

CASE REPORT

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Adult expression of a 3q13.31 microdeletion

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Abstract

Background: The emerging 3q13.31 microdeletion syndrome appears to encompass diverse neurodevelopmental conditions. However, the 3q13.31 deletion is rare and few adult cases have yet been reported. We examined a cohort with schizophrenia (n = 459) and adult control subjects (n = 26,826) using high-resolution microarray technology for deletions and duplications at the 3q13.31 locus.

Results: We report on the extended adult phenotype associated with a 3q13.31 microdeletion in a 41-year-old male proband with schizophrenia and a nonverbal learning disability. He was noted to have a speech impairment, delayed motor skills, and other features consistent with the 3q13.31 microdeletion syndrome. The 2.06 Mb deletion overlapped two microRNAs and seven RefSeq genes, including *GAP43*, *LSAMP*, *DRD3*, and *ZBTB20*. No overlapping 3q13.31 deletions or duplications were identified in control subjects.

Conclusions: Later-onset conditions like schizophrenia are increasingly associated with rare copy number variations and associated genomic disorders like the 3q13.31 microdeletion syndrome. Detailed phenotype information across the lifespan facilitates genotype-phenotype correlations, accurate genetic counselling, and anticipatory care.

Keywords: 3q13 deletion, Schizophrenia, Copy number variation, Genotype-phenotype correlation, Genetic counselling, Genomic disorder, Nonverbal learning disability

Background

Preliminary evidence suggests that individuals with microdeletions at chromosome 3q13.31 (OMIM #615433) may be predisposed to a broad spectrum of neurodevelopmental/neuropsychiatric conditions including global developmental delay/intellectual disability (DD/ID), speech delay, autism spectrum disorder (ASD), and attention deficit hyperactivity disorder (ADHD) [1-5]. Inconsistent molecular and cytogenetic techniques as well as variable genomic breakpoints have made pinpointing the responsible gene(s) within the 3q13.31 region challenging. In a large case series, Molin et al. defined a 580 kb shortest region of overlap (SRO) that includes five RefSeq genes: *DRD3*, *ZNF80*, *TIGIT*, *MIR568*, and *ZBTB20* [1]. Those authors proposed that haploinsufficiency of *DRD3* (OMIM #126451), which codes for the D3 subunit of the dopamine receptor, and *ZBTB20* (OMIM #606025), a DNA transcription repressor expressed in hippocampal neurons, may contribute to the

neurodevelopmental features of the 3q13.31 microdeletion syndrome [1,6]. Recently, a 1.3 Mb deletion at 3q13.31 downstream of this proposed SRO and encompassing just two genes (*LSAMP*, *GAP43*) was identified in a 7-year-old female with ADHD, hypotonia, and postnatal growth above the mean [3]. *LSAMP* (OMIM #603241) encodes a limbic system-associated membrane protein (LAMP) and has been shown to regulate anxiety-like phenotypes in mice [7]. *GAP43* (OMIM #162060) is almost exclusively expressed in neuronal tissue and is a candidate gene for ASD [8].

Later-onset conditions, including neurodevelopmental diseases like schizophrenia, may also be associated with rare copy number variations (CNVs) [9]. To date, few adult cases with 3q13.31 deletions have been described in the literature, highlighting the paucity of phenotypic data across the lifespan needed to inform genetic counselling and anticipatory care. Here we provide a description of the extended adult phenotype associated with a 3q13.31 microdeletion [9] that encompasses all four of the previously proposed neurodevelopmental candidate genes at this locus: *DRD3*, *ZBTB20*, *LSAMP*, and *GAP43*.

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Case presentation

Clinical description

The male proband (Figure 1) was conceived naturally to non-consanguineous parents of European ancestry, a 29-year-old mother and 36-year-old father. There was no known family history of major developmental or neuropsychiatric conditions. The pregnancy and term delivery were unremarkable; birth weight was 3,941 g (75th-90th percentile). There was no evidence of hypotonia. The patient was noted to have delayed motor developmental milestones and "clumsiness" prior to age 3 years, when he was hospitalized for suspected viral meningoencephalitis with decreased level of consciousness and dystonic movements. A speech impairment and enuresis was noted thereafter and persisted into adulthood. At age 9 years, fine motor and perceptual motor skills were noted to be under-developed. A head CT (computed tomography) scan at age 15 years showed focal hypoplasia of the superior cerebellar vermis; a repeat CT scan at age 33 years was read as normal.

