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Examination of Association to Autism of Common Genetic Variation in Genes Related to Dopamine

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Abstract

Autism is a severe neurodevelopmental disorder characterized by a triad of complications. Autistic individuals display significant disturbances in language and reciprocal social interactions, combined with repetitive and stereotypic behaviors. Prevalence studies suggest that autism is more common than originally believed, with recent estimates citing a rate of one in 150. Although this genomic approach has yielded multiple suggestive regions, a specific risk locus has yet to be identified and widely confirmed. Because many etiologies have been suggested for this complex syndrome, we hypothesize that one of the difficulties in identifying autism genes is that multiple genetic variants may be required to significantly increase the risk of developing autism. Thus we took the alternative approach of examining 14 prominent dopamine pathway candidate genes for detailed study by genotyping 28 SNPs. Although we did observe a nominally significant association for rs2239535 (p=.008) on chromosome 20, single locus analysis did not reveal any results as significant after correction for multiple comparisons. No significant interaction was identified when Multifactor Dimensionality Reduction (MDR) was employed to test specifically for multilocus effects. Although genome-wide linkage scans in autism have provided support for linkage to various loci along the dopamine pathway, our study does not provide strong evidence of linkage or association to any specific gene or combination of genes within the pathway. These results demonstrate that common genetic variation within the tested genes located within this pathway at most play a minor to moderate role in overall autism pathogenesis.

Keywords

Autism; Dopamine; SNPs; linkage; association

Introduction

Autism is a highly heritable, genetically complex neurodevelopmental disorder that is neither distinct nor categorical. With an onset early in childhood, autism represents one extreme of a spectrum of social and communication impairment and behavioral problems, referred to as Autism Spectrum Disorders (ASD). The incidence of severe autism is estimated at one in 1,000 individuals, with males affected at a rate four times that of females (Fombonne, 1999; Williams et al., 2006). This rate of incidence increases to approximately

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one in 150 when the broad diagnosis is considered to include milder forms of ASD (Rice et al., 2007). Evidence from various studies indicates that ASDs have a genetically complex etiology, possibly involving epistasis and locus heterogeneity. While rare single mutations and chromosomal abnormalities are responsible for some cases (Abrahams et al., 2008), current models strongly suggest that inheritance of multiple interacting polymorphic loci contributes to a continuum of disease phenotypes in the majority of affected children (Veenstra-Vanderweele et al., 2004a; Veenstra-Vanderweele et al., 2004b).

The high heritability of autism has driven efforts to search for susceptibility loci using genome-wide linkage screens (Barrett et al., 1999; Buxbaum et al., 2001; International Molecular Genetic Study Autism Consortium (IMGSAC), 2001; Liu et al., 2001; Philippe et al., 1999; Risch et al., 1999; Shao et al., 2002; Szatmari et al., 2007; Yonan et al., 2003) and genome wide association studies (Arking et al., 2008). Although this genomic approach has yielded multiple suggestive regions, a specific risk locus has yet to be identified and widely confirmed.

Some evidence supports the involvement of neurobiological pathways, in particular the dopamine pathway (Figure 1). This connection seems compelling because the dopaminergic system has been linked to a variety of behaviors and functions: cognition, attention, motivation, and emotion (Nieoullon, 2002;Nieoullon et al., 2003). When disturbance of dopamine metabolism in autistic children was examined, affected individuals had a higher rate of urinary homovanilic acid (HVA) (Figure 1). A relationship between the severity of autism and the increased HVA levels was also observed (Garreau et al., 1980). For these reasons, the dopaminergic system is a common target for medication used in children with autism (Oswald et al., 2007). Risperidone, an antipsychotic (neuroleptic), is an antagonist of the dopamine D2 and 5HT2 receptors that has been reported to improve the restricted and repetitive stereotype (Malone et al., 2005). Other drugs such as Haldol, a dopamine antagonist, and Welbutrin, a dopamine uptake inhibitor, have proven effective in some autistic children. Thus with substantial evidence of disturbances in the dopamine pathway, we selected a set of functional candidate genes within this pathway that enabled us to examine each gene for variations in more detail. This approach entails selecting genes based on knowledge of the specific phenotypes and of the underlying neurobiology related to expected behavioral abnormalities in individuals with autism.

