Case Report

Tourette Syndrome and Klippel-Feil Anomaly in a Child with Chromosome 22q11 Duplication

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Received 14 July 2009; Accepted 26 October 2009

1. Introduction

Klippel-Feil Syndrome (KFS) involves a congenital fusion of vertebrae in the cervical spine [1]. Tourette Syndrome (TS) is a heritable neuropsychiatric disorder characterized by persistent, childhood-onset tics that fluctuate in intensity, migrate in anatomic location, and are performed in response to sensory urges [2]. Motor stereotypies usually have younger onset, are much more stable phenomenologically, and occur involuntarily with excitement or other stimulation [3]. Longstanding clinical observations that high doses of amphetamines can induce stereotypies and tics [4], while dopamine receptor blocking agents inhibit them [5], support a hyperdopaminergic neurotransmission or receptor hypersensitivity model for these symptoms, although the dopamine/tic relationship is likely much more complex [6].

Large genetic association and linkage studies to date have failed to implicate genes for dopamine synthesis or metabolism as causes of TS, but clinical presentations of rare genetic diseases involving dopamine pathways are supportive, as in a recently reported case of TS in a girl with chromosome 22q11 deletion [7]. This region contains Catechol-O-Methyltransferase (COMT), which degrades dopamine, norepinephrine, and epinephrine. Low-COMT gene copy number has been associated with obsessive compulsive and hyperactive psychopathology in velocardiofacial syndrome [8], and lesser-COMT activity theoretically could increase catecholamines and hyperkinetic movements.

We report clinical and genetic characterization of the first case of 22q11DupS and TS, KFS, and stereotypies, suggesting that both low and high copy numbers of 22q11 may generate hyperkinetic and obsessive compulsive symptoms.

2. Case Presentation

The patient, a Caucasian male diagnosed with KFS, was referred at age of 9 years for evaluation of repetitive movements. He presented with motor stereotypy in the 1st year of life which persists to the present: a patterned movement involving the flapping of both hands, and sometimes body stiffening are occurring daily, with excitement. From age 6 to his present age, 12 years, he has had a series of mild tics including eye blinking, nose twitching, leg and toe pointing, and repetitive coughing and sniffing, consistent with a diagnosis of TS. He also has obsessive compulsive behaviour (OCB) and anxiety, with excessive rumination,
but no Attention Deficit Hyperactivity Disorder (ADHD).
He has seen a psychologist for dysthyemia and adjustment but
takes no neurologic or psychiatric medications. At school,
academic performance is average to above. Past Medical
History includes full-term birth, at 3.1 kg. Development
includes walking by 16 months and speaking normally by
2 years. Surgical history includes a Woodward Procedure
for Sprengel's Deformity of the scapula and Cervical Spine
Decompression and Stabilization. Review of systems includes
parasomnias and migraines. Family history is negative for
tics, OCB, or other neurologic or psychiatric disorders.

General examination revealed a barrel-chested appear-
ance, a short neck with low posterior hairline, abnormal
scapulae, and webbing of toes. At age of 12 years, weight
was 36.6 kg (75%ile), height was 126.4 cm (<5%ile),
body mass index was 34 (>95%ile), and head circumference
was 50.5 cm. Palate and cardiac exams were normal. Neurolog-
ics exam was notable for normal language and gregarious
social interactions. Occasional tics and the stereotypy were
observed. Cranial nerve exam was normal. Distal strength
was diminished in both hands and thumb abductors. Reflexes
were 2+ and symmetric. Fine movements of the hands were clumsy and slow. Sensation was diminished to
light touch in the hands. Current clinical ratings showed Yale
Global Tic Severity Scale (YGTSS) total tic score of 6 (mild),
Child Yale-Brown Obsessive Compulsive Scale (CY-BOCS)
score of 16 (mild/moderate), and the DuPaul ADHD Rating
Scale (ADHDRS) score of 17 (subthreshold).

Imaging studies include CT scans that revealed fusion
of cervical and thoracic vertebrae (Figure 1), scoliosis,
hypoplastinc thumbs, and several digits of the feet and hands.

Due to the complex phenotype, we evaluated the patient's
DNA using comparative genomic hybridization (CGH)
analysis (BeadChip technology with a Single Nucleotide
Polymorphism based array; Illumina HD Human610-quad
BeadChip platform). This revealed a ~3 Mb hemizygous
microduplication of chromosome 22q11.2, the same region
as the classical 22q11 microdeletion syndrome [9], as well
as the 22q11.2 duplication with a less well-characterized
phenotype [10]. This region contains genes coding for
approximately 20 proteins expressed in brain and/or bone.

Followup negative testing of the parents demonstrated
that this duplication was de novo.

To further characterize this boy's COMT genotype,
we generated a lymphocyte cell line. DNA nucleotide
sequence analysis indicated that the patient was heterozy-
gous for the G675A COMT haplotype (Figure 2(a)i) and
that the chromatogram peak height for the 675G variant
was consistently two times higher than that of the 675A
variant (Figure 2(a)ii). This suggests that the 675G (higher-
expressing) allele [11] was duplicated. We then compared
mRNA/cDNA sequence for the patient and a normal indi-
vidual. The G:A ratio for the normal control heterozygote
was slightly >1 (Figure 2(a)iii) consistent with the instability
of the 675G mRNA transcript [11]. In contrast, the G:A ratio
for the patient was >2 (Figure 2(a)ii) which again suggested
that the patient has a higher than normal level of expression
of the COMT gene.

