Neocerebellar abnormalities in a neonate with the FOXP2 mutation
Georgios P.D. Argyropoulos, Rachael Elward, Maneet Saini, Mortimer Mishkin, Faraneh 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 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 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.

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Genetic subtyping and its implications for clinical management: The case of 22q11.2 syndrome
Jos Egger, Willem Verhoeven, Joep Tuirings, Nicole De Leew

Objective: The 22q11.2 deletion syndrome (22qDS), mostly caused by the gene a 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.

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Intellectual development in Noonan syndrome: A longitudinal study
Renee Roelofs, Nikki Janssen, Ellen Wingbermuhle, 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 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.

Discussion: Clinical management of patients with 22q11DS should be guided primarily by its genetic subtype.

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Quality of life in adults with Noonan syndrome
Ellen Wingbermuhle, Floor Nobbe, Renee Roelofs, Ineke Van der Burgt, Roy Kessels, Jos Egger

Objective: Noonan syndrome (NS) is a genetic disorder related to mutations in the RAS-MAPK pathway. Cardinal features include short stature, facial dysmorphism, congenital heart defects, subtle cognitive dysfunctions accompanied by schizophrenia-like psychoses and autism spectrum disorders. The clinical spectrum (CRKL-D-H) comprises the MAPK1 gene and is associated with specific heart defects and the presence of anxiety disorders. The relatively rare central deletion (LCR-B-D) encompasses the CRKL gene and predominantly shows renal/urogenital anomalies in combination with autistic-like behaviours.

Participants and Methods: Thirty patients with genetically proven and subtype 22q11DS were referred to the Dutch national outpatient facility specialized in psychopathology and genetics for detailed neuropsychological and psychopharmacological assessment in order to ascertain the most appropriate neuropsychological and psychospoecological strategy.

Results: Apart from one distal and one central deletion, common deletion was found in 28 patients. They presented with a variable level of intellectual disability. Patients with common deletion had a history of relapsing schizophrenia-like psychoses, partial or non-responsive to conventional antipsychotics, and often accompanied by anxieties and mood instability. The patient with distal deletion displayed anxiety symptoms, whereas in the one with central deletion, autistic-like behaviour was present. Most patients with common deletion could effectively be treated with targeted contextual measures and clozapine or quetiapine, often combined with valproic acid. The patient with distal deletion showed full remission upon treatment with chlorpromazin whereas in the patient with central deletion, behaviour strongly improved upon contextual-neuropsychological and behavioural measures only.

Discussion: Clinical management of patients with 22q11DS should be guided primarily by its genetic subtype.

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