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Brief Research Communication

Parent of Origin Effects in Attention/Deficit Hyperactivity Disorder (ADHD): Analysis of Data From the International Multicenter ADHD Genetics (IMAGE) Program

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There are conflicting reports suggesting that the parental origin of transmitted risk alleles may play a role in the etiology of attention deficit/hyperactivity disorder (ADHD). A recent report by Hawi and colleagues observed a generalized paternal over-transmission of alleles associated with ADHD. This was not replicated in more recent studies. Using data from a large multicenter study we examined the overall and gene-specific parent of origin effect in 554 independent SNPs across 47 genes. Transmission disequilibrium and explicit parent of origin test were performed using PLINK. Overall parent of origin effect was tested by Chi-square. There was no overall parent of origin effect in the IMAGE sample ($\chi^2_1 = 1.82, P = 0.117$). Five markers in three genes, *DDC*, *TPH2*, and *SLC6A2* showed nominal association ($P < 0.01$) with ADHD combined subtype when restricted to maternal or paternal transmission only. Following the initial report by Hawi and co-workers three studies, including this one, found no evidence to support an overall parent of origin effect for markers associated with ADHD. We cannot however, exclude gene-specific parent of origin effect in the etiology ADHD.
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KEY WORDS: ADHD; candidate gene; parent of origin effect

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There is considerable evidence to suggest that expression of particular genes can be influenced by their parental origin. The parent of origin effect cannot be explained through inheritance of differences in DNA sequences alone, but requires additional mechanisms to be evoked. These mechanisms are broadly termed "epigenetic inheritance." Epigenetic inheritance includes stable and heritable alterations of the genetic code, not including change at the DNA sequence. The epigenetic marking of genes altering their expression can be achieved through a number of mechanisms. To date epigenetic modification has been described at the chromatin- and nucleotide-level. The complex packaging of DNA into chromatin and chromosomes is maintained by the histone proteins.

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Consequently, the histone proteins are integral to the regulation of access to the DNA sequence and therefore the expression of genes maintained within these structures. Modifications of histone proteins can include acetylation, methylation, phosphorylation, and ubiquitination [Jaenisch and Bird, 2003]. However, the most notable epigenetic modification occurs at the nucleotide level through methylation of the nucleotide base cytosine. The methylation of cytosine residues at the gene promoter is thought to decrease the transcriptional activity of a gene [Robertson, 2005]. Imprints are removed during early germ cell development, re-established later in germ cell development or after fertilization, and maintained during embryonic development. "Imprinting" of the gene effectively tells the molecular machinery within the cell to express only one allele in the cell and its progeny. There is evidence to suggest that nearly 80 human genes show mono-allelic expression consistent with imprinting [Jirtle, 2002]. The mechanism underlying the reading of the imprint can involve many aspects of gene expression, and the silencing can be stable throughout the individual's life [Federman, 2006].

A high proportion of the imprinted genes that have been identified are highly expressed in the central nervous system and encompass a wide variety of functions including intracellular signaling, RNA processing and neurotransmitter signaling [Davies et al., 2005]. Interestingly, involvement of imprinting has been suggested for a number of common mental disorders, including autism, bipolar disorder, schizophrenia, and Tourette's syndrome. The evidence for this has arisen from observed preferential inheritance of risk alleles from either the maternal or paternal line. Imprinting is only one mechanism contributing to these disorders. However, we must also consider the influence of other biological influences such as the variation in maternally inherited mitochondrial DNA and in utero maternal environment [Weinberg, 1999].

There is evidence to suggest that the parental origin of genetic risk factors may play a role in the etiology of attention deficit/hyperactivity disorder [ADHD (MIM143465)]. ADHD is typically characterized by inattention, excessive motor activity, impulsivity, and distractibility. Individuals with ADHD have significant impairment in family and peer relations. Moreover, they have difficulties in academic functioning and show high comorbidity with antisocial, mood, anxiety, and substance use disorders. ADHD is a common disorder with a prevalence of European children estimated at between 4.6% [Polanczyk et al., 2007]. Family, twin, and adoption studies strongly support the influence of genetic factors in the etiology of ADHD [Thapar et al., 1999; Asherson, 2004; Faraone et al., 2005]. However, the specific mode of inheritance is unknown.

