q20*, some other preliminary findings of gene involvement in the impulsivity of humans have been reported, such as tryptophan hydroxylase 2 (TPH2),11 monoamine oxidase A (MAO-A),12 serotonin 1A receptor (HTR1A),13 serotonin

1Department of Psychiatry, University of Helsinki, Institute of Clinical Medicine, Helsinki, Finland; 2Research and Development, Rinnekoti Foundation, Espoo, Finland; 3Department of Clinical Neuroscience, Karolinska Institutet, Stockholm, Sweden; 4Department of Forensic Psychiatry, University of Eastern Finland, Niuvaniemi Hospital, Kuopio, Finland; 5National Institute for Health and Welfare, Helsinki, Finland; 6Department of Psychiatry, Helsinki University Central Hospital, Helsinki, Finland; 7Department of Psychiatry, New York University School of Medicine, New York, NY, USA and 8Laboratory of Neurogenetics, National Institute on Alcohol Abuse and Alcoholism, Rockville, MD, USA. Correspondence: Dr R Tikkanen, Department of Psychiatry, University of Helsinki, Institute of Clinical Medicine, Valaskarinkatu 12, P.O. Box 22, Helsinki 00260, Finland.

E-mail: roope.tikkanen@helsinki.fi

Received 9 June 2015; revised 18 September 2015; accepted 19 September 2015
18 receptor (HTR1B), serotonin 3B receptor (HTR3B), serotonin transporter (S-HTT) and dopamine transporter (DAT1, SLC6A4). Moreover, preliminary findings suggest genetic involvement in human violent behavior; that is, alleles coding for a low-activity variant of the monoamine oxidase A enzyme (MAO-A) and CDH13 coding for the T-cadherin protein.

Impulse control is a learned protective mechanism against overt reactions to negative emotions, and also has a genetic foundation. Preliminary examples of genes affecting emotion include the presynaptic vesicular monoamine transporter 1 (VMAT1), neurotensin V (NPH), Val158Met common functional polymorphism of catechol-O-methyltransferase (COMT), S-HTT, variations in the FKBPS gene that affects the release of corticotropic-releasing hormone, HTR1B, HTR2B and a polymorphism in the PAC1 gene co-operating with the pituitary adenylate cyclase-activating polypeptide. Despite increasing knowledge of genetic associations with behaviors, strong causal explanations for the heritability of behaviors are missing.

Herein, we examine the effects of HTR2B Q20 on temperament, impulsive and aggressive behaviors while sober and under the influence of alcohol, and alcohol consumption. One gene rarely explains a large proportion of complex phenotypic traits and human behavior. However, we investigated the possibility of finding at least some effect of the HTR2B Q20 on phenotype based on the preliminary work by Bevilacqua et al. The subjects were obtained from a Finnish founder population isolate with a relatively recent bottleneck, which has been estimated to be a reliable group for detection of genetic causal variants with low frequencies (0.5–5%) in complex disorders. Founder populations increase the power to detect effects of rare alleles. Of the 17 Finnish disease alleles, 70–98% of the disease chromosomes are attributable to a single allele.

**MATERIALS AND METHODS**

Participants and groups

Two groups were examined and compared. These two groups were formed from a sample genotyped by Bevilacqua et al. That Finnish cohort comprised violent offenders (n = 228), their relatives (n = 352) and controls (295). Subjects of whom we had complete phenotype data available were included in the present study. The violent offenders were excluded because the majority were alcohol dependent and had a personality disorder diagnosis, and thus probably represent a different extreme phenotype than the nonviolent and nonalcoholic subjects included in the present study. The first group comprised carriers of the HTR2B Q20 (n = 14, 57% were males). These subjects were found among the relatives of the violent offenders and healthy controls genotyped without pre-selection for phenotype or genotype. The second group comprised healthy controls without the HTR2B Q20 (n = 156, 100% were males), who were recruited by newspaper ads. The HTR2B Q20 carriers were all heterozygotes and comprised seven relatives (86% were females) of the violent offenders and seven males from the group of healthy controls. The rationale for combining relatives and healthy controls with different genders into one group was to achieve adequate statistical power. Among the seven HTR2B Q20 relatives, four were first degree relatives, two were second degree relatives and one was a step-sister. The prevalence of the HTR2B Q20 among the relatives was 2.0 and 2.4% among the controls, which matches the allele frequency reported by Bevilacqua et al.