To directly compare COMT gene expression levels,
we optimized a proven two-step, high-temperature, semi-
quantitative RTPCR protocol (denature at 94°C for 30
seconds followed by extension at 71°C for 40 seconds
for 33 cycles) [12] using primers specific for either
the 675G or 675A: the forward 675G primer (COMT-
ValF 5'-ATGTGGATTTCCGCTGGCTG-3') and the 675A
primer (COMT-MetF 5'-ATGGTGGATTTCGCTGGCA
T-3') were specific for sequence from exon 4 and the reverse
primer (COMT-R 5'-CTTCGCCAGCAGGCGCAT
3') for sequence from exon 5. Only the patient (Figure 2(b), lane
2) expressed the 675A allele and both the patient and two
normal controls (lanes 3 and 4) appeared to have comparable
levels of expression of the 675G allele, as evident from the
equivalent intensity of amplicons.

To assess possible clinical implications of this finding,
cerebrospinal fluid was obtained via lumbar puncture for
assessment of neurotransmitter levels. Routine cells (1 white,
1 red blood cell), protein, and glucose were normal. Levels
of CSF neurotransmitter metabolites were obtained through
HPLC testing commercially (Medical Neurogenetics, Atlanta,
Georgia). The level of 3-O-methyldopa, a metabolite of L
DOPA via COMT, was normal at 19 nmol/L (normal <100).
The level of Homovanillic acid, a final common pathway
metabolite of dopamine and norepinephrine via COMT, was
normal at 279 nmol/L (167–563).

3. Discussion

We describe a boy with KFS, TS, stereotypy, and ob ses-
se compulsive symptoms in association with de novo
22q11DupS with normal parental genotype and phenotype.
This is the first report of TS associated with 22q11DupS. The
incidence of TS in the general population is sufficiently high
that this association could be incidental. However, a 22q11.2
deletion has been reported in association with tics and TS [7], and as neither parent had a personal or family history of these neuropsychiatric symptoms, our results suggest that the 22q11DupS may confer risk for the TS phenotype.

Hemizygous microdeletion at 22q11.2 (22q11DS) is the most common microdeletion syndrome, usually involving homologous recombination of the same ∼3 Mb region duplicated in our patient [13]. Within the 22q11.2 duplication region, candidate genes implicated in central nervous system structure or function include CLTCL1, RTN4R, SNAP29, PRODH, GSCL, UFDIL, ES2, and COMT. The COMT gene (MIM no. 116790) has particular interest because of its role in monoamine degradation and because a common 675G>A (Val158Met) substitution results in the dysregulation of the dopaminergic system. The 675A allele of the COMT haplotype codes for the 158Met variant of this membrane-bound enzyme that is expressed at lower levels in the brain compared to the alternate 158Val variant [14]. A recent investigation of 126 normal healthy Caucasian subjects indicated the COMT low-expression/low-activity A allele forms part of a more expansive COMT gene haplotype “G-A-A” that appears to associate with inefficient prefrontal working-memory response [15]. This same COMT haplotype (G-A-A) also appears to be more prevalent in 22q11DS patients with OCD and ADHD [16].

Both low copy number in 22q11DS and reduced COMT expression due to the presence of a COMT 675A allele [14] have been associated with neuropsychiatric symptoms, including anxiety and Obsessive Compulsive Symptoms [17, 18]. Cerebrospinal fluid neurotransmitter and metabolite levels were not altered in our patient. Although this finding might have had treatment implications, it was not surprising. A recent report showed no alterations in these studies in psychiatric patients with COMT gene polymorphisms [19]. Another study found CSF dopamine changes in Restless Legs Syndrome, but mainly in the presence of more severe symptoms [20]; our patient has milder motor tic symptoms. Finally, it is worth pointing out that studies have questioned...
the role for low COMT activity in psychiatric disorders [21, 22]. Our patient was heterozygous for the G675A COMT haplotype with duplication or the 675G<sup>+</sup>, higher-expressing fusion in association with duplication or deletion at 22q11.2. Our patient calls into question a unique role of low COMT activity in the etiopathogenesis of OCD or TS.

Outside the brain, the 22q11DS and 22q11DupS manifest considerable phenotypic overlap, including congenital heart defects, palatal defects and abnormal facies, micrognathia, short stature, dysplastic ears and hearing defects, downsloping palpebral fissures, urogenital anomalies, absent thymus, T cell deficiency, anomalies of the hands and feet, and scoliosis, suggesting diverse effects of both low and high copy numbers [23]. Mouse studies indicate that many of the physical anomalies associated with copy number variation at 22q11.2 are attributable to Tbx1 dosage [24]. Mutations in the GDF6 gene, which is expressed in the developing intervertebral space, are causative for the KF2 class of KFS [25]. Tbx1 is likewise expressed in the developing intervertebral space [25, 26]. The 22q11DS has shown prior association with synostosis in the appendages, scoliosis, and vertebral irregularities [9]; however, this is the first report of vertebral fusion in association with duplication or deletion at 22q11.2. We propose Tbx1 as a candidate gene for broad spectrum KFS where it presents in association with Sprengle’s shoulder, heart, and palatal and/or urogenital anomalies.

4. Conclusion

This study is the first to report an association between TS and 22q11DupS, thereby broadening the link between copy number variation at 22q11.2 and the development of TS and comorbid neurobehavioral disorders including OCD. Further research should delineate the basis for linkage between one or more genes within or near the 22q11.2 ~3 Mb critical recombination region and neuropsychiatric disorders.

Acknowledgments

Data in this case report were presented in part at the 5th International Scientific Symposium on Tourette Syndrome, New York City, New York, USA, June 12-13, 2009. Research support was provided by an Australian Research Council linkage Grant and by National Institute of Neurological Disorders and Stroke R01 NS056276. We gratefully acknowledge this boy and his family for reviewing the manuscript and Matthew W. State, M.D., Ph.D. from the Yale Child Study Center for valuable input.

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