

# ADHD and the DRD4 exon III 7-repeat polymorphism: an international meta-analysis

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**We sought to elucidate the relationship of ADHD (Attention-Deficit Hyperactivity Disorder) to the DRD4 exon III VNTR 7R allele worldwide using analytic techniques and to relate these findings to the field of cultural neuroscience. To focus on a potential moderating role of race/ethnicity, we excluded over 30 papers that have explored the relationship between the DRD4 7R and ADHD but had unclear or lax racial–ethnic inclusion criteria. The papers in this meta-analysis were only included if a single race made up 95% or more of their sample. We searched for and translated papers not published in English, and found a significant difference in the relationship of ADHD and DRD4 7R in people of European-Caucasian (Odds ratio 1.635,  $Z = 3.936$ ,  $P < 0.00001$ ) and South American (Odds ratio 2.407,  $Z = 3.317$ ,  $P = 0.001$ ) descent vs people of Middle Eastern ancestry (Odds ratio 0.717,  $Z = -2.466$ ;  $P = 0.014$ ). We also examined the moderating effect of differing ADHD diagnoses, subject recruitment, control recruitment and male to female ratio. Finally, we consider the implications of these data for cultural neuroscience.**

**Keywords:** ADHD; DRD4; attention deficit hyperactivity disorder; polymorphism

Among psychiatric disorders found worldwide, Attention-deficit hyperactivity disorder (ADHD) is relatively common and characterized by impulsivity, hyperactivity and inattention. As such, ADHD is a major behavioral phenotype and important clinically to understand in detail. Research on the genetic etiology of the disorder has analyzed a variety of genes, focusing on DRD4 and DAT. One of the most robust candidate polymorphisms in the search for a genetic link to ADHD is a 7-repeat allele of the 48-base pair repeat in the DRD4 gene. The DRD4 VNTR is involved in G-protein coupling of the DRD4 neuroreceptor (Wang *et al.*, 2004). The 7-repeat allele is thought to have arisen between 30 000 and 300 000 years ago from a series of rare mutational events, and to have thereafter undergone positive selection, since its worldwide prevalence is higher than what random genetic drift would expect (Ding *et al.*, 2001). Although a previous meta-analysis found a positive association with the 7-repeat allele and ADHD (Faraone, 2001), opposite findings have recently been published (Bakker *et al.*, 2005; Brookes, 2005). Genetic demographic studies demonstrate that the 7-repeat allele is present in highly varying percentages in different populations worldwide (Chang *et al.*, 1996; Borinskaya *et al.*, 2004; Baydala, *et al.*, 2006; Bhaduri *et al.*, 2007; Mansoor *et al.*, 2008), e.g. in up to 78% of native South Americans, but only 0–2% of South Asians. Moreover, it was once thought that the worldwide prevalence of ADHD is homogenous (Hawi, 2000), yet recent research suggests that it is

heterogeneous (Polanczyk *et al.*, 2007). These findings demonstrate the complexity of both the DRD4 gene and ADHD, and hint at potential gene–culture interactions of exactly the sort of major interest in cultural neuroscience (Chiao, forthcoming).

There have been multiple relevant meta-analyses published, but to our knowledge they have focused on either Caucasian subjects (Faraone *et al.*, 2001; Maher *et al.*, 2002; Langley *et al.*, 2004), or only Caucasian and Asian subjects (Li *et al.*, 2006). The present study aims to be the broadest worldwide meta-analysis of the relationship of the DRD4 7R allele and ADHD. As such, the findings are more relevant to cultural neuroscience than previous meta-analyses.

## METHODS

We identified papers related to ADHD and DRD4 by searching through papers available on PubMed and Google Scholar, and by searching through meta-analyses already written on the topic of ADHD and DRD4. We then narrowed our search by selecting papers that were directly related to the 7 repeat DRD4 allele (exon III VNTR). Due to the extremely low numbers of Asians with the 7R allele (Chang *et al.*, 1996), and because the 2R allele's downstream region contains polymorphism patterns identical to the 7R allele (Wang 2004) we searched for papers that contained data on the relationship of the 2R allele and ADHD in Asian subjects. From over 3200 papers retrieved from PubMed and Google Scholar, we retained 600 abstracts on topics related to DRD4 and ADHD. Of these, we identified 61 papers relating directly to DRD4 7R and ADHD and 24 needing translation. Since the 7R allele is highly variant among races (Chang *et al.*, 1996), we decided to include papers with 95% or greater racial homogeneity. We excluded

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16 papers because of low, unclear or unknown ethnic inclusion criteria. All of the 23 papers included in the final analyses were published in journals.