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Materials and Methods

Dataset

Our analysis was conducted on a dataset consisting of 403 non-Hispanic Caucasian American families collected in the Southeast United States by the Center for Human Genetics Research at Vanderbilt University and the Institute for Human Genomics at the University of Miami (Table 1). Probands for the study consisted of individuals between the ages of 3 and 21 years who were clinically diagnosed with autism using Diagnostic and Statistical Manual (DSM)-IV criteria. The clinical diagnosis of autism was confirmed based on clinical evaluation using DSM-IV diagnostic criteria supported by the Autism Diagnostic Interview-Revised (ADI-R) and medical records. Exclusion criteria for participation in the larger genetics study included developmental level below 18 months, severe sensory problems (e.g., visual impairment or hearing loss), significant motor impairments (e.g., failure to sit by 12 months or walk by 24 months), or identified metabolic, genetic, or progressive neurological disorders Parents/caregivers were informed of the purposes, risks, and benefits of participating in this project and provided informed consent.

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Molecular Analysis

Genomic DNA was extracted from blood using standard protocols and a commercial system (Puregene; Gentra Systems, Minneapolis, MN). All single nucleotide polymorphisms (SNPs) were identified using the Ensembl (www.ensembl.org), dbSNP (www.ncbi.nlm.nih.gov/projects/SNP), and AppliedBiosystems (http://www.appliedbiosystems.com/) databases. Multiple SNPs spanning each gene were chosen using a hierarchy of nonsynonymous coding change, minor allele frequency > 0.10, location within the gene, with the goal of capturing as much of the common variation as possible. We calculated the linkage disequilibrium between SNPs to assess the coverage of the genes with the goal of capturing most of the common variations (supplementary material). A total of 28 SNPs were genotyped for nine genes (Table 2). The genes were selected based on the metabolic proximity to the neurotransmitter dopamine, on previous reports of association to neuropsychiatric disorders, and on Michal's publication: Biochemical Pathways: An Atlas of Biochemistry and Molecular Biology" (Michal, 1999). SNPs were genotyped using the ABI 7900 Taqman system (Oliveira et al., 2003). Laboratory personnel were blinded to pedigree structure, affection status, and location of quality control samples. Duplicate quality control samples were placed both within and across 384-well plates, and equivalent genotypes were required for all quality control samples to ensure accurate genotyping. Hardy-Weinberg calculations were performed for each marker, and Mendelian inconsistencies (in the multiplex families) were identified using PedCheck (O'Connell et al., 1998). Suspect genotypes were re-read or retested. All SNPs were required to pass 95% efficiency when genotyped.

Statistical Analysis

Genotype efficiency, Hardy-Weinberg Equilibrium and linkage disequilibrium were checked using Haploview (Barrett et al., 2005). If any SNP fell below 95% genotype efficiency, a SNP in high LD with the failed SNP was added to ensure complete coverage of the gene. Linkage analysis was conducted using two-point heterogeneity LOD scores (HLOD) calculated using FASTLINK and HOMOG (Ott, 1999). Both recessive and dominant models with disease allele frequencies of 0.01 and 0.001, respectively, were analyzed. This approach is robust for detecting linkage signals when the underlying model is unknown or complex (Hodge, 1994). The Pedigree Disequilibrium Test (PDT) for single-locus analysis (Martin et al., 2003) assessed the family based association and the Genotype-PDT (GenoPDT) tested genotypic association to the risk of autism (Martin et al., 2003). Taking into account the 4:1 ratio of males to females affected with autism, the HLOD, PDT, and Geno-PDT were also run in a subset of families containing only affected males (male-only, N=303).

Multifactor Dimensionality Reduction (MDR) analysis was used to detect multilocus interactions (Ritchie et al., 2001; Ritchie et al., 2007). Since MDR is designed for case-control data, we extracted from any family with a complete parent-child trio (one per family for multiplex families) the affected child. We constructed "pseudo" controls, using the non-transmitted alleles of the parents (Collins et al., 2006; Ma et al., 2005). We tested for all two way and three way interactions. All p-values are reported as nominal P values unless otherwise stated.

