Research in Developmental Disabilities 34 (2013) 116–125

Contents lists available at SciVerse ScienceDirect

Research in Developmental Disabilities

Subtypes in 22q11.2 deletion syndrome associated with behaviour and neurofacial morphology

Brooke Sinderberry [b], Scott Brown [a], Peter Hammond [c], Angela F. Stevens [f], Ulrich Schall [b,d,e], Declan G.M. Murphy [f], Kieran C. Murphy [g], Linda E. Campbell [a,d,e,*]

[a] School of Psychology, University of Newcastle, New South Wales, Australia
[b] School of Medicine and Public Health, University of Newcastle, New South Wales, Australia
[c] University College London, London, United Kingdom
[d] Hunter Medical Research Institute, New South Wales, Australia
[e] Schizophrenia Research Institute, Sydney, New South Wales, Australia
[f] King's College London, Institute of Psychiatry, United Kingdom
[g] Department of Psychiatry, Royal College of Surgeons in Ireland, Dublin, Ireland

ARTICLE INFO

Article history:
Received 11 May 2012
Received in revised form 24 July 2012
Accepted 24 July 2012
Available online 30 August 2012

Keywords:
Velo-cardio-facial syndrome (VCFS)
22q11.2 deletion syndrome (22q11DS)
DiGeorge syndrome
Cluster analysis
k-Means
Subtype
Behavioural phenotype

ABSTRACT

22q11.2 deletion syndrome (22q11DS) has a complex phenotype with more than 180 characteristics, including cardiac anomalies, cleft palate, intellectual disabilities, a typical facial morphology, and mental health problems. However, the variable phenotype makes it difficult to predict clinical outcome, such as the high prevalence of psychosis among adults with 22q11DS (~25–30% vs. ~1% in the general population). The purpose of this study was to investigate whether subtypes exist among people with 22q11DS, with a similar phenotype and an increased risk of developing mental health problems. Physical, cognitive and behavioural data from 50 children and adolescents with 22q11DS were included in a *k*-means cluster analysis. Two distinct phenotypes were identified: Type-1 presented with a more severe phenotype including significantly impaired verbal memory, lower intellectual and academic ability, as well as statistically significant reduced total brain volume. In addition, we identified a trend effect for reduced temporal grey matter. Type-1 also presented with autism-spectrum traits, whereas Type-2 could be described as having more 22q11DS-typical face morphology, being predominately affected by executive function deficits, but otherwise being relatively high functioning with regard to cognition and behaviour. The confirmation of well-defined subtypes in 22q11DS can lead to better prognostic information enabling early identification of people with 22q11DS at high risk of psychiatric disorders. The identification of subtypes in a group of people with a relatively homogenous genetic deletion such as 22q11DS is also valuable to understand clinical outcomes.

* Corresponding author at: School of Psychology, University of Newcastle, Science Offices, Ourimbah, NSW 2258, Australia. Tel.: +61 02 43494490; fax: +61 02 43494404.
E-mail addresses: Brooke.Sinderberry@newcastle.edu.au (B. Sinderberry), Scott.Brown@newcastle.edu.au (S. Brown), p.hammond@ucl.ac.uk (P. Hammond), stevens@ot32.wanadoo.co.uk (A.F. Stevens), Ulrich.Schall@newcastle.edu.au (U. Schall), declan.murphy@kcl.ac.uk (Declan G.M. Murphy), KMurphy@rcsi.ie (K.C. Murphy), Linda.E.Campbell@newcastle.edu.au (L.E. Campbell).

0891-4222/$ – see front matter © 2012 Elsevier Ltd. All rights reserved.
http://dx.doi.org/10.1016/j.ridd.2012.07.025

1. Introduction

It is evident that the genetic basis of many psychiatric disorders is heterogeneous. However, there is growing consensus that the study of well-defined genetic disorders with unusually high rates of psychiatric disorders can be used as models to increase understanding of pathways to psychopathology not only in the disorder itself but also in the general population (Murphy & Owen, 2001). One such disorder is 22q11.2 deletion syndrome (22q11DS), a relatively common genetic disorder associated with a spontaneous or inherited single interstitial deletion of ~40 genes on chromosome 22q11.2 (Shprintzen, 2005). This microdeletion disorder occurs de novo in ~85% of cases, and is otherwise inherited. The prevalence of 22q11DS is 1 in 4000 live births (Óskarsdóttir, Vujic, & Fasth, 2004). However, the incidence of 22q11DS is likely to be higher due to the fatality of some associated sequences such as Potter sequence (Devriendt, Moerman, & Van Schoubroeck, 1997; Wraith, Super, Watson, & Phillips, 1985).