He was enrolled in a special education program beginning at age 7 years, with particular difficulties noted in mathematics and writing. At age 33 years, clinical neuropsychological testing revealed a full-scale IQ in the borderline range. Research-based testing at age 39 years using the WASI (Wechsler Abbreviated Scale of Intelligence) demonstrated a full-scale IQ of 75, with a marked difference between verbal (90) and performance (62) scores consistent with a nonverbal learning disability.

The patient developed schizophrenia and was first treated with standard antipsychotic medications at age

24 years. Overall, he has had an unremarkable course of illness (details available upon request); of note, aggressive behaviour at age 28 years prompted a change in his medication regimen. His past medical history also includes type 2 diabetes mellitus treated with insulin and hypercholesterolemia diagnosed in his 20's, mild hypocalcemia first identified at age 31 years, bilateral L5-S1 disc protrusion requiring surgery at 34 years, and hypertension diagnosed at age 34 years. At time of last contact, he was 41 years old and living in a supported situation in the community.

Molecular studies

The patient was recruited into a longitudinal study of the genetics of schizophrenia [9] at age 31 years. Research chromosomal microarray analysis using the Affymetrix® Genome-Wide Human SNP Array 6.0 ultimately demonstrated a deletion at cytoband 3q13.31 (chr3:115,308,450–117,370,859, hg18) [9], which was clinically confirmed at a CLIA (Clinical Laboratory Improvement Amendments) approved laboratory and reported back to the patient. All stringent genome-wide CNV calls in this individual are included in Additional file 1: Table S1 with only the 3q13.31 deletion predicted to be pathogenic [10]. As is common with adult-onset disorders like schizophrenia, both parents were unavailable for testing (deceased). The deletion overlaps two microRNAs (miRNAs) and seven RefSeq genes (Figure 2), including the four promising neurodevelopmental gene candidates highlighted by Gimelli et al. (*GAP43* and *LSAMP*) and Molin et al. (*DRD3* and *ZBTB20*) [1,3]. The 3q13.31 region was inspected for



Figure 1 Physical features of an adult male with a 3q13.31 microdeletion. Anthropometric data demonstrated a post-natal growth pattern above the mean: at 31 years height was 181.5 cm (75th-90th percentile), weight was 90.9 kg (BMI 27.6), and OFC was 60.9 cm (97th percentile). Findings noted on physical examination as an adult included a broad neck and slight kyphosis. Craniofacial features included facial asymmetry, strabismus, narrow palpebral fissures, a long philtrum, a narrow high arched palate, flat occiput, and frontal and occipital hair whorls. He also had bilateral cubitus valgus, short 4th and 5th metacarpals bilaterally, as well as narrow feet with mild clinodactyly bilaterally of all toes and camptodactyly bilaterally of 4th and 5th toes.

