Schizophrenia Research 159 (2014) 340–346

Contents lists available at ScienceDirect

Schizophrenia Research

journal homepage: www.elsevier.com/locate/schres

Does rare matter? Copy number variants at 16p11.2 and the risk of psychosis: A systematic review of literature and meta-analysis

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ARTICLE INFO

Article history:
Received 7 June 2014
Received in revised form 16 September 2014
Accepted 16 September 2014
Available online 11 October 2014

Keywords:
CNV
Copy number variation
16p11.2
Duplication
Psychosis
Schizophrenia
Bipolar disorders
Schizoaffective disorder

ABSTRACT

Background: In the last 5 years an increasing number of studies have found that individuals who have micro-duplications at 16p11.2 may have an increased risk of mental disorders including psychotic syndromes.
Objective: Our main aim was to review all the evidence in the literature for the association between copy number variants (CNVs) at 16p11.2 and psychosis.
Methods: We have conducted a systematic review and a meta-analysis utilising the PRISMA statement criteria. We included all original studies (published in English) which presented data on CNVs at 16p11.2 in patients affected by schizophrenia, schizoaffective disorder or bipolar disorder.
Results: We retrieved 15 articles which fulfilled our inclusion criteria. Eleven articles were subsequently selected for a meta-analysis that showed a 10 fold increased risk of psychosis in patients with proximal 16p11.2 duplications. We conducted a second meta-analysis of those studies with low risk of overlap in order to obtain the largest possible sample with the lowest risk of repeated results: 5 studies were selected and we found an odds ratio (OR) of 14.4 (CI = 5.2–39.8; $p < 0.001$) for psychosis with proximal 16p11.2 duplications. The results were not significant for micro-deletions in the same region. Finally extracting only those studies that included patients with schizophrenia we found an OR = 16.0 (CI = 5.4–47.3: $p < 0.001$)
Conclusions: There is a fourteen fold-increased risk of psychosis and a sixteen fold increased risk of schizophrenia in individuals with micro-duplication at proximal 16p11.2.

1. Introduction

There continues to be a debate as to whether genetic influences on schizophrenia are better explained by a "common disease-common allele model" or a multiple rare variant model where mutations are highly penetrant, individually rare, of recent origin and sometimes specific to individuals or families (Walsh et al., 2008; St Clair, 2009; Vassos et al., 2010). There has also been a growing interest in the study of the different psychiatric conditions (such as autism, ADHD, bipolar disorder and schizophrenia) and copy number variants (CNVs) (Kirov, 2010; Grayton et al., 2012). CNVs are micro-deletions and micro-duplications of segments of genome ranging from a few hundred base pairs to several megabases (Grayton et al., 2012). Genome wide screening for CNVs has become possible with the development of micro-array based technologies, namely array comparative genomic hybridization (aCGH) and genome wide SNP chips.

Micro-deletions at 1q21.1, 15q11.2, and 22q11.2, and micro duplications at 16p11.2 have been associated with an increased risk of schizophrenia (Kirov, 2010). Furthermore it appears that some of the CNVs associated with schizophrenia have a pleiotropic effect: the same CNV can be associated with several different clinically defined conditions such as epilepsy, ADHD, obesity, intellectual disability, schizophrenia, bipolar disorder, autism and even normal phenotype (St Clair, 2009; van Winkel et al., 2010).

Our main aim was to synthesize the current evidence for the association of CNVs at 16p11.2 (proximal and distal loci) and psychosis (encompassing Schizophrenia, Schizoaffective Disorder and Bipolar Disorders). Our secondary aim was to investigate the association between schizophrenia sensu strictu and 16p11.2 CNV.

2. Methods

We applied the PRISMA Statement Criteria (Liberati et al., 2009) to our systematic search of the literature.

All primary genetic studies were included. Primary genetic studies were defined as studies where CNVs were investigated in new case control samples, historic case control samples or a combination of both. We also included meta-analyses of the association between CNVs at

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http://dx.doi.org/10.1016/j.schres.2014.09.025

16p11.2 and psychosis. We did not limit our search based on the age of participants and we did not apply any publication date restrictions.

