Potential Role of Genomic Sequencing in the Early Diagnosis of Treatable Genetic Conditions

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We present cases of 3 children diagnosed with the same genetic condition, Gitelman syndrome, at different stages using various genetic methods: panel testing, targeted single gene sequencing, and exome sequencing. We discuss the advantages and disadvantages of each method and review the potential of genomic sequencing for early disease detection. *(J Pediatr 2017;189:222-6).*

At least 7000 rare diseases have been identified, most of which are genetic disorders. Rare diseases collectively affect approximately 30 million people in the US and have a significant impact on patients and families.[1,2] Many go undiagnosed for years, even after numerous medical evaluations.[3] Rapid advances in genetic testing and sequencing technology, such as gene panel and whole exome sequencing (WES), offer the potential to significantly augment rare disease diagnostics; however, the use of tests in diagnostic workups is often variable. Appropriate and early implementation of genomic sequencing technology could lead to earlier detection of these disorders and possibly identify patients at early symptomatic stages. Especially when treatment is available, early identification of genetic disorders could have profound implications for patients with respect to disease management and the prevention of complications. However, one challenge to the use of genomic sequencing is insufficient familiarity with the yield and limitations of the tests, results interpretation, and optimizing application to different patients.[4-7]

Herein, we examine different approaches to diagnosis of a rare treatable genetic disorder by presenting 3 children with varying presentations that led to the diagnosis of Gitelman syndrome. WES led to a diagnosis in a patient who had only mild nonspecific symptoms that had gone unrecognized. In these examples, we discuss classical genetic testing and the potential of genomic sequencing for early detection of treatable genetic conditions.

Case Presentations

Case 1: Classic Symptomatic Presentation

A 16-year-old boy presented to the hospital with paresthesias, muscle cramps, and perioral numbness and was admitted to the intensive care unit with severe hypokalemia. Initial laboratory work revealed significantly low serum potassium (2.0 mEq/L; normal range 3.5-5.0) and magnesium (0.7 mg/dL; normal range 1.5-2.5), and elevated bicarbonate. An electrocardiogram showed U waves, but no prolonged QT interval or arrhythmia. Prenatal and birth history were uncomplicated. He had normal growth measures. Motor and speech development were delayed (walked at 2.5 years of age, first words at 3 years of age). At 9 years of age, he had also presented to the emergency room with hand cramps in the setting of vomiting and dehydration, but received limited workup. His parents and his 2-year-old brother were reportedly healthy.

Given the history of a prior similar presentation, he underwent further workup to identify the etiology of his electrolyte abnormalities. His urine studies revealed an elevated spot urine potassium:creatinine ratio (65 mEq/g; normal range <13), an elevated fractional excretion of magnesium in the setting of hypomagnesemia (2.7%; where >2% indicates inappropriate renal wasting), and a low 24-hour urinary calcium (<75.4 mg/day; normal range 100-250), which together were suggestive of a renal potassium and magnesium wasting disorder such as Bartter or Gitelman syndrome. During the 4-day hospitalization in the intensive care unit, he received intravenous potassium, his electrocardiogram normalized, and symptoms improved. He was then started on spironolactone and a regimen of potassium, magnesium, and calcium supplements. Genetic testing was performed for definitive diagnosis and to optimize pharmacological therapy. A gene panel for Gitelman and Bartter syndromes (types I-IV) was sent, including testing of *SLC12A1*, *KCNJ1*, *CLCNKB*, *BSND,* and *SLC12A3* genes, which identified a pathogenic variant.

Case 2: Familial Asymptomatic Testing

The 2-year-old brother of patient 1 was subsequently seen for a genetic evaluation to determine his risk of hereditary renal tubulopathy, given patient 1's presentation. His birth, development, and past medical history were unremarkable and physical examination was normal. Electrolytes were checked and targeted DNA sequencing for the familial gene variant was performed.

