Clinically detectable copy number variations in a Canadian catchment population of schizophrenia

Anne S. Bassett^{a,b,*}, Gregory Costain^{a,c}, Wai Lun Alan Fung^{a,b}, Kathryn J. Russell^c, Laura Pierce^a, Ronak Kapadia^c, Ronald F. Carter^d, Eva W.C. Chow^{a,b}, and Pamela J. Forsythe^{c,e}

^a Clinical Genetics Research Program, Centre for Addiction and Mental Health, Toronto, Ontario, Canada

^b Department of Psychiatry, University of Toronto, Toronto, Ontario, Canada

^c Community Mental Health Services, Saint John, New Brunswick, Canada

^d Hamilton Regional Laboratory Medicine Program, Hamilton, Ontario, Canada

^e Department of Psychiatry, Saint John Regional Hospital, Saint John, New Brunswick, Canada

Abstract

Copy number variation (CNV) is a highly topical area of research in schizophrenia, but the clinical relevance is uncertain and the translation to clinical practice is under-studied. There is a paucity of research involving truly community-based samples of schizophrenia and widely available laboratory techniques. Our objective was to determine the prevalence of clinically detectable CNVs in a community sample of schizophrenia, while mimicking typical clinical practice conditions. We used a brief clinical screening protocol for developmental features in adults with schizophrenia for identifying individuals with 22q11.2 deletions and karyotypically detectable chromosomal anomalies in 204 consecutive patients with schizophrenia from a single Canadian catchment area. Twenty-seven (13.2%) subjects met clinical criteria for a possible syndrome, and 26 of these individuals received clinical genetic testing. Five of these, representing 2.5% of the total sample (95% CI: 0.3%–4.6%), including two of ten patients with mental retardation, had clinically detectable anomalies: two 22q11.2 deletions (1.0%), one 47, XYY, and two other novel CNVs – an 8p23.3-p23.1 deletion and a *de novo* 19p13.3-p13.2 duplication. The results support the utility of screening and genetic testing to identify genetic syndromes in adults with schizophrenia in clinical practice. Identifying large, rare CNVs (particularly 22q11.2 deletions) can lead to significant changes in management, follow-up, and genetic counselling that are helpful to the patient, family, and clinicians.

*Corresponding author. Centre for Addiction and Mental Health, 33 Russell Street, Toronto, Ontario M5S 2S1, Canada. Tel.: +1 (416) 535 8501x2734; fax: +1 (416) 535 7199. anne.bassett@utoronto.ca (A.S. Bassett).

Contributors

Author Bassett designed the study. Authors Bassett and Chow contributed to writing the original protocol. Authors Costain, Forsythe, Kapadia, and Russell assisted with data collection and clinical screening. Author Carter supervised the molecular cytogenetic analyses. Author Pierce assisted with the statistical analysis. Authors Bassett, Costain, Fung, Pierce, and Russell wrote the manuscript drafts. All authors contributed to and have approved the final manuscript.

Conflict of interest statement

None of the authors have financial interests that might present a conflict of interest.

Keywords

22q11.2 Deletion Syndrome; Schizophrenia; Copy number variation

1. Introduction

For developmental conditions like autism and mental retardation new genetic technologies such as microarrays have extended longstanding associations with cytogenetic abnormalities to include submicroscopic copy number variations (CNVs) (Edelmann and Hirschhorn, 2009; Liang et al., 2008; Weiss, 2009). Schizophrenia is also considered to have neurodevelopmental pathogenesis but has less evidence for associated cytogenetic anomalies than developmental disorders (Bassett et al., 2001a). Research studies using high-resolution techniques have recently focussed attention on CNVs that may be associated with schizophrenia (Bassett et al., in press; Walsh et al., 2008; Xu et al., 2008), including emerging microdeletion (e.g., 1q21.1, 15q13.3) and microduplication (e.g., 1q21.1, 16p11.2) syndromes (Bassett et al., in press). However, 22q11.2 Deletion Syndrome (22q11DS) (OMIM #188400/#192430) currently represents the only genetic subtype of schizophrenia that is both clinically recognizable and associated with a recurrent CNV for which genetic testing is broadly available (Bassett and Chow, 2008). Typical developmental features involve multiple systems, and include dysmorphic facies, learning difficulties, hypernasality often associated with velopharyngeal insufficiency, and cardiac and other birth defects (Bassett and Chow, 1999). Prevalence of major psychotic disorders in 22q11DS is 20–25% (Fung et al., in press). The estimated general population prevalence of 22q11DS is 0.025% (Goodship et al., 1998) while reported prevalences in schizophrenia range from 0 to 2.0%, likely relating to ascertainment strategies such as not studying a truly representative community sample (Bassett and Chow, 2008).