There was no difference between the mean age of the groups: 31.2 years (s.d. = 10.5) in the HTR2B Q20 group and 30.1 years (s.d. = 9.4) in the control group. There was no difference in the mean scores of the last grade of obligatory school (scale 4–10), which describes average cognitive performance: 7.4 (s.d. = 0.5) in the nonviolent HTR2B Q20 group and 7.7 (s.d. = 0.8) among controls.

Mental disorders

All participants were examined with the DSM-III-R semi-structured interview to detect lifetime mental disorders. Experienced psychiatrists conducted the interviews and two research psychiatrists blind-rated the interview data under the supervision of a senior research psychiatrist. Interrater reliability was high, and any differences were resolved by the senior psychiatrist.
The phenotype of HTR2B Q20* carriers
R Tikkonen et al

The relationship between personality traits (TPQ) and the impulsive, aggressive and alcohol-related risk-behaviors (BGLAS and MAST) in the whole sample

Table 1. The personality traits and impulsive, aggressive, alcohol-related risk-behavior, alcohol consumption and father's drinking of HTR2B Q20* carriers (n = 14), are presented using multivariate logistic analyses, where healthy controls (n = 156) were entered into the models as the comparison group

| HTR2B Q20* male carriers | W | P | R² |
|--------------------------|---|---|---|
| Novelty seeking total score (NS) | −0.15 (0.17) | 4.4 | 0.036 | 0.10 |
| Impulsiveness-regression (NS2) | −0.80 (0.21) | 14.8 | < 0.001 | 0.28 |
| Disorderliness-regulation (NS4) | −1.55 (0.79) | 3.8 | 0.048 | 0.06 |
| Harm avoidance total score (HA) | 0.64 (0.14) | 20.8 | < 0.001 | 0.04 |
| Fear of uncertainty–confidence (H2A) | 0.43 (0.15) | 1.5 | 0.004 | 0.13 |
| Fatigability and asthenia-vigor (H4A) | −0.47 (0.12) | 15.8 | < 0.001 | 0.05 |
| Persistence–irresoluteness (RD2) | −0.48 (0.12) | 15.4 | < 0.001 | 0.09 |
| Attachment-detachment (RD3) | 0.95 (0.21) | 19.9 | < 0.001 | 0.50 |

BGLAS
Total score (S) | 0.08 (0.05) | 3.3 | 0.07 | 0.08 |
Total score (UIA) | 2.28 (0.48) | 22.5 | < 0.001 | 0.60 |
Tantrums (S) | 0.53 (0.18) | 8.4 | 0.004 | 0.13 |
Tantrums (UIA) | 4.0 (0.90) | 19.6 | < 0.001 | 0.32 |
Assaults (S) | 0.48 (0.19) | 6.2 | 0.013 | 0.11 |
Assaults (UIA) | 3.83 (0.79) | 23.4 | < 0.001 | 0.35 |
Impulsive behavior (S) | 1.20 (0.30) | 16.1 | < 0.001 | 0.26 |
Impulsive behavior (UIA) | 4.39 (0.90) | 27.8 | < 0.001 | 0.43 |

MAST
Total score | 0.48 (0.13) | 14.8 | < 0.001 | 0.39 |
Physical fights (UIA) | 2.82 (0.65) | 19.0 | < 0.001 | 0.26 |
Arrest for driving (UIA) | 1.77 (0.40) | 19.9 | < 0.001 | 0.29 |

LDH
Alcohol consumption (kg per year) | −0.11 (0.10) | 1.13 | 0.288 | 0.04 |
Father's drinking | −0.06 (0.22) | 0.52 | 0.472 | 0.04 |

Abbreviations: HA, harm avoidance; NS, novelty seeking; R², Nagelkerke R square test; RD, reward dependence; S, sober; UIA, under the influence of alcohol; W, Wald's test; β, regression coefficient. Personality traits were assessed with the tridimensional personality questionnaire (TPQ). Impulsive and aggressive behavior was assessed with the Brown–Goodwin lifetime aggression scale (BGLAS). Alcohol-related risk-behavior was measured with the BGLAS and the Michigan alcohol screening test (MAST). Mean lifetime alcohol consumption and father’s drinking were assessed with the Lifetime Drinking History inventory (LDH). Analyses were adjusted with a categorical variable dividing the sample into three groups: mainly female relatives carriers of the HTR2B Q20* (n = 7), male HTR2B Q20* carriers found among the healthy controls (n = 7) and male controls (n = 156). The rationale for this was to control for gender, genetic contamination and environmental bias.

