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Meta-analysis of magnetic resonance imaging studies in chromosome 22q11.2 deletion syndrome (velocardiofacial syndrome)

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ABSTRACT

Objectives: 22q11.2 deletion syndrome (22q11.2DS), also known as velocardiofacial syndrome (VCFS) or DiGeorge Syndrome, is a genetic disorder due to a micro deletion on chromosome 22q11.2. VCFS is associated with abnormalities in brain structure and with an increased risk of psychiatric disorders, particularly schizophrenia. The aim of this review was to statistically summarize the structural imaging literature on VCFS which due to the relatively rarity of the disorder tends to consider small sample sizes.
Method: A systematic review and meta-analysis of region of interest (ROI) studies comparing VCFS with healthy controls was carried out. Significant heterogeneity was explored using meta-regression.
Results: Subjects with VCFS were characterised by global brain volumetric reduction including several cortical regions, cerebellum and hippocampus. The area of the corpus callosum was increased.
Conclusions: Many regions extensively studied in schizophrenia were not covered in the existing VCFS literature. However, the studies considered support volumetric abnormalities which may help explain why VCFS is associated with a greatly increased risk of psychosis and other psychiatric disorders.

1. Introduction

Chromosome 22q11.2 deletion syndrome (22q11.2DS), affects approximately 1 in 5000 live births (Tézenas Du Montcel et al., 1996) and refers to a group of previously distinct genetically determined disorders (velocardiofacial syndrome, Shprintzen syndrome, DiGeorge syndrome, conotruncal anomaly face syndrome, Cayler cardiofacial syndrome, and CATCH 22 syndrome) caused by a microdeletion on the long arm of chromosome 22 (Scambler et al., 1992). VCFS is characterised by a distinct phenotype including a typical facial appearance, cleft palate, velopharyngeal insufficiency, cardiac anomalies (McDonald-McGinn et al., 1999; Swillen et al., 1997), learning disabilities and by an increased risk for psychotic disorders (Henry et al., 2002; Gothelf et al., 2004a,b; Baker and Skuse, 2005; Papolos et al., 1996; Niklasson et al., 2002) particularly schizophrenia (Murphy et al., 1999). More specifically, psychotic symptoms have been diagnosed in up to 30% of adolescents and adults with 22q11.2DS (Murphy et al., 1999). Moreover, the deletion has been found in 1–6% of people with schizophrenia (Murphy et al., 1998; Yan et al., 1998).

This association has led to considerable research to morphologically characterise 22q11.2DS brain abnormalities and potential similarities with schizophrenia. Magnetic

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resonance imaging (MRI) has allowed detailed in vivo examination of brain structures in people with 22q11.2DS but the evidence is inconclusive (Eliez et al., 2000; Kates et al., 2001; Simon et al., 2005; Eliez et al., 2002; Kates et al., 2006; Campbell et al., 2006; Gothelf et al., 2007; DeBoer et al., 2007; Shashi et al., 2004). This is in part due to the relative rarity of the disorder and the tendency for studies to be small and potentially underpowered. Nevertheless, even taking this into account, the literature appears heterogeneous and published significant effect sizes differ in both direction and magnitude.

The aim of this meta-analysis was to apply quantitative methods to characterise morphometric differences in 22q11.2DS in comparison with healthy controls by 1) identifying region of interest (ROI) studies which offered measurements of brain regions in 22q11.2DS and 2) synthesizing findings using random effects meta-analysis. We also assessed heterogeneity to clarify the role of a number of variables including year of publication, age, sex, IQ, scanner strength and slice thickness.

2. Materials and methods

2.1. Search strategy and inclusion/exclusion criteria

A comprehensive search from a range of electronic databases, including Medline, EMBASE, PsycINFO, and PubMED was conducted up to March 2008 that reported structural MRI data in people with 22q11.2DS and unaffected controls. Search terms used to identify the studies included 'Velocardiofacial syndrome', 'DiGeorge syndrome', '22q11.2 deletion syndrome' and related terms combined using the AND operator with 'Magnetic Resonance Imaging'. The search was also supplemented by a manual and bibliographic cross-referencing. We placed no limit on year of publication. Studies were included if they were published as a peer reviewed article and presented original data which compared a sample of genetically diagnosed 22q11.2DS subjects with a group of healthy controls. Only studies reporting structural MRI data where means and standard deviations were available (or could be extracted) for each group were included. Researchers were contacted if this information was not immediately available in an otherwise acceptable report. Studies were excluded if data were included in more recent larger studies. Data were extracted from all included studies by one author (GMT) and checked by another author (DA). Characteristics including age, sex and IQ of the 22q11.2DS and control groups which may have confounded any observed difference were also recorded as was the year of publication, scanner strength and slice thickness. Data were utilised when volume or area results were available for a region of interest (ROI) from three or more studies. Whereas volumes were acquired from more than one slice, callosal area was measured from one mid-sagittal slice. Volume and area data were never combined in the same analysis.

2.2. Statistical analysis

Statistical analysis was conducted using STATA 9.0 (Stata Corp, College Station, Texas) supplemented by 'Metan' software downloadable from the Centre for Statistics in Medicine, Oxford, UK. Standardised mean differences were calculated using Cohen's d statistic:

$$\text{Cohen}'s\, d = \frac{\overline{X}_1 - \overline{X}_2}{\text{SD}_p}$$

where $\overline{X}_1$ and $\overline{X}_2$ are the mean volumes from the first and second groups respectively and SD_p is the pooled standard deviation estimated from both groups:

$$\text{SD}_p = \sqrt{\frac{(n_1-1)\text{SD}_1^2 + (n_2-1)\text{SD}_2^2}{(n_1 + n_2 - 2)}}$$

where n_i and SD_i are the mean and standard deviation of the 'ith' group. Standardised effect sizes were then combined using the inverse variance method. The standard deviation of Cohen's d is estimated as:

$$\text{SD}(d)\sqrt{\frac{N}{n_1 n_2} + \frac{d^2}{2(N-2)}}$$

where N is the total sample size for the study, d is Cohen's d and n_1 and n_2 are as defined above. Random effects analyses (DerSimonian and Laird, 1986) were used throughout to weight each study. The presence of heterogeneity was tested using the Q-test and its magnitude estimated using I^2 and can be interpreted as the proportion of variance in effect size due to heterogeneity (Higgins et al., 2003). When the Q-test was significant, a Galbraith plot was used to identify those studies contributing the greatest amount to that heterogeneity to investigate potential causes. Publication bias which describes the excess of low-precision studies providing effect sizes of magnitude greater than the average was tested with the Egger's test (Egger et al., 1997). Significance level was set at $P<0.05$.

To further investigate causes for heterogeneity, meta-regression analyses were performed for the following variables: mean age, sex, IQ, scanner strength, slice thickness and year of publication. The STATA program "metareg.ado" was used throughout and the REML (restricted maximum likelihood) method used to estimate the model parameters.

3. Results

3.1. Systematic search

The literature search identified 156 publications of which 48 were retrieved in full text format. Fig. 1 summarises the study flow and reasons for exclusion. Twenty-two studies met inclusion criteria and were included in the final analysis which provided information on 35 regions of interest (Table 1). Images were manually traced reflecting similar anatomical borders and used different software programs to aid image processing. In some cases a semiautomated stereotactic based parcellation method was used (e.g. Eliez et al., 2000). All the studies used the same in-situ hybridization technique but did not report on the extent of the microdeletion. Three of these studies were included after