Tourette syndrome is associated with recurrent exonic copy number variants

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ABSTRACT

Background: Multiple rare copy number variants (CNVs) including genomic deletions and duplications play a prominent role in neurodevelopmental disorders such as mental retardation, autism, and schizophrenia, but have not been systematically studied in Tourette syndrome (TS).

Methods: We performed a genome-wide screening of single nucleotide polymorphism (SNP) genotyping microarray data to identify recurrent or de novo rare exonic CNVs in a case-control association study of patients with TS.

Results: We identified 5 exon-affecting rare CNVs that are either de novo or recurrent in 10 out of 111 patients with TS but were not found in 73 ethnically matched controls or in the entries of the Database of Genomic Variants (containing 21,178 CNVs at 6,558 loci). Three out of the 5 CNVs have been implicated previously by other studies in schizophrenia, autism, and attention-deficit hyperactivity disorder, suggesting that these CNVs produce a continuum of neuropsychiatric disturbances that manifest in different ways depending on other genetic, environmental, or stochastic factors.

Conclusions: Rare, recurrent exonic copy number variants are associated in a subset of patients with Tourette syndrome. *Neurology*® 2010;74:1583-1590

GLOSSARY

ADHD = attention-deficit hyperactivity disorder; **CEPH** = Centre d'Etude du Polymorphisme Humain; **CN** = copy number; **CNV** = copy number variant; **OCD** = obsessive-compulsive disorder; **M** = minimum number of markers in CNV; **PCA** = principal components analysis; **SNP** = single nucleotide polymorphism; **SVS** = SNP and Variation Suite; **TS** = Tourette syndrome.

Tourette syndrome (TS) is a common neurodevelopmental disorder characterized by motor and vocal tics, often associated with obsessive-compulsive disorder (OCD) and attention-deficit hyperactivity disorder (ADHD). Genetic and environmental factors are postulated to play an important role in TS. Support for a genetic component in the etiology of TS comes from twin and family studies.¹⁻⁴ There has been limited success with respect to identifying specific genes that are affected in TS. Genome-wide linkage studies have been inconsistent in reproducing the results.⁵ Partly, such limited success could be due to an incorrect genetic model, uncertainty regarding optimal phenotypic definition for linkage studies, genetic heterogeneity, bilineal transmission, or sporadic and de novo cases.

Multiple rare copy number variants (CNVs), especially exonic CNVs, seem to play a prominent role in several neurodevelopmental disorders, such as autism, ADHD, and schizophrenia.⁶⁻¹⁰ For example, whole-genome studies assessing copy number variation in autism reported large de novo copy number variants in 7% to 10% of simplex families, 2% to 3% of multiplex families, and only 1% of control families.⁶ A similar situation may exist for TS, especially in families where only 1 or 2 family members have TS. While linkage studies may be useful in the study of large TS pedigrees, alternative approaches such as screening for copy number variation may be useful for smaller pedigrees and sporadic cases. In the present study,

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Supplemental data at
www.neurology.org

e-Pub ahead of print on April 28, 2010, at www.neurology.org.

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Supported by the Clinical and Translational Science Award UL1 RR024139, National Center for Research Resources, NIH.

Disclosure: Author disclosures are provided at the end of the article.

we hypothesized that multiple rare copy number variants may be associated with a subset of TS cases.

METHODS Study design and setting. A case-control study of 118 (4 samples that failed quality control were excluded later; see below) white patients with TS and 73 white (Centre d'Etude du Polymorphisme Humain [CEPH]) controls was designed to investigate rare recurrent exonic CNVs. In addition, CNV data from 100 TS-unaffected family members were used to verify the inheritance status of the CNVs. Of 118 patients with TS, DNA samples of 28 patients were obtained at Wayne State University/Children's Hospital of Michigan gene bank (PI Dr. A.M. Hug) between 2006 and 2008. Ninety DNA samples were obtained from Coriell cell repository (Coriell Institute for Medical Research, Camden, NJ). Since rare CNVs are generally identifiable in 7%–10% of other neurodevelopmental disorders,⁶ we expected that using at least 100 samples may lead to the identification of some significant rare CNVs.

