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Prevalence of 22q11.2 deletions in 311 Dutch patients with schizophrenia

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Abstract

The objectives of this study were 1) to examine whether the prevalence of 22q11.2 deletion syndrome (22q11DS) in schizophrenia patients with the Deficit syndrome is higher than the reported ~2% for the population of schizophrenia patients as a whole, and 2) to estimate the overall prevalence of 22q11DS among schizophrenia patients by combining all available studies. Our sample, enriched for patients with the Deficit syndrome, had 88% power to detect an estimated prevalence of 5% of 22q11.2 deletions. No 22q11.2 deletions were detected in 311 schizophrenia patients, 146 of whom met criteria for the Deficit syndrome. Our literature research revealed that in eight studies sixteen deletions were identified in 2133 patients with schizophrenia. This corresponds to a prevalence of 0.75% (95%CI: 0.5%–1.2%). In conclusion: The prevalence of 22q11.2DS in schizophrenia patients with the Deficit syndrome is not higher than in the population of schizophrenia patients as a whole. The prevalence of 22q11.2DS in schizophrenia patients is lower than the frequently reported prevalence of 2% or more.

Keywords

22q11 deletion syndrome; 22q11DS; Schizophrenia; VCFS; Deficit syndrome; Prevalence

1. Introduction

The 22q11.2 deletion syndrome (22q11DS) is associated with a range of congenital physical defects, including velopharyngeal anomalies, cardiac anomalies and typical dysmorphic

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Contributors

Mechteld Hoogendoorn and Jacob Vorstman performed the MLPA analyses, the statistical analyses and wrote the first draft of the manuscript. Gholam Jalali and Beverly Emanuel assisted in testing the schizophrenia sample with MLPA and Beverly Emanuel was also involved in critically proof-reading the manuscript. Jean-Paul Selten performed the confidence interval calculations and assisted in proofreading the manuscript. Richard Sinke provided the laboratory to perform the MLPA analyses. René Kahn supervised the entire study as head of the Department of Psychiatry at University Medical Center Utrecht.

Conflict of Interest

All authors declare that they have no conflicts of interest.

features of the face, hence the name Velo Cardio Facial Syndrome or VCFS. It is also associated with a very high risk (20–30%) of schizophrenia (Murphy et al., 1999; Pulver et al., 1994). It is uncertain, however, which proportion of schizophrenia patients carries a 22q11.2 deletion. Results of studies vary widely from 0.3% to 5.3% (see overview in Table 1). Knowledge of the true rate of 22q11.2 deletions in schizophrenia patients is important for several reasons; from a clinical perspective the identification of a 22q11.2 deletion in patients has consequences for genetic counseling. Identification may also lead to the detection of other physical anomalies associated with the clinical syndrome that may need treatment, such as hypocalcaemia. Furthermore, from a research perspective it is important to better define the relationship between 22q11DS and schizophrenia.

We have screened a sample of 311 Dutch patients with schizophrenia, including a relatively large sub-sample of patients meeting the criteria for the Deficit syndrome. The Deficit syndrome in schizophrenia is characterized by enduring, idiopathic negative symptoms, and is generally associated with a poor prognosis (Kirkpatrick et al., 1989). It is diagnosed in approximately 25%–30% of chronic schizophrenia patients. A number of observations indicate that the Deficit syndrome represents a distinctive subgroup within schizophrenia, with an increased heritability (Carpenter et al., 1999; Kirkpatrick et al., 2000, 2001). Remarkably, the negative symptoms of schizophrenia resemble some behavioral features of 22q11DS patients (with and without schizophrenia). These features are “lack of mental energy” (Niklasson et al., 2001), “social withdrawal”, “bland affect with minimal spontaneous facial expression”, “monotonous voice” (Golding-Kushner et al., 1985) and “poor social skills” (Heinemande Boer et al., 1999).

Consequently, the present study tested the hypothesis of a higher prevalence of 22q11.2 deletions in the subpopulation of schizophrenia patients with the Deficit syndrome. A second aim of the study was to update the current estimations with regard to the prevalence of 22q11DS among schizophrenia patients. To that end we included the results of this study and the study by Drazinic et al., which is presently in review.

2. Materials and methods

To achieve a maximum number of participants with prominent negative symptoms, the majority of patients were assessed through psychiatric hospitals in the Netherlands. Patients with congenital malformations were not recruited preferentially. Patients underwent diagnostic screening using the Comprehensive Assessment of Symptoms and History (CASH (Andreasen et al., 1992)) and additional information from medical records and clinicians. All patients were diagnosed by trained raters. Consensus diagnosis was established in the presence of a psychiatrist (e.g., J.P.S). All participating patients provided written an informed consent according to the Declaration of Helsinki and the Medical Research Ethics Board of each participating institution approved the project. A total of 311 unrelated patients (230 male, 81 female) received a primary diagnosis of schizophrenia (DSM-IV). Mean age of patients was 41 years (SD 14.2); mean age of onset of first psychotic symptoms was 22 years (SD 5.4). Of the 311 patients, 284 were further assessed using the Schedule for the Deficit Syndrome (SDS) (Kirkpatrick et al., 1989).