We identified all relevant studies by searching PubMed, Web of Knowledge and OMIM. The search was run on 13 October 2013 and re-run again on 5 March 2014.

We used the following search terms to browse the three databases:

- PubMed, (title/abstract): {16p11.2 OR 16p11 2} AND {Schizophrenia OR Bipolar OR Psychosis OR Schizoaffective};
- OMIM, by searching for 16p11.2 and 16p11 2;
- Web of Knowledge, by searching (topic) {16p11.2 OR 16p11 2} AND {Schizophrenia OR Bipolar OR Psychosis OR Schizoaffective}.

The eligibility assessment was performed by GG.

We excluded studies published in languages other than English, studies that focused on animal samples, narrative reviews, systematic reviews, commentaries, letters to the editor, editorials, PhD theses, book chapters and any data presented orally or in the form of posters.

We developed our own quality control grid as we could not find any standardized methodology applicable to psychiatric genetic studies.

GG conducted initial quality assessment of the included studies, and afterwards NB checked the quality controlled data. Any disagreement was resolved by discussion between the two authors and if an agreement could not be reached, a third author (AM) adjudicated an outcome.

2.1. Statistical analysis

We extracted relative risks and calculated their standard errors and confidence interval. The pooled relative risk (95% confidence interval) was estimated using a fixed effect model, weighting for the inverse variance. The fixed effect approach assumes that all the studies are estimating the same effect and only random variation between subjects leads to the observed study effect to vary. This approach has been shown to be more conservative compared to using a random effects model (Poole and Greenland, 1999). We explored heterogeneity using a forest plot. We tested for the presence of heterogeneity amongst studies using Cochran's Q statistics where a value close to 0 indicates there is no heterogeneity and we used I^2 statistic to quantify the degree of heterogeneity. The I^2 statistics ranges from 0% to 100% and provides a measure of the level of inconsistency across studies. Sensitivity analyses included combining studies of low risk of overlapping. We also assessed the impact of each study on the pooled estimate by omitting one study at a time to see the extent to which inferences depended on a particular study. We visually examined estimated effect sizes against their standard errors using funnel plots as recommended by Sterne et al. (2008) for evidence of bias and heterogeneity. Analyses were carried out in Stata V.13.

3. Results

3.1. Study selections for the systematic review

A total of 15 studies were identified for inclusion in our review (please see Fig. 1 for a flowchart summary). The search of Web of Knowledge, PubMed and OMIM databases provided a total of 100 citations. After adjusting for duplicates, 76 remained. After reviewing by title and abstract 56 were discarded as they clearly did not meet our inclusion criteria. Four articles were retrieved after hand searching references in articles already selected and by hand searching references in previous reviews of the literature regarding the topic. One further article (Zheng et al., 2013) which was originally excluded due to it being a letter to the editor was later retrieved as it communicated original results. Therefore, a total of 25 articles were retrieved and fully analysed with their supplements.