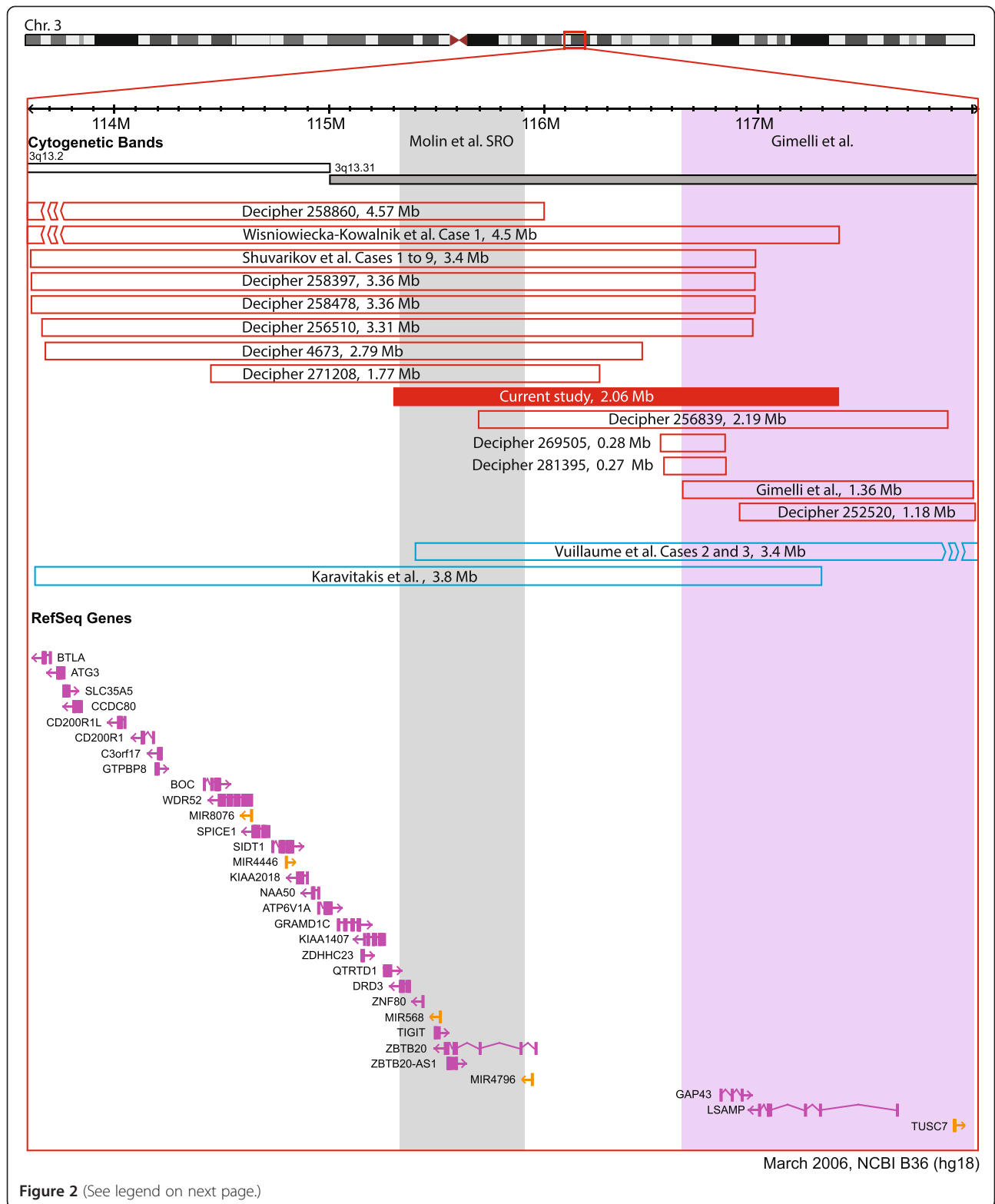


Figure 2 (See legend on next page.)

(See figure on previous page.)

Figure 2 3q13.31 deletions and duplications overlapping neuropsychiatric candidate genes *DRD3*, *ZBTB20*, *LSAMP*, and *GAP43*. The image was modified from the Database of Genomic Variants (<http://dgv.tcag.ca>), NCBI Build 36 (hg 18) [13]. Only deletions and duplications <5 Mb in size and overlapping at least one of *DRD3*, *GAP43*, *ZBTB20*, and *LSAMP* are shown. Deletions and duplications are represented by red and blue bars, respectively. All genes (purple) and miRNAs (orange) within the 3q13.2-q13.31 region are shown; splice variants are not included. The grey bar outlines the coordinates for the 580 kb (chr3:115,335,356-115,916,848) shortest region of overlap (SRO) defined by Molin et al. [1]. The purple bar outlines the boundaries for the Gimelli deletion (chr3:116,640,577- 118,002,810, hg 18) that overlapped *GAP43* and *LSAMP* [3]. The 4.5 Mb deletion reported by Wisniewicka-Kowalnik [14], the 4.57 Mb deletion in DECIPHER Case 258860, and the 3.4 Mb duplication by Vuillaume [4] extend beyond the boundary of the figure and are represented by line breaks. Where necessary, all deletion and duplication coordinates (i.e., excluding the Molin et al. SRO and the case described in this report) were converted from hg 19 to hg 18 using The UCSC Genome LiftOver tool (<http://genome.ucsc.edu>).

CNVs in the DECIPHER (<http://decipher.sanger.ac.uk>) database and 10 patients were found to have deletions overlapping the one presented in this case report (Figure 2) [11]. In the 26,826 adult control subjects with genome-wide CNV data available to our colleagues at The Centre for Applied Genomics (TCAG), no similar 3q13.31 deletions or duplications were identified using a 50% reciprocal overlap criterion (Additional file 2: Table S2) [9,12].