HTR2B Q20* female relatives; 16.3 (s.d. = 2.5) vs 7.4 (s.d. = 4.5), P = 0.02, which seems to match the finding of histrionic personality that was only found among females. The HTR2B Q20* males also had a higher BGLAS total score; 17.7 (s.d. = 6.8) vs 8.6 (s.d. = 4.7), P = 0.006. This finding seems logical, as male sex is thought to be associated with aggression.

Our most important effort to rule out bias caused by genetic contamination, gender and environment was to perform reanalyses of the regression analyses adjusting the analyses with a categorical variable comprising the categories (1) HTR2B Q20* relatives to violent offenders (n = 7), (2) HTR2B Q20* controls (n = 7) and (3) healthy controls (156). The concern was that the relatives could have a considerably different genome as compared with the controls due to that the violent offenders represent an extreme phenotype. Moreover, the relatives were mostly females, which may affect gene expression through epigenetic mechanisms. The relatives could also have experienced challenging environments, as many violent offenders have, that could have induced psychosocial problems. However, adjusting analyses with this categorical variable was the best we could do to control for the possibility of bias. The adjusted reanalyses did not significantly change the results. The adjusted results are presented in the tables.

DISCUSSION

One of our main findings was that the HTR2B Q20* predicted alcohol-related risk-behaviors. The HTR2B Q20* carriers demonstrated aggressive out-bursts, got into fights and behaved in an impulsive manner under the influence of alcohol. They were also arrested for driving while under the influence of alcohol more often than the controls. The HTR2B Q20* carriers were not alcoholics per se, as measured by average alcohol consumption, and were not diagnosed as alcoholics, but they had a tendency to lose behavioral control while under the influence of alcohol.

Another central finding was the high prevalence of mood disorder symptoms and emotional dysregulation among the HTR2B Q20* carriers. This was surprising, as the focus of our hypothesis was on impulsivity. However, impulsivity and emotional dysregulation are closely related phenomena. The putative effect of HTR2B Q20* on emotional regulation was reported by the study by Diaz et al.,2 where 5-HTR2B was shown to be required for pharmacological anti-depressive action in mice.

Apart from overt behavior, we observed an effect of the HTR2B Q20* on temperament, as a persistent tendency to react to stimuli in a certain way. Though not fully consistent, a pattern matching that of a passive-dependent personality31 emerged. Personality features such as relatively low interest in novelty and exploratory activities (low NS total score, NS2 and NS4), anxiety (high HA), fear of uncertainty (high HA2), attachment or dependence (high RD3) and low persistence (low RD2) were characteristic of the HTR2B Q20* carriers. Cloninger31,32 originally proposed that the personality traits described by the TPQ correlate with underlying neurobiological functions, and, for example, the monoamines serotonin33,34 and dopamine37 have been shown to play a critical role in human impulsive-aggressive behavior.

Relating results to Cloninger’s neurobiological proposal,31 the HTR2B Q20* carriers may have a low neurophysiological dopaminergic activity. Cloninger associated a high dopaminergic state with impulsivity and high NS.31 However, novel neurogenetic research suggests that impulsive decision-making may be associated with low dopamine levels in the prefrontal cortex38,39 which could explain the impulsive behavior of the HTR2B Q20* carriers in our sample. Impulsivity caused by high dopaminergic activity is probably a separate construct of impulsive behavior that is mediated primarily by other neuronal pathways.

The high HA finding among the HTR2B Q20* carriers is supported by earlier research, as low serotonergic states have been...
been shown to correlate with depression and impulsive–aggressive behavior. Differences found in RD subscales, which are thought to correlate with underlying noradrenergic activity, increase the probability that the HTR2B Q20* contributes to neurotransmitter variances, yet the mechanisms are unclear. However, a desynchronization in a variety of neuronal networks is thought to cause inhibitory dyscontrol and impaired executive functioning, which suggests that the observed deviant temperamental features may be linked with alcohol-related impulsive–aggressive behavior and the observed emotional dysregulation.