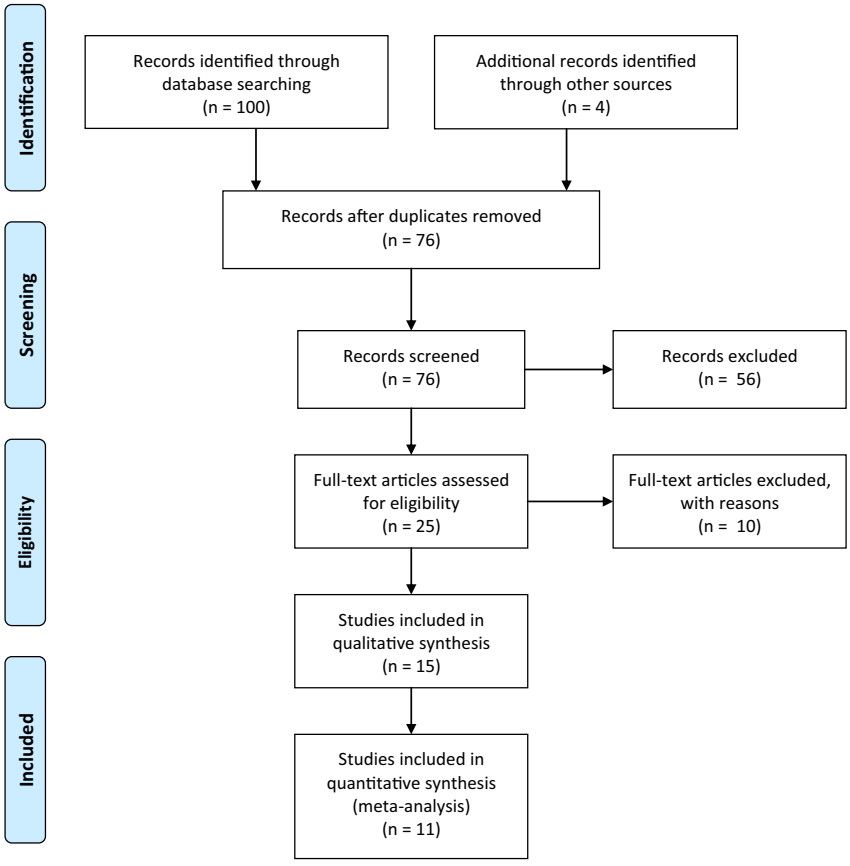

Fig. 1. Flowchart of study selection.

Of these 25 articles, one was excluded as it did not contain original data (a). Two studies were excluded because they focused on the detection of CNVs in intellectual disability (b,c). One article was excluded as it repeated data from a previous study by the same author (d). Four studies were excluded either because we could not retrieve specific information regarding the association between 16p11.2 CNV and schizophrenia or because the data was a mixture of both historical and new data focused on a different mental health disorder than the ones in our search criteria (e,f,g,h). One study was excluded as it presented data on a single nucleotide polymorphism in 16p11.2 (i). A further study (J) was excluded as its full data set was included in the study by Guha et al. (2013) (progressive alphabetical letters refer to supplementary references found in supplementary material table C).

For a summary of the results of each individual study please see Table 1 (for more details for each study please see supplementary material text D).

3.2. Study selection for the meta-analyses, summary of results and quality appraisal

For the meta-analysis we explored deletions and duplications at proximal 16p11.2. 11 studies were included. The studies by Guha et al. (2013) and Rees et al. (2014) were excluded because they focused on a distal region of 16p11.2. The study by Ahn et al. (2014) was excluded because the study design differed from all the others i.e. it hypothesized a higher frequency of 16p11.2 CNVs in COS vs healthy siblings and vs adult onset SCZ and did not therefore represent a straight forward case control study design. Likewise the study Levinson et al. (2012) was also excluded because their study was not a case control study, and the Grozeva et al. (2010) study was excluded because they had focused their analysis on a healthy control group compared with historical results in patients with SCZ.

In our pre-quality control meta-analysis, we utilized a fixed effect (M-H) method and found a pooled OR = 10.0 (CI = 6.3–15.8; heterogeneity chi-squared = 13.34 (d.f. = 16); $p = 0.647$; $I^2 = 0\%$; test of OR = 1; $z = 9.87$; $p < 0.001$) for duplication and psychosis (see Fig. 2.); whereas for deletions we found a pooled OR = 0.736 (CI = 0.334–1.622; heterogeneity chi-squared = 3.04 (d.f. = 5); $p = 0.694$; $I^2 = 0\%$; test of OR = 1; $z = 0.76$; $p = 0.447$).

Two studies (Guha et al., 2013; Rees et al., 2014) focused on CNVs in a distal region of 16p11.2. Whilst Guha et al. showed a six fold increased risk for SCZ and SCD for deletions, Rees et al. failed to replicate these findings. The latter provided a combined analysis which showed an overall OR = 3.39 (CI = 1.21–9.52; $p = 0.017$).

Four studies that analysed the relationship between 16p11.2 CNV duplications and BD, only the meta-analysis of McCarthy et al. (2009) found a statistically significant increased risk of four times in patients with the duplication (OR = 4.3; CI = 1.3–14.5; $p = 0.017$), whilst the others failed to replicate significant results (Grozeva et al., 2010; Bergen et al., 2012; Rees et al., 2014).