Discussion

3q13.31 deletion expression in adults

Including the present case, four adults (≥ 18 years) with 3q13.31 microdeletions have been reported in the literature to date (Table 1) [1,2]. Several features present in this patient, including DD/ID, speech delay, enuresis, postnatal growth above the mean, structural brain abnormalities, high arched palate, and skeletal anomalies, are consistent with previous reports of adults with 3q13.31 microdeletions (Table 1) [1,2]. Of all forty-one cases previously in the literature, the 3q13.31 deletion was reported as occurring de novo in thirty-eight (92.7%) and of unknown inheritance in three (7.3%) [1-4,14,15].

Neuropsychiatric phenotypes (i.e., ADHD and ASD) have been previously associated with the 3q13.31 microdeletion; however, this is the first report of schizophrenia in an individual with a 3q13.31 microdeletion. Moreover, the patient described in this report had a >25 point discrepancy between his performance and verbal IQ scores, consistent with a nonverbal learning disability [16]. Interestingly, the 42 year old female (Case 6) reported in Shuvarikov et al. [2] demonstrated a similar trend in IQ scores (Table 1). Raw IQ scores were not given for many of the paediatric cases, however Vuillaume et al. [4] described an affected 16 year old female (Case 1) as “being able to read and write but educational learning was difficult,” potentially describing a nonverbal learning disability. Detailed neuropsychological phenotyping of additional cases will help determine if nonverbal learning disabilities are part of the emerging 3q13.31 microdeletion syndrome.

Candidate genes for neuropsychiatric expression

The four genes (*GAP43*, *DRD3*, *LSAMP*, and *ZBTB20*) that have been posited as contributing to the brain phenotype of the 3q13.31 microdeletion syndrome are all overlapped by this patient's deletion (Figure 2) [1,2]. Regarding these genes and their potential role in schizophrenia and related neuropsychiatric conditions, non-synonymous point mutations in *GAP43* were recently identified in two unrelated schizophrenia cases in a next-generation sequencing study [17]. *DRD3* has been a longstanding candidate gene for schizophrenia, largely based on its affinity to bind antipsychotic drugs and its localization in limbic brain structures [18]. Further, *LSAMP* and *ZBTB20* have each been implicated in various brain regions associated with schizophrenia. In a post-mortem study of schizophrenia, *LSAMP* expression was noted to be increased by ~20% in the dorsolateral prefrontal cortex of individuals with schizophrenia compared to controls [19]. In mice, *ZBTB20* knockdowns were noted to have faulty hippocampal cytoarchitecture and selective ablation of *ZBTB20* in mature hippocampal CA1 neurons led to disruptions in learning and memory [20,21].

In addition to genic haploinsufficiency, other molecular mechanisms may contribute to the phenotype of the 3q13.31 microdeletion syndrome. In particular, recent reports suggest miRNAs may play a role in mediating the risk for neurodevelopmental disorders [22,23]. Both miRNAs overlapped by the 3q13.31 deletion in this patient (miR-4796, miR-568) have predicted targets that are additional candidate genes for schizophrenia and related disorders, including *SHANK2* and *FMRI* [24,25]. The individual and collective influence of the above mentioned genes and miRNAs on the neuropsychiatric expression of the 3q13.31 microdeletion is deserving of further study. Of interest with respect to genotype-phenotype correlations are the few reports to date of the reciprocal 3q13.31 duplication, in which individuals appear to share some (i.e., DD/ID, hypotonia) but not all of the same clinical features as the 3q13.31 microdeletion [4,26]. The fact that neither deletions nor duplications at 3q13.31 were identified in 26,826 controls suggest that