There have been many association studies examining the role of individual candidate genes in ADHD. Meta-analysis of these data suggests that variation in the genes that code for the dopamine receptors D4 (*DRD4*) and D5 (*DRD5*), the 5-hydroxytryptamine (serotonin) transporter (*SLC6A4*), the serotonin 1B receptor (*HTR1B*), synaptosomal protein of 25kD (*SNAP25*) and the dopamine transporter [*SLC6A3* (*DAT1*)] influence susceptibility to ADHD [Faraone et al., 2005]. In examination of putative risk alleles, Hawi and colleagues observed a generalized parent of origin effect in an Irish ADHD study. Using data from genetic variants that showed at least a trend toward association with ADHD ($P < 0.01$) they observed that the previously identified risk allele was more likely to be transmitted with the paternal chromosome than the maternal chromosome (paternal vs. maternal $\chi^2 = 9.6; P = 0.0019$) [Hawi et al., 2005]. More recently, two further studies have failed to confirm an overall paternal origin effect [Kim et al., 2007; Laurin et al., 2007a]. Gene-specific parent of origin effects have been observed for *BDNF* [Kent et al., 2005], *DDC* [Hawi et al., 2001], *GNAL* [Laurin et al., 2007b], *HTR1B* [Hawi et al., 2002], *SLC6A4* [Hawi et al., 2005; Banerjee et al., 2006], *SNAP25* [Mill et al., 2004], *TPH2*, *DRD4*, *DRD5*, and *SLC6A3* [Hawi et al., 2005].

This report describes findings of a test for overall and gene-specific parent of origin effects in 47 autosomal genes examined in the large International Multicenter ADHD Genetics (IMAGE) study.

The participants described in this manuscript have previously been reported by the IMAGE consortium [Brookes et al., 2006]. Ethical approval for the study was obtained from National Institute of Health registered ethical review boards for each center. Sample collection, SNP selection and genotyping described in this manuscript have previously been reported by the IMAGE consortium [Brookes et al., 2006]. Candidate genes were selected according to a "biological systems" approach. Forty-six genes were identified that play important roles in the regulation of dopamine, serotonin, and norepinephrine neurotransmission. A further six genes important in circadian rhythm were also selected. Genes fell into the following functional groups: dopamine receptors, serotonin receptors, norepinephrine receptors, neurotransmitter metabolic and catabolic enzymes, neuronal transporters, synaptic vesicle associated proteins, fatty acid desaturase enzymesm and circadian rhythm genes. For detailed summary of these genes see Brookes et al. [2006]. Genes located on the X-chromosome were not examined in the parent of origin analysis. The decision not to analyze female probands for transmission from the X-chromosome, was made to prevent confounding by X-inactivation.

Pair-wise linkage disequilibrium statistics were calculated using PWLD in STATA9 [Clayton, 2002]. Transmission disequilibrium test and explicit parent of origin test were performed using PLINK [Purcell et al., 2007]. To exclude bias due to non-independence of the tested markers we performed parent of origin analysis on a pruned subset of SNPs that were in approximate linkage equilibrium with each other. Markers were pruned where they showed a variance inflation factor (VIF) of 2 or greater. A VIF of 1 would imply that the SNP is completely independent of all other SNPs [Purcell et al., 2007]. Additional quality control parameters for the data were applied within PLINK. Fifty-two individuals with $\leq$90% completed genotyping across the SNP panel were excluded. After pruning the final analysis was performed across 554 SNPs in 590 nuclear families, accounting for 659 affected offspring trios. For comparative analysis data from the non-pruned set of 905 SNP markers were examined along side SNP data from five published studies [Hawi et al., 2005; Kent et al., 2005; Kim et al., 2007; Laurin et al., 2007a,b].

Five markers showed an association with ADHD-CT at the unadjusted $P < 0.01$ level. Using the explicit parent of origin test, none show a significant difference in the transmission from the maternal and the paternal lineage (see Table I). An overall parent of origin effect was examined by comparing all maternal and paternal transmissions in the five associated markers. There was no overall parent of origin effect in these data ($\chi^2_1 = 1.82$, $P = 0.117$). Five additional markers showed association with ADHD-CT when restricted to maternal or paternal transmission only (see Table II). Using the explicit parent of origin test on these SNPs only the dopamine decarboxylase (*DDC*) linked marker rs11575454 showed a weak parent of origin effect ($P = 0.039$).