Blood was collected from each participant; screening for 22q11DS was done by means of Multiplex Ligation-dependent Probe Amplification (MLPA). MLPA is a Polymerase Chain Reaction (PCR) variant using two oligonucleotide hemiprobcs complementary to the target DNA sequence (Schouten et al., 2002). In a single reaction up to 45 target sequences can be quantified. The two hemiprobcs on each target sequence (two PCR primers, one with added variable unique length sequence) are ligated after hybridization, and subsequently amplified, each of the ligated probes producing an amplification product of unique length, which can be

detected and quantified. The resulting quantification of each probe product allows for the definition of a normal or abnormal copy number (euploidy versus a deletion or duplication) of that probe. Deletions and other rearrangements at 22q11.2 are thought to be mediated by Low Copy Repeats (LCRs) (Edelmann et al., 1999; Shaikh et al., 2000). For the detection of copy number changes occurring in the region between these LCRs, the MLPA 'Di George kit' was used (Fernandez et al., 2005). MLPA has been demonstrated to be a highly accurate assay for the detection of copy number changes at 22q11.2 (with a sensitivity and specificity of respectively 0.95 and 0.99 (Vorstman et al., 2006a)). The MLPA DiGeorge kit is commercially available (www.mrc-holland.com). In order to verify reliable detection of the 22q11.2 deletion, in each run two positive controls were included, consisting of DNA from two patients with proven 22q11.2 deletions (one common LCRA-LCRD deletion and one LCRA-LCRB deletion, assessed with fluorescence *in situ* hybridization (FISH) analysis). Quality of each run was verified by assessing the variance of the results of the control probes, which query sequences outside the 22q11.2 region.

A power calculation for comparison of the estimated prevalence in the sample size with a known prevalence was based on methods described by Machin et al. (1997). Since a prevalence of 2% of 22q11.2 deletions among schizophrenia has frequently been quoted in literature, we considered this prevalence as the 'known prevalence' in the power estimation. To detect an estimated 22q11.2 deletion prevalence of 5% in our sample, enriched for patients with the Deficit syndrome, the power of the sample was 88% at $\alpha=0.05$.

In order to calculate the prevalence of 22q11DS in the population of schizophrenia patients as a whole, we synthesized findings that were previously reported on this topic. For this purpose, the key words "22q11", "22q11DS", "VCFS" and "schizophrenia" were used in a computerized search of MEDLINE. Bibliographies from identified articles were cross-referenced. Only studies that screened random samples of schizophrenia patients were included in this calculation; studies in which samples of schizophrenia patients were screened for 22q11DS after selection for its phenotypic hallmarks were excluded. Prevalence and 95% confidence intervals were estimated for patients with schizophrenia in general, as derived from all available studies. Since patients with childhood onset schizophrenia (age of onset <13 years) may represent a homogeneous subgroup with more neuro-developmental and more cytogenetic abnormalities (Kumra et al., 2001), we also estimated the prevalence of 22q11DS in childhood onset patients and in adult onset patients with schizophrenia separately. Prevalences and their 95% confidence intervals were calculated using the Confidence Interval Analysis statistical package (CIA) (Gardner et al., 1989).

3. Results

A total of 146 out of 311 patients met the criteria for Deficit syndrome as defined by the SDS. Following SDS criteria, 138 patients were classified as non-deficit patients. Among these, 29 patients exhibited negative symptoms that could be secondary to substance abuse or medication. However, in accordance with the SDS criteria, they were classified as non-deficit schizophrenia.

In each run the two positive controls were identified, indicating the reliability of the MLPA kit. In the total sample, including the Deficit subgroup, no 22q11.2 deletions were detected with MLPA.

The results of the literature search on the prevalence of 22q11DS are shown in Table 1. Adding the results of the current study and the report of Drazinic et al. (in review) to the results from the literature search, to date a total of sixteen 22q11.2 deletions have been identified in 2133 patients with schizophrenia (0.75%, 95% confidence interval: 0.5%–1.2%). In a total of 82

childhood onset schizophrenia patients (combining the results of Ivanov et al. (2003) and Sporn et al. (2004), four 22q11.2 deletions were identified (4.9%, 95% confidence interval: 1.9%–11.9%). As a result, twelve 22q11.2 deletions have been identified in 2051 adult onset schizophrenia patients (0.6%, 95% confidence interval: 0.3%–1%).

4. Discussion

In the present study we tested the hypothesis of a higher prevalence of 22q11DS in the deficit form of schizophrenia. Furthermore, a literature search was performed to re-estimate the prevalence of 22q11DS among schizophrenia patients. Results that were previously reported on this topic were combined.