Mimicking typical clinical practice conditions, we previously showed the value of brief clinical screening for developmental features in adults with congenital cardiac disease for identifying individuals with 22q11.2 deletions and karyotypically detectable chromosomal anomalies (Fung et al., 2008). Using the same protocol to identify those with possible genetic syndromes (Fung et al., 2008), we investigated 204 consecutive patients with schizophrenia from a single Canadian catchment area.

2. Methods

Unrelated patients aged 18–70 years meeting DSM-IV criteria for chronic schizophrenia or schizoaffective disorder with onset age 13 years or older were sequentially recruited from the only community mental health clinic in a catchment area of 150,000 people in New Brunswick, Canada. The study was approved by local and university institutional review boards.

We approached 234 consecutive patients meeting inclusion criteria. Thirty were too ill to provide informed consent, refused participation, and/or had no surrogate consent provider. After obtaining informed consent, participants were assessed by trained research assistants using a standardized clinical screening protocol (Fung et al., 2008) which documented

physical features and recorded medical, developmental, psychiatric, and family history (first degree relatives with psychotic illness), supplemented by medical records. Age at onset was the age at first treatment for psychosis.

Using previously determined criteria (Fung et al., 2008), subjects meeting either of the following criteria were deemed “Syndromal”: 1) subjects ($n = 11$) having learning difficulties, dysmorphic facies, and hypernasality, or 2) subjects ($n = 16$) having two of these features and a birth defect or short stature (height <3rd percentile) or mental retardation. Data for all subjects were reviewed to verify inclusion in the Syndromal group. Subjects meeting these criteria had clinical karyotype at the 450–650 band level and fluorescence in-situ hybridization (FISH) studies using a standard 22q11.2 probe (e.g., TUPLE1/Vysis) from the commonly deleted region (Bassett and Chow, 2008; Fung et al., 2008). Seven non-Syndromal subjects, including the only one with mental retardation and four others with one or two of the other syndromal features, also had this genetic testing. Analyses using SAS 9.1 determined statistical significance at the $p < 0.05$ level (2-sided) (SAS Institute Inc., 1997).

3. Results

Table 1 shows the demographic and clinical features of the 204 participants. Mean age at onset was significantly younger for males (24.0 years, SD 6.9) than females (27.7 years, SD 10.7; $t = 2.9$, $df = 202$, $p = 0.004$). Twenty-seven (13.2%) subjects met Syndromal criteria. Mean educational level was significantly lower, age nonsignificantly younger and seizures non-significantly more prevalent in this group (Table 1).

Of 26 Syndromal subjects tested (one died before testing), five (19.2%) had a chromosomal anomaly involving a CNV. Two had a 22q11.2 deletion (men aged 40 and 35 years; age at onset 27 and 28 years; full scale IQ 73 and 62, respectively). Three subjects had other anomalies detected on karyotype: 1) 47, XYY in a 60 year old man with age at onset 32 years, borderline intellect, subtle dysmorphic facies, hypocalcemia, myopia, history of marijuana and alcohol abuse, and minor legal involvement; 2) an 8p23.1 interstitial hemizygous deletion without inversion or duplication in a 53 year old woman, not present in her father (unaffected mother deceased), with age at onset 26 years, borderline intellect, mild dysmorphic facies, and hypocalcemia; and 3) a *de novo* 19p13.3 interstitial hemizygous duplication in a 26 year old woman with age at onset 24 years, mild mental retardation, dysmorphic facies, pes planus requiring orthotics, and short stature. Clinical array CGH analysis of DNA extracted from peripheral blood lymphocytes further delineated the extent of the latter two anomalies [8p: Perkin Elmer Constitutional Chip 4.0 (~5200 BAC clones), including 18 from the region of interest; 19p: Agilent 4x44k (~44,000 oligonucleotide probes), including 384 from the region of interest]. Estimated breakpoints (NCBI Build 36) were 200,000 and 6,310,000 for the 6.1 Mb interstitial deletion at 8p23.3-p23.1 and 2,789,838 and 12,284,090 for the 9.5 Mb interstitial duplication at 19p13.3-p13.2. Of the five individuals with chromosomal anomalies, four had no family history of psychosis; one was adopted. All five received genetic counselling (Bassett et al., 2008; Hodgkinson et al., 2001). None of seven subjects tested in the non-Syndromal group had a detectable anomaly.