The acute effects of ethanol on neurotransmission (for example, dopamine release) and behavior may explain these results, in combination with the passive-dependent personality observed in the present study. A causal mechanism would suggest that ethanol enhances an inherent tendency towards impulsive decision-making and subsequently causes acute disinhibition of behavior. Another mechanism could be acute behavioral disinhibition caused by the anxiolytic effects of ethanol since anxiety was high among the HTR2B Q20* carriers. Bevilacqua et al. observed an increased motor activity, in Htr2b knockout mice, after a D1 receptor agonist challenge (parallel to acute alcohol exposure). Acute ethanol intake could cause a similar fast increase in dopaminergic and motor activity among HTR2B Q20* carriers.

We also examined the entire sample’s personality trait associations with behavior and found that a passive-aggressive personality structure (high NS, HA and RD) corresponded with alcohol-related, impulsive–aggressive risk behavior. Separately, antisocial alcoholic violent offenders have been shown to exhibit an explosive personality that featured high NS, high HA and low RD. It seems as if several distinct personality patterns, scoring higher or lower on the scales as compared with controls, are associated with impulsive–aggressive behavior. The HTR2B Q20* carriers with a passive-dependent personality may be one distinct subgroup, as the passive-dependent personality has been suggested to be linked with alcohol-related ‘loss of control’ behavior.

Even though an impact of the HTR2B Q20* on monoaminergic function in the brain would be the most obvious explanation of the results, direct pleiotropic effects of the HTR2B Q20* on endocrine function of the body holds explanatory potential since gene–endocrine interactions may alter the risk for impulsivity and alcohol-related problem behavior. For example, an interaction between the functional MAO-A polymorphism and testosterone has been shown to alter the risk for antisocial behavior. Also, the metabolism of glucose and insulin has been shown to directly predict impulsive–aggressive behavior. A potential molecular mechanism for this could be that high glycogen synthase kinase 3β (GSK3β) activity downregulates insulin-mediated glycogen synthesis and glucose homeostasis, but a role for HTR2B Q20* in this scenario is partly speculative at this point. The HTR2B Q20*, however, may have a role in insulin and glucose metabolism, as the 5-HT2B receptor is required for prolactin-induced β-cell expansion during pregnancy in mice. Htr2b knockout mice remained normo-glycemic after an effort to create a diet-induced, insulin-resistance state.

Despite the fact that one gene rarely explains a large proportion of behaviors, these preliminary results suggest that the HTR2B Q20* may have a role in the inter-individual differences of behavior after exposure to alcohol. The study sample belongs to a unique fonder population, which increases the possibility to detect links between genes and behavior. A primary preventive measure against risk-behavior in HTR2B Q20* carriers would be to decrease alcohol consumption or achieve abstinence, and increase cognitive control over impulsive behavior and emotions through cognitive psychotherapy, pharmacological treatment and psychosocial interventions.

A potential source of bias of the result was the small sample size, which increases the possibility of spurious results. Sampling, gender bias, genetic contamination and varying environments are also potential sources of bias. The sampling was compromised by the fact that it was not originally designed for this particular study, but on the other hand the sample was genotyped without pre-selection for phenotype or genotype, and the prevalence of the HTR2B Q20* equaled that of the general population. The major concern of bias was that half of the HTR2B Q20* group comprised mainly female relatives of violent offenders, which could bias...
results in several ways. The relatives may have had an essentially differing genome from the HTR2B Q20* individuals found among the healthy controls due to that the violent offenders represent an extreme phenotype. The female sex of the relatives may also have biased results. Last, the relatives could have shared psychosocially challenging environments and experiences that often occur in the lives of violent offenders. We tried to rule out all these three potentially biasing factors by adjusting the regression analysis with a categorical variable separating the relative HTR2B Q20* individuals from the control HTR2B Q20* individuals. The reported results are based on this adjustment. Our study setting would need to be replicated in a more homogenous sample. On the other hand, a study setting examining the effect of gender in a mixed sample would be valuable. Our study would also be worth replicating among homozygous individuals, as abnormal phenotypic characteristics are probably more evident among homozygotes. We were not able to control for specific gene–gene or gene–environment interactions specifically, but tried to rule out the potential bias by using a categorical variable in the regression analyses as described above. Nevertheless, we think that these preliminary results contribute towards behavioral genetic understanding of impulsivity and related diseases and risk-behaviors.