In the explicit parent of origin analysis, two additional markers showed nominally significant parent of origin effects at $P < 0.01$. These were rs518511 and rs3730315 linked to the *FADS2* gene on chromosome 11 and *ADRBK2* on chromosome 22, respectively. Association with ADHD for rs518511 was due to paternal transmissions whilst association for rs3730315 occurred through maternal transmissions (see Table III). The

TABLE I. Summary of Transmission Disequilibrium Test and Parent of Origin Analysis in Markers Showing Nominal Association in the IMAGE Sample at $P < 0.01$

						All transmissions					Maternal transmissions only					Paternal transmissions only					Parent of origin effect	
CHR	Position	Gene	Marker	GT	Risk	T	NT	χ^2	OR	*P*	T	NT	χ^2	OR	*P*	T	NT	χ^2	OR	*P*	Z-score	*P*
3	144849528	SLC9A9	rs1242075	G|A	G	287	228	6.8	1.3	0.009	150	116	4.35	1.3	0.037	137	113	2.3	1.2	0.129	−0.36	0.716
3	195343944	HES1	rs4686673	G|A	A	302	239	7.3	1.3	0.007	163	120	6.53	1.4	0.011	139	120	1.4	1.2	0.238	−0.92	0.358
12	70641446	TPH2	rs1386493	G|A	A	204	150	8.2	1.4	0.004	116	75	8.85	1.6	0.003	90	75.5	1.2	1.2	0.276	−1.25	0.213
17	4567246	ARRB2	rs7208257	G|A	G	101	67	6.9	1.5	0.009	53	36	3.25	1.5	0.072	48	31	3.7	1.5	0.056	0.16	0.873
17	35078615	PNMT	rs200173	G|A	A	27	11	6.7	2.5	0.009	16	6	4.55	2.7	0.033	11	5	2.3	2.2	0.134	−0.27	0.790
					All	921	695	32	1.3	1.4E−07	498	353	24.7	1.4	4.3E−06	425	345	8.3	1.2	1.6E−02		0.117[a]

[a]Test statistic derived from χ^2 of total maternal and paternal transmissions.

TABLE II. Summary of Transmission Disequilibrium Test and Parent of Origin Analysis in Markers Showing Nominal Association From Maternal-Only or Paternal-Only Transmissions in the IMAGE Sample at $P < 0.01$

						All transmissions					Maternal transmissions only					Paternal transmissions only					Parent of origin effect	
CHR	Position	Gene	Marker	GT	Risk	T	NT	χ^2	OR	*P*	T	NT	χ^2	OR	*P*	T	NT	χ^2	OR	*P*	Z-score	*P*
7	50322022	DDC	rs11575454	G|C	C	21	9	5	2.3	0.028	12	1	9	12	0.002	9	8	0.1	1.1	0.808	−2.1	0.039
7	50381415	DDC	rs1466163	G|A	A	160	129	3	1.2	0.068	69	70	0	1	0.932	92	60	6.8	1.5	0.009	1.9	0.062
12	70641446	TPH2	rs1386493	G|A	A	204	150	8	1.4	0.004	116	75	9	1.6	0.003	90	76	1.2	1.2	0.276	−1.2	0.213
12	79712221	TPH2	rs17110747	G|A	G	175	134	5	1.3	0.020	100	66	7	1.5	0.008	76	69	0.3	1.1	0.560	1.4	0.164
16	54252607	SLC6A2	rs3785143	G|A	A	130	95	5	1.4	0.020	56	51	0	1.1	0.629	75	44	8.1	1.7	0.004	1.6	0.105

TABLE III. Summary of Transmission Disequilibrium Test and Parent of Origin Analysis in Markers Showing Nominal Parent of Origin Effects in the IMAGE Sample at $P < 0.01$

						All transmissions				Maternal transmissions only				Paternal transmissions only				Parent of origin effect	
CHR	Position	Gene	Marker	GT	Risk	T	NT	χ^2	OR	*P*	T	NT	χ^2	OR	*P*	T	NT	χ^2	OR	*P*	Z-score	*P*
11	61388030	FADS2	rs518511	A|C	C	123	120	0	1	0.847	47.5	67.5	3.5	0.7	0.062	76	53	4.1	1.4	0.04	2.74	0.006
22	24424591	ADRBK2	rs3730315	G|A	A	31	27	0.3	1.1	0.599	19.5	7.5	5.3	2.6	0.021	12	20	2.1	0.59	0.15	2.61	0.009

parent of origin effects at these markers did not remain significant when corrected for the 545 comparisons examined in the "pruned" dataset.