In this 204 patient sample, the minimum prevalence of any chromosomal anomaly was 2.5% (95% CI: 0.3%–4.6%) and of 22q11.2 deletions was 1.0% (95% CI: 0%–2.3%).

4. Discussion

The results of this study support the value of clinical screening for features of genetic syndromes in schizophrenia. The high prevalence of anomalies discovered in the Syndromal subgroup (19.2%) indicates that our clinical protocol successfully identified individuals for standard genetic testing who had an elevated *a priori* probability of an anomaly (Fung et al., 2008). Although developmentally- based, the protocol did not rely on comorbid mental retardation. There are several other emerging microdeletion (e.g., 1q21.1, 15q13.3) and microduplication (e.g., 1q21.1, 16p11.2) syndromes associated with schizophrenia that our genetic testing methods would not have detected (Bassett et al., in press). Thus the true yield in the Syndromal group is likely to be even higher.

Notably, most of the Syndromal group, including individuals with detected anomalies, did not have mental retardation, as expected for schizophrenia in the general population (Bassett et al., 2008). Two of the 10 individuals with mental retardation had a detectable anomaly, in line with expectations for mental retardation (Edelmann and Hirschhorn, 2009; Koolen et al., 2009; Liang et al., 2008). Notably, for studies of mental retardation in general, schizophrenia status would usually be unknown due to young age of patients. Only one other study investigated dual diagnosis patients for 22q11.2 deletions (Murphy et al., 1998). The trend for recurrent seizures to be more prevalent in the Syndromal group may be consistent with more complex neuropsychiatric expression in individuals with developmental forms of schizophrenia, including those with large, rare CNVs (Bassett et al., in press).

The prevalence of 22q11.2 deletions identified in the overall sample was consistent with most studies of schizophrenia (Table 2), and consistent with 22q11DS representing a true genetic subtype of schizophrenia, as are syndromic forms of other complex disorders like hearing loss (Bassett et al., 2001b). The total prevalence of all 22q11.2 deletions in our catchment population, given 46 subjects not attending the clinic and 30 unable to participate, cannot be less than 2 in 280 (0.7%; 95% CI, 0%–1.7%), and may be higher. Possible reasons for lower prevalence figures in some studies include selection bias such as high IQ or familial schizophrenia (Bassett and Chow, 2008) and premature death of individuals with 22q11DS (Bassett et al., 2009; Fung et al., 2008) in addition to low power with small sample sizes. Sample sizes in consortium studies appear large but are comprised of individual smaller samples (Bassett et al., in press).

In addition to the 22q11.2 deletions discovered using FISH, we identified two large, rare CNVs at the borderline of the low-resolution genome-wide technique used (karyotyping). To our knowledge, the 8p23.3-p23.1 deletion and 19p13.3-p13.2 duplication have not been previously reported. There are other chromosomal abnormalities associated with schizophrenia that involve these regions (Bassett et al., 2000); however, there is no direct overlap with linkage or “top” association findings highlighted in the January 2010 SzGene Database (Allen et al., 2008). There are 11 genes in the 8p23.3-p23.1 region and approximately 250 genes in the 19p13.3-p13.2 region. As would be the case for most

regions of the genome, many of these genes, including DLGAP2 in 8p23.3 and ARHGEF10 in 19p13.2, are of potential interest for schizophrenia. There are previous reports of the sex chromosome abnormality identified (47, XYY) in psychotic disorders (Mors et al., 2001; Walsh et al., 2008).

CNVs account for a large proportion of variation within every human genome (Conrad et al., 2010; Sebat et al., 2004). Those that are rare, of larger size, and of *de novo* origin are more likely to have a causal link to a disease phenotype such as schizophrenia (Bassett et al., in press). The 19p duplication meets all these criteria, while the 8p deletion meets at least two of these criteria, is a deletion, and is flanked on the proximal side by a segmental duplication like many emerging genomic disorders (Lupski and Stankiewicz, 2005; Miller et al., 2010). Neither CNV has been reported in control populations, and both are multigenic. Both of these CNVs would be classified as likely pathogenic according to a recently published consensus statement (Miller et al., 2010).