Three undergraduate translators from Yale University were hired for the Portuguese, Spanish and German papers. We found Google Translate to be of comparable translation quality for our purpose, and thereafter we translated 20 additional papers using this website. One non-English paper passed all inclusion criteria to become part of the final group of studies to be analyzed (Carrasco *et al.*, 2004).

For each paper, we recorded the number of subjects with ADHD and the risk allele (RA), with ADHD without RA, without ADHD with RA and without ADHD without RA. This formed the basis of our statistical analysis. Some papers specified whether subjects were heterozygous or homozygous for the 7R allele, although 7R homozygotes are rare. In case-control studies, we counted these both heterozygous and homozygous individuals as one count in our analyses. Some papers used Haplotype relative risk rather than case-control study design. Papers using this method were also included as well since the control subjects are even better genetic matches to the ADHD subjects (Knapp *et al.*, 1993). In the European/Caucasian category, we also coded for subject recruitment strategies, the rigor of ADHD diagnoses, the ratio of males to females in the ADHD sample, which ADHD criteria were used in the diagnoses, and the male to female ratio of the control group. Control recruitment was divided into three groups: random/ local population samples, subjects part of longitudinal studies and low scorers on ADHD diagnostic measures. ADHD recruitment was also split into three groups: subjects that came from hospitals and clinics or were referred by psychiatrists, those that had been part of longitudinal studies not related to ADHD, and high scoring individuals on ADHD diagnostic measures. Rigor of ADHD diagnoses was also split into three categories, low, medium and high. Low rigor referred to subjects put into the ADHD category based solely on a teacher or parent interview of the child. High rigor denoted that the ADHD subjects had undergone a formal diagnosis from one or more psychiatrists or similarly highly trained individuals; this was almost always combined with parent or teacher interviews of the child's behavior. The medium rigor category was used for all papers in which the ADHD group was composed of individuals subjected to diagnostic measures somewhere in between the two aforementioned categories.

We analyzed these data using Comprehensive Meta-analysis (Biostat, 2005), a software program that can compute a large variety of meta analytical statistics, and used it to compute all statistics. We combined ethnic groups into four overarching groups which we label European-Caucasian, South American, Middle Eastern and Asian. The European-Caucasian group was composed of studies of individuals with British, German, American, Norwegian and Irish ancestry. The South American group was composed of Chilean and

Brazilian individuals (of non-native-American descent). The Middle Eastern grouping was composed of individuals of Turkish and Israeli descent, and the Asian grouping was made up of Han Chinese, Korean, Indian and Taiwanese individuals.

## RESULTS

We found a significant difference between the European-Caucasian and Middle Eastern groups in the relationship of ADHD to the 7R allele (Figures 1 and 2). Specifically, as previously reported, the Caucasian group showed a positive relationship between ADHD and the 7R allele, Odds ratio (OR) 1.64 (1.28–2.09,  $Z=3.94$ ,  $P=0.0001$ ). In contrast, the Middle Eastern group showed a negative relationship between ADHD and the 7R allele, OR 0.72 (0.55–0.93;  $Z=-2.47$ ;  $P=.014$ ). The South American group also demonstrated a positive relationship between ADHD and the 7R allele: OR 2.41 (1.43–4.05;  $Z=3.32$ ,  $P=0.001$ ). Although both the South American and Middle Eastern findings are statistically significant, it is important to recognize that both groupings were composed of three studies each. The Asian group demonstrated a positive relationship between the 2R allele and ADHD, but the results were insignificant: OR 1.65 (0.40–6.73,  $Z=0.69$ ,  $P=0.49$ ). We also assessed publication bias for the European-Caucasian group and found that publication bias does exist in this field (see Figure 3).

