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The NIH Undiagnosed Diseases Program and Network: Applications to modern medicine

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Abstract

Introduction—The inability of some seriously and chronically ill individuals to receive a definitive diagnosis represents an unmet medical need. In 2008, the NIH Undiagnosed Diseases Program (UDP) was established to provide answers to patients with mysterious conditions that long eluded diagnosis and to advance medical knowledge. Patients admitted to the NIH UDP undergo a five-day hospitalization, facilitating highly collaborative clinical evaluations and a detailed, standardized documentation of the individual's phenotype. Bedside and bench investigations are tightly coupled. Genetic studies include commercially available testing, single nucleotide polymorphism microarray analysis, and family exomic sequencing studies. Selected gene variants are evaluated by collaborators using informatics, *in vitro* cell studies, and functional assays in model systems (fly, zebrafish, worm, or mouse).

Insights from the UDP—In seven years, the UDP received 2954 complete applications and evaluated 863 individuals. Nine vignettes (two unpublished) illustrate the relevance of an undiagnosed diseases program to complex and common disorders, the coincidence of multiple rare single gene disorders in individual patients, newly recognized mechanisms of disease, and the application of precision medicine to patient care.

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Conflicts of interest statement

The authors declare no conflict of interest.

Web resources

The URLs for information presented here are: Online Mendelian Inheritance in Man, <http://www.omim.org/>, <http://www.ncbi.nlm.nih.gov/omim>, Human Phenotype Ontology, <http://human-phenotype-ontology.github.io/>, and Phenotips, <https://phenotips.org/>.

Conclusions—The UDP provides examples of the benefits expected to accrue with the recent launch of a national Undiagnosed Diseases Network (UDN). The UDN should accelerate rare disease diagnosis and new disease discovery, enhance the likelihood of diagnosing known diseases in patients with uncommon phenotypes, improve management strategies, and advance medical research.

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1. Introduction

In 2008, the NIH established an Undiagnosed Diseases Program (UDP), designed to help patients who had long sought a precise diagnosis and to discover new pathways and mechanisms of disease [1–3]. Ongoing annotation of the human genome, combined with advances in DNA sequencing, provided a huge impetus to the UDP and bolstered the promise of precision medicine [4]. Initiated within the NIH Intramural Research Program, the UDP has now evolved into the Undiagnosed Diseases Network (UDN), supported by the NIH Common Fund. The Network consists of the UDP, six additional clinical sites around the nation, a coordinating center, two DNA sequencing cores, a model organisms screening center, a metabolomics core, and a central biorepository. The UDN functions under a common IRB protocol with reliance agreements and data sharing procedures. On September 16, 2015, the UDN was launched with an online portal for patient applications (<https://gateway.undiagnosed.hms.harvard.edu>) [5]; it is modeled after the UDP, whose methods and illustrative cases are presented here.

Patients and their families were enrolled in a protocol approved by the NHGRI Institutional Review Board, and gave written informed consent. They applied to the UDP by providing a referral letter from a clinician, along with medical records, laboratory results, imaging studies, and biopsy slides. UDP experts evaluated each application for the presence of objective findings, novel phenotypic manifestations, and the likelihood of obtaining a diagnosis. A signature feature of the UDP was compression of the clinical evaluation at the NIH Clinical Center into five inpatient days, free of charge to the patient, with no insurance approvals. The UDP diagnostic process emphasized highly collaborative clinical evaluations, detailed and standardized documentation of patient's phenotype, and tightly coupled bedside and bench investigations. Standardized documentation of patient phenotypes employed Human Phenotype Ontology (HPO) terms, using PhenoTips software [6]. Clinical consultations were conducted by multiple specialists, and imaging studies and laboratory testing were tailored to the patient's individual manifestations. Examples of specialized assays included cerebrospinal fluid neurotransmitters and plasma glycomics. Biologic samples, including plasma, serum, DNA, urine, and fibroblasts from skin biopsies, were routinely collected and stored. Genetic studies included commercially available testing, panels of genes, single nucleotide polymorphism (SNP) analysis, and family exomic sequencing. Variant analysis utilized both commonly applied variant annotations and manually curated data, including SNP chip correlation, regions of low coverage, and non-coding regions. Some potentially pathogenic variants were evaluated by collaborators using informatics, cultured cell studies, and animal models for functional assays (fly, zebrafish, worm, or mouse).

2. Insights from the UDP

From its inception in 2008 through May 2015, the UDP received 2954 complete applications and accepted 863 (29%) for evaluation. Of these, we know 64 (7%) have died. Of the 863 patients evaluated, we present nine vignettes, seven published (Table 1) [7–38] and two unpublished, comprising 20 patients in ten families. (The number in column of Table 1 identifies the vignette's section number in this article.) The patients demonstrate how investigating undiagnosed individuals advances understanding of: 1) common and complex disorders, 2) the coincidence of rare diseases, 3) newly recognized mechanisms of disease, and 4) the practice of precision medicine.