Karyotyping provides genome-wide coverage of CNVs down to about 5–10Mbin size (Miller et al., 2010). Based on studies of mental retardation and/or multiple congenital anomalies (Li and Andersson, 2009), one might expect up to a doubling of the detection rate of such CNVs in the Syndromal group using high resolution techniques such as microarrays. While microarrays targeted to CNVs associated with genomic disorders are now a standard of care in many jurisdictions for individuals with such developmental features (Koolen et al., 2009), the yield in individuals without multiple developmental features would be expected to be lower. With respect to genome-wide microarrays, current costs and challenges with interpretation of findings suggest that such testing may not be justified at this time for individuals without syndromic and/or neurodevelopmental features (Miller et al., 2010).

The results support a clinically driven approach of identifying adults likely to have genetic syndromes. This strategy has a high yield, at a reasonable cost, using standard genetic testing (Fung et al., 2008). Clinics with a sizeable schizophrenia population, anywhere in the world, are likely to have one or more patients with a 22q11.2 deletion or other genetic abnormality (Bassett and Chow, 2008). Identifying 22q11DS leads to significant changes in management, follow-up, and genetic counselling that are helpful to the patient, family, and clinicians (Bassett and Chow, 2008). Genetic counselling, if not anticipatory care, would also change for patients with other anomalies (Bassett et al., 2008). Parental testing, when possible, is essential to determine whether changes are *de novo* or inherited, in which case family studies will help delineate the penetrance. Further information about clinically relevant changes to care will be forthcoming as more patients with CNVs are identified, assessed for multisystem involvement, followed, and reported in sufficient numbers (Bassett et al., in press). Further large, well-designed prevalence studies are needed.

Acknowledgments

The authors thank the patients and their families for their participation, colleagues for referring patients, research assistants, staff at the Saint John Community Mental Health Services, fellows and students who assisted in the collection and analysis of data for the study, and Gladys Wong for helping to prepare the manuscript.

Role of funding source

This research was supported by a Canadian Institutes of Health Research grant (MOP-79518), and a Canada Research Chair in Schizophrenia Genetics (Author Bassett). These funding sources had no further role in study design; in the collection, analysis and interpretation of data; in the writing of the report; or in the decision to submit the paper for publication.

Abbreviations

22q11DS	22q11.2 Deletion Syndrome
BAC	bacterial artificial chromosome
FISH	fluorescence in-situ hybridization

References

- Allen NC, Bagade S, McQueen MB, Ioannidis JP, Kavvoura FK, Khoury MJ, et al. Systematic meta-analyses and field synopsis of genetic association studies in schizophrenia: the SzGene database. *Nature Genetics*. 2008; 40:827–34. [PubMed: 18583979]
- Arinami T, Ohtsuki T, Takase K, Shimizu H, Yoshikawa T, Horigome H, et al. Screening for 22q11 deletions in a schizophrenia population. *Schizophrenia Research*. 2001; 52:167–70. [PubMed: 11705710]
- Bassett AS, Scherer SW, Brzustowicz LM. Copy number variations in schizophrenia: critical review and new perspectives on concepts of genetics and disease. *American Journal of Psychiatry*. in press.
- Bassett AS, Chow EWC. 22q11 deletion syndrome: a genetic subtype of schizophrenia. *Biological Psychiatry*. 1999; 46:882–91. [PubMed: 10509171]
- Bassett AS, Chow EWC. Schizophrenia and 22q11.2 deletion syndrome. *Current Psychiatry Reports*. 2008; 10:148–57. [PubMed: 18474208]
- Bassett, AS., Chow, EWC., Hodgkinson, KA. Chapter 5. Schizophrenia and psychotic disorders. In: Smoller, JW, Sheidley, BR., Tsuang, MT., editors. *Psychiatric genetics: applications in clinical practice*. Arlington, VA: American Psychiatric Publishing, Inc; 2008. p. 99-130.
- Bassett AS, Chow EWC, Husted J, Hodgkinson KA, Oechslein E, Harris L, et al. Premature death in adults with 22q11.2 deletion syndrome. *Journal of Medical Genetics*. 2009; 46:324–30. [PubMed: 19246480]
- Bassett AS, Chow EWC, O'Neill S, Brzustowicz LM. Genetic insights into the neurodevelopmental hypothesis of schizophrenia. *Schizophrenia Bulletin*. 2001a; 27:417–30. [PubMed: 11596844]
- Bassett AS, Chow EWC, Waterworth D, Brzustowicz LM. Genetic insights into schizophrenia. *Canadian Journal of Psychiatry*. 2001b; 46:131–7. [PubMed: 11280081]
- Bassett AS, Chow EWC, Weksberg R. Chromosomal abnormalities and schizophrenia. *American Journal of Medical Genetics*. 2000; 97C:45–51.
- Brunet A, Armengol L, Pelaez T, Guillamat R, Valles V, Gabau E, et al. Failure to detect the 22q11.2 duplication syndrome rearrangement among patients with schizophrenia. *Behavioral and Brain Functions*. 2008; 4:10. [PubMed: 18284679]
- Chen CH, Lee YR, Chung MY, Wei FC, Koong FJ, Shaw CK, et al. Systematic mutation analysis of the catechol O-methyltransferase gene as a candidate gene for schizophrenia. *American Journal of Psychiatry*. 1999; 156:1273–5. [PubMed: 10450274]
- Conrad DF, Pinto D, Redon R, Feuk L, Gokcumen O, Zhang Y, et al. Origins and functional impact of copy number variation in the human genome. *Nature*. 2010; 464:704–12. [PubMed: 19812545]
- Edelmann L, Hirschhorn K. Clinical utility of array CGH for the detection of chromosomal imbalances associated with mental retardation and multiple congenital anomalies. *Annals of the New York Academy of Sciences*. 2009; 1151:157–66.
- Fung WLA, Chow EWC, Webb GD, Gatzoulis MA, Bassett AS. Extracardiac features predicting 22q11.2 deletion syndrome in adult congenital heart disease. *International Journal of Cardiology*. 2008; 131:51–8. [PubMed: 18191243]

