PPM1D

Tutorial with Parents (Dec. 13, 2017)
Both parents attended the tutorial, along with their affected son, which occurred in the Kennedy IDDRC office and was hosted by Dr. Steve Walkley. Dr. Marion was the presenting pediatrician who outlined the clinical condition in the child and in general. This was further expanded upon by the parents in terms of their experiences. Dr. Herb Lachman was the scientist who presented a lay summary of the gene, its protein, and how its functional absence might be causing the developmental disability. He also outlined the advantage of using iPSC methodology to explore how specific mutations in this gene could be causing disease. The parents were extremely positive in their response. Later they raised funds to support *PPM1D* research in Dr. Lachman's lab through their child's school and other activities, a story that was publicized by a local TV station. With this, Dr. Lachman's lab generated iPSCs from the patient and his unaffected brother and made CRISPR-edited iPSC lines containing a null mutation similar to that found in the patient. They also generated the same mutation in a neuroblastoma cell line using CRISPR. NIH funding is current being sought to continue these studies. The family also participated in the Rare Disease Day program sponsored by the Rose F. Kennedy IDDRC in February, 2018 and later appeared in a 2018 Kennedy Center newsletter. They remain in contact with Dr. Marion and Dr. Lachman.

Patient Description:
RS was initially seen at 16 months of age because of developmental disability, hypotonia, and slightly dysmorphic facial features. Born at full term after an uncomplicated gestation, he had had difficulties with feeding from the newborn period, which were attributed to his generalized hypotonia. Feeding was also complicated by gastroesophageal reflux disease. His motor development had been globally delayed: he had rolled over (belly to back) at six months, sat unassisted at 9 months, and when seen at 16 months, he was standing holding on. Though he made sounds, his only words were "mama" and "dada."

RS at Rare Disease Day 2017

On exam at that time, he was noted to be below 5th centile for height and weight; head circumference was normal. He had slightly dysmorphic facial features (low set, posteriorly rotated ears, small epicanthal folds, thin upper vermilion border of the lip, and a generalized coarsening of the facial features) and small hands and feet, He was hypotonic and extremely sensitive to noises.

Testing at initial evaluation included microarray comparative genomic hybridization, which showed a small deletion in 17q. Parental studies confirmed that the deletion was inherited from RS's father, and therefore felt to be not pathogenic. DNA analysis for fragile X was negative. An X ray of his hand ruled out signs of dysostosis multiplex.

Development continued to be slow. RS manifested a series of behavioral abnormalities, including ADHD, hyperacusis, and sensory integration issues.

Whole exome sequencing revealed a de novo pathogenic mutation in PPM1D (c.1210C>T; p.Gln404). Review of the literature reveals one individual with similar phenotypic features who had the same mutation (subject 4 in https://repository.icr.ac.uk/bitstream/handle/internal/627/PPM1D%20truncating%20muts%20published.pdf?sequence=2&isAllowed=y)

Disease/Syndrome Features:
Recent meta-analyses have identified *de novo* mutations in *PPM1D* as a likely cause of intellectual disability [Lelieveld 2016]. Deep phenotyping of 14 individuals with intellectual or developmental disabilities and truncating *PPM1D* mutations has revealed a syndrome typified by cognitive impairment, gastrointestinal difficulties, and a high pain threshold. In addition to mild to severe intellectual disability, most individuals from this cohort had behavioral problems ranging from anxiety disorders to autism spectrum disorder. Half of all individuals showed hypersensitivity to sound. Other common conditions included hypotonia, short stature, feeding difficulties, periods of illness with fever and/or vomiting, vision problems, and small hands and feet with brachydactyly [Jansen 2017]. An additional patient has been reported who shares some features with the cohort originally described but who also presents with cleft palate and an aberrant right subclavian artery. Furthermore, this patient did not have any of the previously described gastrointestinal difficulties. Therefore, patients with *PPM1D* mutations may have wide phenotypic variability [Porrmann 2018].

Protein/Pathway:
Protein phosphatase, Mg^{2+}/Mn^{2+}-dependent 1D, *PPM1D*, encodes a 605-amino-acid protein with an N-terminal phosphatase domain and a C-terminal nuclear localization signal. PPM1D is upregulated by p53 in response to DNA damage. When activated, PPM1D dephosphorylates and inhibits a number of tumor suppressors including p53, p38, ATM, Chk1, and Chk2. In so doing, PPM1D negatively regulates the DNA damage response and other cellular stress-response pathways [Ruark 2013, Jansen 2017].

As such, *PPM1D* has oncogenic properties and is amplified in around 11% of primary breast tumors. Specifically, PPM1D regulates the p38 mitogen-activated protein kinase (MAPK) which itself activates p53 by phosphorylating two serine residues at positions 33 and 46. Overexpression of PPM1D therefore reduces p53 phosphorylation and activity and promotes tumor formation in cells expressing oncogenic Ras [Bulavin 2002]. Recently, mosaic *PPM1D* mutations in lymphocytes were identified in patients with breast cancer and hypothesized to confer a predisposition to cancer. These truncating mutations were shown to encode hyperactive PPM1D isoforms and suppress p53 activity in response to ionizing radiation (IR) [Ruark 2013]. However, further analysis revealed that these mutations arose after chemotherapy and were absent in germline DNA samples [Pharoah 2016]. Fibroblasts from patients with *PPM1D*-associated intellectual disability showed normal p53 activity in response to IR but did show a growth delay in response to this challenge. PPM1D controls cell-cycle activity by positively upregulating G1-to-S

transition, and it is possible that this function is perturbed in patient cells. In addition to *PPM1D*, other genes that cause intellectual disability when mutated in the germline and cancer when mutated somatically include *SETBP1* and *CTNNB1* [Jansen 2017].

Interrogation of cDNA libraries shows that *PPM1D* is expressed in both the fetal and adult brain. It appears to be more widely expressed during development, with transcripts also found in fetal liver and skeletal muscle. In mice, *Ppm1d* expression is highest in the cerebellum [Jansen 2017]. *PPM1D* mutations associated with intellectual disability currently described in the literature are located in the last or penultimate exons of the gene and are predicted to generate a premature stop codon. As such, these mRNAs are expected to escape nonsense-mediated decay and produce a protein that maintains its protein phosphatase activity but lacks its nuclear localization signal [Jansen 2017].

Publications:

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Support Groups and Information:

None currently

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