2.1. Understanding common and complex diseases

Most common and complex disorders are polygenic or multifactorial, and their diverse determinants are difficult to sort out. In contrast, rare disorders are largely monogenic, *i.e.*, explained by a single genetic aberration. Three rare patients exemplify insights into common conditions (osteoporosis, nephrolithiasis, and viral infections).

2.1.1. Osteoporosis—A 15-year-old male had perinatal thrombocytopenia with intraventricular hemorrhage, hypoglycemia, tracheomalacia, aspiration pneumonias, congenital hip dislocations, infantile spasms at 15 months, and severe developmental delay by 2 years [35]. By age 6, he had renal tubular acidosis, nephrocalcinosis, nephrolithiasis, and fractures of the fibula and humerus. At age 15, he was microcephalic and noninteractive, with short stature, facial dysmorphisms, drooling, hearing loss, seizures, flexion contractures, scoliosis, cryptorchidism, retinitis pigmentosa, and cortical blindness. Brain MRI showed decreased white matter volume and delayed myelination in the frontal lobes. Bone age was delayed. Plain radiographs of lower extremities showed osteoporosis (Fig. 1A); DEXA scan Z scores were -2.9 in the spine and -6.5 in the forearm. Bone biopsy showed no trabecular meshwork, low cancellous bone volume, thick cortex, and decreased osteoblast and osteoclast activity. Differentiated bone marrow stem cells exhibited poor calcium phosphate mineralization.

Exome sequencing of the boy and his 9-year-old brother revealed a maternally inherited missense variant in the *SMS* gene on chromosome X, *i.e.*, c.443A>G (p.Gln148Arg). *SMS* encodes the enzyme spermine synthase, whose level was decreased 2.6-fold in the proband's cultured fibroblasts (Fig. 1B). Hemizygous mutations in *SMS* result in the Snyder-Robinson syndrome, characterized by facial dysmorphisms, neurological deficits, and osteoporosis [39–41].

Osteoporosis is a major public health problem whose mechanism is not completely understood. Snyder-Robinson syndrome can serve as a monogenic disorder in which to study the role of polyamines [42,43] in preventing osteoporosis in humans.

2.1.2. Nephrolithiasis—A 38-year-old man had recurrent episodes of nephrolithiasis [14]; stone analysis revealed calcium phosphate, and the patient had osteopenia and fractures. Serum ionized calcium was 1.32–1.41 mmol/L (normal, 1.12–1.32), the serum parathyroid hormone was suppressed to 3–10 pg/mL (normal, 16–87), urine calcium/

creatinine ratio was persistently high (median 0.33; normal, <0.22), and the fractional excretion of phosphate was 34% (normal, <20%). The serum $1\alpha,25(\text{OH})_2\text{D}_3$ was elevated at 83–160 pg/mL (normal, 18–64); specialized studies showed that the ultimate, inactive vitamin D metabolite, $24,25(\text{OH})_2\text{D}$, was 0.33 ng/mL (normal, 1.2–2.6). Ketoconazole therapy normalized the patient's calcium axis. Fibroblasts showed no metabolites of $1\alpha,25(\text{OH})_2\text{D}_3$ and reduced expression of CYP24A1 protein. Sequencing of the *CYP24A1* gene revealed a paternally inherited deletion, p.E143del, and a maternally inherited transition in exon 9, c.1226T>C (p.L409S).

The *CYP24A1* gene encodes 1,25(OH) $_2$ D-24-hydroxylase, the enzyme responsible for inactivating vitamin D [44]. Biallelic mutations in this gene result in increased active vitamin D levels, hypercalcemia, nephrocalcinosis, and nephrolithiasis. The frequency of deleterious *CYP24A1* variants in the general population is estimated at 0.06–0.14. Since 10% of all people have nephrolithiasis, *CYP24A1* mutations could account for 4–20% of patients with calcium kidney stones [14]. Individuals at risk for this common disease could be screened for high $1\alpha,25(\text{OH})_2\text{D}_3$ levels for consideration of a low calcium diet, less vitamin D- fortified foods, and minimal sun exposure.

2.1.3. Viral infections—A brother and sister, ages 11 and 6 years, presented with dysmorphic facial features, global developmental delays, hypotonia, optic atrophy, cerebral atrophy, and severe hypogammaglobulinemia with no increase in the number of infections [26]. Plasma levels of IgG were 317 and 142 mg/dL (normal, 574–1474), IgA <7 and 17 mg/dL (normal, 34–305), and IgM 21 and 21 (normal 32–208), respectively. Antibodies to measles, mumps, and varicella were negative or equivocal, despite adequate vaccine administration. Antibodies to tetanus toxoid, diphtheria toxoid, *Haemophilus influenza*, and *Streptococcus pneumonia* were adequate after vaccination. Thin layer chromatography of urine revealed a tetrasaccharide, identified on mass spectrometry as glucose $_3$ -mannose, making the diagnosis of Congenital Disorder of Glycosylation type IIb, now known as MOGS-CDG; this was confirmed by finding heterozygous mutations in the gene *MOGS*, encoding glucosidase I. Affected individuals fail to synthesize complex glycans on glycoproteins, creating a devastating, multisystem disease seen in only one prior patient [45] (Fig. 1C).