Table 1 Clinical features of four adults with 3q13.31 deletions

	Current report	Molin et al. Case 1	Molin et al. Case 8	Shuvarikov et al. Case 6
Age (years)	41	19.5	18	42
Sex	Male	Male	Male	Female
Ethnicity	European	NR	NR	NR
OFC (percentile)	97 th	90 th	97 th	50-75 th
Height (percentile)	75 th -90 th	95 th	99 th	10-25 th
Weight (category)	Overweight	NR	NR	Obese
Neurocognitive	Borderline intellectual disability (VIQ 90, PIQ 62)	[Developmental delay]	[Severe intellectual disability] (FSIQ < 50)	[Borderline intellectual disability] (VIQ 94, PIQ 61)
Speech delay	Yes	No	Yes	Yes
Neuropsychiatric	[Schizophrenia], aggressive behaviour	ADHD	ADHD, some repetitive behaviours	Social and emotional immaturity
Neurologic	Delayed motor development, focal hypoplasia of the superior cerebellar vermis (15 y), enuresis	Hypotonia	Hypotonia	Cerebellar agenesis, EEG abnormalities, hypotonia, enuresis
Musculoskeletal	Bilateral L5-S1 disc protrusion, slight kyphosis	Kyphosis	NR	NR
Genitalia	NA	Small testes (8 ml)	Normal	Small introitus
Craniofacial	Broad neck, facial asymmetry, strabismus, narrow palpebral fissures, long philtrum, narrow high arched palate, flat occiput, frontal and occipital hair whorls (Figure 1)	Dolichocephaly, prominent broad forehead, strabismus, myopia, ptosis, antimongoloid slant, short philtrum, high arched palate, large ears, crowded teeth, soft enamel	Prominent/broad forehead, high arched palate, large fleshy ears, pointed chin	Absent eyebrows, epicanthal folds, down slanting palpebral fissures, ptosis, high palate, nystagmus, microstomia, small teeth, large palatine tori
Hands and feet	Cubitus valgus, bilateral short 4 th and 5 th metacarpals, narrow feet with mild bilateral clinodactyly and camptodactyly of toes	Small hands, long fingers	Tapering fingers	Pes cavus, middle finger clinodactyly bilaterally
Pregnancy and birth	Uneventful pregnancy, birth weight 3941 g (75 th -90 th percentile)	NR	Birth weight 3430 g (50-85 th percentile)	Placental calcifications, marginally small for dates
Other	Insulin dependent Type 2 diabetes mellitus, hypercholesterolemia, hypocalcemia, hypertension	NR	NR	Large angioma in right shoulder, dorsocervical fat pad

OFC, occipital frontal circumference; NR, not reported; NA, not assessed; FSIQ, full scale intelligence quotient; VIQ, verbal intelligence quotient; PIQ, performance intelligence quotient; ADHD, attention deficit hyperactivity disorder; EEG, electroencephalography. Square brackets used to highlight ascertainment feature.

copy number aberrations in this region, rather than haploinsufficiency alone, may be associated with the deleterious phenotypic consequences.

Implications for clinical practice

Cytogenetic anomalies may be found in up to 5-8% of cases with schizophrenia, suggesting a potential future role for clinical microarray testing in this population [9]. The occurrence of schizophrenia in the patient reported here could be unrelated to the 3q13.31 microdeletion. However, multiple lines of evidence, including the variable expression of many other recurrent large, rare CNVs, suggest a genetically-related neuropsychiatric spectrum of disease that includes both DD/ID and schizophrenia [9,27,28]. This is, to our knowledge, the first report of a

3q13.31 deletion discovered in a schizophrenia cohort. This attests to the overall rarity of these variants, and to the relative paucity of available data (almost all of which are research-based) compared with diseases like DD/ID where clinical microarray testing is now the first-tier diagnostic test [9,29]. More data are needed to delineate the role of pathogenic CNVs in the dual-diagnosis (schizophrenia and premorbid ID) population to which this patient would belong, where the yield may be significantly higher and where clinical testing is already indicated [30].

Conclusions

In conclusion, we have identified an adult male with schizophrenia and a 3q13.31 deletion overlapping four promising neurodevelopmental candidate genes: *DRD3*,

ZBTB20, *GAP43*, and *LSAMP*. Later-onset conditions like schizophrenia are increasingly associated with rare CNVs. Detailed phenotypic information across the lifespan facilitates genotype-phenotype correlations, accurate genetic counselling, and anticipatory care.

Consent

Written informed consent was obtained from the patient for publication of this Case report and any accompanying images. A copy of the written consent is available for review through the Editor-in-Chief of this journal.

Additional files

Additional file 1: Table S1. Genome-wide copy number variation detected by Affymetrix 6.0 microarray in the proband with a 3q13.31 deletion described in this report.

Additional file 2: Table S2. Overview and negative results of 13 control datasets (total n=26,826) searched for 3q13.31 deletions and duplications.

