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# Phelan-McDermid Syndrome Presenting as a Puzzling Case of Regressive Autism

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## Introduction

Phelan-McDermid Syndrome is a genetic neurodevelopmental disorder characterized by intellectual disability, severe speech delay, hypotonia and autism spectrum disorder (ASD). Variable dysmorphic features are also described; the most common of which are large fleshy hands, long eyelashes, pointed chin, prominent/dysplastic ears, bulbous nose, full lips, hypoplastic/dysplastic nails, and dolichocephaly. An associated seizure disorder is relatively common and brain MRIs report variable abnormalities including thinning or hypoplasia of the corpus callosum, generalized white matter atrophy, and nonspecific white matter hyper intensities. Other more common associated features include feeding difficulties with GERD, renal abnormalities such as ureteric reflux and hydronephrosis are considered relatively common [1]. Phelan-McDermid Syndrome is most often caused by a deletion involving chromosome 22q 13.3, a region that includes the SHANK3 gene [2]. Mutations within this gene have also been associated with the Phelan-McDermid phenotype. The SHANK3 gene codes for a protein that appears to be critical in forming postsynaptic connections between neurons as well as being involved in the formation and maturation of the dendritic spines, outgrowths from the dendrites that help connect and transmit nerve impulses. Therefore absence or decreased levels of this protein will lead to impaired neuronal interconnectivity and this is likely to be responsible for the neurodevelopmental outcomes of the Phelan-McDermid Syndrome.

Phelan-McDermid Syndrome is one of the more common monogenic causes of ASD accounting for about 0.5% to 2% of cases [3]. It may become more common as techniques improve to detect smaller chromosome deletions or mutations in SHANK3 that can cause the phenotypic syndrome. Previous reports have suggested that smaller deletions tend to cause more cases of autism and the larger deletions more severe phenotypes. In our case we have a very small mutation and the clinical presentation was that of regressive autism with fewer physical features [4].

## Case Report

JD is a 3 year old girl who presented to the Early Intervention Program at NYPH at the age of 26 months with a concern for ASD. JD was the product of a normal pregnancy and delivery to a 33 year old mother. JD was born outside the US and her family travelled extensively during her first 2 years. Some prior medical records were available and did not indicate any developmental concerns. She was reported at 6 months to be sitting with support, rolling over, transferring objects, babbling, laughing and responding to voices with a normal neurological exam.

JD's parents first became concerned with her development when she was about 12 months of age; they noted that she was not speaking or pointing and her eye contact appeared diminished. She started walking at 15 months but she was very unsteady and was constantly falling. At about 18 months she had a severe varicella infection accompanied by high fevers. After this time there was reported to be clear regression. She was falling more and behaviors such as mouthing, head shaking and hand tapping were increasing. Language was not developing and she seemed to be increasingly withdrawn.

At this point JD's parents sought treatment in Europe where they were living at the time. JD was provided with occupational therapy and behavioral therapy for 10 h a week and parents were told she probably had autism.

As JD approached 2 years of age and her development was not progressing the family made plans to move to the US and contacted the Early Intervention Program in New York. JD was 26 months when she was seen by the Early Intervention Program. At that evaluation JD was active and distracted, her balance and coordination were poor. She was noted to mouth many objects and frequently put her hands in her mouth. Eye contact was limited and she had no purposeful play skills or communicative efforts. In addition to mouthing she would frequently bang toys on the wall in a repetitive fashion. Based on developmental assessment using standardized tools JD was found to be significantly delayed with standard scores falling more than 2 standard deviations below the mean across all developmental domains.

A Clinical Autism Rating Scale 2nd Edition (CARS2) was also performed and JD's score fell in the severe range at 40.

At this time JD was given a definitive developmental diagnosis of severe global developmental delay and autism. Due to the history of regression it was felt that JD could have Rett Syndrome and she was

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referred by her pediatrician for a genetics consultation. She also had an EEG which showed left frontal lobe spikes and she was started on anticonvulsants. MRI showed scattered areas of subtle FLAIR hyper intensity but was otherwise reported as a normal MRI. Diagnostic testing continued while ongoing therapies were provided.

## Genetics

After a comprehensive medical genetics consultation, a karyotype and whole genome single nucleotide polymorphism (SNP) microarray analysis was sent and identified no abnormalities. Microarrays are currently performed on children referred for developmental delays/intellectual disability/congenital anomalies to rule out the presence of chromosomal micro deletions or duplications greater than approximately 50 kilo bases [5]. Screening for metabolic disorders, including urine organic acids and plasma amino acids were also within normal limits for our patient.

Given reported history of regression and lack of speech, single gene panel testing for Rett syndrome and other overlapping disorders, such as Angelman, Pitt-Hopkins and Mowat-Wilson syndromes, was performed. Next generation sequencing (GeneDx Laboratory) of MECP2, CDKL5, CNTNAP2, FOXG1, MBD5, MEF2C, NRXN1, SLC9A6, TCF4, UBE3A and ZEP2 and deletion duplication testing of all respective genes, with the exception of FOXG1, revealed no disease causing mutations. Methylation studies of the Angelman/Prader Willi critical region on chromosome 15q11-13 were also normal.