For a summary of the quality check list and risk of overlapping of each study please see Table 2 (also see supplementary table SA for the methodology used to detect CNV and supplementary table SB for the samples used in the analyses).

We defined a "high quality" study as those which fulfilled any three of the first five quality criteria in the grid. If the study didn't meet the

Table 1
Summary of the results for duplication and their odds (i.e. odds ratios) ratios for each individual study.

Study	Type of study	Definition of caseness	*N* cases	*N* with dup (%)	*N* controls	*N* dup (%)	OR for dup (CI, *p*)
Walsh et al., 2008	Prim	COS	83	2 (2.4)	77	0	4.75 (0.2–100.6, 0.32)
	Prim	SCZ	150	0	268	0	NA
McCarthy et al., 2009	Prim	SCZ	1906	12 (0.63)	3971	1 (0.03)	25.2 (3.3–193.6, 2×10^{-5})
	Rep	SCZ	2645	9 (0.34)	2420	1 (0.04)	8.3 (1.3–50.5, 0.022)
	Comb	SCZ	5877	21 (0.36)	6391	2 (0.03)	14.5 (3.3–62.0, 4.3×10^{-5})
	Rep	BD	3315	4 (0.12)	NR	NR	NR
	MA	SCZ	8590	26 (0.30)	28,406	8 (0.03)	8.4 (2.8–25.4, 4.8×10^{-7})
	MA	BD	4822	6 (0.12)	25,225	7 (0.03)	4.3 (1.3–15.5, 0.017)
Grozeva et al., 2010	Prim	BD + SCD	1697	3 (0.18)	2806	1 (0.03)	5.0 (0.5–47.8, 0.16)
Levinson et al., 2011	Prim	SCZ + SCD	3945	13 (0.33)	3611	1 (0.03)	11.9 (1.56–91.28, 0.003)
	MA	SCZ + SCD	9890	31 (0.31)	29,597	8 (0.03)	11.8 (35.4–25.6, 1.5×10^{-8})
Vacic et al., 2011	Prim	SCZ	802	4 (0.50)	742	0	8.4 (0.5–155.7, 0.15)
	Rep	SCZ	7488	18 (0.24)	6689	1 (0.01)	16.1 (2.1–120.8, 0.007)
	Comb	SCZ	8290	22 (0.26)	7431	1 (0.01)	19.8 (2.7–146, 0.003)
Bergen et al., 2012	Prim	SCZ	1505	9 (0.60)	2087	1 (0.05)	12.6 (1.6–99.2, 0.02)
	Prim	BD	834	1 (0.12)	2087	1 (0.05)	2.5 (1.2–40.0, 0.54)
Van Den Bossche et al., 2012	Prim	SCZ	1270	2 (016)	1145	2 (0.17)	0.9 (0.1–6.4, 0.9)
	Prim	BD	598	2 (0.33)	1145	2 (0.17)	1.9 (0.3–13.7, 0.51)
Levinson et al., 2012	Prim	SCZ + SCD	1357	2 (0.15)	1104	1 (0.09)	1.63 (0.14–17.98, 0.70)
Grozeva et al., 2012	Hx	NA	NA	NA	10,259	4 (0.039)	NA
	Hx-Comb	SCZ	8590	26 (0.3)	38,665	12 (0.031)	9.8 (4.9–19.4, 1.8×10^{-15})
	Rep	BD	7333	NA	43,779	NA	1.1 (1.0–1.1, >0.0001)
Szatkiewicz et al., 2013	Prim	SCZ	3962	9 (0.23)	5318	1 (0.02)	11.7 (1.5–92.3, 0.02)
Ahn et al., 2014	Prim	COS	126	2 (1.59)	69	0	2.8 (0.1–59.0, 0.50)
Priebe et al., 2013	Prim	SCZ + SCD	1637	1 (0.61)	1627	0	3.0 (0.1–73.3, 0.50)
Zheng et al., 2013	Prim	SCZ	882	3 (0.34)	954	0	7.6 (0.4–147.3, 0.18)
	Rep	SCZ	779	2 (0.26)	926	0	6.0 (0.3–124.3, 0.24)
Guha et al., 2013	Prim	SCZ + SCD	790	0	1347	1 (0.07)	NA
	Prim	SCZ + SCD	662	1 (0.15)	662	0	NA
	Rep	SCZ + SCD	12,398	5 (0.04)	17,945	12 (0.067)	NA
	Rep	SCZ + SCD	13,850	6 (0.04)	19,954	13 (0.06)	NA
Rees et al, 2014	Prim	SCZ	6882	27 (0.39)	6316	0	50.7 (3.1–inf, 2.3×10^{-8})
	Meta	SCZ	16,772	58 (0.35)	63,068	19 (0.03)	11.52 (6.86–19.34, 2.9×10^{-24})
Rees et al, 2014 (distal)	Prim	SCZ	6882	0	6316	2 (0.03)	NA (0–3.82,1)
	Meta	SCZ	20,732	13 (0.06)	27,045	5 (0.02)	3.39 (1.21–9.52, 0.017)

