Psychiatry Research: Neuroimaging 285 (2019) 47–50

Contents lists available at ScienceDirect

Psychiatry Research: Neuroimaging

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

Short communication

Hypogyrification and its association with cognitive impairment in children with 22q11.2 deletion Syndrome: A preliminary report

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ARTICLE INFO

Key words:
Velocardiofacial syndrome
Schizophrenia

ABSTRACT

22q11.2 Deletion Syndrome (22qDS) is a neurogenetic disorder resulting in cognitive deficits and hypogyrification, but relationships between these processes have not been established. 22qDS youth and healthy controls (HC) were administered a battery of cognitive tasks. Gyrification measurements were extracted from structural T1 scans using Freesurfer, contrasted between groups, and correlated to cognition. Data was adjusted for age, sex, socio-economic status and intracranial volume. 22qDS displayed significant hypogyrification which was associated with poorer executive functioning and verbal learning in orbitofrontal and anterior cingulate cortex. Our preliminary findings identified neurodevelopmental deficits in 22qDS shown by hypogyria, which relate to cognitive impairments.

1. Introduction

22q11.2 Deletion Syndrome (22qDS), also known as velocardiofacial syndrome, is a neurogenetic disorder caused by a hemizygous microdeletion of 1.5–3 megabases (Mb) on chromosome 22 and results in medical manifestations including congenital heart disease and immune dysfunction (Shprintzen, 2008; Tezenas Du Montcel et al., 1996). 22qDS has been associated with abnormalities in motor development, learning, intelligence, and behavior (Shprintzen, 1999; Swillen et al., 1998). Individuals with 22qDS have a greater risk factor for psychiatric disorders with executive functioning deficits such as autism and schizophrenia (Schneider et al., 2014). Approximately 25–32% of individuals with 22qDS develop psychosis (Green et al., 2009; Murphy et al., 2000), thus is an important model for studying genetic risk factors for psychosis.

Gyrification (cortical folding) is important for understanding the neurodevelopmental markers of psychosis and has been proposed as an endophenotype for psychosis (Nanda et al., 2014; White and Gottesman, 2013). Gyrification develops when neuronal migration and proliferation processes are complete (Gertz and Kriegstein, 2015; Neal et al., 2006). Disruptions in these processes impact human sulcal and gyral patterns (Rakic, 1995; Stewart et al., 1975) and have been demonstrated in 22qDS mouse models (Maynard et al., 2003; Meechan et al., 2009). These reported disruptions suggest a plausible cause for gyrification alterations shown in MRI studies of 22qDS patients (Karayiorgou et al., 2010). Hypogyrification has been consistently reported in 22qDS (Kunwar et al., 2012; Schaer et al., 2006), specifically in regions including the midline cortex (medial prefrontal, cingulate, precuneus, and orbitofrontal) as well as middle frontal, inferior frontal gyrus, motor and parietal cortex (Schaer et al., 2009; Schmitt et al., 2015; Srivastava et al., 2011).

While gyrification alone has been examined in individuals with neurodevelopmental disorders, including 22qDS, its relationship to cognition has not been well documented. Despite some studies showing that higher gyrification is associated with better cognition in healthy individuals (Chung et al., 2017; Gregory et al., 2016), this finding has not been replicated in 22qDS. Though one study reported increased occipital gyral complexity in 22qDS compared to controls, there were no significant relationships to IQ (Bearden et al., 2009). To our knowledge, no studies have reported the relationships between gyrification and cognition in 22qDS. Our goals are to: 1. Investigate gyrification in 22qDS youth compared to healthy children in regions typically reported in the literature (bilateral anterior cingulate (ACC), superior frontal, dorsal lateral prefrontal cortex (DLPFC), medial and lateral orbitofrontal (mOFC and lOFC), precuneus and superior parietal cortex) and 2. Assess their relationship to cognition (executive

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https://doi.org/10.1016/j.pscychresns.2019.01.007
Received 21 June 2018; Received in revised form 25 January 2019; Accepted 26 January 2019
Available online 31 January 2019