With uninformative results at this point and an evolving unclear phenotype, clinical whole exome sequencing (WES) was sent to Columbia University Laboratory. After several months, testing identified a heterozygous frame shift mutation, c.2994_2997delCCGC (p.R999fs), in the SHANK3 gene on chromosome 22q13.3. No mutation was detected in parents as part of routine trio testing for WES. This novel mutation has not been reported previously but is suspected to alter translation and thus is consistent with a diagnosis of Phelan-McDermid syndrome (Phelan gene reviews). This gene is thought to be a major mediator of the neurodevelopmental phenotype of this condition. With the advent of genomic sequencing, intragenic SHANK3 mutations have been reported in individuals with developmental delays, autism spectrum disorders and one female with a Rett-like phenotype [6].

Given a history of developmental delays and an initial report of 'regression', this patient went through an extensive series of testing without informative answers. The lack of major facial dysmorphisms, absence of congenital anomalies, along with her evolving behavioral concerns or autism-like features made clinical diagnosis difficult until her WES identified this four base pair deletion. Since the majority of reported patients with Phelan-McDermid syndrome have a much larger deletion on chromosome 22q13.3 involving the SHANK3 gene detected by chromosome/microarray testing, our patient would not have obtained a definitive diagnosis without WES to detect this single frameshift mutation. JD's younger sibling was also tested and was not found to carry this mutation.

## Discussion

In this report we presented a case of a girl with Phelan-McDermid Syndrome initially presenting as a case of regressive autism. Regressive autism is thought to occur in up to a third of all cases of ASD [7]. In these cases infants and toddlers appear to be developing typically as JD did and many develop some language but then, usually around 18 months, there is a loss of previously acquired skills and the development of social avoidance, decreased eye contact and increasing repetitive behaviors. Our case showed many of these characteristics and what appeared to be quite a dramatic regression in skills and behavior after 18 months. Our patient did not have the more obvious dysmorphic features of Phelan-McDermid syndrome, but did have seizure activity and MRI findings consistent with this diagnosis.

Patients with a typical symptoms or complex medical histories may often go through years of stressful, time consuming and costly testing by multiple health care providers without a diagnosis. Accurately defining a genetic disorder can now provide valuable information about prognosis, anticipatory guidance, and recurrence risk. In children, this knowledge becomes increasingly important for therapies, treatment and future health care prevention. In this case, through the use of the newly available WES techniques, a small deletion in the SHANK3 gene on chromosome 22q13.3 was found which provided the definitive diagnosis of Phelan-McDermid syndrome as an explanation for the symptoms.

The true prevalence of this disorder remains unknown as this syndrome likely remains under diagnosed. The use of WES is becoming increasingly available in the clinical setting and expands our understanding of new genes and rare syndromes. The improvements in sequencing technology and bioinformatics turnaround time as a commercial service, and better insurance coverage for testing have allowed patients and family to access this diagnostic tool. WES is becoming more cost effective compared to traditional protocols involving serial genetic testing, particularly for conditions characterized by genetic heterogeneity [8,9].

Without multidisciplinary collaboration, families may continue to struggle through an unclear diagnostic journey. Often with developmental delays and/or hypotonia, definitive diagnosis from DNA testing can help young children avoid invasive procedures such as muscle biopsies.

Nevertheless there are limitations to WES which are often over looked by individuals not familiar with this test. This method may not identify deep intronic mutations or mutations in a promoter region. The technology also does not cover all regions of interest and thus causal variants may be missed from low or sub optimal coverage. As with any genetic test, it is important that families have pretest and posttest counseling about risks, benefits, and limitations of genetic testing by certified geneticists and/or genetic counselors.

From a therapeutic stand point, with a known diagnosis of monogenic ASD interventions can be tailored as there is phenotypic variability among children with ASD/neurodevelopmental disorders. In our patient we hope to improve verbal and nonverbal communication using newer educational technologies since we now have knowledge that these patients' receptive language is often more advanced than expressive language. In addition, emphasis on oral-motor therapy can also help to alleviate common chewing and swallowing difficulties in younger children. Diagnosis can provide opportunities for families to participate in clinical trial(s) for medical therapy and novel treatment options. In addition diagnosis allows

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families to connect with each other to share ideas and resources as well as consult with experts in the field.

We also anticipate that as WES and whole genome sequencing become increasingly used in the clinical setting, more accurate diagnosis will be available and our knowledge of mutations and rare variants may lead to a better understanding of the pathogenesis in both common and rare neurodevelopmental disorders.

JD currently receives intensive therapies through the Early Intervention program. She receives 25 h of applied behavior analysis (ABA) per week, and center based occupational therapy, physical therapy and speech therapy. The speech therapy also includes feeding therapy as JD has poor biting and chewing skills. Further neurological assessment, including video EEG, did not show any unusual motor movements to be associated with seizure activity and she will be weaned off the anticonvulsants. She is continuing follow up with specialists in this area.

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