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De novo PIK3CB mutation associated with macrocephaly and diffuse polymicrogyria

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Background: Phosphatidylinositol-4,5-bisphosphate 3-kinase catalytic subunit beta (PIK3CB) is a member of the PI3K complex. This complex has two p110 members; PIK3CA (p110a) and PIK3CB (p110b) which are both ubiquitously expressed. PI3K complex functions to phosphorylate PIP2 to PIP3 which activates AKT and subsequently mTOR. PIK3CA mutations have been previously linked with macrocephaly and developmental delay. **Methods:** An 18 month old girl was investigated for severe hypotonia, developmental delay and macrocephaly. Head circumference was >97%ile at birth and 53.0 cm (>99%ile, +5.4 SD) at 13 months old. She had no hydrocephalus or epilepsy. MRI brain (18 months old) re-identified megalencephaly and diffuse polymicrogyria. Symmetric signal abnormality was noted in the periventricular white matter, unchanged between 8 and 18 month images. MR spectroscopy was unrevealing. At 18 months she remains unable to sit independently. Exome sequencing was performed and functional studies to further support variant pathogenicity. **Results:** Exome sequencing identified de novo variant in PIK3CB: c.1735G>T; p.Asp579Tyr. No mutations were noted in other genes known to cause developmental delay, macrocephaly or overgrowth syndromes. Functional studies in patient cells showed dysregulation of PIK3CB and downstream signalling, providing support for causality of this novel disease gene. **Conclusions:** We believe that our patient's macrocephaly (+5.4 SD) and diffuse polymicrogyria results from altered PIK3CB function.

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Redesign of a neuropsychology service in a tertiary pediatric hospital (CHEO)

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Background: Neuropsychological assessments are used in hospitals to examine brain-behaviour relationships, and are an integral part of care for medically complex patients. Unfortunately, waitlists can be lengthy. We gathered information regarding best-practice guidelines and physician referral patterns in an effort to better manage the neuropsychology waitlist at a pediatric hospital. **Methods:** We conducted: 1) A semi-structured telephone survey with 4 Canadian, pediatric, hospital-based neuropsychology services; 2) An electronic survey distributed to referring physicians at CHEO; 3) A focus group for CHEO neurologists and neurosurgeons. **Results:** The telephone survey indicated that there are no clear, best-practice guidelines for pediatric neuropsychologists working in a tertiary, pediatric hospital. The electronic survey revealed some confusion about neuropsychology services and indicated the need for better communication between neuropsychology and referral sources. The focus group revealed that demand for neuropsychology services far outstrips supply and confirmed the need for better communication. **Conclusions:** The results confirmed the need for best-practice guidelines to be developed around delivering neuropsychology services within a pediatric tertiary care setting, as well as continuing to work closely with neurology and neurosurgery to ensure that the neuropsychological needs of their patients are met.

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Expanding the phenotype of TRNT1 mutations to include Leigh syndrome

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Background: Children with biallelic mutations in *TRNT1* have multi-organ involvement with congenital sideroblastic anemia, B-cell immunodeficiency, periodic fevers, and developmental delay (SIFD) as well as seizures, ataxia and sensorineural hearing loss. The *TRNT1* gene encodes the CCA-adding enzyme essential for maturation of both nuclear and mitochondrial transfer RNAs accounting for phenotypic pleitropy. Neurodegenerative Leigh syndrome has not been previously reported. **Methods:** Case summary: A Portuguese boy presented with global developmental delay, 2 episodes of infantile Leigh encephalopathy at 8 mo and 4 yr responsive to high-dose steroids, slow neurodegeneration of cognitive, language and motor functions with optic atrophy, pigmentary retinopathy, spasticity, dystonia, and focal dyscognitive seizures, pancytopenia, transfusion dependent sideroblastic anemia, recurrent febrile infections (pulmonary, gastrointestinal), hypernatremia, with tracheostomy dependence at age 5 yr, malabsorption and TPN dependence at 9 yr, and survival to early adulthood. Neuroimaging showed symmetric hemorrhagic lesions in the thalamus, brain stem (periaqueductal grey) and cerebellum consistent with Leigh syndrome but no lactate peak on MRS. **Results:** Whole exome sequencing identified a homozygous missense pathogenic variant in *TRNT1*, c.668T>C (p.I223T) in the affected individual. **Conclusions:** This report expands the neurological phenotype of *TRNT1* mutations and highlights the importance of considering this gene in the evaluation of Leigh syndrome.

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Infantile Onset Multisystem Neurologic, Endocrine and Pancreatic Disease: case series and review

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Background: We report three brothers born to consanguineous parents of Syrian descent with a novel homozygous c.324G>A (p.W108*) mutation in PTRH2 that encodes mitochondrial peptidyl-tRNA hydrolase 2. Mutations in PTRH2 have recently been identified in the autosomal recessive condition, Infantile Onset Multisystem Neurologic, Endocrine and Pancreatic Disease (IMNEPD). To our knowledge, this is the first case of IMNEPD described in a Canadian centre. **Methods:** Clinical phenotyping enabled a targeted approach in which all exons of PTRH2 were sequenced. We identified a novel mutation and compared our patients with those recently described. **Results:** We identified a homozygous nonsense mutation in PTRH2, c.324G>A (p.W108*). This G to A mutation results in a premature stop at codon 108 that produces a truncated protein, removing most of the amino acids at the enzymatic active site. This mutation is not