Abbreviations

DD/ID: Developmental delay/intellectual disability; ASD: Autism spectrum disorder; ADHD: Attention deficit hyperactivity disorder; SRO: Shortest region of overlap; CNV: Copy number variation; CT: Computed tomography; IQ: Intelligence quotient; WASI: Wechsler Abbreviated Scale of Intelligence; CLIA: Clinical Laboratory Improvement Amendments; miRNA: microRNA; TCAG: The Centre for Applied Genomics.

Competing interests

SWS is on the Scientific Advisory Board of Population Diagnostics, Inc. and is a co-founder of YouNique Genomics. The other authors declare no conflicts of interest.

Authors' contributions

CL organized the clinical data and drafted and revised the manuscript. RM organized the clinical data for the manuscript. DJS carried out the clinical cytogenetic studies. ACL, CRM, and SWS carried out the molecular studies. GC carried out the study and helped draft and revise the manuscript. ASB conceived, designed, carried out the study, reviewed the detailed phenotypic data, and helped draft the manuscript. All authors read and approved the final manuscript.

Acknowledgements

The authors thank the patient for his participation, research assistants and staff at Saint John Community Mental Health Services and the Saint John Regional Hospital, and staff at The Centre for Applied Genomics (TCAG). The authors would also like to thank the anonymous reviewers for their valuable feedback. This study was supported by Canadian Institutes of Health Research (CIHR) grants (MOP-111238 and MOP-89066 to A.S.B.). A.S.B. holds the Canada Research Chair in Schizophrenia Genetics and Genomic Disorders, and the Dalglish Chair in 22q11.2 Deletion Syndrome. Control datasets were obtained, along with permission for use, from the database of Genotypes and Phenotypes (dbGaP) found at <http://ncbi.nlm.nih.gov/gap> through accession numbers phs000143.v1.p1 (Starr County Health Studies' Genetics of Diabetes Study), phs000091.v2.p1 (GENEVA NHS/HPFS Diabetes study), phs000169.v1.p1 (Whole Genome Association Study of Visceral Adiposity in the HABC Study), phs000303.v1.p1 (Genetic Epidemiology of Refractive Error in the KORA Study) and phs000404.v1.p1 (COGEND; The Genetic Architecture of Smoking and Smoking Cessation). The Starr County Health Studies Genetics of Diabetes Study was supported by the National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK) and the NIDDK Central Repositories. Support for the GWAS of Gene and Environment Initiatives in Type 2 Diabetes was provided through the NIH Genes, Environment and Health Initiative [GEI] (U01HG004399). The human subjects participating in the GWAS derive from The Nurses' Health Study and

Health Professionals' Follow-up Study and these studies are supported by National Institutes of Health (NIH) grants CA87969, CA55075 and DK58845. Assistance with phenotype harmonization and genotype cleaning, as well as with general study coordination, was provided by the Gene Environment Association Studies, GENEVA Coordinating Center (U01 HG004446) and the National Center for Biotechnology Information. Support for genotyping, which was performed at the Broad Institute of MIT and Harvard, was provided by the NIH GEI (U01HG004424). Support for the 'CIDR Visceral Adiposity Study' was provided through the Division of Aging Biology and the Division of Geriatrics and Clinical Gerontology, National Institute on Aging. Assistance with phenotype harmonization and genotype cleaning, as well as with general study coordination, was provided by Health ABC Study (HABC) Investigators. The KORA dataset was obtained from the NEI Refractive Error Collaboration (NEIREC) Database, support for which was provided by the National Eye Institute. Support for genotyping of the COGEND samples, which was performed at the Center for Inherited Disease Research (CIDR), was provided by 1X01 HG005274-01. Assistance with genotype cleaning of the COGEND samples, as well as with general study coordination, was provided by the Gene Environment Association Studies (GENEVA) Coordinating Center (U01HG004446). Support for the collection of COGEND datasets and samples were provided by the Collaborative Genetic Study of Nicotine Dependence (COGEND; P01 CA089392) and the University of Wisconsin Transdisciplinary Tobacco Use Research Center (P50 DA019706, P50 CA084724).

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Received: 30 December 2013 Accepted: 11 March 2014

Published: 20 March 2014

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doi:10.1186/1755-8166-7-23

Cite this article as: Lowther et al.: Adult expression of a 3q13.31 microdeletion. *Molecular Cytogenetics* 2014 **7**:23.

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