Prim = primary; Rep = replication; Comb = combination; MA = meta-analysis, Hx = historical, Hx-Comb = historical combined, SCZ = schizophrenia; BD = bipolar disorder; SCD = schizoaffective disorder; PSY = psychosis; COS = childhood onset schizophrenia; NA = not applicable; NR = not reported, Dup = duplication, Del = deletions, OR = odds (i.e. odds) ratio, CI = confidence interval, distal = focused on the distal portion of 16p11.2.

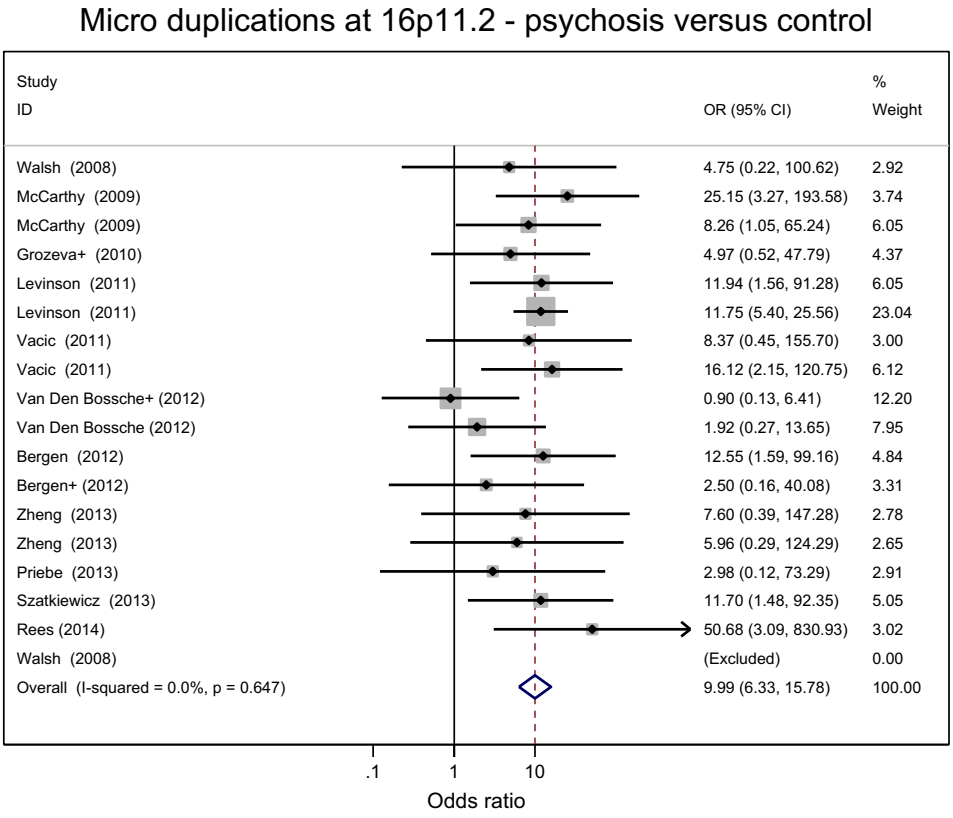

Fig. 2. Forest plots displaying the effect of 16p11.2 micro-duplications in patients with psychosis versus controls (please note that some studies are repeated as they present different sets of original data; the studies marked with + refer to BD). Note on case samples included (for greater detail please see Supplementary Table B): Walsh et al.(1)—original data only included; McCarthy et al.(1)—original data (discovery sample), McCarthy et al.(2)—original data (replication sample); Grozeva, et al.—WTCCC (BD); Levinson et al.(1)—original data (MGS), Levinson et al.(2)—meta analysis (ISC, McCarthy discovery and replication samples and MGS); Vacic et al.(1)—original data, Vacic et al.(2)—replication (MGS and ISC); Van Den Bossche et al.(1)—original data (BD), Van Den Bossche et al.(2)—original data (SCZ); Bergen et al.(1)—original data (SCZ; Swedish register cohort and original sample), Bergen et al.(2)—original data (BD), Zheng et al.(1)—original data (discovery sample), Zheng et al.(2)—original data (replication sample); Priebe et al.—original data; Szatkiewicz et al.—original data and Swedish register cohort; Rees et al.—original sample (CardiffCOGS and CLOZUK); Walsh et al.(2)—original data (family sample study design therefore excluded).