- Fung WLA, McEvilly R, Fong J, Silversides C, Chow E, Bassett AS. Elevated prevalence of generalized anxiety disorder in adults with 22q11.2 deletion syndrome. *American Journal of Psychiatry*. in press.
- Goodship J, Cross I, LiLing J, Wren C. A population study of chromosome 22q11 deletions in infancy. *Archives of Disease in Childhood*. 1998; 79:348–51. [PubMed: 9875047]
- Hodgkinson KA, Murphy J, O'Neill S, Brzustowicz L, Bassett AS. Genetic counselling for schizophrenia in the era of molecular genetics. *Canadian Journal of Psychiatry*. 2001; 46:123–30. [PubMed: 11280080]
- Hoogendoorn ML, Vorstman JA, Jalali GR, Selten JP, Sinke RJ, Emanuel BS, et al. Prevalence of 22q11.2 deletions in 311 Dutch patients with schizophrenia. *Schizophrenia Research*. 2007; 98:84–8. [PubMed: 17964762]
- Horowitz A, Shifman S, Rivlin N, Pisante A, Darvasi A. A survey of the 22q11 microdeletion in a large cohort of schizophrenia patients. *Schizophrenia Research*. 2005; 73:263–7. [PubMed: 15653270]
- Ivanov D, Kirov G, Norton N, Williams HJ, Williams NM, Nikolov I, et al. Chromosome 22q11 deletions, velo-cardio-facial syndrome and early-onset psychosis. *Molecular genetic study*. *British Journal of Psychiatry*. 2003; 183:409–13. [PubMed: 14594915]
- Karayorgou M, Morris MA, Morrow B, Shprintzen RJ, Goldberg R, Borrow J, et al. Schizophrenia susceptibility associated with interstitial deletions of chromosome 22q11. *Proceedings of the National Academy of Sciences USA*. 1995; 92:7612–6.
- Koolen DA, Pfundt R, de Leeuw N, Hehir-Kwa JY, Nillesen WM, Neefs I, et al. Genomic microarrays in mental retardation: a practical workflow for diagnostic applications. *Human Mutation*. 2009; 30:283–92. [PubMed: 19085936]
- Li MM, Andersson HC. Clinical application of microarray-based molecular cytogenetics: an emerging new era of genomic medicine. *Journal of Pediatrics*. 2009; 155:311–7. [PubMed: 19732576]
- Liang JS, Shimojima K, Yamamoto T. Application of array-based comparative genome hybridization in children with developmental delay or mental retardation. *Pediatrics & Neonatology*. 2008; 49:213–7. [PubMed: 19166117]
- Lupski JR, Stankiewicz P. Genomic disorders: molecular mechanisms for rearrangements and conveyed phenotypes. *PLoS Genetics*. 2005; 1:e49. [PubMed: 16444292]
- Miller DT, Adam MP, Aradhya S, Biesecker LG, Brothman AR, Carter NP, et al. Consensus statement: chromosomal microarray is a first-tier clinical diagnostic test for individuals with developmental disabilities or congenital anomalies. *American Journal of Human Genetics*. 2010; 86:749–64. [PubMed: 20466091]
- Mors O, Mortensen PB, Ewald H. No evidence of increased risk for schizophrenia or bipolar affective disorder in persons with aneuploidies of the sex chromosomes. *Psychological Medicine*. 2001; 31:425–30. [PubMed: 11305850]
- Murphy KC, Jones RG, Griffiths E, Thompson PW, Owen MJ. Chromosome 22q11 deletions. An under-recognised cause of idiopathic learning disability. *British Journal of Psychiatry*. 1998; 172:180–3. [PubMed: 9519073]
- Pawlowska B, Tomankiewicz-Zawadzka A, Ilnicka A, Bogdanowicz J, Wciorka J, Szafranski T, et al. A study on the occurrence of the deletion 22q11.2 in patients affected with a psychiatric disease. *Psychiatria Polska*. 2007; 41:251–60. [PubMed: 17598434]
- SAS Institute Inc. SAS/STAT software: changes and enhancements through release 6.12. Cary, NC: SAS Institute Inc; 1997.
- Sebat J, Lakshmi B, Troge J, Alexander J, Young J, Lundin P, et al. Large-scale copy number polymorphism in the human genome. *Science*. 2004; 305:525–8. [PubMed: 15273396]
- Walsh T, McClellan JM, McCarthy SE, Addington AM, Pierce SB, Cooper GM, et al. Rare structural variants disrupt multiple genes in neurodevelopmental pathways in schizophrenia. *Science*. 2008; 320:539–43. [PubMed: 18369103]
- Weiss LA. Autism genetics: emerging data from genome-wide copy-number and single nucleotide polymorphism scans. *Expert Reviews of Molecular Diagnostics*. 2009; 9:795–803.

