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CASE REPORT

Autism spectrum disorder with microdeletion 10q26 by subtelomere FISH

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Abstract: An 11-year-old female with early feeding problems, mild motor delays, normal speech, subtle facial changes, social difficulties, anxiety and a diagnosis of Asperger disorder was found to have deletion of 10q26.3 by subtelomere fluorescent in situ hybridization (stF) analysis. Our patient and others with 10q26 aneuploidy add this region to 11 other autism susceptibility loci qualified by converging genome linkage/association, high resolution chromosome, and mutation studies in our review. We summarize these loci and the current spectrum of terminal 10q deletion cases.

Keywords: autism disorder, Asperger disorder, subtelomere FISH, microarray analysis, 10q26 deletion, gene changes in autism

Introduction

The introduction of high resolution chromosome studies has greatly increased the yield of positive findings in children with intellectual disability (ID), from 3% for routine chromosome analysis to 5%–6% for subtelomere FISH (stF) and 12%–20% for comparative genomic hybridization-microarray analysis (aCGH).[1,2] These submicroscopic aneuploidies have greatly enlarged the repertoire of genetic anomalies in children with normal cognitive function and minimal dysmorphology including those with high-functioning autism.[3–5] The many copy number variants (CNVs) now correlated with autism corroborate its multifactorial determination suggested by familial risks of 60%–90% for monozygotic twins, 0%–10% for dizygotic twins, and 2%–8% for siblings.[6,7] Genetic linkage, chromosome aberration, and family mutation studies are converging to highlight significant autism loci and their candidate genes, promoting consideration of genetic screening that could recognize autism susceptibility when therapy can be most effective.[8–10] Here we describe a girl with high functioning autism and 10q26.3 de novo deletion by stF who, with similar patients, adds another key locus to the genomics of autism.

Case report

The patient had a birth weight of 6.13 lb after a 35-week uncomplicated gestation to a 27-year-old mother and 36-year-old father. Family history indicated that she was the first child and that there were no relatives with ID or autism. She remained in the nursery only two days but had poor breast feeding and jaundice requiring early monitoring and eventual switch to bottle feeding. She required surgeries for strabismus at ages 8 and 15 months, plus surgery for adenoids and myringotomy tubes at age

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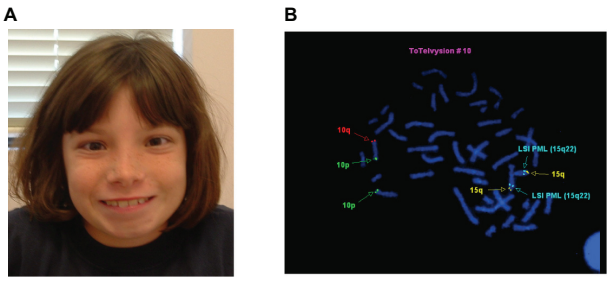

Figure 1 A) Frontal view of the patient; **B**) Portion of stF analysis showing 10q26.3 deletion.

26 months. Her motor development was on the upper side of normal with walking at 18 months, but her speech progressed normally and she was not accepted by early intervention programs. Her parents arranged private occupational therapy because of clumsiness; she had mild sensory symptoms with sensitivity to loud noises and certain food textures but her eye contact, pointing to objects, and imaginative play were normal. Problems with socialization appeared in kindergarten when the patient kept to herself or manifested outbursts or tantrums when challenged by other students. She was evaluated by neurologic specialists because of learning difficulties, diagnosed with attention deficit disorder, and given methylphenidate leading to an improvement in her school work. Her parents noted prosody with rigid responses and anxiety in social situations, refusing to attend parties or school functions; she has always interacted better with adults than children her own age. Habits include pulling out her eyebrows or biting her nails, and she can watch television or draw in her room for hours. She has made average grades in school and is in regular classes at the appropriate grade level. School and neuropsychology evaluations have documented average intelligence (IQ 95-100) with anxiety symptoms and a diagnosis of Asperger disorder based on her social anxieties, language peculiarities (prosody), and restricted interests. Review of systems including sleep, digestive, or muscle problems was unremarkable.

On physical examination, the patient had a height of 49 1/2 inches, weight of 55 1/2 lbs, and head circumference of 19 1/2 inches (all at third percentile for age). Her craniofacial morphology was grossly normal (Figure 1A) with mild hypertelorism (interpupillary distance of 6 cm) and a high palate. Her somewhat narrow eyes and long nose are reminiscent of Shprintzen/del(22q) syndrome. She had two café-au-lait spots of about 3 cm in diameter on her left back and thigh. Her muscle mass and strength was normal but she exhibited immature coordination for age as shown by mirror movements, finger-to-nose tracking, and tandem walking. She made eye contact but had little interaction with the examiner and exhibited anxiety when undergoing measurements or