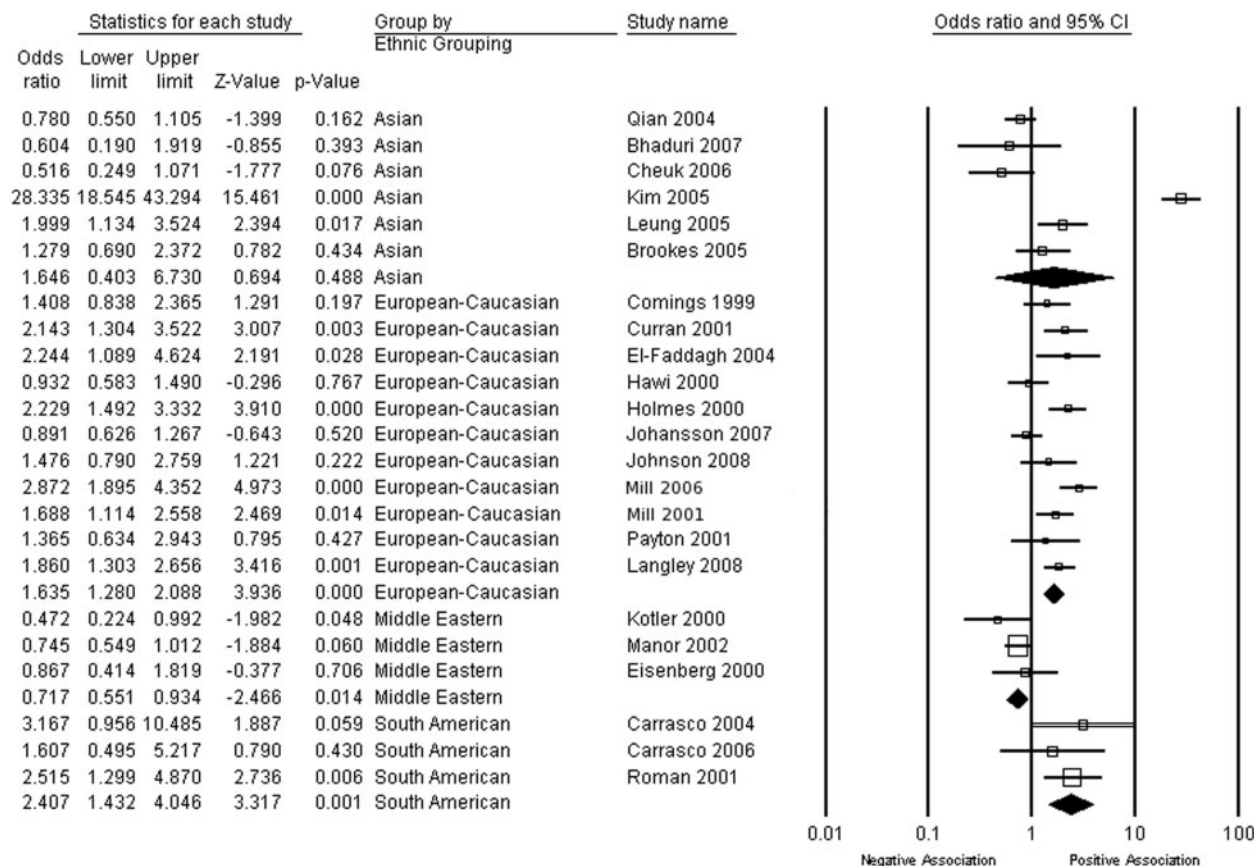
### Heterogeneity among studies

$I^2$  is a test for percentage of variability between studies due to heterogeneity of the studies themselves rather than sampling error. An  $I^2$  value over 50 is significant cause to question whether grouping studies together is valid. When grouped together, our original 12 studies in the Caucasian category yielded a high  $I^2$  of 65.9. After removing Hawi *et al.*, 2000 and Johansson *et al.*, 2007,  $I^2$  was 29.691. Removing these two studies also lowered the  $Q$ -value (another test for heterogeneity of studies) from 32.4 to 12.8, and changed the OR for European-Caucasians from 1.64 to 1.84 (1.52–2.22;  $Z=6.25$ ,  $P=0.00002$ ).

Similarly, when grouped together, our original six studies in the Asian category yielded a high  $I^2$  value: 97.5. After removing Kim *et al.*, 2005 we saw a drop in  $I^2$  to 66.7 as well as a large drop in the association between the 2R allele and ADHD from OR 1.65 to OR 0.96 (0.59–1.55,  $Z=-0.17$ ,  $P=0.87$ ). The following results are all calculated based on the studies with Caucasian subjects (including Hawi *et al.*, 2000; Johansson *et al.*, 2007) unless stated otherwise.

### Sex differences

Among the studies of Caucasian subjects, the percentage of males made no difference to the size of the odds ratio. Groups with 49.5–72% males were classified in the Low category; studies with 81.3–100% males were classified in the High Category. No studies fell into the 73–81% range



Meta Analysis

Fig. 1 Papers have been grouped into one of the following racial categories: Asian, European-Caucasian, Middle Eastern and South American. Darkened diamonds correspond to group values while the white squares and line that cross through show the OR for each paper and the corresponding confidence interval.

between High and Low groupings. The Low male percentage category had a slightly higher OR 1.74 (1.07–2.82,  $Z=2.23$ ;  $P=0.026$ ) than the High male percentage category OR 1.44 (0.79–2.60,  $Z=1.19$ ,  $P=0.24$ ). Since the relationship between the 7R and ADHD is similar the same in both Caucasian and South American groupings, we added the South American studies to this analysis and found an even greater similarity between High and Low categories: High OR 1.63 (1.06–2.51,  $Z=2.21$ ,  $P=0.027$ ), Low OR 1.74 (1.07–2.83,  $Z=2.23$ ,  $P=0.026$ ).

