A New Approach to Rare Diseases of Children: The Undiagnosed Diseases Network

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A 5-year-old boy presented to the Undiagnosed Diseases Network (UDN) with a history of global developmental delay, postnatal microcephaly, hypotonia, jerking movements concerning for seizures, minimal speech, severe gastroesophageal reflux disease, dysmorphic features, and partial agenesis of the corpus callosum on brain magnetic resonance imaging.

The patient was born at term after an uncomplicated pregnancy. Birth weight and length were in the 30th and 20th percentiles, respectively; head circumference at birth was unknown but not reported to be abnormal. He had poor feeding in the newborn period and gastroesophageal reflux disease was diagnosed in the first month of life. Weight gain and height progressed normally. Head circumference measured at the sixth percentile at 5 weeks of age and fell below the third percentile at 3 months of age.

Reduced muscle tone and truncal hypotonia were first appreciated at 6 months of age, as were mild motor delays. His first words were spoken at 11 months of age, but he was slow to gain vocabulary. Of note, he had no regression of developmental milestones.

Unexplained spasms concerning for seizures began at 12 months of age. Thought to correlate with gastrointestinal discomfort and gas, the episodes were characterized by extension and body stiffening, followed by a scream, hyperextension of arms, head turn, and opisthotonic posturing. In the absence of epileptiform activity on electroencephalogram, his neurologists favored myoclonic spasms over seizures. Over time, the spells evolved to be more consistent with dyskinetic and choreiform movement. In addition to his myoclonic spasms, the patient also experienced myoclonic jerks characterized by downward and inward hyperextension of the arms. Trials of various anticonvulsants showed only marginal effect. He had intermittent hand stereotypies.

The patient's medical history was significant for intermittent esotropia, mild obstructive sleep apnea, and dysmorphic features, including mild pectus excavatum, epicanthal folds, widely spaced teeth, high-arched palate, telecanthus, and broad mouth. Throughout his workup, the patient underwent extensive diagnostic imaging and laboratory studies (**Table I**; available at www.jpeds.com). There was no reported family history of similarly affected individuals. Both medical and biochemical geneticists who evaluated him indicated that his constellation of features was suggestive of an underlying genetic etiology, but not consistent with any known syndrome. With all evaluations failing to reveal an underlying etiology, the medical geneticist recommended whole exome sequencing (WES). Unfortunately, access to WES on a clinical basis was unavailable owing to lack of insurance coverage by a commercial insurance provider. As a result, the child's rare disease remained undiagnosed and the family was left without answers.

UDN	Undiagnosed Diseases Network
WES	Whole exome sequencing

The UDN

Approximately 25-30 million individuals in the United States are living with a rare disease.[1] Many children with rare diseases remain undiagnosed throughout life, leading to excess medical care, expensive diagnostic odysseys, and frustration for patients and their families.[2,3] Advances in genomic technology have allowed for more comprehensive genetic analyses of patients with rare diseases.

In an effort to better characterize patients with rare and undiagnosed diseases, the National Institutes of Health launched a single-site project, the Undiagnosed Diseases Program, to improve our understanding of the etiology of these disorders. After initial success, the program expanded to encompass additional clinical and research institutions, thus establishing the UDN.[4] The UDN is a network of investigators across 13 institutions designated to serve public need by bringing expertise in clinical diagnostics, translational research, and multiomics technologies to solve medical mysteries (**Figure 1**).

Delineated by the National Institutes of Health Common Fund, the UDN's main objectives are 3-fold: (1) to improve the level of diagnosis and care for patients with undiagnosed diseases, (2) to facilitate research into the etiology of