aforementioned standard then it was defined as "low quality". In total, ten of the studies met the threshold for high quality. As this quality appraisal did not manage to screen for the risk of repeated measure we therefore analysed only those studies which showed a low likelihood of overlapping results (Walsh et al., 2008; Priebe et al., 2013; Zheng et al., 2013; Rees et al., 2014). We also included the most recent and largest study (Vacic et al., 2011), which despite presenting a high risk of overlapping results actually showed a low likelihood to overlap with the four aforementioned studies. This was done in order to maximize the pool of patients and controls selected with a minimum risk of overlapping results.

Out of the 5 studies which passed our quality control measure for low risk of overlapping we found a M-H pooled OR = 14.4 (CI = 5.2–39.8; heterogeneity chi-squared = 2.85 (d.f. = 6); $p = 0.827$; $I^2 = 0\%$; test of OR = 1; z = 5.13; $p < 0.001$) for duplications (see Fig. 3).

The meta-analysis was then repeated focusing only on cases with schizophrenia and therefore the study by Priebe et al. (2013) was excluded. For this meta-analysis we found M-H pooled OR of 16.0

Table 2
Summary of the quality grid and risk of overlapping for each study for duplication and their odd ratios for each individual study.

Study	Description of population	Use of standardized measurement for diagnosis	Screening of control group	Validation experiments	Use of historical control	Likelihood of overlapping with previous studies (low, high)
Walsh et al. (2008)	Yes	Yes	No	No	No	Low
McCarthy et al. (2009)	Yes	Yes	Yes	Yes	No	High
Grozeva et al. (2010)	Yes	Yes	Yes	No	Yes	High
Levinson et al. (2011)	Yes	Yes	Yes	Yes	No	High
Vacic et al. (2011)	Yes	Yes	Yes	Yes	No	High
Bergen et al. (2012)	Yes	Yes	Yes	Yes	No	High
Van Den Bossche et al. (2012)	Yes	Yes	Yes	No	No	High
Levinson et al. (2012)	Yes	Yes	Yes	Yes	No	High
Grozeva et al. (2012)	Yes	Yes	Yes	Yes	Yes	High
Szatkiewicz et al. (2013)	Yes	Yes	Yes	Yes	No	High
Ahn et al. (2014)	Yes	Yes	Yes	Yes	Yes	Low
Priebe et al. (2013)	Yes	Yes	No	Yes	No	Low
Zheng et al. (2013)	No	No	No	Yes	No	Low
Guha et al. (2013)	Yes	Yes	Yes	Yes	No	High
Rees et al. (2014)	Yes	Yes	Yes	Yes	Yes	Low