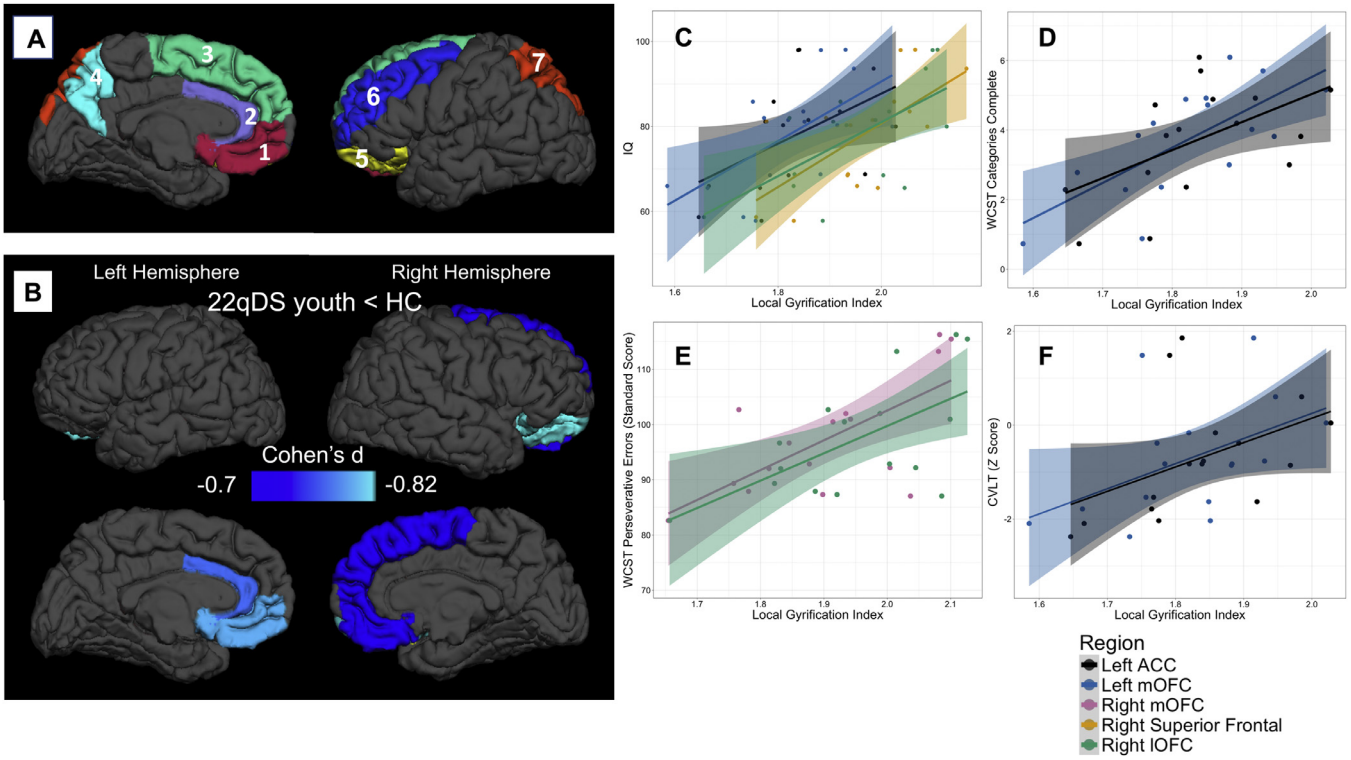

Fig. 1. Group Comparisons and Partial Correlations Between LGI (local gyrification index) regions and Cognition in 22q11.2 deletion syndrome (22qDS) youth. A) FreeSurfer Region of Interest Atlas; 1. medial orbitofrontal (mOFC), 2. anterior cingulate (ACC), 3. superior frontal, 4. precuneus, 5. lateral orbitofrontal (lOFC), 6. dorsal lateral prefrontal cortex (DLPFC) and 7. superior parietal. B) Effect sizes (Cohen's d) displaying significant ($p < 0.05$, corrected) decreases in gyrification for 22qDS youth compared to HC. Regions include left ACC, left mOFC, right superior frontal, right mOFC and right lOFC. Correlations in 22qDS youth Between C) IQ and left ACC, left mOFC, right superior frontal and right lateral orbitofrontal LGI; D) Wisconsin Card Sorting Test (WCST) Categories Complete (CC) and left ACC and left mOFC LGI; E) WCST Perseverative Errors (PE) and right mOFC and right lOFC LGI; and F). California Verbal Learning Test (CVLT) *Z*-Score and left ACC and left mOFC LGI. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

functioning, verbal memory, fine-motor sequencing and set-shifting, and attention). We predict that these regions will show hypogyrification and will associate with poorer cognition in 22qDS youth.

2. Material and methods

2.1. Participants

Children diagnosed with 22qDS with no history of psychosis ($n = 16$) were age-matched to healthy controls (HC, $n = 22$).

The measurement battery included previously reported cognitive tasks that showed impairments in 22qDS (Hooper et al., 2013): WISC-IV Full-Scale IQ, Continuous Performance Task (CPT) Fast and Slow Numbers *d'*, California Verbal Learning Test (CVLT) Children's Version Total Z score, fine-motor sequencing and set-shifting (Trail Making Test A and B), and Wisconsin Card Sorting Test (WCST) Categories Complete (CC) and Perseverative Errors (PE) Standard Scores (higher scores indicating better performance).

2.2. Imaging

T1 Spoiled GRASS (3T) images were processed using Freesurfer 4.3 to obtain local gyrification index (LGI) (Schaer et al., 2008). LGI was calculated using the ratio of the surface area of cortex within the sulcal folds compared to the surface area of cortex on the outer surface (Schaer et al., 2008). LGI values ranges from one to five such that lower cortical folding (hypogyrification) would have a smaller gyrification index and would correspond to abnormal neurodevelopment. ACC LGI was calculated by averaging the rostral and caudal anterior cingulate cortex and DLPFC LGI by averaging the rostral and caudal middle frontal cortex.