WES Whole exome sequencing

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Case 3: Early Diagnosis

A 7-year-old boy was evaluated for developmental delay, hypotonia, and possible autism spectrum disorder after being referred to genetics clinic. He was an only child of nonconsanguineous parents. There were no known maternal prenatal exposures. His motor and language development were delayed. He spoke in short sentences with a paucity of spontaneous speech, although he was able to understand well and convey his needs. He had difficulty with reading and spelling, but was comfortable with numbers, counting, and addition. Socially, he seemed interested in interacting with other children and exhibited play behaviors, but seemed more engaged with objects. Parents also reported unique stereotypical behaviors. Past medical history included constipation, poor sleep, and unexplained knee arthralgias with normal radiographs. There was no known family history of autism. On examination, he had normal growth measures and no physical anomalies. He made limited eye contact and had low tone. Audiology and ophthalmology assessments were normal. He had a normal brain magnetic resonance imaging study with spectroscopy and prior electroencephalographs were negative for seizure activity. A biochemical workup for inborn errors of metabolism was unrevealing. He had a normal karyotype, fragile X testing, and microarray. Diagnostic WES, trio, was performed in clinical laboratory testing as part of his developmental delay and autism workup. Written informed consent was obtained and the family chose to receive results of secondary findings. Exon capture was performed using Agilent's SureSelect XT2 All Exon V4 kit (Agilent, Santa Clara, California). DNA was sequenced using the Illumina HiSeq 2000 sequencing system (Illumina, San Francisco, California) with 100 bp paired-end reads. Resulting reads were aligned to the human reference genome (hg19). Variants in genes associated with autism, intellectual disability, metabolic, and other neurologic disorders, hypotonia, and speech delay were assessed in accordance with the phenotype information provided.

Diagnosis and Outcome

Genetic testing identified mutations in the solute carrier family12, member 3 (*SLC12A3)* gene encoding the thiazide-sensitive sodium-chloride co-transporter in all 3 patients. *SLC12A3* mutations are associated with Gitelman syndrome, an autosomal-recessive, salt-losing tubulopathy that results in hypokalemia, hypomagnesemia, metabolic alkalosis, and hypocalciuria. Patients often present in adolescence or early adulthood with muscle cramping, paresthesias, low blood pressure, and cardiac arrhythmia. It is a treatable condition with management of electrolytes by administration of potassium and/or potassium-sparing diuretics. The prognosis is generally good if patients are recognized, treated, and monitored to prevent episodes of electrolyte imbalance that can lead to complications such as fatal cardiac arrhythmias, especially in the setting of intercurrent illness.[8]

In patient 1, gene panel testing revealed a homozygous missense variant in the *SLC12A3* gene (c. 533C>T; p. Ser178Leu). Two previous reports have demonstrated this specific gene alteration (p. Ser178Leu) in patients with Gitelman syndrome.[9,10] At follow-up, he was without signs of electrolyte imbalance. He continued on magnesium oxide, potassium chloride, calcium carbonate, and spironolactone with serial monitoring of electrolyte levels. Genetic testing was offered to other family members including his 2-year-old sibling (patient 2), who was asymptomatic at testing. By familial targeted DNA sequencing, patient 2 was also found to be homozygous for the missense variant in the *SLC12A3* gene (c.533C>T; p.Ser178Leu). Laboratory evaluation for him revealed intermittently low serum potassium (range 3.1-5.6 mmol/L) and elevated urine potassium (82.3 mmol/L). Serum magnesium, calcium, and bicarbonate were consistently normal. He was followed for long-term monitoring. On 2 separate occasions, he presented with severe hypokalemia in the setting of viral illnesses with poor intake and diarrhea, but quickly responded to potassium supplementation. Eventually, spironolactone was initiated with stabilization of serum potassium levels.

Exome sequencing for patient 3 surprisingly found compound heterozygous disease-associated variants in *SLC12A3* (p.(P643L) and p.(G741R)), but did not find any definitive pathogenic variants in well-known disease genes associated with developmental delay or the autism spectrum. Both of the *SLC12A3* mutations identified in him have been previously reported in Gitelman syndrome.[9,11] On follow-up, his electrolytes demonstrated borderline low potassium, mildly low magnesium, and low urine calcium consistent with Gitelman syndrome on multiple tests. He was also noted to have polydipsia, polyuria, and enuresis, which had not been brought to clinical attention. Potassium and magnesium supplementation was started to prevent complications. Notably, his unexplained arthralgias resolved after the initiation of treatment, suggesting that these symptoms were an early manifestation of his condition. Developmental delay and autism were not the expected presentations for this renal condition, but interestingly growth retardation and developmental delays have been reported in a few patients with Gitelman syndrome.[12]

Discussion

The cases presented herein demonstrate different paths to diagnosis for a treatable genetic condition and highlight the usefulness of each genetic diagnostic approach. The first 2 patients were diagnosed by more traditional testing methods after a severe presentation (patient 1, gene panel testing) or in an asymptomatic sibling (patient 2, familial targeted genetic testing). The third patient, who had mild symptoms from the disease that had gone unrecognized, was diagnosed via exome sequencing.

Genetic testing is increasingly performed by high-throughput sequencing for a gene panel or an exome.[13] Exome sequencing interrogates the protein-coding regions of the genome, which is the approximately 2% of the genome where 85% of disease-causing mutations have been found.[14] Compared with more traditional targeted sequencing, it has the advantage of

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