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Case Report

De novo ATP1A3 and compound heterozygous *NLRP3* mutations in a child with autism spectrum disorder, episodic fatigue and somnolence, and muckle-wells syndrome

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ABSTRACT

Complex phenotypes may represent novel syndromes that are the composite interaction of several genetic and environmental factors. We describe an 9-year old male with high functioning autism spectrum disorder and Muckle-Wells syndrome who at age 5 years of age manifested perseverations that interfered with his functioning at home and at school. After age 6, he developed intermittent episodes of fatigue and somnolence lasting from hours to weeks that evolved over the course of months to more chronic hypersomnia. Whole exome sequencing showed three mutations in genes potentially involved in his clinical phenotype. The patient has a predicted pathogenic *de novo* heterozygous p.Ala681Thr mutation in the *ATP1A3* gene (chr19:42480621C > T, GRCh37/hg19). Mutations in this gene are known to cause Alternating Hemiplegia of Childhood, Rapid Onset Dystonia Parkinsonism, and CAPOS syndrome, sometimes accompanied by autistic features. The patient also has compound heterozygosity for p.Arg490Lys/p.Val200Met mutations in the *NLRP3* gene (chr1:247588214G > A and chr1:247587343G > A, respectively). *NLRP3* mutations are associated in an autosomal dominant manner with clinically overlapping auto-inflammatory conditions including Muckle-Wells syndrome. The p.Arg490Lys is a known pathogenic mutation inherited from the patient's father. The p.Val200Met mutation, inherited from his mother, is a variant of unknown significance (VUS). Whether the *de novoATP1A3*mutation is responsible for or

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plays a role in the patient's episodes of fatigue and somnolence remains to be determined. The unprecedented combination of two NLRP3 mutations may be responsible for other aspects of his complex phenotype.

1. Introduction

Gene mutations associated with impairing behavioral disorders that present in childhood may hold the key to discovering highly penetrant mutations and actionable genetic mechanisms that lead to these disorders. We describe a child with autism spectrum disorder, as well as worsening fatigue and somnolence. We present the analysis performed in the de-convolution of the genetic origins of this patient's complex genetic disease.

1.1. Patient description

The proband is a 9 year-old male with a history of motor and speech developmental delays, autism spectrum disorder, low vision, and strabismus. He has fixed interest in superheroes consistent with his autism spectrum disorder. At 5 years of age, he manifested severe perseveration, which interfered with functioning in the school and home. This perseveration improved with risperidone and later with aripiprazole treatment. At age 6 years, his parents and teachers noted intermittent fatigue and excessive daytime sleepiness with longer nocturnal sleep times (13–16 h/night) than expected for age [1]. He was difficult to arouse in the morning from this long sleep. These symptoms would last 2–3 days and occur approximately every two weeks. No other mood, behavior or eating changes were reported with these hypersomnia episodes. In between episodes, sleep patterns were normal and daytime sleepiness less severe. Over the course of months, sleepiness and fatigue with long sleep times became more of a chronic, daily issue. The patient was falling asleep through the day and began to rely on brief scheduled naps through the school day to manage excessive daytime sleepiness. The patient denied symptoms of narcolepsy including sleep paralysis, hypnagogic/hypnopompic hallucinations and cataplexy. Physical examinations have consistently revealed his weight and height to be in the 60th percentile, and head circumference between the 15th and 25th percentile. He has no dysmorphic features or neurocutaneous stigmata. His hair is blonde and thin. He can follow commands and speak fluently but he is talkative and impulsive. He had significantly decreased visual acuity, decreased visual field bilaterally, bilateral nystagmus and limitation of abduction of the left eye (status post-operative procedure for strabismus), and a form of dyspraxia of horizontal movements on lateral gaze. Motor exam showed generalized hypotonia but no spasticity, dystonia, or tremor. He has full strength. Reflexes were 1+ and symmetric without evident clonus. He had occasional overflow movements with stressed gait testing. Plantar response was bilaterally flexor. His coordination when running was mildly impaired but his cerebellar and gait examinations were otherwise normal.

1.2. Neurological evaluation

Brain MRIs demonstrated small nonspecific white matter hyperintensities in the bilateral centrum semiovale and right corona radiata (Supplemental Fig. 1) stable over multiple exams. There was no edema, atrophy, or other parenchymal signal alteration. MRI of the temporal bones demonstrated a hypoplastic right posterior semicircular canal, dysmorphic and enlarged left posterior semicircular canal (no bone

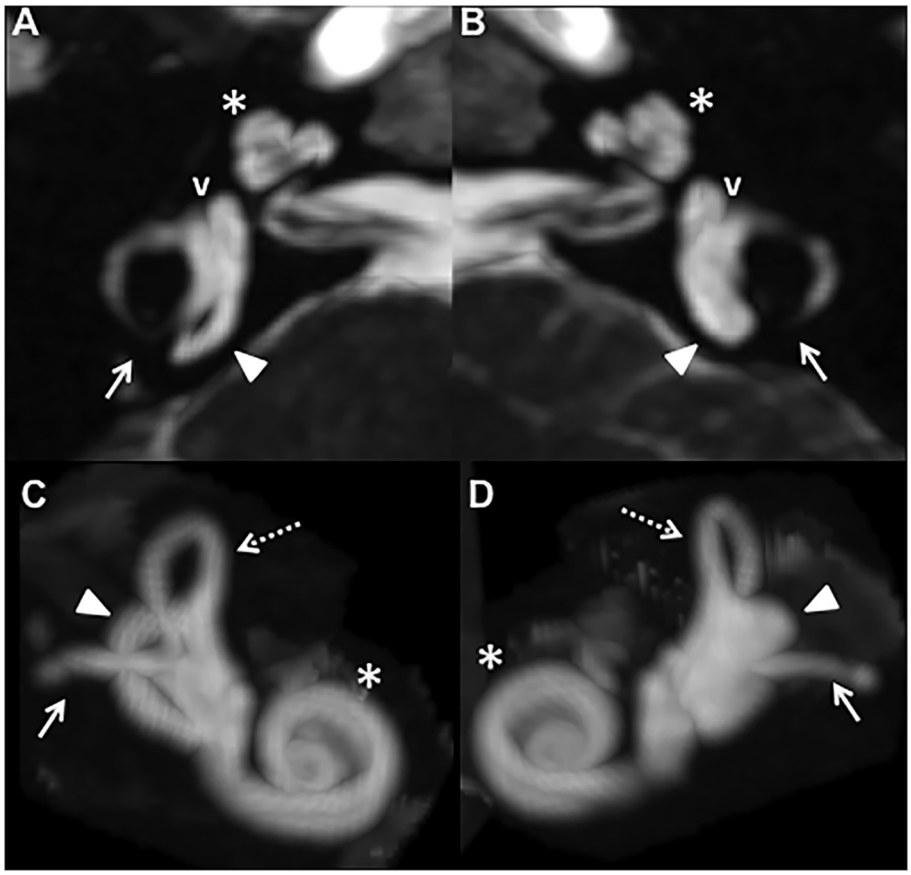

Fig. 1. Temporal bone MRI obtained at 7 years of age. Segmented axial 3D FIESTA (fast imaging employing steady-state acquisition) images (A,B) and MIP (maximum intensity projection) images (C, D) of the right (A,C) and left (B, D) temporal bones demonstrate hypoplastic appearance of the right posterior semicircular canal (arrowhead), dysmorphic left posterior semicircular canal with no bone island (arrowhead), and a globular left vestibule ("v"). The cochlea (*), lateral semicircular canals (arrows), and superior semicircular canals (dashed arrows) appear normal bilaterally.