2.3. Statistical analysis

Demographic variables were compared between groups via chi-squared tests and t-tests. LGI contrasts between 22qDS and HC were examined using an analysis of covariance. Significant regions ($p < 0.05$, corrected) were assessed in the secondary analysis in relation to cognition using partial Spearman correlations. Neurocognitive relationships with significant LGI regions were evaluated within its respective category: IQ, attention and executive functioning (CPT), fine-motor sequencing and set-shifting (Trail Making Test), verbal memory (CVLT), and executive functioning (WCST).

All data were adjusted for age, sex, and socioeconomic status (SES), and LGI was also adjusted for total intracranial volume (ICV). Correlations were reported with and without IQ as a covariate. False Discovery Rate (FDR) correction was performed across seven regions (within hemisphere) for group contrasts. Partial correlations were FDR corrected for significant LGI regions (bilateral mOFC, left ACC, right superior frontal, and right lOFC) by cognitive domains (IQ, CPT, Trail Making Test, CVLT, WCST). Effect sizes were calculated using Cohen's d.

Refer to supplementary methods for more information pertaining to inclusion criteria, neurocognitive testing, imaging and statistical analyses.

3. Results

3.1. Demographics

Our sample contained 16 22qDS (8 males, 8 females, 11.25 ± 1.86 years old) and 22 HC (8 males, 14 females, 12 ± 1.39 years old; Supplementary Table 1). The groups showed no significant sex, age, or ICV differences, but 22qDS showed significantly lower SES than HC ($F = 12$, $p < 0.01$).

3.2. Group differences

22qDS showed significantly ($p < 0.05$, corrected) lower LGI compared to HC in the mOFC (bilateral), left ACC, right superior frontal, and right lOFC (Fig. 1B). These regions were then included in the secondary analysis. LGI group differences that were significant before multiple comparisons are listed in supplementary results.