Effects of different ADHD diagnoses

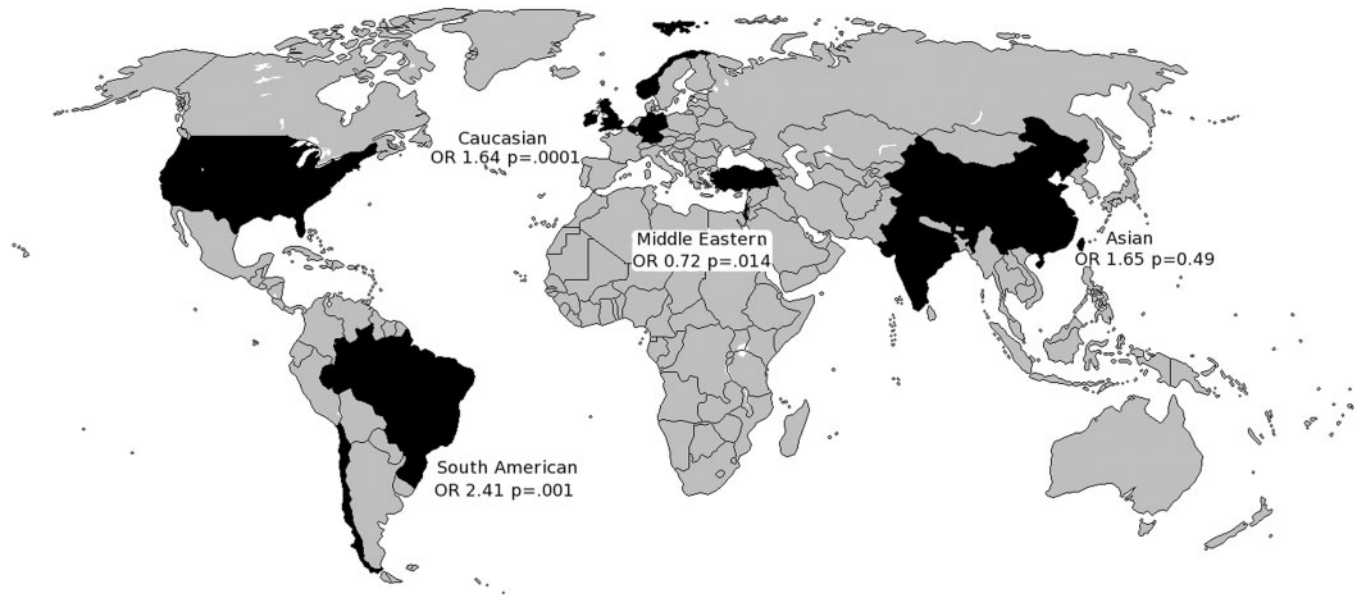
There was a slight variation in the strength of the DRD4 7R ADHD association depending on the confidence in which the ADHD diagnoses were made. Low confidence grouping demonstrated relatively high OR 1.92 (1.44–2.55,  $Z=4.49$ ,  $P<0.001$ ); the High grouping demonstrated a lower OR 1.34 (0.54–3.28,  $Z=0.63$ ,  $P=0.53$ ), and the Medium grouping also showed an even lower OR 1.32 (0.90–1.94,  $Z=1.44$ ,  $P=0.15$ ).