Xu B, Roos JL, Levy S, van Rensburg EJ, Gogos JA, Karayiorgou M. Strong association of de novo copy number mutations with sporadic schizophrenia. *Nature Genetics*. 2008; 40:880–5. [PubMed: 18511947]

Table 1

Demographic features and clinical features related to identifying possible genetic syndromes in a catchment population of schizophrenia.

	Total sample (<i>n</i> = 204)			Syndromal (<i>n</i> = 27)			Non-Syndromal (<i>n</i> = 177)			Statistics ^a	
	Mean	SD		Mean	SD		Mean	SD			<i>p</i>
Age (y)	44.5	12.1		41.2	12.6		45.0	11.9		0.13	
Age at onset of psychosis (y)	25.1	8.5		24.6	6.9		25.2	8.7		0.74	
Educational level (y)	10.8	2.9		8.9	3.3		11.1	2.7		0.0001	
	Number	Percent		Number	Percent		Number	Percent			<i>p</i>
Male sex	142	69.6		16	59.3		126	71.2		0.21	
Caucasian	187	91.7		25	92.6		162	91.5		>0.9995	
Schizoaffective	20	9.8		4	14.8		16	9.0		0.33	
Family history of psychosis ^b	19 (of 188)	10.1		2 (of 26)	7.7		17 (of 162)	10.5		>0.9995	
Possible syndromal features	Number	Percent		Number	Percent		Number	Percent			<i>p</i>
Global dysmorphic faces ^c	50	24.5		27	100.0		23	13.0		<0.0001	
Hypnasal speech ^c	20	9.8		13	48.2		7	4.0		<0.0001	
Learning difficulties ^{c,d}	101	49.5		26	96.3		75	42.4		<0.0001	
Mental retardation	10	4.9		9	33.3		1	0.6		<0.0001	
Birth defects ^{c,e}	18	8.8		10	37.0		8	4.5		<0.0001	
Short stature (<3rd percentile) ^c	17 (of 198)	8.6		5 (of 26)	19.2		12 (of 172)	7.0		0.05	
Other features	Number	Percent		Number	Percent		Number	Percent			<i>p</i>
Microcephaly (<3rd percentile)	10 (of 195)	5.1		2 (of 26)	7.7		8 (of 169)	4.7		0.61	
Hypocalcemia	8 (of 66)	12.1		3 (of 17)	17.7		5 (of 49)	10.2		0.43	
Recurrent seizures	12	5.9		4	14.8		8	4.5		0.06	

^a Syndromal vs. non-Syndromal comparison, using unpaired *t*-test for continuous variables and chi-square test/Fisher's exact test for categorical variables.