Table 1 Chromosome 10q aberrations with autistic behaviors

Chromosome region	Aberration/inheritance	Clinical findings
10q25–10qter	Del(10)(q25/q26–10qter)-Cr[11]	>30 cases: ID, MCA (neural, cardiac, urogenital defects),
	De novo or from translocation parent	ADHD (~80%), autism (~10%)
10q11.23–q21.2	Dup(10)(q11.23–q21.2)-aCGH[6]	1 patient with autism
10q23.2–q23.32	Del(10)(q23.2q23.32)-Cr/aCGH[12]	8 patients, three families: Mild ID, ADHD, autism, possible
	(all but one familial)	psychiatric disease, one with BRRS
10q25–10qter	Del(10)(q25/q26–10qter)-Cr[11]	>30 cases: ID, MCA (neural, cardiac, urogenital defects),
	De novo or from translocation parent	ADHD (~80%), autism (~10%)
10q26 (del)	Del(10)(q26)-stF (de novo)	Present case: ID, Asperger, ADHD
	Del(10)(q26)-stF[13] (1/3 studied from parent)	8 patients: ID, MCA (cardiac defects), short stature, precocious puberty, hearing loss, 1 with autism
	Dim(10)(q26)-stF[13] (7/8 studied were from parent)	14 patients: ID, MCA (microcephaly, hydrocephaly, polymicrogyria, hypospadias), 1 with autism
	Del(10)(q26)-stF[15]	1 patient: ID
	Del(10)(q26)-stF[16]	1 patient: ID, MCA/DYS, ataxia
	Del(10)(q26)-stF[18]	1 patient: mild ID, dysmorphology, hearing loss
	t(10;11)der(11)del(10)(q26)-stF[19]	1 patient: ID, MCA/DYS, aplastic anemia, thrombocytopenia
	Del(10)(q26.2/.3)-aCGH[14]	3 patients: 2 with ID, 1 with autism
	Del(10)(q26.2/.3)-aCGH[17]	2 patients: ID
	t(10;11)der(11)del(10)(q26)-aCGH[20]	1 patient: ID and autism
10q26 (dup)	Dup(10q26)-aCGH[1]	2 patients: ID
	Dup(10q26)-aCGH[19]	2 patients with ID, autism

Abbreviations: Del, deletion (absent fluorescent signal); Dim, partial deletion (diminished signal); Cr-routine chromosome analysis; stF, subtelomere FISH analysis; aCGH, CGH microarray analysis; ID-mental retardation/developmental delays/intellectual disability; DYS-dysmorphic appearance and/or birth defects; BRRS, Bannayan-Riley-Ruvalcaba syndrome (153480-25).

Table 2 Summary of loci implicated in autism through stFISH/aCGH and gene association/mutation

Locus	Implicated genes grouped by potential mechanism					
	Pattern formation	**Synapse-channels**	**Synapse-metabotropic**	**Synapse-adhesion**	**Immune**	**Unknown-other**
1q21.1+/–						
1q42.2–						
2q21q24–/–		*SCN1A (m)*				
2q35–, q37–	*PAX3*					*CENTG2 (m)*
3p26–, –/–				*CNTN3 (m)*		*OXTR (m)*
3q24–		*NHE9/SLC9A9*				
7q11+/–		*KIAA0442*				
7q31–	*MET (m)*		*CADPS2 (m)*			*FOXP2*
10q11–			*REEP3*			*TRIP8*
10q23–	*PTEN (m)*					
10q26–	*PTPRE, EMX2*		*GPR2*			
11p13–						*SCT (m)*
13q14–				*NBEA*		
15q11+/–						*APBA2*
15q13.3+/–			*CHRNA7*			
16p13+/–						*MBD3*
16p11+/–			*PRKCB1*			
22q11–						
22q13–				*SHANK3 (m)*		*ADSL (m)*
Xp22–				*NLGN4 (m)*	*IL1IRAPL1 (m)*	*VCX (m)*
Xq28+/–						*FMR2 MECP2*

Notes: Loci deleted (–, –/– homozygous) or duplicated (+) in >5 patients with autism spectrum disorders using subtelomere FISH (stFISH) or comparative genomic hybridization-microarray analysis (aCGH). Genes within deletion intervals that have been implicated in association, expression, or mutation (m) studies of autistic patients are listed beside each locus in columns corresponding to their potential mechanism. Listed loci do not include those for characterized disorders like Rett or Fragile X syndromes (the listed MECP2 mutation was in a patient with autism, not Rett syndrome).

Gene abbreviations and descriptions are from Online Mendelian Inheritance in Man®. McKusick numbers are listed as references to disorders and genes – go to the database and search on the listed number.[24]