3.3. LGI and cognition correlations

In 22qDS youth, higher LGI in left ACC, left mOFC, right superior frontal, and right lOFC significantly correlated with higher IQ ($p < 0.05$, corrected, Fig. 1C, Supplementary Table 3). In 22qDS youth, higher left ACC and mOFC LGI was significantly ($p < 0.05$, corrected) associated with higher WCST CC and (Fig. 1D, Supplementary Table 4). Poorer performance in WCST PE significantly correlated ($p < 0.05$, corrected) with lower right mOFC and lOFC LGI (Fig. 1E, Supplementary Table 4). 22qDS youth also showed significant associations ($p < 0.05$, corrected) between both the higher left mOFC and left ACC LGI and better CVLT performance (Fig. 1F, Supplementary Table 5). After including IQ as a covariate, LGI was not significantly related to WCST or CVLT (data not shown).

In HC, no significant correlations between gyrification and cognitive function or intelligence were observed (see Supplementary Tables 3–5 for LGI correlations with IQ, WCST and CVLT).

Additional correlations that are significant before multiple comparison correction in 22qDS youth and HC between LGI and IQ, Trail Making Test Parts A and B, CPT, and WCST are described in Supplementary Results.

4. Discussion

In our study, 22qDS youth displayed hypogyrification compared to HC in bilateral mOFC, right lOFC, left ACC, and right superior frontal cortex. In 22qDS youth, higher LGI in left ACC, left mOFC, right superior frontal, and right lOFC significantly correlated with higher IQ. Better executive functioning associated with increased gyrification in the bilateral mOFC, right lOFC, and left ACC in 22qDS youth, greater verbal learning performance correlated to increased left mOFC and left ACC gyrification and these results were no longer significant after controlling for IQ. In HC, no significant gyrification-cognition relationships were observed.

Our observation that 22qDS youth show hypogyrification in the medial prefrontal and lateral orbitofrontal cortex is consistent with previous hypogyrification findings in the medial frontal and parietal cortex (Schaer et al., 2006; Schmitt et al., 2015; Srivastava et al., 2011). With regards to a neurobiological mechanism, 22qDS animal models showed neuronal migration disruptions after a 1.5Mb deletion (Maynard et al., 2003; Meechan et al., 2009; 2012). Separate studies have shown that neuronal migration lays a foundation for gyrification in ferrets (Neal et al., 2006), and both pachygyria and lissencephlia are associated with reduced cortical neuronal migration in humans (Guerrini and Marini, 2006; Sheen et al., 2006). We infer that 22qDS in humans results in neuronal migration disruptions, leading to gyrification abnormalities. Furthermore, Cao et al. observed a logarithmic decrease in human gyrification using in vivo MRI in ages 4 to 83 such that patients with schizophrenia show accelerated reductions in dorsal lateral prefrontal cortex, ACC and supramarginal cortex (Cao et al., 2017). Our data supports that patients' with 22qDS show hypogyrification at a young age, suggesting that accelerated gyrification reductions may have important implications in the onset of psychosis.

To our knowledge, we are the first study to report that hypogyrification associates with poorer cognition in 22qDS youth, which have been reported in other populations with neurocognitive deficits like Prader-Willi Syndrome (Lukoshe et al., 2014). Additionally, a LgDel (Large Deletion) mouse model of 22qDS displayed diminished cortical circuit elements (interneurons, synaptic terminals and projection neurons) in the medial anterior frontal cortex, and the altered projection neuron frequencies predicted subsequent executive functioning deficits in affected mice (Meechan et al., 2015). Given that both a diminished 22q11 dosage alters cortical circuitry and reduces gyrification, and these neurodevelopmental findings have demonstrated associations with cognition, subsequent studies should replicate these findings in humans and other animal models with human-like gyrification patterns such as ferrets (Neal et al., 2006). Our gyrification-cognition relationships were no longer significant after controlling for IQ in 22qDS youth, which could be explained by the collinearity between IQ and cognition (Dennis et al., 2009). Therefore, controlling for IQ in a neurodevelopmental population with cognitive deficits is likely to remove any major source of variance contributed by cognition (Dennis et al., 2009).

