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Neocerebellar abnormalities in a neonate with the FOXP2 mutation
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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 articulate 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 Vlla 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.

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Genetic subtyping and its implications for clinical management: The case of 22q11.2 syndrome
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Objective: The 22q11.2 deletion syndrome (22q11DS) is a common deletion syndrome with a high prevalence, and a large variability in phenotype. Deletion size and position determine the phenotype and clinical manifestations. Given the phenotypic spectrum, a genetic subtyping approach is necessary to clarify the relationship between genotype and phenotype. We describe a genetic subtyping of 22q11DS patients in the Dutch national 22q11DS registry, and we discuss the implications for clinical management.

Methods: Genetic subtyping was performed using a specific copy-number variant (CNV) panel. The 22q11DS registry, which is included in the Dutch Genotype-Phenotype (DGP) cohort, contains extensive clinical information and a complete set of molecular analysis for 22q11DS patients. The genetic subtyping results were used to identify subgroups with specific genotype-phenotype relationships.

Results: Among the 22q11DS patients, 30% had a central deletion, 40% had a distal deletion, and 30% had an interstitial deletion. A central deletion was associated with intellectual disability, autism spectrum disorders, and renal/urogenital anomalies, whereas a distal deletion was associated with cardiac defects and a central deletion was associated with congenital heart defects and endocrine disorders.

Conclusions: Genetic subtyping of 22q11DS patients is crucial for clinical management. The identification of distinct genotype-phenotype relationships can inform the selection of appropriate diagnostic and therapeutic strategies.

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Intellectual development in Noonan syndrome: A longitudinal study
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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 intellectual development 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, η² = .36; PIQ: t(15) = 5.49, p < .001, η² = .67). Adult PIQ was higher than VIQ (t(15) = 2.23, p = .04, η² = .25). Childhood PIQ and VIQ together predicted all adult IQ and index scores (adjusted R² = .82, F = 13.32, p < .001), 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.

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Quality of life in adults with Noonan syndrome
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Objective: Noonan syndrome (NS) is a genetic disorder related to mutations in the RAS-MAPK pathway. Cardiac features include short stature, facial dysmorphism, congenital heart defects, subtle cognitive dysfunctions and a slightly lowered mean IQ (≈ 90). These characteristics may bring about lowered levels of quality of life (QoL). In this study, 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 global 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.

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