Effects of different recruitment techniques

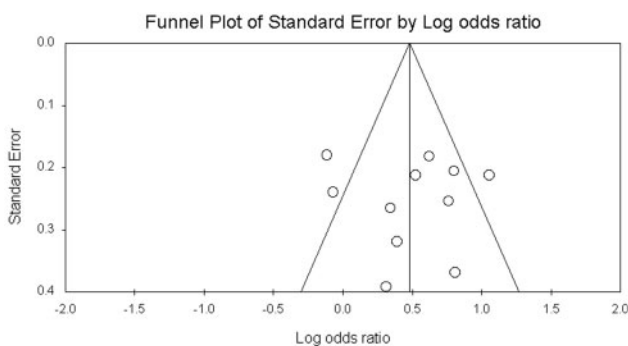
The strength of the association between ADHD and the DRD4 7R was also mediated partly by the method in which the control groups were recruited. ADHD subjects and control groups initially recruited as part of an ongoing longitudinal study unrelated to ADHD showed an OR of 1.82 (0.88–3.77,  $Z=1.61$ ,  $P<0.11$ ). Control subjects that were recruited either randomly from blood donation banks or were volunteers from local schools showed lower OR 1.43 (1.08–1.89,  $Z=2.50$ ,  $P=0.012$ ). These same studies all had ADHD subjects recruited from nearby clinics or hospitals or referred by local psychiatrists. Some papers split their sample into two groups, those with high scores on ADHD diagnostic assessments, the ADHD group, and those with low scores, the control group. This categorization demonstrated a high OR 1.88 (1.24–2.85,  $Z=2.96$ ,  $P=0.003$ ).

DISCUSSION

The strength of association between ADHD and the DRD4 7-repeat allele was significantly different for the Caucasian and Middle Eastern subgroups. We also found that the



**Fig. 2** The countries that were included in this meta-analysis have been darkened on the map. The odds ratio and *P*-values are displayed for each race category. Odds ratio for the Asian category was not significant.



**Fig. 3** Publication Bias measures the tendency that significant results are published while those that are not significant are kept from publication. This graph measures the publication bias of the European–Caucasian group. A scatterplot shaped similar to the isosceles triangle indicates little publication bias, while a scatterplot that varies from the triangle shows that publication bias is an issue. This figure shows that publication bias is an issue in reporting the relationship between ADHD and the 7R allele.

association was comparable between South American and Caucasian groups. Although the effect size was substantial and statistically significant, it is important to keep in mind that the Middle Eastern and South American groups only had three studies; the inclusion of more studies could potentially reduce or nullify this effect. Future studies in psychiatric genetics could easily add cultural specificity to their conclusions by stratifying groups according to ancestral background when analyzing data.

We did not find strong moderators of the ADHD DRD4 7R association, although again were limited in power to detect such effects. More studies would have to be combined in order for future research to come to definite conclusions

about the effects of methodological differences. We also found that the strength of the association was not affected by gender differences in the sample, in apparent conflict with a previous report (El-Faddagh *et al.*, 2004). However, we note that our data was lacking in male / female ratios in control groups, and such data as well as more studies might be necessary to elucidate the relationship between sex and the strength of the ADHD DRD4 7R connection.

The rigor of ADHD diagnosis did not have a significant impact on the strength of the association, but again our power was limited to assess this with high confidence. Previous research on diagnostic quality affecting diagnosis rates has demonstrated that studies using higher diagnostic standards diagnosed fewer individuals (Rohde *et al.*, 2005). This would imply that the lower diagnostic standards used by a study the lower OR assessing ADHD and DRD4 7R, which conflicts with our findings.

### Relation to cultural neuroscience

This world-wide meta-analysis examined the association of ADHD and the DRD4 VNTR in several racial–ethnic groups, which, given the data we had access to, were confounded with potential effects of culture. These cultural differences are important for several reasons. Perhaps the most interesting possibility is that cultural environment can interact with the genotype to alter the phenotypic expression within a given culture. We also note that there are differences in defining and diagnosing psychiatric disorders (Mezzich 1995). It is possible that differences in ADHD diagnosis may also serve as an explanation for the difference in associations between DRD4 and ADHD between European and Middle Eastern people, although it would be surprising if

this could account for all of the differences we found. In our samples, the rigor of ADHD diagnosis did not strongly moderate the association, and so culture based differences in diagnostic criteria might be small as well, in terms of their impact on the strength of the ADHD-DRD4 7R association. Another factor contributing to the difference in association across cultures may have to do with differences in parenting and the children's response to parenting types. Studies have demonstrated that genotype and race may have an effect on how children react towards parenting behavior (Sheese *et al.*, 2007; Propper *et al.*, 2007) and how it is interpreted by the child (Deater-Deckard and Dodge, 1996). Socio-economic status been found to moderate externalizing behavior and may also contribute to the difference in association between ADHD and DRD4 across racial groups (Deater-Deckard *et al.*, 1998).