Standard protocol approvals, registrations, and patient consents. The study protocol was approved by the Institutional Review Board at Wayne State University and informed consent was obtained from parents.

Subjects. DNA samples from whole blood samples of 118 white subjects with TS (87 male and 31 female) were used in the study. Subjects were included after thorough neurologic evaluation by a pediatric neurologist. The following criteria were used to establish a diagnosis of TS: 1) motor tics fluctuating for more than 2 years; and 2) presence of vocal tics. Patients diagnosed with various other conditions associated with TS (e.g., autism) or other established chromosomal disorders (except ADHD and OCD) were excluded from the present study. Comorbid OCD and ADHD and family information were evaluated and diagnosed by the pediatric neurologist who made the initial diagnosis of TS. No formal diagnostic instruments were used for this purpose or to exclude the presence of autism or mental retardation. A total of 46 subjects had TS only without OCD and ADHD, 16 subjects had comorbid ADHD, 27 subjects had comorbid OCD, and 29 subjects had comorbid OCD and ADHD. No subject had comorbid autism.

We also isolated DNA from 100 TS-unaffected parents of patients with TS, who did not meet the diagnostic criteria for TS. Eleven families had 2 affected family members, including 1 family with identical twins and 1 family with a parent–child concordant pair. A total of 96 families had only 1 affected member. Only 30 out of 118 patients with TS had both parents genotyped, 40 had 1 parent genotyped, and 48 had no parental data. Sixteen TS-unaffected parents had a diagnosis of ADHD; 21 TS-unaffected parents had OCD. The TS-unaffected parents were not used as control due to concerns about incomplete penetrance and variable expressivity, uncertainty about phenotypic definition, and concerns whether ADHD and OCD may be due to same underlying genetic lesions as TS. The TS-unaffected parent group was only used to verify the inheritance status of any CNVs that would be identified in this study. We used genotype data from 73 CEPH controls using the same Illumina 610 Quad platform as controls for our study.

Initially, genomic DNA from 118 white subjects with TS was extracted and genotyped using Illumina 610 Quad platform. Genotyping call rate and SD of log *R* values were used as quality control measures. The genotyping call rate in 4 subjects was less than 98% and these samples were excluded from further analysis.

The lowest call rate in the remaining 114 TS samples (84 male and 30 female) was 99.4%. It is well-known that raw log *R* data show significant sample-to-sample variability and hence the SD of log *R* values after *z*-normalization were primarily used for quality control purposes. Three additional samples were excluded based on SD of log *R* values. SD of log *R* values of the remaining 111 patients and 73 CEPH controls are shown in figure e-1 on the *Neurology*[®] Web site at www.neurology.org.

We downloaded the whole genome log *R* ratios of 73 white CEPH controls from Illumina. The CEPH samples were primarily used as controls in this study. These data were obtained from the same platform (610 Quad) used to analyze our patient samples. In addition, entries in the Database of Genomic Variants (containing 21,178 CNVs at 6,558 loci) were used as controls. The same quality control procedures were used for the TS-unaffected family members and 73 CEPH controls. The lowest call rate in these subjects was 99.1% and thus all these samples were included in the analysis. We also used a set of 128 ancestry informative markers to confirm the self-reported ethnicity in TS cases and controls.¹¹ In addition, we performed principal components analysis (PCA) on the entire set of SNP genotypes (figure e-3). The residual variance inflation factor (λ) was 1.16, suggesting some difference between cases and controls in sample source/batch/population stratification. The PCA analysis was used to correct for these differences (see Normalization).

Microarray experiment. Genotyping was performed and validated at the Yale University microarray center, which is a member of the NIH neuroscience microarray consortium. Illumina 610 Quad platform was used to perform the microarray experiments and raw hybridization intensity measurements and genotype calls were obtained for downstream processing.

Normalization. Illumina Beadstudio was used to obtain the log *R* ratio from raw hybridization intensities of the TS and control samples. The log *R* ratio of 111 patients with TS, 100 TS-unaffected family members, and 73 CEPH controls were *z*-normalized to account for both sample-to-sample and probe-to-probe variability (e-Methods and figures e-2 and e-10). Subsequently, SNP and Variation Suite (SVS; Golden Helix, Inc.) was used to perform a PCA of the *z*-normalized log *R* data to detect any residual batch/stratification effects (figures e-4 and e-9). Six principal components determined by elbow of scree plot (figures e-9 and e-11) and binary segmentation of eigenvalues accounted for residual batch/stratification effects and these effects were subsequently removed (e-Methods). Only the PCA-corrected data were used for identifying the CNVs reported in table 1.