To date a number of reports have described markers showing a parent of origin effect in ADHD. As mentioned above, three studies have examined overall parent of origin effects in ADHD [Hawi et al., 2005; Kim et al., 2007; Laurin et al., 2007a]. Additional gene-specific parent of origin effects has been observed for *BDNF* [Kent et al., 2005], *DDC* [Hawi et al., 2001], *GNAL* [Laurin et al., 2007b], *HTR1B* [Hawi et al., 2002], *SLC6A4* [Hawi et al., 2005; Banerjee et al., 2006], *SNAP25* [Mill et al., 2004], *TPH2*, *DRD4*, *DRD5*, and *SLC6A3* [Hawi et al., 2005]. In a post-hoc analysis we tested whether markers examined in more than one study showed evidence of a parent of origin effect (see Table IV). Briefly, seven SNP markers across seven genes have been examined in the IMAGE and at least one other study. No evidence of a parent of origin effect was observed for any of the tested markers.

In conclusion, in this report we showed parent-specific associations with ADHD-CT ($P < 0.01$) for five independent markers linked to three genes, namely *DDC*, *TPH2*, and *SLC6A2* (see Table II). Assuming all of the 554 markers are independent and a type 1 error of 1% we would expect to observe 11 associations from both the paternal and maternal transmissions by chance alone. This would suggest that these observations may be due to chance alone.

However, previous data from analysis of *DDC* show that the association signals are stronger from the paternal chromosome in ADHD [Hawi et al., 2001] and bipolar affective disorder [Borglum et al., 2003]. *DDC* is located on chromosome 7p11, 27kb from *GRB10* (encoding growth factor receptor-bound protein 10), that has been demonstrated to be imprinted in various human and mouse tissues. Imprinting of *GRB10* is partial with tissue and isoform specificity [Blagitko et al., 2000]. Since imprinted genes are often found in clusters regulated by imprinting centers the *DDC* gene locus may also be imprinted. The direct examination of the imprinting status of the *DDC* gene shows evidence of asynchronous replication, a phenomenon suggestive of imprinting. However, SNP expression analysis shows biallelic expression of transcribed *DDC* SNPs in various human and mouse tissues, which is counter-indicative of imprinting [Hitchins et al., 2002]. The imprinting status of *DDC* is therefore not conclusive but does not exclude the possibility of partial or tissue and developmental phase specific imprinting for this gene. *Tph1*, the mouse homologue to human *TPH1*, shows some evidence of paternal imprinting in the mouse cerebellum using a custom murine chromosome 7 microarray [Buettner et al., 2004]. However, there is evidence to suggest that *Tph1* is not expressed in the brain, and that the tryptophan hydroxylase in the brain is generated from *Tph2* [Walther et al., 2003]. It would therefore be prudent to further examine the human *TPH2* gene in cerebellum and other brain regions to examine potential imprints. Moreover, paternal imprinting of the *TPH2* gene would support the association with ADHD stemming from transmission from the maternal chromosomes observed in this study.

Two markers showed an explicit parent of origin effect, namely markers linked to *FADS2* and *ADRBK2*. However, it is important to consider that the significance of these findings is driven not only by an over-transmission of a putative risk allele from one parent but a combined under-transmission of the risk allele from the other parent. This would suggest conflicting selection at the maternal and paternal chromosome as opposed to a one-way selection bias as observed for *DDC*, *TPH2*, and *SLC6A2* described above.