Previous studies have reported gyrification-cognition relationships in healthy adolescents (Chung et al., 2017; Gregory et al., 2016); however, we observed no such relationships in HC. Decreases in gyrification during adolescence may reflect the emergence of higher cognitive functions such that cognitive-gyrification relationships are strengthened during mid-adolescence (Chung et al., 2017; White et al., 2010). Our HCs' ages ranged 9.12–14.44 years, so it is possible that these relationships will not mature until later in neurodevelopment. Furthermore, longitudinal gyrification in 22qDS youth remains lower than in healthy controls throughout childhood and adolescence (Kates et al., 2011; Kunwar et al., 2012), suggesting abnormal neurodevelopment that may lead to incomplete maturation that could underlie cognitive dysfunction.

Our work suggests that cognitive deficits observed in 22qDS youth are associated with underlying gyrification abnormalities. Adolescence is a crucial period for cognitive development, and is also a time where the incidence of psychosis begins to increase. Cognitive decline has shown to be a predictive factor in conversion to psychosis in 22qDS (Antshel et al., 2017; Tang and Gur, 2017) as well as gyrification in relation to psychotic symptoms (Kunwar et al., 2012), but the latter has not been largely replicated. We acknowledge our limitations; we had a small sample size with cross-sectional data, so we could not assess longitudinal gyrification-cognitive relationships. Future studies should investigate gyrification-cognition relationships in 22qDS youth across all stages of development using larger sample sizes, in longitudinal studies, as well as in later adolescence and examine how these associations may differentiate those who convert to psychosis.

Acknowledgments

We would like to thank all participants who were involved in the study, all staff who supported the study and the National Institute of Mental Health who funded the grant.

Funding

This work was supported by the grant from the National Institute of Mental Health R01MH078015 (to VS).

Contributors

VS, MK and SH designed and implemented the study and both VS

and SH supervised data collection. AJ and NT were involved in quality control and data processing in Freesurfer. SSM, PL, and NT assisted OL with statistical analyses. OL wrote the manuscript with the help of LO, PL, NT and SSM. All authors provided feedback on data interpretation and have approved the final article.

Conflict of Interest

The authors declare no conflict of interest.

Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.pscychresns.2019.01.007.

References

Antshel, K.M., Fremont, W., Ramanathan, S., Kates, W.R., 2017. Predicting cognition and psychosis in young adults with 22q11.2 deletion syndrome. Schizophr. Bull. 43, 833–842. https://doi.org/10.1093/schbul/sbw135.

Bearden, C.E., Van Erp, T.G.M., Dutton, R.A., Lee, A.D., Simon, T.J., Cannon, T.D., et al., 2009. Alterations in midline cortical thickness and gyrification patterns mapped in children with 22q11.2 deletions. Cereb. Cortex 19, 115–126. https://doi.org/10.1093/cercor/bhn064.

Cao, B., Mwangi, B., Passos, I.C., Wu, M.-J., Keser, Z., Zunta-Soares, G.B., et al., 2017. . Lifespan gyrification trajectories of human brain in healthy individuals and patients with major psychiatric disorders. Sci. Rep. 7, 511. https://doi.org/10.1038/s41598-017-00582-1.

Chung, Y.S., Hyatt, C.J., Stevens, M.C., 2017. Adolescent maturation of the relationship between cortical gyrification and cognitive ability. Neuroimage 158, 319–331.

Dennis, M., Francis, D.J., Cirino, P.T., Schachar, R., Barnes, M.A., Fletcher, J.M., 2009. Why IQ is not a covariate in cognitive studies of neurodevelopmental disorders. J. Int. Neuropsychol. Soc. 15, 331.

Gertz, C.C., Kriegstein, A.R., 2015. Neuronal migration dynamics in the developing ferret cortex. J. Neurosci. 35, 14307–14315. https://doi.org/10.1523/JNEUROSCI.2198-15.2015.