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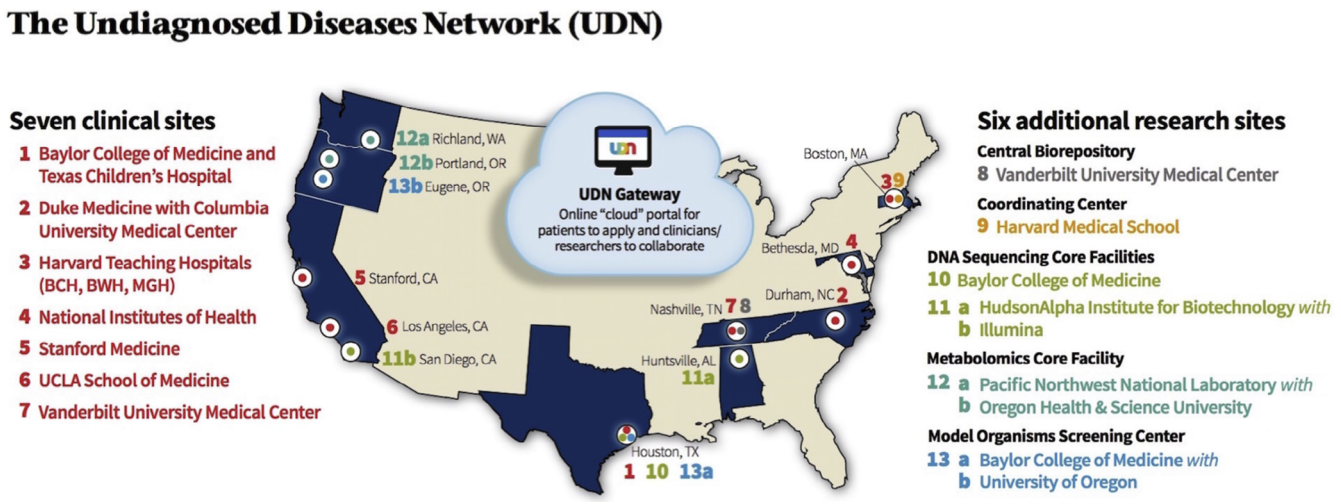

Figure 1. Geographical representation and structure of UDN clinical and research sites as of January 4, 2018. *BCH*, Boston Children's Hospital; *BWH*, Brigham and Women's Hospital; *MGH*, Massachusetts General Hospital; *UCLA*, University of California at Los Angeles.

undiagnosed diseases, and (3) to create an integrated and collaborative research community to identify improved options for optimal patient management. With these goals in mind, the UDN began accepting applications in September 2015.

The UDN accepts applications from both pediatric and adult patients. Applicants are eligible if they have a condition with at least 1 objective clinical finding that remains undiagnosed despite thorough evaluation by a healthcare provider. The most common disease domains of applicants include neurology, musculoskeletal, and allergy/immunology. Participation in the UDN requires consent to store and share information and biomaterials among both UDN centers and collaborating research institutions. A UDN-wide committee of clinicians reviews each patient before acceptance into the study. Patients are seen at 1 of the 7 clinical sites by expert clinicians for an evaluation that often spans several days. Specific evaluations and additional research studies are determined on a case-by-case basis by UDN clinician-scientists (**Figure 2**).

Teams of clinicians and medical researchers join together to conduct precise clinical evaluations, analyze genomic data, and pursue state-of-the-art follow-up studies to understand complex disease mechanisms. Ultimately, the UDN aims to reduce the burden of undiagnosed diseases on patients, families, and providers. In this report, we use a case example to illustrate the function and mission of the UDN.

Evaluation at a Clinical Site of the UDN

Initial Evaluation

Upon exhausting all clinically available diagnostic evaluations, the treating medical geneticist referred the patient to the UDN with the hope of revealing a unifying diagnosis. The patient's parents submitted an application to the UDN via the online portal (http://gateway.undiagnosed.hms.harvard.edu) with the required short medical practitioner referral letter. The patient's application, 1 of 1978 applications received by the UDN, was then subject to detailed medical record review and discussion with a multidisciplinary team of experts at 1 of the 7 UDN clinical sites. The site expert review panel and the network-wide panel accepted this patient's case for enrollment in the UDN. The patient's application was 1 of 848 accepted as of January 4, 2018.

Once accepted and regardless of socioeconomic status, patients receive the benefit of extensive clinical evaluations with appropriate specialists in addition to access to clinical and translational research studies, including genomic testing when appropriate. The initial encounter for this patient consisted of an in-person research study consent with a genetic counselor and clinical research coordinator, and blood and urine sample collection for genomic and metabolomic analyses. DNA was extracted from blood from the patient and his unaffected parents, who served as controls, to perform trio WES analysis via the CLIA-certified exome sequencing core (**Table II**; available at www.jpeds.com). Clinical variant interpretation by the sequencing laboratory was guided by American College of Medical Genetics and Genomics recommendations.[5] In parallel, research personnel at the clinical site applied a variety of computational algorithms for genomic analysis with the goal of increasing the likelihood of finding a molecular diagnosis for this patient. Relevant findings on genetic testing would guide subsequent clinical evaluations with physicians.

Genetic and Clinical Evaluations

Trio WES of this patient and his unaffected parents revealed 2 variants: a *de novo* heterozygous truncating variant in the *FOXG1* gene (c.624C>A; p.Tyr208X; NM_005249.4; GRCh37) and a maternally inherited heterozygous missense variant in the *SCN5A* gene (c.3911C>T; p.Thr1304Met; NM_198056.2; GRCh37). The *FOXG1* variant had been previously reported in a patient with FOXG1 syndrome.[6] The *SCN5A* variant had

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