CONFLICT OF INTEREST
The authors declare no conflict of interest.

ACKNOWLEDGMENTS
We thank Rickard L Sjöberg for his important scientific guidance, and Aija Räsanen, Viivi Mjuunen and Eero Saukkonen for their assistance in practical matters.

REFERENCES
1 Bevilacqua L, Doly S, Kaprio J, Yuan Q, Tikkanen R, Paunio T et al. A population-specific HTR2B stop codon predisposes to severe impulsivity. Nature 2010; 468: 1061–1066.
2 Diaz SL, Doly S, Narboux-Neme N, Fernandez S, Mazot P, Banas SM et al. The 5-HT(2B) receptors are required for serotonin-selective antidepressant actions. Mol Psychiatry 2012; 17: 154–163; doi:10.1038/mp.2001.159.
3 Doly S, Valjent E, Setola V, Callebert J, Herve D, Launay JM et al. Serotonin 5-HT2B receptors are required for 3,4 methylenedioxyamphetamine-induced hyperlocomotion and SHT release in vivo and in vitro. J Neurosci 2008; 28: 2933–2940.
4 Launay JM, Schneider B, Loric S, Da Prada M, Kellerman O. Serotonin transport and serotonin transporter-mediated antidepressant recognition are controlled by 5-HT2B receptor signaling in serotonergic neuronal cells. FASEB J 2006; 20: 1843–1854.
5 Choi DS, Ward SJ, Messaddeq N, Launay JM, Maroteaux L. 5-HT2B receptor-mediated serotonin morphogenetic functions in mouse cranial neural crest and myocardin cells. Development 1997; 124: 1745–1755.
6 Nebigil CG, Choi DS, Dierich A, Hickel P, Le Meur M, Messaddeq N et al. Serotonin 2B receptor is required for heart development. PNAS 2000; 97: 9508–9513.
7 Launay JM, Birraux G, Bondoux D, Callebert J, Choi DS, Loric S et al. Risperidone in the treatment of schizophrenia: a randomised, placebo-controlled, double-blind, parallel-group study. Lancet 1998; 349: 3141–3147.
8 Launay JM, Herve P, Callebert J, Mallat Z, Collet C, Doly S et al. Serotonin 5-HT2B receptors are required for bone-marrow contribution to pulmonary arterial hypertension. Blood 2012; 119: 1772–1780.
9 Bevilacqua L, Goldman D. Genetics of impulsive behaviour. Phil Trans R Soc B 2013; 368: 2012380; doi:10.1098/rstb.2012.0380.
10 Psychiatric Genomics Consortium (PGC) Genetic relationship between five psychiatric disorders estimated from genome-wide SNPs. Nat Genet 2013; 45: 984–994; doi:10.1038/ng.2599.
11 Zhou Z, Roy A, Lipsky R, Kuchipudi K, Zhu G, Taubman J et al. Haplo-type-based linkage of tryptophan hydroxylase 2 to suicide attempt, major depression, and cerebrospinal fluid 5-hydroxyindoleacetic acid in 4 populations. Arch Gen Psychiatry 2005; 62: 1109–1118; doi:10.1001/archpsyc.62.10.1109.
12 Brunner HG, Nelen M, Breakfield XO, Ropers HH, van Oost BA. Abnormal behavioral association with a point mutation in the structural gene for monamine oxidase A. Science 1993; 262: 578–580; doi:10.1126/science.8211166.
13 Benko A, Lazary J, Molnar E, Gonda X, Tothfalusi L, Pap D et al. Significant association between the C1019G functional polymorphism and the HTR1A gene and impulsivity. Am J Med Genet B Neuropsychiatr Genet 2010; 153B: 592–599; doi:10.1002/ajmg.b.61025.
14 Lappalainen J, Long JC, Eggert M, Ozaki N, Robin RW, Brown GL et al. Linkage of antisocial alcoholism to the serotonin 5-HT1B receptor gene in 2 populations. Arch Gen Psychiatry 1998; 55: 989–994; doi:10.1001/archpsyc.55.11.989.
15ucci F, Enoch MA, Yuan Q, Shen PH, White KV, Hodkinson C et al. HTR3B is associated with alcoholism with antisocial behavior and alpha EEG power—an intermediate phenotype for alcoholism and comorbid behaviors. Alcohol 2009; 43: 73–84; doi:10.1016/j.alcohol.2008.09.005.
16 Sakado K, Sakado M, Muratake T, Mundt C, Someya T. A psychometrically derived impulsive trait related to a polymorphism in the serotonin transporter gene-linked polymorphic region (5-HTTLPR) in a Japanese nonclinical population: assessment by the Barratt impulsiveness scale (BIS). Am J Med Genet B Neuropsychiatr Genet 2003; 121B: 71–75; doi:10.1002/ajmg.b.20063.
17 Paloyelis V, Asherson P, Mehta MA, Farooq SV, Kunutsor S, DAT1 and CDMT effects on delay discounting and trait impulsivity in male adolescents with attention...
deficit/hyperactivity disorder and healthy controls. Neuropsychopharmacology 2010; 35: 2414–2426; doi:10.1038/npp.2010.124.