Results

A marginal association was detected for the DBH (dopamine-β-monooxygenase) p=0.03 in the overall dataset for rs161115. COMT (Catechol-O-methyl transferase) showed a marginal association p=0.05 (whole dataset) and p=0.03 (male only dataset). We also observed a marginal association (p=0.01) for PTS (6-pyruvoyl-tetrahydropterin synthase). The strongest

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association, p=0.008 (0.018 when corrected for multiple comparisons), was observed for rs2239535 (chromosome 20) for YWHAB (tyrosine 3-monooxygenase/tryptophan 5-monooxygenase activation protein, beta polypeptide), TH's (tyrosine 3-monooxygenase) activation protein. Linkage analysis was performed and the only result of note was a LOD score of 2.49 (recessive model) for DBH in the male only subset (supplementary material). MDR was run, but it detected no gene-gene interaction (supplementary material).

Discussion

Compelling evidence has linked dysfunction in the dopamine pathway with autism, fostering studies of genes along this pathway. Variation in genes within the dopamine pathway has been implicated in various genetic linkage and/or association studies, but the results have been inconsistent. This lack of replication across the studies might be explained by the extreme genetic and phenotypic heterogeneity of the samples. To overcome this inconsistency, examination of families with only affected males has been suggested as a method of looking at a more homogeneous autism subset (Cantor et al., 2005; Stone et al., 2004). However, the subsetting of our samples into a male only subset did not improve the consistency of our results. Ultimately, our study does not provide overwhelming evidence of a main effect of any specific gene in the pathway.

This led us to hypothesize that interactions between genes might represent a more consistent genetic effect. To test the possibility that interactions might result in stronger joint effects, we performed MDR analysis. Although MDR has >80% power to detect both main and interactive effects in a dataset of this size, even in the presence of locus or genetic heterogeneity (Ritchie et al., 2007), this analysis did not identify any strong or moderate interactive effects..

That we found no significantly strong effects suggests that none of these genes, alone or in combination, carries a pervasive effect in autism. . There could be variation in regulatory elements for these genes outside of the coding regions covered by our analysis or an extreme level of locus heterogeneity that has a significant negative impact on power both for PDT and MDR analyses. Since we only examined common variations, the underlying effects could arise from multiple rare variants in one or more of these genes. Furthermore, genes part of the dopamine pathway but not genotyped in this study could harbor susceptibility alleles.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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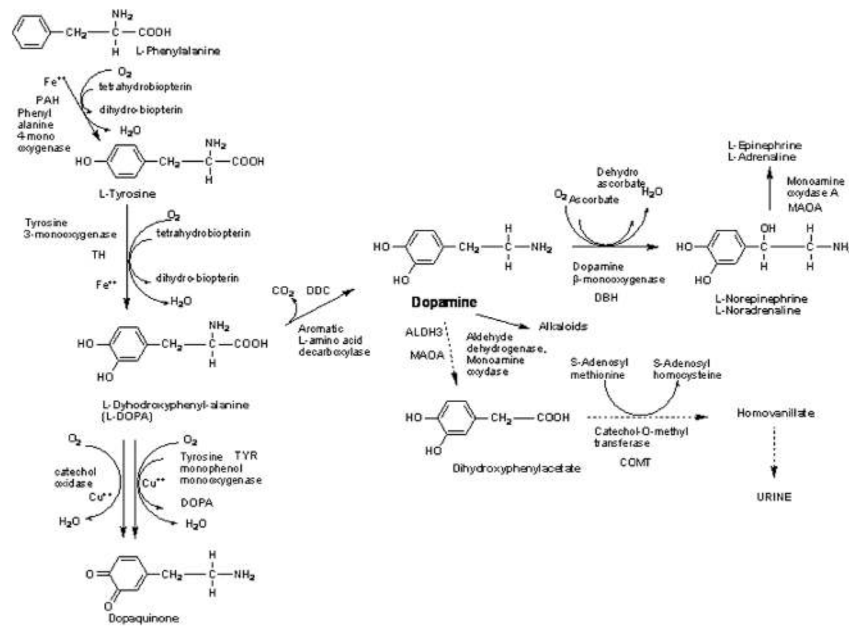

Figure 1. Dopamine pathway

Representation of the dopamine pathway with the metabolic genes indicated. The other genes genotyped in this study are SLC6A3, the dopamine transporter. PTS (6-pyruvoyltetrahydropterin synthase) an enzyme part of the tetrahydrobiopterin pathway, and YWHAB (Tyrosine-3-monooxygenase activation protein).