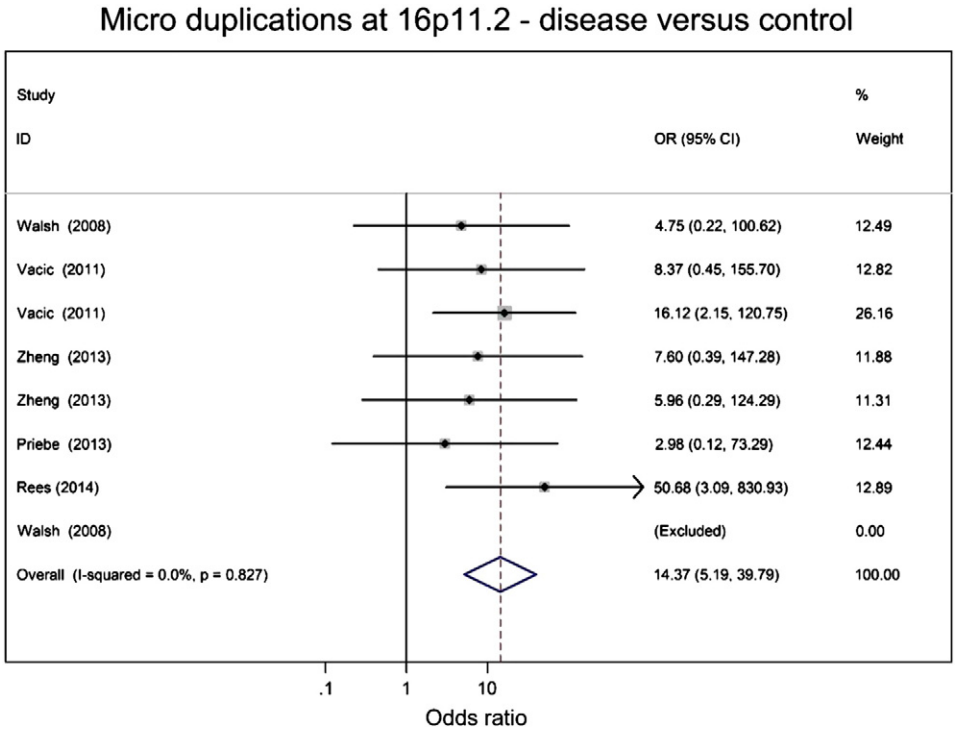

Fig. 3. Forest plots displaying the effect of 16p11.2 micro-duplications in patients with psychosis versus controls after selection of low risk of overlapping studies (please note that some studies are repeated as they present different sets of original data). Note on case samples included (for greater detail please see Supplementary Table B): Walsh et al.(1)—original data only included; Vacic et al.(1)—original data, Vacic et al.(2)—replication (MGS and ISC); Zheng et al.(1)—original data (discovery sample), Zheng et al.(2)—original data (replication sample); Priebe et al.—original data; Rees et al.—original sample (CardiffCOGS and CLOZUK); Walsh et al.(2)—original data (family sample study design therefore excluded).

(CI = 5.4–47.3; heterogeneity chi-squared = 2.10 (d.f. = 5) $p = 0.836$; I-squared = 0.0%; test of OR = 1; $z = 5.00$ $p < 0.001$).

4. Discussion

There is increasing interest in CNVs at 16p11.2 because of their association with psychosis. Of the 15 studies that we retrieved, seven had reported significant association between adult onset SCZ and SCD and 16p11.2 duplications, with frequencies ten times higher (ranging from approximately 0.2% to 0.6%) in cases compared to controls (0% to 0.07%). They also found an increased risk of SCZ or SCD that was between 8 and 25 times higher in individuals with 16p11.2 duplications (McCarthy et al., 2009; Levinson et al., 2011; Vacic et al., 2011; Bergen et al., 2012; Szatkiewicz et al., 2013; Rees et al., 2014) (we can confidently approximate the OR to the risk ratio because the disorder is rare). On the other hand three studies which showed increased frequencies of duplications in cases still failed to find a statistical significance, possibly due to smaller datasets (Van Den Bossche et al., 2012; Priebe et al., 2013; Zheng et al., 2013).

