The following full text is a publisher's version.

For additional information about this publication click this link.
http://hdl.handle.net/2066/166234

Please be advised that this information was generated on 2018-11-23 and may be subject to change.
Neocerebellar abnormalities in a neonate with the FOXP2 mutation

Georgios P.D. Argyropoulos, Rachael Elward, Maneet Saini, Mortimer Mishkin, Faraneeh Vargha-Khadem

Objective: A dominantly inherited verbal and orofacial dyspraxia in half the members of the multi-generational ‘KE family’ is linked to a mutation in FOXP2, the first gene implicated in the developmental processes culminating in articulated speech and language. Neural and genetic substrates of this disorder may inform the ontogeny and developmental trajectory of human speech. FOXP2 expression is known to occur strikingly early during embryonic development and is prominent in the human, rodent and avian olivo- and ponto-cerebellar circuits. Indeed, imaging studies from our laboratory on affected KE family members aged 9-77 years have previously reported structural and functional abnormalities in the cerebellum as well as other cortical and subcortical structures. However, up to now, it had not been possible to document the emergence of FOXP2-dependent abnormalities in the brain of affected neonates from this large pedigree.

Methods: We analysed structural T1- and T2-weighted magnetic resonance images acquired from a neonate with the FOXP2 mutation, his unaffected twin, and 12 healthy control neonates (6-16 weeks-old). We used voxel-based morphometry and volumetry to investigate grey- and white-matter abnormalities in the affected neonate.

Results: We report a marked reduction of neocerebellar lobule VIIa Crus I in the affected member as compared to his unaffected sibling and unrelated controls.

Conclusions: FOXP2 mutation is associated with cerebellar Crus I volume reduction from the early stages of neonatal life, consistent with the gene’s expression in the human embryonic cerebellum. These findings highlight the significance of cerebellar abnormalities in developmental orofacial dyspraxia in the pre-linguistic infant.

Correspondence: Georgios P.D. Argyropoulos, UCL Institute of Child Health, garygropoulos@gmail.com

Genetic subtyping and its implications for clinical management: The case of 22q11.2 syndrome

Jos Egger, Willem Verhoeven, Joep Tuertlings, Nicole De Leeuw

Objectives: The 22q11.2 deletion syndrome (22qDS), mostly caused by a large deletion on chromosome 22 that encompasses the FOXP2 gene and is associated with specific heart defects and subtle cognitive processing and alexithymic traits, which have been demonstrated in neurocognitive deficit, such as slower speed of information processing and alexithymic traits, which have been demonstrated in neurocognitive deficit, such as slower speed of information processing. In line with this, we describe the first study to investigate the genetic subtyping in patients with 22qDS, and link specific neuropsychological impairments to specific genetic substrates.

Participants: We included 28 patients who were referred to our outpatient facility specialized in psychiatry and genetics for psychopathology and genetics for psychopathology and genetics for psychosis.

Methods: Participants were classified into three groups based on genetic subtyping, with the common deletion and the central deletion each encompassing a different genetic subtype. We investigated the profiles of various neuropsychological measures, including verbal and nonverbal intelligence (FSIQ), memory, attention, executive functioning, and social cognition. Additionally, we analyzed the relationship between genetic subtyping and a range of other factors, such as age, gender, and clinical status.

Results: Patients with the common deletion showed a significantly lower FSIQ compared to those with the central deletion, which in turn was lower than in the control group. In terms of executive functioning, participants with the common deletion performed worse on the Stroop test and Trails B, while those with the central deletion showed a trend toward worse performance on the Stroop test. No significant differences were found in memory and attention tasks.

Conclusions: Our findings suggest that genetic subtyping can provide valuable information about the specific neuropsychological profiles in 22qDS. This information can help tailor clinical management and support individualized treatment planning.

Correspondence: Jos Egger, Vincent van Gogh Institute for Psychiatry, j.egger@donders.ru.nl

Intelligent development in Noonan syndrome: A longitudinal study

Renée Roelofs, Nikki Janssen, Ellen Wingbermühle, Roy Kessels, Jos Egger

Objective: While cognitive impairments in adults with Noonan syndrome (NS) seem to be limited to a low-average intelligence and slower processing speed, studies in children with NS have demonstrated more extensive cognitive problems (e.g., deficits in language, memory, attention, and executive functioning). This longitudinal study is the first to investigate the developmental trajectories in patients with NS. Although childhood IQ is expected to be lower than adult IQ, it is assumed to be a significant predictor of adult intelligence.

Participants and Methods: Sixteen patients with NS underwent intelligence assessment in childhood and in adulthood, using Wechsler’s intelligence scales. IQ scores and Wechsler standard scores achieved in childhood and adulthood were compared. Childhood verbal and performance IQ (VIQ/PIQ) were included as predictors in multiple regression analyses for adult IQ and index scores.

Results: Compared with childhood scores, adult full-scale IQ (FSIQ) and PIQ significantly increased (FSIQ: t(15) = 2.88, p = .01, r² = .36; PIQ: t(15) = 5.49, p < .001, r² = .67). Adult PIQ was higher than VIQ (t(15) = -2.23, p = .04, r² = .25). Childhood PIQ and VIQ together predicted all adult IQ and index scores (adjusted R² = .62, P < 13.32, r² = .80), except for processing speed.

Conclusions: In accordance with the hypothesis, childhood IQ significantly predicted adult intelligence in patients with NS. PIQ advanced to a normal level in adulthood, while VIQ did not develop proportionately, resulting in a discrepancy between adult PIQ and VIQ. This may suggest a delay in the development of executive functioning in patients with NS, which seems to be outgrown in adulthood.

Correspondence: Renée Roelofs, Vincent van Gogh Institute for Psychiatry, roelofs@vgvi.nl

Quality of life in adults with Noonan syndrome

Ellen Wingbermühle, Floor Nobbe, Renée Roelofs, Ineke Van der Burgt, Roy Kessels, Jos Egger

Objective: Noonan syndrome (NS) is a genetic disorder related to mutations in the RAS-RAF-MAPK pathway. Cardial features include short stature, facial dysmorphism, congenital heart defects, subtle cognitive impairments and lower levels of quality of life (QoL). In this study, the QoL was evaluated in adults with NS.

Participants and Methods: Forty-five adult patients with NS and 26 IQ-matched, healthy controls completed the Dutch version of the Lancashire Quality of Life Profile (LQoLP), a comprehensive structured interview covering nine domains of QoL, as well as general measures on wellbeing. Groups were compared using ANOVA and chi-square tests.

Results: Patients with NS demonstrated significantly lower levels of QoL on two out of four general outcome measures (Happiness with life and Cantril’s ladder, p<0.05). Contrary to the controls, the majority of patients did not have a relationship (p<0.05). A history of being bullied in youth was more prevalent in the NS group (p<0.01) and patients presented with significantly lower levels of self-esteem (p<0.05). No difference was found in satisfaction with health, in spite of the medical burden in the NS group.

Conclusions: The QoL profile of adult NS patients differs from that of controls with respect to both subjective measures, such as happiness with life and self-esteem, and objective measures, such as relationship status. Lowered QoL in NS may be moderated by neurocognitive deficit, such as slower speed of information processing and alexithymic traits, which have been demonstrated in this group before.

Correspondence: Ellen Wingbermühle, Vincent van Gogh Institute for Psychiatry, wingbermuhle@vgvi.nl