Abbreviations: UK, unknown; ADSL, adenylosuccinate lyase (608222); APBA2, amyloid beta A4 precursor protein-binding, family A (602712); CADPS2, calcium-dependent activator protein for secretion 2 (609978); CENTG2, centaurin, gamma-2 (608651); CHRNA7, cholinergic receptor neuronal nicotinic alpha polypeptide 7 (118511); CNTN3, contactin 3 (601325); EMX2, empty spiracles, Drosophila, 2 homolog homeotic gene (600035); FMR2, fragile site, folic acid type, rare, FRAXE (300806); FOXP2, forkhead box P2 (605317); GPR26, G protein-coupled receptor 26 (608847); IL1RAPL1, interleukin 1 receptor accessory protein-like calcium-related; KIAA0442, Kazusa DNA Institute brain cDNA clone 0442 (607270); MBD3, methyl-CpG-binding domain protein (603573); MET, MET protooncogene (164860); MECP2, methyl-CpG-binding protein 2 (30005); NHE9/SLC9A9 sodium/hydrogen exchanger 9/solute carrier family 9 (608396); NLGN4, neuroligin 4 (300427); NBEA, neurobeachin fragile site 13 A (604889); OXTR, oxytocin receptor (167055); PRKCB1, protein kinase C beta-1 (176970); PTPRE, protein tyrosine phosphatase (600926); PAX3, paired box gene 3 (606597); REEP3, receptor expression-enhancing protein 3; *SCN1A*, sodium channel neuronal type I alpha subunit (182389); SHANK3, SH3 and multiple ankyrin repeat domains 3 (606230); TRIP 8, JMJD1C, thyroid hormone receptor interactor 8, jumonji domain-containing protein 1 (604503); VCX, variably charged, X chromosome (300229); VCX2 (300532); VCX3A (300533).

changing rooms. FISH analysis was performed on the case as well as her parents according to the manufacturer's specifications (Vysis, Inc.; Downers Grove, IL). The patient had a normal karyotype with absence of signal on one chromosome 10 homolog by stF (Figure 1B); parental karyotypes were normal with signals at band 10q26.3 evident on both chromosomes 10.

Discussion

The presence of deletion 10q26.3 in our patient but not in her parents correlates with other studies linking that chromosome region with mental disability and autistic behaviors as shown in Table 1. The phenotypic effects of terminal 10q deletion become more specific as the amount of missing material becomes less: those with larger deleted regions spanning bands q24/q26 to the terminus have a variable but convergent pattern of mental retardation, autistic behavior, growth failure, and diverse anomalies of the craniofacial, cardiac, digestive, skeletal, and urogenital systems (Table 1).[11–21] Patients with small or submicroscopic 10q deletions associate three chromosome regions with minimal dysmorphology, mild intellectual disability (ID), and autism – 10q11.21–q21.2,[6] 10q23.2/23.32[12] and 10q26,[1,13–20] see Table 1. Our patient brings the total of 10q26 microdeletion/microduplication patients with mental disability to 33 with 6 described as autistic.

The purported increase in prevalence of autism spectrum disorders, recently cited as 1 in 100 children from a 2008 study,[21] has drawn attention to environmental exposures including vaccines or their preservatives.[6,7] While no

environmental agent has satisfied evidential criteria, new technologies for chromosome analysis (stF, aCGH) have supplemented prior studies associating numerous genes and gene regions with autism.[1–7] The expanding repertoire of genetic change confirms a view of autism as a multifactorial disorder analogous to diabetes mellitus, with the associated genes acting to enhance susceptibility.[6,7]

Genetic testing can document perinatal autism susceptibility and lead to early objective diagnosis by eye-tracking or imaging technologies that are being developed.[8–10] In consonance with these goals, and with the expectation that conditions with autism and minimal cognitive disability will be most helpful in defining the neurogenetic basis of autism, we have described a girl with normal IQ and classic features of Asperger disorder that included clumsiness, impaired social interactions, attention deficit disorder, obsessive-compulsive symptoms, and unusual focus on activities like drawing. Her early subtle symptoms – mild facial alterations, feeding problems, sensory alterations, motor delays, poor reciprocal communication – did not draw attention or qualify her for therapy until social anxieties and school problems became manifest in kindergarten. Earlier forecast of autism susceptibility through genetic testing and consequent therapies would possibly have ameliorated her later difficulties.

Our patient and others with 10q26 deletions add another autism-susceptibility region to those we list as well-characterized in Table 2. Genome-wide linkage, association, or homozygosity mapping studies implicate chromosomes 1–7, 8–11, 13, 15, 16–17, 19, 22, and X with stF and aCGH refining specific autism-related regions: 2q32–34, 4q28–33, 7q22–36, 15q11–13.3, 16p11–13, 22q11–13, Xp11–22, Xq13 and Xq28.[1–7] Plausible candidate genes affecting neurogenesis and pattern formation;[22] synaptic channels, neurotransmitter paths, or adhesion;[23] and miscellaneous functions (immunity, oxytocin) are present in these regions with several elected by gene mutation (Table 2, right columns). Similar candidates in the 10q26 region include protein tyrosine phosphatase (*PTPRE*-600926[24]), transforming acidic, coiled-coil containing protein 2 (*TACC2*-605302) neighboring the fibroblast growth factor receptor type 2 (*FGFR2*-176943), a G protein-coupled receptor 26 (*GPR26*-608847); and the empty spiracles, Drosophila, 2 homolog homeotic gene (*EMX2*-600035) – all are expressed in brain and the latter gene was mutated in a form of schizencephaly.[25] Multifactorial determination predicts interaction among genes on 10q with others summarized in Table 2, many involved in signal transduction pathways that coordinate neurogenesis and synaptic function.

Disclosure

The authors report no conflicts of interest in this work.

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