Green, T., Gothelf, D., Glaser, B., Debbané, M., Frisch, A., Kotler, M., et al., 2009. . Psychiatric disorders and intellectual functioning throughout development in velo-cardiofacial (22q11.2 deletion) syndrome. J. Am. Acad. Child Adolesc. Psychiatry 48, 1060–1068.

Gregory, M.D., Kippenhan, J.S., Dickinson, D., Carrasco, J., Mattay, V.S., Weinberger, D.R., et al., 2016. . Regional variations in brain gyrification are associated with general cognitive ability in humans. Curr. Biol. 26, 1301–1305.

Guerrini, R., Marini, C., 2006. Genetic malformations of cortical development. Exp. Brain Res. 173, 322–333.

Hooper, S.R., Curtiss, K., Schoch, K., Keshavan, M.S., Allen, A., Shashi, V., 2013. A longitudinal examination of the psychoeducational, neurocognitive, and psychiatric functioning in children with 22q11.2 deletion syndrome. Res. Dev. Disabil. 34, 1758–1769.

Karayiorgou, M., Simon, T.J., Gogos, J.A., 2010. 22q11.2 microdeletions: linking DNA structural variation to brain dysfunction and schizophrenia. Nat. Rev. Neurosci. 11, 402–416.

Kates, W.R., Bansal, R., Fremont, W., Antshel, K.M., Hao, X., Higgins, A.M., et al., 2011. Mapping cortical morphology in youth with velocardiofacial (22q11.2 deletion) syndrome. J. Am. Acad. Child Adolesc. Psychiatry 50, 272–282 e2.

Kunwar, A., Ramanathan, S., Nelson, J., Antshel, K.M., Fremont, W., Higgins, A.M., et al., 2012. Cortical gyrification in velo-cardio-facial (22q11.2 deletion) syndrome: a longitudinal study. Schizophr. Res. 137, 20–25.

Lukoshe, A., Hokken-Koelega, A.C., van der Lugt, A., White, T., 2014. Reduced cortical complexity in children with Prader-Willi syndrome and its association with cognitive impairment and developmental delay. PLoS One 9, e107320.

Maynard, T.M., Haskell, G.T., Peters, A.Z., Sikich, L., Lieberman, J.A., LaMantia, A.-S., 2003. A comprehensive analysis of 22q11 gene expression in the developing and adult brain. Proc. Natl. Acad. Sci. U. S. A. 100, 14433–14438. https://doi.org/10.1073/pnas.2235651100.

Meechan, D.W., Rutz, H.L.H., Fralish, M.S., Maynard, T.M., Rothblat, L.A., LaMantia, A.S., 2015. Cognitive ability is associated with altered medial frontal cortical circuits in the LgDel mouse model of 22q11.2DS. Cereb. Cortex 25, 1143–1151.

Meechan, D.W., Tucker, E.S., Maynard, T.M., LaMantia, A.-S., 2009. Diminished dosage of 22q11 genes disrupts neurogenesis and cortical development in a mouse model of 22q11 deletion/DiGeorge syndrome. Proc. Natl. Acad. Sci. 106, 16434–16445.

Meechan, D.W., Tucker, E.S., Maynard, T.M., LaMantia, A.S., 2012. Cxcr4 regulation of interneuron migration is disrupted in 22q11.2 deletion syndrome. Proc. Natl. Acad. Sci. 109, 18601–18606.

Murphy, K.C., Jones, L.A., Owen, M.J., 2000. High rates of schizophrenia in adults with velo-cardio-facial syndrome (VCFS). Schizophr. Res. 41, 29.

Nanda, P., Tandon, N., Mathew, I.T., Giakoumatos, C.I., Abhishekh, H.A., Clementz, B.A., et al., 2014. . Local gyrification index in probands with psychotic disorders and their first-degree relatives. Biol. Psychiatry 76, 447–455.