It is likely that the 7R allele has undergone positive selection for thousands of years (Ding *et al.*, 2001). Given the worldwide heterogeneity of the 7R allele (Chang *et al.*, 1996) this evidence brings up a question: if this allele has been undergoing positive selection, then why is it that many people possess this gene in such varying percentages? Most species inhabit generally the same environment and remain endemic to a single ecological terrain. Humans on the other hand occupy wide ranges of ecological climates. Just as different terrain types contribute to the variability of human environments, differences in human culture add entirely new levels of complexity to the environment humans occupy as well. Additionally, greater rates of migration have been associated with higher prevalence of the 7R allele (Chen *et al.*, 1999), and research studying worldwide prevalence of the 7R allele has demonstrated its highest prevalence in groups who underwent the most long distance migrations (Chang *et al.*, 1996). This finding relates to the modern population of colonized lands. Are these populations composed of individuals more likely to have the 7R allele? Are there cultural ramifications of the above average presence of this phenotype in populations of countries that were colonized?

It is difficult to define whether or not cultural differences actually influence selection pressure enough to influence the biology of a people, but future research in the field of cultural neuroscience may reveal insight into this question. This meta-analysis demonstrates the importance of making ethnic/cultural distinctions in neuropsychiatric genetics, but more importantly our findings broach the need for medical research to be wary of applying techniques and treatments equally to all racial groups. Cultural and genetic factors may both play a role in European Caucasians' and Middle Eastern individuals' difference in ADHD DRD4 7R association. Future research could attempt to parse these moderating factors apart by studying individual ethnic groups within a larger non-ethnic specific cultural context. For example, obtaining a sample pool of people of Middle Eastern ancestry within America.

## REFERENCES

- Bakker, S.C., van der Meulen, E.M., Oteman, N., et al. (2005). DAT1, DRD4, and DRD5 polymorphisms are not associated with ADHD in Dutch families. *American Journal of Medical Genetics Part B (Neuropsychiatric Genetics)*, 132B, 50–2.
- Baydala, L., Sherman, J., Rasmussen, C., Wikman, E., Janzen, H. (2006). ADHD characteristics in Canadian aboriginal children. *Journal of Attention Disorders*, 9, 642–7.
- Bhaduri, N., Das, M., Das, A.B., Mukhopadhyay, K. (2007). Dopamine receptor D4 exon 3 variable number of tandem repeat polymorphism: distribution in eastern Indian population. *Indian Journal of Human Genetics*, 13, 54–8.
- Borinskaya, S.A., Kozhekbaeva, Z.M., Gorbunova, E.V., et al. (2004). Analysis of the DRD4 gene polymorphism in populations of Russia and neighboring countries. *Russian Journal of Genetics*, 40, 835–40.
- Brookes, K.J., Xu, X., Chen, C.K., Huang, Y.S., Wu, Y.Y., Asherson, P. (2005). No evidence for the association of DRD4 with ADHD in a Taiwanese population within family study. *BMC Medical Genetics*, 6, 31.
- Carrasco, X.C., Rothhammer, P.A., Moraga, M.V., Henriquez, H.B., Aboitiz, F.D., Rothhammer, F.E. (2004). Presencia de los alelos DRD4/7R y DAT1/10R en miembros de familias chilenas con syndrome de deficit atencional con hiperactividad. *Revista Medica de Chile*, 132, 1047–52.
- Carrasco, X., Rothhammer, P., Moraga, M., et al. (2006). Genotypic interaction between DRD4 and DAT1 loci is a high risk factor for attention deficit hyperactivity disorder in Chilean families. *American Journal of Medical Genetics Part B (Neuropsychiatric Genetics)*, 141B, 51–4.
- Chang, F.M., Kidd, J.R., Livak, K.J., Pakstis, A.J., Kidd, K.K. (1996). The world-wide distribution of allele frequencies at the human dopamine D4 receptor locus. *Human Genetics*, 98, 91–101.
- Chen, C., Burton, M., Greenberger, E., Dmitrieva, J. (1999). Population migration and the variation of dopamine D4 receptor (DRD4) allele frequencies around the globe. *Evolution and Human Behavior*, 20, 309–24.
- Cheuk, D.K.L., Li, S.Y.H., Wong, V. (2006). Exon 3 polymorphisms of dopamine D4 receptor (DRD4) gene and attention deficit hyperactivity disorder in Chinese children. *American Journal of Medical Genetics Part B (Neuropsychiatric Genetics)*, 141B, 907–11.
- Chiao, J.Y. (in press). Cultural neuroscience: Visualizing culture-gene influences on brain function. In: Decety, J., Cacioppo, J., editors. *Handbook of Social Neuroscience*. UK: Oxford University Press.
- Comings, D.E., Gonzalez, N., Wu, S., et al. (1999). Studies of the 48 bp repeat polymorphisms of the DRD4 gene in impulsive, compulsive, addictive behaviors: Tourette syndrome, ADHD, pathological gambling, and substance abuse. *American Journal of Medical Genetics Part B (Neuropsychiatric Genetics)*, 88, 358–68.
- Curran, S., Mill, J., Sham, P., et al. (2001). QTL association analysis of the DRD4 exon 3 VNTR polymorphism in a population sample of children screened with a Parent Rating Scale for ADHD symptoms. *American Journal of Medical Genetics Part B (Neuropsychiatric Genetics)*, 105, 387–93.
- Deater-Deckard, K., Dodge, K.A., Bates, J.E., Pettit, G.S. (1998). Multiple risk factors in the development of externalizing behavior problems: group and individual differences. *Development and Psychopathology*, 10, 469–93.
- Deater-Deckard, K., Dodge, K.A. (1997). Externalizing behavior problems and discipline revisited: nonlinear effects and variation by culture, context, and gender. *Psychological Inquiry*, 8, 161–75.
- Ding, Y.C., Chi, H.C., Grady, D.L., et al. (2002). Evidence of positive selection acting at the human dopamine receptor D4 gene locus. *PNAS*, 99, 309–14.
- El-Faddagh, M., Laucht, M., Maras, A., Vöhringer, L., Schmidt, M.H. (2004). Association of the dopamine D4 receptor (DRD4) gene with attention-deficit/hyperactivity disorder (ADHD) in a high-risk community sample: a longitudinal study from birth to 11 years of age. *Journal of Neural Transmission*, 111, 883–9.