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Table 1

Dataset Distributions

	Total	**Multiplex**	**Trios**	**Unaffected sibs**
All	403	151	252	231
Male Only Subset	303	89	214	185

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Table 2

Tested Genes and Single Nucleotide Polymorphisms (SNPs)

SNP[a]	Gene	Chr[b]	NCBI built 36	MAF[c]	MA[d]
rs37020	SLC6A3	5	1471374	0.42	C
rs1611115	DBH	9	133530069	0.22	T
rs2797849	DBH	9	133531495	0.35	C
rs3025388	DBH	9	133532810	0.17	G
rs1108581	DBH	9	133534795	0.21	G
rs1611125	DBH	9	133538866	0.47	C
rs2797853	DBH	9	133542069	0.34	T
rs2073833	DBH	9	133549836	0.44	C
rs2073837	DBH	9	133552482	0.31	A
rs2070762	TH	11	2142911	0.48	G
rs7129973	TYR	11	88555218	0.41	C
rs12419949	TYR	11	88562111	0.11	T
rs2000554	TYR	11	88575589	0.41	G
rs7123206	TYR	11	88590980	0.12	A
rs3819331	PTS	11	111604249	0.14	C
rs1801153	PAH	12	101735233	0.35	T
rs1522307	PAH	12	101800984	0.34	G
rs1006556	ALDH3A1	17	19580307	0.24	C
rs2072330[e]	ALDH3A1	17	19585064	0.40	A
rs4646787	ALDH3A1	17	19589841	0.34	A
rs2239535	YWHAB	20	42949570	0.24	A
rs2425672	YWHAB	20	42959551	0.43	A
rs2425675	YWHAB	20	42968348	0.28	A
rs2020917	COMT	22	18303438	0.30	T
rs1055503	COMT	22	18316065	0.13	A
rs4646312	COMT	22	18322891	0.40	C

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SNP[a]	Gene	Chr[b]	NCBI built 36	MAF[c]	MA[d]
rs4633[e]	COMT	22	18324789	0.48	C
rs165774	COMT	22	18327115	0.34	A

[a]Single Nucleotide Polymorphism designation

[b]Chromosome

[c]Minor Allele Frequency

[d]Minor Allele

[e]synonymous changes

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Table 3

Pedigree Disequilibrium Test (PDT) and Geno-PDT Results

		Overall		MO*	
		PDT		PDT	
SNP	**Gene**	**SUM****	**GENO****	**SUM**	**GENO**
rs37020	SLC6A3	0.655	0.324	0.304	0.151
rs161115	DBH	0.070	**0.033**	0.239	0.134
rs2797849	DBH	0.084	0.237	0.089	0.242
rs3025388	DBH	1.000	0.668	0.265	0.220
rs1108581	DBH	0.852	0.050	0.456	0.125
rs1611125	DBH	0.429	0.768	0.897	0.951
rs2797853	DBH	0.472	0.489	0.164	0.376
rs2073833	DBH	0.558	0.274	0.827	0.216
rs2073837	DBH	0.492	0.329	0.850	0.816
rs2070762	TH	0.297	0.590	0.478	0.768
rs7129973	TYR	0.591	0.150	0.898	0.781
rs12419949	TYR	0.273	0.456	0.848	0.963
rs2000554	TYR	0.306	0.509	0.967	0.951
rs7123206	TYR	0.876	0.973	0.948	0.997
rs3819331	PTS	**0.012**	**0.029**	0.087	0.157
rs1801153	PAH	0.906	0.927	0.621	0.795
rs1522307	PAH	0.412	0.143	0.131	0.024

SNP	Gene	Overall PDT SUM**	Overall PDT GENO**	MO* PDT SUM	MO* PDT GENO
rs1006556	ALDH3A1	0.928	0.740	0.673	0.685
rs17857757	ALDH3A1	0.798	0.926	0.582	0.700
rs4646787	ALDH3A1	0.365	0.255	0.268	0.136
rs2239535	YWHAB	**0.008**	**0.017**	**0.013**	**0.028**
rs2425672	YWHAB	0.687	0.721	0.559	0.756
rs2425675	YWHAB	0.072	0.178	0.083	0.209
rs2020917	COMT	0.501	0.468	1.000	0.517
rs1055503	COMT	0.152	0.192	0.060	0.090
rs4646312	COMT	0.405	0.729	0.528	0.833
rs4633	COMT	0.704	0.676	0.371	0.675
rs165774	COMT	0.075	**0.046**	**0.028**	0.083

[*] Families where only males are affected

[**] The Sum-PDT is an allelic test; the Geno-PDT is a genotype test

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