Neal, J., Takahashi, M., Silva, M., Tiao, G., Walsh, C.A., Sheen, V.L., 2006. Insights into the gyrification of developing ferret brain by magnetic resonance imaging. J. Anat. 210, 66–77.

Rakic, P., 1995. A small step for the cell, a giant leap for mankind: a hypothesis of neocortical expansion during evolution. Trends Neurosci 18, 383–388.

Schaer, M., Cuadra, M.B., Tamarit, L., Lazeyras, F., Eliez, S., Thiran, J.P., 2008. A surface-based approach to quantify local cortical gyrification. IEEE Trans. Med. Imaging 27, 161–170.

Schaer, M., Schmitt, J.E., Glaser, B., Lazeyras, F., Delavelle, J., Eliez, S., 2006. Abnormal patterns of cortical gyrification in velo-cardio-facial syndrome (deletion 22q11.2): an MRI study. Psychiatry Res. 146, 1–11.

Schaer, M., Glaser, B., Cuadra, M.B., Debbane, M., Thiran, J.P., Eliez, S., 2009. Congenital heart disease affects local gyrification in 22q11.2 deletion syndrome. Dev. Med. Child Neurol. 51, 746–753. https://doi.org/10.1111/j.1469-8749.2009.03281.x.

Schmitt, J.E., Vandekar, S., Yi, J., Calkins, M.E., Ruparel, K., Roalf, D.R., et al., 2015. . Aberrant cortical morphometry in the 22q11.2 deletion syndrome. Biol. Psychiatry 78, 135–143.

Schneider, M., Schaer, M., Mutlu, A.K., Menghetti, S., Glaser, B., Debbané, M., et al., 2014. . Clinical and cognitive risk factors for psychotic symptoms in 22q11.2 deletion syndrome: a transversal and longitudinal approach. Eur. Child Adolesc. Psychiatry 23, 425–436.

Sheen, V.L., Ferland, R.J., Harney, M., Hill, R.S., Neal, J., Banham, A.H., et al., 2006. . Impaired proliferation and migration in human Miller-Dieker neural precursors. Ann. Neurol. 60, 137–144.

Shprintzen, R.J., 1999. Velo-cardio-facial syndrome: a distinctive behavioral phenotype. Dev. Disabil. Res. Rev. 6, 142–147.

Shprintzen, R.J., 2008. Velo-cardio-facial syndrome: 30 years of study. Dev. Disabilies Res. Rev. 14, 3–10. https://doi.org/10.1002/ddrr.2.Velo-Cardio-Facial.

Srivastava, S., Buonocore, M.H., Simon, T.J., 2011. Atypical developmental trajectory of functionally significant cortical areas in children with chromosome 22q11.2 deletion syndrome. Hum. Brain Mapp. 33, 213–223.

Stewart, R.M., Richman, D.P., Caviness, V.S., 1975. Lissencephaly and pachygyria. Acta Neuropathol 31, 1–12. https://doi.org/10.1007/BF00696881.

Swillen, A., Devriendt, K., Legius, E., Prinzie, P., Vogels, A., Ghesquière, P., et al., 1998. . The behavioural phenotype in velo-cardio-facial syndrome (VCFS): from infancy to adolescence. Genet. Couns. 10, 79–88.

Tang, S.X., Gur, R.E., 2017. Longitudinal perspectives on the psychosis spectrum in 22q11.2 deletion syndrome. Am. J. Med. Genet. Part A 168, 800.

Tezenas Du Montcel, S., Mendizabai, H., Ayme, S., Levy, A., Philip, N., 1996. Prevalence of 22q11 microdeletion. J. Med. Genet. 33, 719.

White, T., Gottesman, I., 2013. Brain connectivity and gyrification as endophenotypes for schizophrenia: weight of the evidence. Curr. Top. Med. Chem. 12, 2393–2403.

White, T., Su, S., Schmidt, M., Kao, C.-Y., Sapiro, G., 2010. The development of gyrification in childhood and adolescence. Brain Cogn 72, 36–45.