18 Tiihonen J, Rautiainen M-R, Ollila HM, Repo-Tiihonen E, Virkkunen M, Palotie A et al. Genetic background of extreme violent behavior. Mol Psychiatry 2014; 20: 786–792; doi:10.1038/mp.2014.130.

19 Bevilaqua L, Goldman D. Genetics of emotion. Trends Cogn Sci 2011; 15: 401–408; doi:10.1016/j.tics.2011.07.009.

20 Lohoff FW, Hodge R, Narasimhan S, Nall A, Ferraro TN, Mickey BJ et al. Functional genetic variants in the vesicular monoamine transporter 1 modulate emotion processing. Mol Psychiatry 2014; 19: 129–139; doi:10.1038/mp.2012.193.

21 Zhou Z, Zhu G, Hariri AR, Enoch MA, Scott D, Sinha R et al. Lohoff FW, Hodge R, Narasimhan S, Nall A, Ferraro TN, Mickey BJ et al. Functional genetic variants in the vesicular monoamine transporter 1 modulate emotion processing. Mol Psychiatry 2014; 19: 129–139; doi:10.1038/mp.2012.193.

27 Lim ET, Wurtz P, Havulinna AS, Nall A, Ferraro TN, Mickey BJ et al. Functional genetic variants in the vesicular monoamine transporter 1 modulate emotion processing. Mol Psychiatry 2014; 19: 129–139; doi:10.1038/mp.2012.193.

22 Ducci F, Goldman D. Genetic approaches to addiction: genes and alcohol. Addiction 2008; 103: 1414–1428.

23 Lesch KP, Bengel D, Heils A, Sabol SZ, Greenberg BD, Petri S et al. Association of anxiety-related traits with a polymorphism in the serotonin transporter gene regulatory region. Science 1996; 274: 1527–1531.

24 Binder EB, Salyakina D, Lichtner P, Wochnik GM, Ising M, Putz B et al. Polymorphisms in FKBP5 are associated with increased recurrence of depressive episodes and rapid response to antidepressant treatment. Nat Genet 2004; 36: 1319–1325.

25 Ressler KJ, Mercer KB, Jovanovic T, Joffe R, Narasimhan S, Nall A, Ferraro TN, Mickey BJ et al. Functional genetic variants in the vesicular monoamine transporter 1 modulate emotion processing. Mol Psychiatry 2014; 19: 129–139; doi:10.1038/mp.2012.193.

26 Goldman D. The missing heritability of behavior: the search continues. Translational Psychiatry (2015), 1: 103; doi:10.1038/mp.2014.130.

28 Peltonen L, Jalanko A, Varilo T. Molecular genetics of the Finnish disease heritage. Science 2004; 305: 1527–1531.

29 APA. American Psychiatric Association. Diagnostic and statistical manual of mental disorders. 3rd revised ed. American Psychiatric Press: Washington, DC, 1987.