Not a single 22q11.2 deletion was found in a sample of 311 Dutch schizophrenia patients, of whom 146 met the criteria for the Deficit syndrome. A possible explanation for this negative result is that, contrary to our hypothesis, schizophrenia in 22q11DS patients is not characterized by more prominent negative symptoms as compared to schizophrenia in the general population. Indeed, Bassett et al. (2003) reported no significant differences in the core symptoms of schizophrenia, including negative symptoms, between schizophrenia patients with 22q11DS and those without 22q11DS. Also, Murphy et al. (1999) reported fewer negative symptoms in schizophrenia patients with 22q11DS than in patients without 22q11DS. However, the sample size of the deficit schizophrenia subgroup in the present study does not allow definite conclusions regarding this issue.

In the entire studied sample of schizophrenia patients, no deletions were detected. This result differs from previous studies reporting up to 2.4% of 22q11.2 deletions in random samples of schizophrenia patients with adult onset (see Table 1). Additionally, in concordance with our results, Drazinic et al. (in review) did not find any 22q11.2 deletions in a sample of 171 patients treated with clozapine, 158 of whom met the criteria for schizophrenia or schizoaffective disorder.

The prevalence derived from our literature search is less than the 2% which is often quoted in literature. Nevertheless, given an estimated prevalence of 22q11DS in the general population of 1/4 000–1/6 000 (Botto et al., 2003; Goodship et al., 1998; Oskarsdottir et al., 2004; Tezenas Du Montcel et al., 1996; Zori et al., 1998), the prevalence of 22q11DS in schizophrenia patients is still approximately 30–45 times higher than expected. The results of our literature study also show that the prevalence of 22q11DS in schizophrenia patients with childhood onset (1.9–11.9%) is considerably higher than the prevalence in schizophrenia patients with adult onset (0.3–1%). This finding is in keeping with an onset of psychotic symptoms at an early age in subjects with 22q11DS (Vorstman et al., 2006b).

In summary, in the current study no 22q11.2 deletions were detected in a sample of 311 Dutch patients with schizophrenia, in which 146 patients met the criteria for the deficit syndrome. Thus, the present study provided no evidence that this deletion is more common among deficit schizophrenia patients. Contrary to the frequently reported prevalence of 2% of 22q11DS in schizophrenia, a lower prevalence of 0.5%–1.2% of 22q11DS is calculated when summing up the total of schizophrenia patients that have been tested so far.

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Table 1

Overview of prevalence of 22q11DS in samples of patients with schizophrenia

Study	Number of 22q11DS/total number of randomly selected schizophrenia patients	Prevalence of 22q11 deletion	Population	A.O. of psychotic symptoms in 22q11DS patients	Method
Karayorgou et al. (1995)	2/100	2%	U.S., ethnicity not specified	20 y; 32 y	FISH
Arinami et al. (2001)	1/300	0.3%	Japan, unrelated patients	15 y	4 microsatellite markers + 1 single nucleotide polymorphism (SNP); confirmation by FISH
Ivanov et al. (2003)	1/329 adult onset	0.3%	United Kingdom (N=415), unrelated patients; Bulgaria (N=55).	Unclear: between 17 and 21 y	5 microsatellite markers + 1 SNP; confirmation by semi-quantitative PCR
	0/134 early onset ^a	0%			
	0/7 childhood onset ^b	0%	Exclusion: IQ < 70		
Wiehahn et al. (2004)	2/85	2.35%	South Africa, Afrikaner e.o.	19 y; 22 y	FISH and SNPs ^c
Sporn et al., (2004) ^d	4/75 childhood onset	5.33%	U.S., ethnicity not specified. Exclusion: premorbid IQ < 70	Information not provided in paper	FISH and MLPA
Horowitz et al. (2005)	6/634	0.95%	Israel, Ashkenazi Jewish e.o.	Unknown; anonymous	7 microsatellite markers + 3 SNPs
Drazinic et al. (in review)	0/158	0%	U.S., ethnicity not specified	–	FISH
Hoogendoorn (present study)	0/311	0%	The Netherlands, Dutch e.o.	–	MLPA

e.o.=ethnic origin.

A.O.=age at onset.

y=years.

^aEarly onset patients with schizophrenia (N=134) with age of onset 13–17 years (derived from Table 1, Ivanov et al., 2003).

^bSeven childhood onset patients with schizophrenia with age of onset 7–12 years (derived from Table 1, Ivanov et al., 2003).

^cIn the study of Wiehahn et al. (2004), 85 patients with schizophrenia were only subjected to FISH when they met two or more positive screening criteria for 22q11DS. Six patients met these criteria and were tested by FISH; two were found to have a deletion on the 22q11 locus. However, as the authors mention, in an independent set of studies by Liu et al. (2002a,b), the entire sample of 85 patients was genotyped using a panel of single nucleotide polymorphisms (SNPs) from the 22q11 locus. The same two patients identified by FISH as carrying a deletion were homozygous for all SNPs. The other 83 patients were heterozygous for at least one marker locus, therefore the presence of a 22q11 deletion was excluded in these patients.

^dUsiskin et al. (1999) reported a prevalence of 6.4% of 22q11 deletions in childhood onset schizophrenia (COS) patients (3 patients with a deletion out of 47 COS patients). However, the sample of Usiskin et al. was not included in our prevalence calculation as these 47 patients are all included in the sample that is described by Sporn et al. (2004).