- Eisenberg, J., Zohar, A., Mei-Tal, G., et al. (2000). A haplotype relative risk study of the dopamine D4 receptor (DRD4) exon III repeat polymorphism and attention deficit hyperactivity disorder (ADHD). *American Journal of Medical Genetics (Neuropsychiatric Genetics)*, 96, 258–61.
- Faraone, S.V., Doyle, A.E., Mick, E., Biederman, J. (2001). Meta-analysis of the association between the 7-repeat allele of the dopamine D4 receptor gene and attention deficit hyperactivity disorder. *American Journal of Psychiatry*, 158, 1052–7.
- Hawi, Z., McCarron, M., Kirley, A., Daly, G., Fitzgerald, M., Gill, M. (2000). No association of the dopamine DRD4 receptor (DRD4) gene polymorphism with attention deficit hyperactivity disorder (ADHD) in the Irish population. *American Journal of Medical Genetics Part B (Neuropsychiatric Genetics)*, 96, 268–72.
- Holmes, J., Payton, A., Barrett, H.J., et al. (2000). A family-based and case control association study of the dopamine D4 receptor gene and dopamine transporter gene in attention deficit hyperactivity disorder. *Molecular Psychiatry*, 5, 523–30.
- Johansson, S., Halleland, H., Halmøy, A., et al. (2007). Genetic analyses of dopamine related genes in adult ADHD patients suggest an association with the DRD5-Microsatellite repeat, but not with DRD4 or SLC6A3 VNTRs. *American Journal of Medical Genetics Part B (Neuropsychiatric Genetics)*, 147B, 1470–5.
- Johnson, K.A., Kelly, S.P., Roberston, I.H., et al. (2008). Absence of the 7-repeat variant of the DRD4 VNTR is associated with drifting sustained attention in children with ADHD but not in controls. *American Journal of Medical Genetics Part B (Neuropsychiatric Genetics)*, 147B, 927–37.
- Kim, Y.S., Leventhal, B.L., Kim, S.J., et al. (2005). Family-based association study of DAT1 and DRD4 polymorphism in Korean children with ADHD. *Neuroscience Letters*, 290, 176–81.
- Knapp, M., Seuchter, S.A., Baur, M.P. (1993). The haplotype-relative-risk (HRR) method for analysis of associatio in nuclear families. *American Journal of Human Genetics*, 52, 1085–93.
- Kotler, M., Manor, I., Sever, Y., et al. (2000). Failure to replicate an excess of the long dopamine D4 exon III repeat polymorphism in ADHD in a family-based study. *American Journal of Medical Genetics Part B (Neuropsychiatric Genetics)*, 96, 278–81.
- Langley, K., Fowler, T.A., Grady, D.L., et al. (2008). Molecular genetic contribution to the developmental course of attention deficit hyperactivity disorder. *European Child & Adolescent Psychiatry*, 18, 26–32.
- Langley, K., Marshall, L., van den Bree, M., Owen, M., O'Donovan, M., Thapar, A. (2004). Association of the dopamine D4 receptor gene 7-repeat allele with neuropsychological test performance of children with ADHD. *American Journal of Psychiatry*, 161, 133–8.
- Li, D., Sham, P., Owen, M.J., He, L. (2006). Meta-analysis shows significant association between dopamine system genes and attention deficit hyperactivity disorder (ADHD). *Human Molecular Genetics*, 15, 2276–84.
- Leung, P.W.L., Lee, C.C., Hung, S.F., et al. (2005). Dopamine receptor D4 (DRD4) gene in Han Chinese children with attention-deficit hyperactivity disorder (ADHD): increased prevalence of the 2-repeat allele. *American Journal of Medical Genetics Part B (Neuropsychiatric Genetics)*, 133B, 54–6.