CNV identification. PCA-corrected, *z*-normalized log *R* data were partitioned into copy number segments (CN segments) using the circular binary segmentation algorithm implemented by SVS. In order to isolate large and robust CNVs from the whole set of CN segments, 3 filtering criteria were used: 1) minimum number of markers in CNV ($M \geq 10$), 2) CN segment absolute mean *z*-score ($CN \geq 1$), and 3) $M \times CN > 40$. The purpose of these filtering criteria was to initially eliminate small ($M < 10$) and noisy ($CN < 1$) CNVs. The filtering criteria were specifically designed to identify only large and robust CNVs. The CNV analysis performed by HelixTree resulted in 112,457 CN segments across 184 subjects (111 patients with TS, 73 controls). This included CN segments that correspond to all copy numbers including the normal copy number of 2. A CNV was considered TS-specific if it was >10 kb, contained at least 10 probes, and was not found in controls or in the entries of the Database of Genomic Variants (containing 21,178 CNVs at 6,558 loci).

Table 1 The rare exon-affecting CNVs that are either de novo or recurrent in the TS population

Patient no.	Phenotype	Father	Mother	CNV no.	Chromosome	Start position	End position	No. of markers	Size	Type of CNV	Genes	Prior disease association
1	TS, no OCD, ADHD	Asymptomatic, CNV–	ND	1	2	50,845,531	51,105,641	74	260,110	Del	NRXN1	ASD, SCHZ, MR
2	TS, no OCD, no ADHD	ND	ND		2	50,912,249	51,145,937	59	233,688	Del	NRXN1	ASD, SCHZ, MR
3	TS, no OCD, no ADHD	ND	Asymptomatic, CNV–	2	3	152,997,280	153,028,731	19	31,451	Del	AADAC	None
4	TS, no OCD, ADHD	ND	ND		3	152,997,280	153,028,731	19	31,451	Del	AADAC	None
5	TS, no OCD, no ADHD	ND	Asymptomatic, CNV–		3	152,997,280	153,028,731	19	31,451	Del	AADAC	None
6	TS, no OCD, ADHD	Asymptomatic, CNV +	Asymptomatic, CNV–	3	10	67,990,005	68,167,990	74	177,985	Del	CTNNA3	ASD, SCHZ
7	TS, OCD, no ADHD	Asymptomatic, CNV–	Asymptomatic, CNV +		10	68,124,816	68,216,254	34	91,438	Del	CTNNA3	ASD, SCHZ
8	TS, no OCD, no ADHD	ND	Asymptomatic, CNV–	4	14	43,786,417	44,231,181	94	444,764	Del	FSCB	None
9	TS, no OCD, ADHD	ND	Asymptomatic, CNV–		14	43,786,417	44,231,181	94	444,764	Del	FSCB	None
10	TS, OCD, no ADHD	Asymptomatic, CNV–	Asymptomatic, CNV–	5	21	34,647,599	34,826,567	55	178,968	Dup	KCHE1, KCHE2, RCAN1	DS

Abbreviations: ADHD = attention-deficit hyperactivity disorder; ASD = autism spectrum disorder; CNV = copy number variant; DS = Down syndrome; ND = CNV status not determined; OCD = obsessive-compulsive disorder; MR = mental retardation; SCHZ = schizophrenia; TS = Tourette syndrome.

Furthermore, at least 20% of the CNV's total length had to be unique when compared to the controls. These criteria are similar to those in a recently published study of structural genomic variation in autism.¹² To identify recurrent CNVs, CNVs that were present in only 1 patient with TS (singletons) were removed. The log *R* values of the probes of each of these CNVs were subsequently visually displayed for robustness, rarity/absence in the normal population, and recurrence in TS population as a quality control procedure of the filtering process (figures e-5 through e-8).