Data from the Irish ADHD study presented by Hawi et al. [2005] suggested that the risk alleles for ADHD are, in general,

TABLE IV. Summary of Combined Transmission Disequilibrium Test and Parent of Origin Statistics in SNP Markers Examined Across Multiple Published Studies

						All transmissions				Maternal transmissions only				Paternal transmissions only				Parent of origin effect	
CHR	Position	Gene	Marker	GT	Risk	Study	T	NT	χ^2	OR	*P*	T	NT	χ^2	OR	*P*	T	NT	χ^2	OR	*P*	χ^2	*P*
5	1447521	SLC6A3	RS27072	A|G	A	a,e	201	242	3.8	0.83	0.05	98.5	131.5	4.7	0.75	0.03	102.5	110.5	0.3	0.93	0.58	1.25	0.26
6	78228978	HTR1B	RS6296	G|C	G	a,b,e	379	366	0.2	1.04	0.63	180	187	0.1	0.96	0.71	199	179	1.1	1.11	0.30	0.97	0.33
11	27636491	BDNF	RS6265	A|G	A	a,c	244	262	0.6	0.93	0.42	123.5	113.5	0.4	1.09	0.52	115.5	143.5	3	0.8	0.08	2.79	0.09
12	70634964	TPH2	RS1843809	C|A	C	a,b	229	151	16	1.52	1.0E−04	124.5	75.5	12	1.65	5.0E−04	104.5	75.5	4.7	1.38	0.03	0.69	0.40
13	46307034	HTR2A	RS6314	A|G	A	a,e	132	148	0.9	0.89	0.34	70.5	76.5	0.2	0.92	0.62	61.5	71.5	0.8	0.86	0.39	0.05	0.83
20	10164901	SNAP25	RS363026	A|C	A	a,d	100	117	1.3	0.85	0.25	42	51	0.9	0.82	0.35	58	66	0.5	0.88	0.47	0.06	0.81
20	10206653	SNAP25	RS6039806	C|A	C	a,e	395	381	0.3	1.04	0.62	203.5	184.5	0.9	1.1	0.33	191.5	196.5	0.1	0.97	0.80	0.68	0.41

Key to studies: (a) Hawi et al. [2005], (b) Laurin et al. [2007a], (c) Kent et al. [2005], (d) Kim et al. [2007], (e) IMAGE sample.

preferentially transmitted via the paternal chromosome. In three follow-up studies, including data presented here, no evidence to support an overall parent of origin effect for markers associated with ADHD was found. We cannot, however, exclude gene-specific parent of origin effects in the etiology ADHD.

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REFERENCES

Asherson P. 2004. Attention-deficit hyperactivity disorder in the post-genomic era. Eur J Child Adolesc Psychiatry 13(Suppl 1):I50–I70.

Banerjee E, Sinha S, Chatterjee A, Gangopadhyay PK, Singh M, Nandagopal K. 2006. A family-based study of Indian subjects from Kolkata reveals allelic association of the serotonin transporter intron-2 (STin2) polymorphism and attention-deficit-hyperactivity disorder (ADHD). Am J Med Genet Part B 141B(4):361–366.

Blagitko N, Mergenthaler S, Schultz U, Wollmann HA, Craigen W, Eggermann T, Ropers HH, Kalscheuer VM. 2000. Human GRB10 is imprinted and expressed from the paternal and maternal allele in a highly tissue- and isoform-specific fashion. Hum Mol Genet 9(11):1587–1595.

Borglum AD, Kirov G, Craddock N, Mors O, Muir W, Murray Y, McKee I, Collier DA, Ewald H, Owen MJ, et al. 2003. Possible parent-of-origin effects of Dopa decarboxylase in susceptibility to bipolar affective disorder. Am J Med Genet Part B 117B(1):18–22.

Brookes K, Xu X, Zhou K, Lowe N, Anney R, Franke B, Gill M, Ebstein R, Buitelaar J, Sham P, et al. 2006. The analysis of 51 genes in DSM-IV combined type attention deficit hyperactivity disorder: Association signals in DRD4, DAT1 and 16 other genes. Mol Psychiatry 11(10): 934–953.

Buettner VL, Longmate JA, Barish ME, Mann JR, Singer-Sam J. 2004. Analysis of imprinting in mice with uniparental duplication of proximal chromosomes 7 and 15 by use of a custom oligonucleotide microarray. Mamm Genome 15(3):199–209.

Clayton D. 2002. Clayton, Geneassoc: STATA modules for gene association analyses. Cambridge, UK; Cambridge Institute for Medical Research: (2002).

Davies W, Isles AR, Wilkinson LS. 2005. Imprinted gene expression in the brain. Neurosci Biobehav Rev 29(3):421–430.

Faraone SV, Perlis RH, Doyle AE, Smoller JW, Goralnick JJ, Holmgren MA, Sklar P. 2005. Molecular genetics of attention-deficit/hyperactivity disorder. Biol Psychiatry 57(11):1313–1323.