- Maher, B.S., Marazita, M.L., Ferrell, R.E., Vanyukov, M.M. (2002). Dopamine system genes and attention deficit hyperactivity disorder: a meta-analysis. *Psychiatric Genetics*, 12, 207–15.
- Manor, I., Tyano, S., Eisenberg, J., Bachner-Melman, R., Kotler, M., Ebstein, R.P. (2002). The short DRd4 repeats confer risk to attention deficit hyperactivity disorder in a family based design and impair performance on a continuous performance test (TOVA). *Molecular Psychiatry*, 7, 790–4.
- Mansoor, A., Mazhar, K., Qamar, R. (2008). VNTR polymorphism of the DRD4 locus in different Pakistani ethnic groups. *Genetic Testing*, 12, 299–304.
- Mezzich, J.E. (1995). Cultural formulation and comprehensive diagnosis. Clinical and research perspectives. *The Psychiatric Clinics of North America*, 18, 649–57.
- Mill, J., Caspi, A., Williams, B., et al. (2006). Prediction of heterogeneity in intelligence and adult prognosis by genetic polymorphisms in the dopamine system among children with attention-deficit/hyperactivity disorder. *Archives of General Psychiatry*, 63, 462–9.
- Mill, J., Curran, S., Kent, L., et al. (2001). Attention deficit hyperactivity disorder (ADHD) and the dopamine D4 receptor gene: evidence of association but no linkage in a UK sample. *Molecular Psychiatry*, 6, 440–4.
- Payton, A., Holmes, J., Barrett, J.H., et al. (2001). Susceptibility genes for a trait measure of attention deficit hyperactivity disorder: a pilot study in a non-clinical sample of twins. *Psychiatry Research*, 105, 273–8.
- Polanczyk, G., de Lima, M.S., Horta, L.B., Biederman, J., Rohde, L.A. (2007). A worldwide prevalence of ADHD: a systematic review and metaregression analysis. *American Journal of Psychiatry*, 164, 942–8.
- Propper, C., Willoughby, M., Halpern, C.T., Carbone, M.A., Cox, M. (2007). Parenting quality, DRD4, and the prediction of externalizing and internalizing behaviors in early childhood. *Developmental Psychobiology*, 10, 619–32.
- Qian, Q., Wang, Y., Zhou, R., Yang, L., Faraone, S.V. (2004). Family-based and case control association studies of DRD4 and DAT1 polymorphisms in Chinese attention deficit hyperactivity disorder patients suggest long repeats contribute to genetic risk for the disorder. *American Journal of Medical Genetics Part B (Neuropsychiatric Genetics)*, 128B, 84–9.
- Rohde, L.A., Szobot, C., Polanczyk, G., Schmitz, M., Martins, S., Tramontina, S. (2005). Attention-deficit/hyperactivity disorder in a diverse culture: do research and clinical findings support the notion of a cultural construct for the disorder? *Biological Psychiatry*, 57, 1436–41.
- Roman, T., Scmitz, M., Polanczyk, G., Eizirik, M., Rohde, L.A., Hutz, M.H. (2001). Attention-deficit hyperactivity disorder: a study of association with both the dopamine transporter gene and the dopamine D4 receptor gene. *American Journal of Medical Genetics Part B (Neuropsychiatric Genetics)*, 105, 471–8.
- Sheese, B.E., Voelker, P.M., Rothbart, M.K., Posner, M.I. (2007). Parenting quality interacts with genetic variation in dopamine receptor D4 to influence temperament in early childhood. *Development and Psychopathology*, 19, 1039–46.
- Wang, E., Ding, Y.C., Flodman, P., et al. (2004). The genetic architecture of selectin at the human dopamine receptor D4 (DRD4) gene locus. *American Journal of Medical Genetics Part B (Neuropsychiatric Genetics)*, 74, 931–44.