RESULTS A total of 523 CNVs were identified from 184 subjects (111 subjects with TS and 73 CEPH controls). The mean CNV size was 234.42 ± 21.3 kb (mean $\pm$ SE). A total of 307 CNVs belonged to the TS group (*n* = 111) whereas 216 CNVs belonged to the control group (*n* = 73). TS and control groups did not differ with respect to the overall CNV burden (table 2). Out of the 307 CNVs in the TS group, 87 CNVs were identified as CN polymorphisms (present in at least 2 normal controls) on initial comparison with 73 normal controls and were removed from the analysis. Of the remaining 220 CNVs, 85 were recurrent CNVs and 135 were singletons. Similarly, the singleton CNVs were evaluated for their inheritance status. Only de novo singleton CNVs containing genes were considered as promising candidate CNVs of TS. One of the singletons was found to be a de novo duplication that contained voltage gated potassium channel genes (*KCNE2*, *KCNE1*) and regulator of calcineurin 1 (*RCAN1*) genes (CNV 5 in table 1). In most cases,

we could not ascertain whether these singleton CNVs were de novo because of lack of both parents' samples. The 85 recurrent CNVs corresponded to 34 unique genomic regions. A total of 24 out of these 34 CNVs either did not contain genes or were reported to be present in the Toronto database of genomic variants and thus were excluded from further evaluation. Out of the remaining 10 promising variants, 4 were found to affect only the introns and 6 affected exons. One of the 6 exonic CNVs affected an identical twin and the other affected a mother-son duo. Thus, while each of these 2 CNVs affected 2 individuals with TS and is perhaps significant from a pathogenic point of view, they were not considered as recurrent because they arose from a single mutation event. Thus, the remaining 4 CNVs were considered as recurrent CNVs (CNV 1–4 in table 1). All the promising CNVs were visually inspected to verify that the CNV is unambiguously identifiable from adjacent region (some of these CNVs are displayed in figures e-5 through e-8). As shown in table 1, there were 4 deletions. The 9 cases with recurrent exonic CNVs included 4 cases with TS only, 1 case with comorbid OCD, and 4 cases with comorbid ADHD, while the rest of the 102 cases included 39 cases with TS only, 23 cases with comorbid OCD, 11 cases with comorbid ADHD, and 29 cases with comorbid ADHD and OCD. Due to small sample size of cases with exonic CNVs, we cannot exclude the possibility that the distribution of TS-related phenotypes

Table 2 Rare CNV burden analysis by event type and size^a

CNV type and size (kb)	No. of CNVs in TS group (n = 111)	No. of CNVs in control group (n = 73)	TS patients/CEPH control ratio	p Value	No. of CNVs in unaffected family (n = 100)	TS patients/unaffected family member ratio	p Value
All							
<10	10	6	1.096		9	1.001	
10-100	138	89	1.02		103	1.207	
100-500	125	103	0.798		129	0.873	
>500	34	18	1.242		21	1.459	
All sizes	307	216	0.935	NS	262	1.056	NS
Deletions							
<10	10	6	1.096		7	1.287	
10-100	120	76	1.038		85	1.272	
100-500	72	71	0.667		87	0.746	
>500	10	8	0.822		9	1.001	
All sizes	212	161	0.866	NS	188	1.016	NS
Duplications							
<10	0	0	NA		2	0	
10-100	18	13	0.911		15	1.081	
100-500	53	32	1.089		46	1.038	
>500	24	10	1.578		13	1.663	
All sizes	95	55	1.136	NS	76	1.126	NS

Abbreviations: CEPH = Centre d'Etude du Polymorphisme Humain; CNV = copy number variant; NA = not available; NS = not significant; TS = Tourette syndrome.

^a The ratios represent the ratio of CNV frequencies normalized by the respective sample sizes of cases and controls.

among cases with exonic CNV and the rest of the cases are different. In order to ensure that the 10 positive cases harboring the 5 CNVs (recurrent or de novo) did not systematically differ from the remaining 101 cases due to ancestry, quality control, or other technical differences, a PCA analysis that included the 111 patients with TS was performed. Figure e-4b shows PCA primary eigenvalues of log *R* of 10 cases with recurrent or de novo CNVs and the rest of the cases.