People with 22q11DS often have a typical facial morphology and a high frequency of congenital physical defects including cardiac and palatal anomalies. In addition it has been argued that people with 22q11DS have a specific behavioural phenotype, defined as "the characteristic behavioural, psychiatric, neuropsychological and linguistic components of a genetic disorder" (Murphy, 2004). In particular, people with 22q11DS have mild intellectual disabilities and specific impairments in areas such as numeracy, visuo-spatial processing, and executive function. Having 22q11DS also constitutes a very significant risk factor for a number of psychiatric disorders. For example, the risk of developing schizophrenia-like psychotic disorders in 22q11DS is second only to the risk experienced by having two parents or a monozygotic co-twin with schizophrenia (Murphy, Jones, & Owen, 1999). The syndrome is also associated with a high prevalence of anxiety, autistic spectrum, obsessive-compulsive, mood, and attention-deficit/hyperactivity disorders (Campbell et al., 2010; Fine et al., 2005; Gothelf et al., 2004; Gothelf, Schaer, & Eliez, 2008; Green et al., 2009; Swillen, 2001). The behavioural phenotype in 22q11DS is increasingly being linked with brain morphology and volumetric differences (Campbell et al., 2006; Chow, Robert, Zipursky, Mikulis, & Bassett, 2002; Eliez, Schmitt, White, & Reiss, 2000; Gothelf, Penniman, Gu, Reiss, & Eliez, 2007; Kates et al., 2001, 2004; Sundram et al., 2010; van Amelsvoort et al., 2004). People with 22q11DS have an overall smaller brain volume compared with age-matched typically developing peers, with a disproportionate loss of volume in the posterior part of the brain (Campbell et al., 2006; Eliez et al., 2000). In addition, white matter loss is more pronounced than grey matter loss (Campbell et al., 2006; Kates et al., 2001). Regional brain changes and function, especially in the fronto-striatal and fronto-parietal networks, have been linked with cognitive deficits such as working memory (Azuma et al., 2009), emotional problems, atypical pro-social behaviours and schizotypal traits (Campbell et al., 2006; Sundram et al., 2010).

One of the complicated features of 22q11DS is its phenotypic heterogeneity. There is a significant variability between the expressed phenotype in affected individuals within the same family (Driscoll et al., 1992; Leana-Cox, Pangkanon, Supovitz, Curtin, & Wulfsberg, 1995; McLean, Saal, Spinner, Emanuel, & Driscoll, 1993) and even between monozygotic twins with the deletion (Singh, Murphy, & O'Reilly, 2002). In some cases, one individual can be very severely affected whilst a sibling, parent or child is much less affected by the deletion. The variability in both the type and severity of symptoms is problematic for the families and the healthcare professionals involved in the care of people with the syndrome. While some characteristics of 22q11DS can have a causal relationship, for example the presence of cleft palate and velopharyngeal insufficiency, others appear unrelated. Curiously, until the deletion was identified in 1992 (Scambler et al., 1992), children with the syndrome were usually given more clinically homogenous diagnoses such as velo-cardio-facial syndrome (VCFS) or Di George syndrome (sequence) depending on the clinical features present. Children with VCFS were usually diagnosed due to the co-occurring palatal anomalies with cardiac defects and a typical facial morphology, whilst children with Di George syndrome more typically had severe cardiac anomalies with co-occurring immunological deficiencies. However, since the deletion was identified nearly twenty years ago, all children with the deletion are recognised as having the same syndrome regardless of how many symptoms they share; hence the syndrome may be an example of multiple phenotypes arising from one deletion.

In the last couple of years, longitudinal studies of people with 22q11DS have outlined specific risk factors for the development of psychosis (Antshel et al., 2010; Gothelf et al., 2005; Gothelf, Feinstein, et al., 2007; Gothelf, Penniman, et al., 2007; Gothelf et al., 2010; Kates, Antshel, et al., 2011; Kates, Bansal, et al., 2011; Schaer et al., 2009). Debbané and colleagues report that auditory hallucinations can be present as early as the age of 9 among children with 22q11DS, these hallucinations may be a risk factor for later psychosis or may indeed, represent a prodrome (Debbane, Glaser, David, Feinstein, & Eliez, 2006). Further, a decrease of verbal IQ has been found to be linked to more psychotic symptoms among adolescents with 22q11DS (Gothelf et al., 2005; Kates et al., 2011a) whilst longitudinal volumetric grey matter reductions in the temporal cortex are associated with a higher prevalence of positive symptoms (Kates et al., 2011a). However, despite our rapidly increasing knowledge of the risk factors for developing psychosis, it is not currently possible to predict the types of cognitive impairments or psychiatric disorders that an individual child with 22q11DS will experience. This makes it difficult to implement early intervention strategies to improve quality of life and reduce the burden of disease. In order to identify reliable precursors (of severe psychiatric disorders) and to improve care, it would be useful to identify homogenous phenotypic subtypes. This would enable more targeted investigations of the genetic influences on the phenotypic variability in 22q11DS as well as enabling the syndrome to be utilised as a genetic model to understand the ontogeny of psychosis, obsessive-compulsive disorder and other psychiatric disorders in the general population.

Hence, the objective of the current study was to investigate the presence of subtypes, based on clinical features, in order to refine the extensive phenotypic spectrum in 22q11DS so as to improve clinical diagnosis. We analysed an existing dataset pertaining to a large cohort of children and adolescents with 22q11DS. To identify homogenous phenotypes within the