Federman D. 2006. The biology of human sex differences. N Eng J Med 354(14):1507–1514.

Hawi Z, Foley D, Kirley A, McCarron M, Fitzgerald M, Gill M. 2001. Dopa decarboxylase gene polymorphisms and attention deficit hyperactivity disorder (ADHD): No evidence for association in the Irish population. Mol Psychiatry 6(4):420–424.

Hawi Z, Dring M, Kirley A, Foley D, Kent L, Craddock N, Asherson P, Curran S, Gould A, Richards S, et al. 2002. Serotonergic system and attention deficit hyperactivity disorder (ADHD): A potential susceptibility locus at the 5-HT(1B) receptor gene in 273 nuclear families from a multi-centre sample. Mol Psychiatry 7(7):718–725.

Hawi Z, Seguardo R, Conroy J, Sheehan K, Lowe N, Kirley A, Shields D, Fitzgerald M, Gallagher L, Gill M. 2005. Preferential transmission of paternal alleles at risk genes in attention-deficit/hyperactivity disorder. Am J Hum Genet 77(6):958–965.

Hitchins MP, Bentley L, Monk D, Beechey C, Peters J, Kelsey G, Ishino F, Preece MA, Stanier P, Moore GE. 2002. DDC and COBL, flanking the imprinted GRB10 gene on 7p12, are biallelically expressed. Mamm Genome 13(12):686–691.

Jaenisch R, Bird A. 2003. Epigenetic regulation of gene expression: How the genome integrates intrinsic and environmental signals. Nat Genet 33(Suppl):245–254.

Jirtle RL. 2002. www.geneimprint.com.

Kent L, Green E, Hawi Z, Kirley A, Dudbridge F, Lowe N, Raybould R, Langley K, Bray N, Fitzgerald M, et al. 2005. Association of the paternally transmitted copy of common Valine allele of the Val66Met polymorphism of the brain-derived neurotrophic factor (BDNF) gene with susceptibility to ADHD. Mol Psychiatry 10(10):939–943.

Kim JW, Waldman I, Faraone S, Biederman J, Doyle AE, Purcell S, Arbeitman L, Fagerness J, Sklar P, Smoller JW. 2007. Investigation of parent-of-origin effects in ADHD candidate genes. Am J Med Genet Part B 144(6):776–780.

Laurin N, Feng J, Ickowicz A, Pathare T, Malone M, Tannock R, Schachar R, Kennedy JL, Barr CL. 2007. No preferential transmission of paternal alleles at risk genes in attention-deficit hyperactivity disorder. Mol Psychiatry 12(3):226–229.

Laurin N, Ickowicz A, Pathare T, Malone M, Tannock R, Schachar R, Kennedy JL, Barr CL. 2007. Investigation of the G protein subunit Galpha(olf) gene (GNAL) in attention deficit/hyperactivity disorder. J Psychiatry Res (in press).

Mill J, Richards S, Knight J, Curran S, Taylor E, Asherson P. 2004. Haplotype analysis of SNAP-25 suggests a role in the aetiology of ADHD. Mol Psychiatry 9(8):801–810.

Polanczyk G, de Lima MS, Horta BL, Biederman J, Rohde LA. 2007. The worldwide prevalence of ADHD: A systematic review and metaregression analysis. Am J Psychiatry 164(6):942–948.

Purcell S, Neale B, Todd-Brown K, Thomas L, Ferreira MAR, Bender D, Maller J, de Bakker PIW, Daly MJ, Sham P. 2007. PLINK: A toolset for whole-genome association and population-based linkage analysis. Am J Hum Genet 81(3):559–575.

Robertson KD. 2005. DNA methylation and human disease. Nat Rev Genet 6(8):597–610.

Thapar A, Holmes J, Poulton K, Harrington R. 1999. Genetic basis of attention deficit and hyperactivity. Br J Psychiatry 174:105–111.

Walther DJ, Peter JU, Bashammakh S, Hortnagl H, Voits M, Fink H, Bader M. 2003. Synthesis of serotonin by a second tryptophan hydroxylase isoform. Science 299(5603):76.

Weinberg CR. 1999. Methods for detection of parent-of-origin effects in genetic studies of case-parents triads. Am J Hum Genet 65(1):229–235.