Similar filtering of 216 CNVs from 73 controls revealed that 2 exonic CNVs were present in 2 controls (a total of 4 CNVs). A Fisher exact test to determine the probability of finding 9 recurrent CNVs out of 111 cases vs 4 out of 73 controls revealed no significant difference. Similarly, considering recurrent CNV at a specific locus, the Fisher exact test comparing 2/111 vs 0/73 also did not show any significant difference.

Candidate TS genes and recurrent loci from CNVs. A deletion of 5' exons of the neurexin 1 gene (*NRXN1*, CNV 1 in table 1, figure 1) was identified in 2 unrelated subjects (figure 1). Figure 1 also shows CNVs containing *NRXN1* gene, which has been reported in autism and schizophrenia. *NRXN1* CNVs identified in autism studies are labeled as ASD_Marshall,¹² ASD_AGP,¹³ and ASD_Glessner.¹⁴ The schizophrenia-

associated CNVs are labeled as SCHZ_Vrij¹⁵ and SCHZ_Kirov.¹⁶ The 2 CNVs identified in TS are labeled as TS_patient1 and TS_patient2. CNVs containing the *NRXN1* gene were not found in our controls, but nonexonic CNVs were found in controls in the Database of Genomic Variants.

A deletion containing 5' regions of microsomal arylacetamide deacetylase (*AADAC*) was present in 3 unrelated patients with TS (table 1, CNV 2). A deletion (CNV 3 in table 1) containing α -T catenin (*CTNNA3*) was recurrent in 2 patients.

A 450-Kb deletion containing the entire *FSCB* gene (fibrous sheath CABYR-binding protein) was found in 2 unrelated patients (CNV 4, table 1). A 180-Kb de novo duplication involving voltage-gated potassium channel genes (*KCNE1*, *KCNE2*) and a regulator of calcineurin 1 (*RCAN1*) genes in the Down syndrome critical region was identified in 1 patient (CNV 5, table 1).

Other potential singleton TS candidate CNVs. A 1q21 deletion (not shown in table 1 due to not being a recurrent event, figure 2) was present in identical twins who both had TS. A duplication involving *CTTNBP2*, *LSM8*, and *ANKRD7* genes (not shown in table 1 due to not being a recurrent event, figure 3) was found in a mother-son duo, both with TS.

Figure 1 Copy number variants (CNVs) containing *NRXN1* in autism, schizophrenia, and Tourette syndrome (TS)

NRXN1 CNVs identified in autism studies are labeled as ASD_Marshall, ASD_AGP, and ASD_Glessner. The schizophrenia-associated CNVs are labeled as SCHZ_Vrij and SCHZ_Kirov. The 2 CNVs identified with TS are labeled as TS_patient1 and TS_patient2. The RefSeq Genes track refers to the genes represented in NCBI RefSeq database and structural variation refers to the structural variants reported in different studies of normal control populations.

DISCUSSION We identified 5 exon-affecting rare CNVs that are either de novo (CNV 5 in table 1) or recurrent (CNV 1–4 in table 1) in the TS population in 10 out of 111 patients with TS. We found that genes/loci in 3 out of the 5 CNVs have been implicated by other studies in closely related neurodevelopmental disorders, notably in schizophrenia, autism, and ADHD. In addition, while not recurrent, a large 1q21 deletion in a pair of identical twins (both with TS) was reported previously in association with autism, schizophrenia, and mental retardation.

We identified several CNVs containing genes that are highly expressed in brain and play a prominent role in cell–cell interaction and synaptic connectivity and function. Several of these genes encode cell adhesion molecules (*NRXN1*, *CTTNBP2*, and *CTNNA3*). *NRXN1* belongs to the neurexin family of proteins. In humans, alterations in genes encoding neurexins or neuroligins have recently been implicated in autism, schizophrenia, and other neurodevelopmental diseases, linking synaptic cell adhesion to cognition and its disorders.^{10,17} Familial deletion within the X-linked neuroligin 4 (*NLGN4*) gene has been associated with autism and TS with affected individuals represented by an autistic boy with a motor tic, his brother with TS and ADHD, and their carrier mother with learning disorder,