^b Excluding adopted subjects.

^c Feature used to determine Syndromal designation.

^dSelf-described.

^eBirth defects included hypoplastic nasal cartilage, strabismus, pretragal ear buds, bronchial cysts, breast asymmetry, hernia, fused ribs, cervical rib, scoliosis, bilateral hip dislocation, brachycephaly, spastic monoplegia of lower limb, bilateral contractures, pes planus, camptodactyly.

Table 2

Reported prevalence of 22q11DS in schizophrenia samples with 95% confidence intervals (CI).^a

22q11.2 deletion syndrome		Total number of patients screened	Total number of patients tested for 22q11DS	Mean age at screening, y (range)	Male (%)	Population	Ascertainment issues	Method of molecular confirmation	Family history of SZ	Reference
% (95% CI) ^a	<i>n</i>									
2.00 (0–4.74)	2	100	3	NI	78	US (Baltimore), mostly SZ	Re-contact of participants in an epidemiological study	FISH	<i>n</i> = 14 (14.0%)	Karayiorgou et al. (1995)
1.97 (0–4.18)	3	152	NI	NI	NI	Afrikaaner, Caucasian, SZ	Of a subset of <i>n</i> = 85 assessed, 6 had mildly dysmorphic facial features (2 with 22q11.2 deletion)	SNP Array	0% (by design)	Xu et al. (2008)
1.10 (0–2.41)	3	265	NI	NI	NI	Polish, psychosis	NI	FISH	NI	Pawlowska et al. (2007)
1.05 (0–2.50)	2	190	160 tested with MLPA; 30 tested with DiGeorge syndrome test kit	33.3	81	Spanish/Catalan (Barcelona), SZ	Hospitalized patients	MLPA confirmed with FISH	NI	Brunet et al. (2008)
0.98 (0–2.33)	2	204	33	44.5 (18–70)	69.6	Canadian, most Caucasian, SZ or SA	<i>n</i> = 27 met clinical criteria for possible genetic syndrome; adult onset (13 y), community sample	FISH	<i>n</i> = 19/188 (10.1%)	(present study)
0.95 (0.19–1.70)	6	634	NI	45.8 (18–83)	63	Israeli, Ashkenazi Jewish, SZ	Hospitalized patients, genetic association study	7 ms, 3 SNP markers from 600-kb COMT region	NI	Horowitz et al. (2005)
0.30 (0–0.99)	1	300	300	44.3 (19–78)	56	Japanese, SZ	Hospitals within 200 km of Tokyo; hospitalized patient sample	3 ms, 1 SNP (COMT) markers	NI	Ainami et al. (2001)
0.20 (0–0.63)	1	470	470	NI	69	British (<i>n</i> = 415; <i>n</i> = 86 onset age <18 y), SZ; Bulgarian (<i>n</i> = 55; onset age <18 y), SZ	Recruited for a genetic association study; in-patients and out-patients	3–5 ms markers	NI	Ivanov et al. (2003)
0	0	177	50	47	54	Han Chinese (Taiwan), SZ	Private psychiatric hospital; hospitalized patient sample	4 COMT SNPs; 5 ms markers for 28 homozygous patients	NI	Chen et al. (1999)

<u>22q11.2 deletion syndrome</u>		Total number of patients screened	Total number of patients tested for 22q11DS	Mean age at screening, y (range)	Male (%)	Population	Ascertainment issues	Method of molecular confirmation	Family history of SZ	Reference
% (95% CI) ^a	<i>n</i>									
0	0	311	311	41	74	Dutch, SZ	146 (47%) patients with a deficit (negative syndrome) subtype recruited for a genetic study; hospitalized patient sample	MLPA (DiGeorge kit)	NI	Hoogendoorn et al. (2007)

SZ – schizophrenia; SA – schizoaffective disorder; MLPA – multiplex ligation-dependent probe amplification; NI – no information; SNP – single nucleotide polymorphism; FISH – fluorescence in-situ hybridization; CI – confidence interval; MR – mental retardation.

Consortium studies were not included (see text).

^a2-sided 95% CI were calculated with lower bound for negative results set to zero as true prevalence cannot be less than zero.