30 Am J Physiol Endocrinol Metab 2013; 305: E1327–E1328; doi:10.1152/ajpendo.00425.2013.

31 Cloninger CR. Neurogenetic adaptive mechanisms in alcoholism. Science 2004; 305: 1527–1531.

32 Cloninger CR. Neurogenetic adaptive mechanisms in alcoholism. Science 2004; 305: 1527–1531.

33 Cloninger CR. Neurogenetic adaptive mechanisms in alcoholism. Science 2004; 305: 1527–1531.

34 Virkkunen M, Tiihonen J, Kiiuka J, Bergstrom K, Hakola P, Karhu J, Rynanen OP et al. Altered striatal dopamine re-uptake site densities in habitually violent and non-violent alcoholics. Nat Med 1995; 1: 654–657; doi:10.1038/nm298-654.

35 Linnoila M, Virkkunen M, Scheinin M, Nuutila A, Franssila-Kallunki A, Linnoila M, Rissanen A, Franssila-Kallunki A, Tiihonen J. Low non-oxidative glucose metabolism and violent offending: an 8-year prospective follow-up study. Psych Psychiatry 2007; 150: 287–295; doi:10.1016/j.psyct.2006.01.013.

36 Virkkunen M, Rissanen A, Naukkari M, Franssila-Kallunki A, Linnoila M, Tiihonen J. Energy substrate metabolism among habitually violent alcoholic offenders having antisocial disorder. Psychiat Res 2007; 150: 287–295; doi:10.1016/j.psyct.2006.01.013.

37 Tiihonen J, Kuikka J, Bergstrom K, Hakola P, Karhu J, Rynanen OP et al. Altered striatal dopamine re-uptake site densities in habitually violent and non-violent alcoholics. Nat Med 1995; 1: 654–657; doi:10.1038/nm298-654.

38 Barnett JH, Jones PB, Robbins TW, Muller U. Effects of the catechol-O-methyltransferase Val158Met polymorphism on executive function: a meta-analysis of the Wisconsin Card Sort Test in schizophrenia and healthy controls. Mol Psychiatry 2007; 12: 502–509.

39 Malhotra AK, Kessler LJ, Mazzanti C, Bates JA, Goldberg T, Goldman D et al. A functional polymorphism in the COMT gene and performance on a test of prefrontal cognition. Am J Psychiatry 2002; 159: 652–654.

40 Walidie KE, Saunders A. The neural basis of autism: a review. Int J Sch and Cogn Psychol 2014; 1: 113; doi:10.47172/3425-1000113.

41 Tikkainen R, Hori M, Lindberg N, Virkkunen M. Tridimensional Personality Questionnaire data on alcoholic violent offenders: specific connections to severe impulsive cluster B personality disorders and violent crime. BMC Psychiatry 2007; 7: 36; doi:10.1186/1471-244X-7-36.

42 Sobbing RL, Ducci F, Barr CS, Newman TK, Dell’osso L, Virkkunen M et al. A non-additive interaction of a functional MAO-A VNTR and testosterone predicts antisocial behavior. Neuropsychopharmacology 2008; 33: 425–430.

43 Virkkunen M, Rissanen A, Naukkari M, Franssila-Kaljunki A, Linnoila M, Tiihonen J. Low non-oxidative glucose metabolism and violent offending: an 8-year prospective follow-up study. Psychiat Res 2009; 168: 26–31; doi:10.1016/j.psychiatr.2008.03.026.

44 Virkkunen M, Rissanen A, Franssila-Kallunki A, Tiihonen J. Low non-oxidative glucose metabolism and violent offending: an 8-year prospective follow-up study. Psychiat Res 2009; 168: 26–31; doi:10.1016/j.psychiatr.2008.03.026.

45 Okula KP, Tiihonen J, Repo-Tiihonen E, Tikkanen R, Virkkunen M. Basal insulin secretion, PCL-R and recidivism among impulsive violent alcoholic offenders. Psychiatric Res 2015; 225: 420–424; doi:10.1016/j.psychres.2014.11.073.

46 Beurle E, Criego SF, Jope RS. Glycogen synthase kinase-3 (GSK3): Regulation, actions, and diseases. Pharmacol Ther 2015; 148: 114–131.

47 Pasek RC, Gannon M. Advancements and challenges in generating accurate material. To view a copy of this license, visit http://creativecommons.org/licenses/