anxiety, and depression.¹⁸ A common genetic basis for autism and schizophrenia has been noted previously.^{19–21} Rare recurrent exonic CNVs affecting *NRXN1*, *NLGN3*, *NLGN4*, and *CNTNAP2* have been previously implicated in autism, schizophrenia, and ADHD.^{9,10} Many patients with TS have ADHD as a comorbid condition. The same genes involved in different neurodevelopmental disorders suggests that additional modifying factors play an important role in determining whether a given subject develops TS, autism spectrum disorder, or schizophrenia. However, we have not used any formal diagnostic instrument in all cases to evaluate for comorbid conditions such as autism, ADHD, and schizophrenia. Hence, we cannot differentiate between true pleiotropy and a missed comorbidity.

There are some limitations to the present study. No significant difference in rare CNV burden was found between cases and controls. The rare CNV burden could be potentially used to assess germline chromosome instability. However, the small sample size did not allow us to infer about the importance of germline chromosome instability in this group.

This study also showed that there were 2 exonic CNVs that were present in 2 or more controls but in none of the cases. These included genes *LIN28B*, *BVES*, *SRPK2*, and *PUS7* that have never been im-

Figure 2 1q21 Copy number variants (CNVs) in autism, schizophrenia, and Tourette syndrome (TS)

CNVs identified in autism study are labeled as ASD.ACRD whereas the schizophrenia-associated CNVs are labeled as SCHZ.ISC and SCHZ.EUR. The 2 CNVs identified with TS are labeled as TS_patient1 and TS_patient2. The RefSeq Genes track refers to the genes represented in NCBI RefSeq database and structural variation refers to the structural variants reported in different studies of normal control populations.

plicated in any neurodevelopmental disorders and may represent some rare nondisease phenotypes unique to these individuals. In addition, asymptomatic parents of 2 patients with TS (patients 6 and 7 in table 1) harbored the CNV. This may perhaps be due to reduced penetrance of the CNV.

As seen in figure e-4, there were batch/population stratification effects in our raw data. We checked 6 principal components determined based on elbow of scree plot (figure e-9) and binary segmentation of

eigenvalues and corrected for these components that account for batch and population stratification effects. Only the PCA-corrected data were used for identifying the CNVs reported in table 1 and hence these are unlikely to be due to batch/stratification effects.

A Fisher exact test to determine the probability of finding 9 instances of recurrent CNVs out of 111 cases vs 4 instances of recurrent CNVs out of 73 controls revealed no significant difference. Consider-

Figure 3 7q31 Copy number variants (CNVs) in Tourette syndrome (TS)

CNV (TS.IMMP2L) containing IMMP2L that was identified in a previous study lies 7 Mb proximal to the 2 CNVs identified in the present study (TS.patient1, TS.patient2). The CNV identified in the present study contains CTTNBP2 in a mother-son duo, both of whom have TS. The RefSeq Genes track refers to the genes represented in NCBI RefSeq database and structural variation refers to the structural variants reported in different studies of normal control populations.

ing recurrent CNV at a specific locus, the Fisher exact test comparing 2/111 vs 0/73 also did not show any significant difference. This is perhaps due to the smaller sample size of the study. Future studies with larger sample size will further clarify the role of identified CNVs in the pathogenesis of TS.

ACKNOWLEDGMENT

The authors thank Rosalie and Bruce Rosen for supporting these studies and the NIH Neuroscience Microarray Consortium/Yale Neuroscience Microarray Center for performing the microarray experiments.

DISCLOSURE

Dr. Sundaram receives research support from the NIH (NICHD 1R01HD059817-01A1 [PI]). Dr. Huq serves as an Associate Editor of *MedLink Neurology* and receives research support from the NIH (NICHD 1R01HD059817-01A1 [Co-I]) and from Festival of Trees. B.J. Wilson reports no disclosures. Dr. Chugani serves on the editorial boards of *Journal of Child Neurology*, *Journal of Pediatric Neurology*, *Brain and Development*, and *Pediatric Neurology*, and receives research support from the NIH (NINDS R01 NS 34488 [PI] and NICHD R01HD059817-01A1[Co-I]).

Received July 22, 2009. Accepted in final form February 3, 2010.

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