Walsh et al. (2008) and Ahn et al. (2014) focused their analysis on COS; a more severe and possibly more genetically loaded form of SCZ. Despite finding an increased frequency of duplications in cases with SCZ compared with controls (2.4% and 0.61% respectively) than in similar studies of adult onset SCZ, their results did not reach statistical significance.

The role of deletions at the distal region of 16p11.2 and psychosis is still highly uncertain with one study finding an association and one study that failed to replicate this finding (Guha et al., 2013; Rees et al., 2014). Similar uncertainty is also seen in the evidence for the role of duplications at the proximal 16p11.2 and the risk of bipolar disorder (Grozeva et al., 2010; Bergen et al., 2012; Van Den Bossche et al., 2012).

4.1. Strength of our study

To our knowledge we have been the first to have rigorously applied the PRISMA statement criteria to conduct a meta-analysis of the risk for CNVs at 16p11.2 and psychosis. Furthermore, in doing so, we believe this to be the first study to have applied a systematic quality control and incorporate the risk of overlapping results criteria to our meta-analysis. Several previous publications (Levinson et al., 2011; Rees et al., 2014) have provided original results and combined/meta-analytical results with previous datasets; however we argue that the choice of previous dataset appeared at times arbitrary and not supported by a rigorous selection.

4.2. Limitations of our study

Despite the low heterogeneity within our selected studies there are intrinsic limitations in combining observational studies as reported by Stroup et al. (2000).

We encountered a systematic *positive results bias*; in fact by utilizing the standard search methods we have only been able to detect studies which showed positive results either in the cases or in the controls. Hence studies which find no CNVs at 16p11.2 usually do not report their analysis in their text or tables and so escaping the search engine search. For example our own study of CNV in BD was not detected by the search parameters utilized here (McQuillin et al., 2011). We have however investigated though rigorous criteria all literature in different search engines.

Finally we did not go further than searching data presented in the original article or in the supplementary information published in the same journal. To access the entire database was going beyond the scope of our study; unfortunately this causes an intrinsic risk of

re-counting the same findings more than once with a risk of the over-inflation of positive findings (either deletions or duplications). However, the frequency in cases and controls is fairly consistent across studies and large numbers have been included in the meta-analysis giving the best possible estimate of the effect sizes of CNV at this locus in SCZ.

5. Conclusions

The concept that certain recurrent CNVs, including 16p11.2, are important risk factors for a small proportion of patients with Schizophrenia is rapidly gaining credence. A number of rare CNVs that appear to have pleiotropic CNS effects can be considered strong susceptibility loci for a broad range of neurodevelopmental disorders. In other words the risk associated with these CNVs is not exclusively for schizophrenia. It will be important to investigate whether healthy controls with 16p11.2 duplications have neuropsychological intermediate phenotypes (Stefansson et al., 2014).

In our meta-analysis on 11 studies we robustly confirmed a ten-fold increased risk of psychotic illness in patients with proximal 16p11.2 duplications. Moreover in our "post-screening for risk of overlapping sample" analysis we found a fourteen fold increased risk for psychosis in patients with the duplications.

We found no statistical association between micro-deletions and psychosis at proximal 16p11.2. Guha et al. (2013) and Rees et al. (2014) were the only studies that explored in two independent samples the distal portion of the same region, the first finding a strong association between micro-deletions and psychosis but the other failing to observe any deletion in 6882 cases with SCZ.

The robust association of 16p11.2 duplications and psychosis argues for a detailed study of the duplicated region. It is important to determine how the duplication confers this increased risk of psychosis e.g. by gene or micro RNA dosage effect.

Role of funding source

This study was not funded by any public, private or not-for-profit grants.

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Conflict of interests

Dr Giaroli has received honoraria for serving on a speaker bureau for Ely Lilly, Shire and FlynnPharma; also he has served as board advisor for Shire.

The other authors declare no conflict of interests.

Acknowledgement

This study did not receive funding from any public, private or not-for-profit grants.

Appendix A. Supplementary data

Supplementary data to this article can be found online at http://dx.doi.org/10.1016/j.schres.2014.09.025.

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