The children were hypogammaglobulinemic because immune globulins are N-linked glycoproteins stabilized by their glycans; Dr. Sergio Rosenzweig and colleagues demonstrated that the half-life of the patients' IgG was 6 days compared with 21 days for normal IgG. However, this defect did not significantly increase their susceptibility to infections, because their T cells failed to produce normal amounts of infective envelope-glycosylated virus (Fig. 1D).

MOGS-CDG represents a rare example of a genetic disorder that confers *resistance*, rather than *susceptibility*, to an environmental agent. It emphasizes the importance of glycans for immunoglobulin stability as well as infectivity of viruses; interference with viral glycosylation could be a therapeutic strategy for halting viral replication. Moreover, the patient's cells provide a model system for studying the infectivity of microbes that require glycoprotein synthesis.

2.2. Coincidental rare Mendelian diseases: Dulling Occam's razor

A law of parsimony in diagnostic medicine, Occam's razor, is to seek a single explanation for various manifestations of a patient's condition. However, multiple rare diseases are bound to coexist in some patients with unusual phenotypes, raising the question of how one best defines a disease.

2.2.1. Multiple diagnoses in a consanguineous sibship—Two sibs were products of a first cousin marriage (Fig. 2A). The older, a 6-year-old boy, was born with microcephaly and by 4 months had failure to thrive, distal renal tubular acidosis, nystagmus, and optic nerve atrophy. He fell frequently following a febrile illness at 2½ years; neurologic evaluation, including a nerve biopsy, revealed a diffuse motor axonal polyneuropathy. A muscle biopsy showed myofiber atrophy. By the time of his UDP evaluation, he had lost all developmental milestones. His 2-year-old sister exhibited a similar course.

SNP analysis showed 5% homozygosity. Sequencing revealed a homozygous *ATP6VOA4* mutation (c.1185delC; p.Y396TfsX12) in both sibs, explaining their renal tubular acidosis and hearing loss [46]. Exome sequencing identified homozygous, predicted deleterious mutations in *SLC52A2* (c.1327T>C; p.C443R) in both affected siblings; mutations in this riboflavin transporter are associated with Brown-Vialetto-van Laere syndrome type 2, a progressive neurologic disorder with deafness, bulbar dysfunction, and axial and limb hypotonia [47]; the children were treated with riboflavin. Homozygous, predicted deleterious mutations in *TOP1MT* (c.1030C>T; p.R344C) were also present in both affected siblings. *TOP1MT* encodes a mitochondrial DNA topoisomerase not previously associated with human disease. The proband's cultured fibroblasts responded to the drug EPI-743 (alphatocotrienol quinone; Fig. 2C), rendering the boy eligible for a clinical trial of this drug, which has demonstrated clinical response in Leigh encephalopathy and Leber hereditary optic neuropathy [48,49].

This case illustrates the importance of reconsidering the principle of Occam's razor, especially in cases of consanguinity.

2.2.2. Multiple diagnoses in a sibship independent of consanguinity—An 11-year-old girl (Fig. 2D, Sibling 1, left) born with microcephaly, had motor delay at 6 months, intellectual disability, easy fatigability, hypotonia, and an unexplained neuropathy [28]. At 20 months, she suffered the first of a dozen episodes of fever, lethargy, fasting hypoglycemia, ketonuria, undetectable insulin and, on one occasion, lactic acidemia. She had coarse facial features, midfacial hypoplasia, hypotelorism, synophrys, widely spaced teeth, brachydactyly, fifth finger clinodactyly, hypoplastic toenails, aggressive and obstinate behavior, and abdominal striae. BMI, weight, and head circumference were >97th centiles. Her younger sister (Sibling 2) had a similar presentation, but with more severe developmental delay and hypotonia and no dysmorphisms. At age 5 years, milestones ranged from 4 to 15 months. Gait was unsteady, hand movements stereotypic, and pincher grasp absent. There was no consanguinity.

The two sisters displayed a homozygous variant in *PCK1* (c.134T>C; p.I45T) on exome sequencing [28]; this variant conferred a short half life on the PCK protein, which is

cytosolic phosphoenolpyruvate carboxykinase, a gluconeogenic enzyme that maintains glucose homeostasis. The older sister had a *de novo* nonsense variant in *RAI1* (c.2273G>A; p.W758X), producing reduced mRNA consistent with Smith-Magenis syndrome [50]; this accounted for her dysmorphisms, intellectual disability, and behavior issues. The younger sister had a *de novo* mutation in *GRIN2B* (c.1238A>G; p.E413G), the gene for N-methyl-D-aspartic glutamate receptor subunit 2B. This variant accounted for her specific neurological deficits [51].

Even in the absence of consanguinity, multiple rare diseases can occur in the same patient.

2.3. Newly recognized mechanisms of disease

The discovery of novel diseases in undiagnosed patients often reveals a previously unrecognized metabolic or cell biological pathway.

2.3.1. Arterial calcification—In 2011, the UDP reported nine adults in three families with a rare disease, arterial calcification due to deficiency of CD73 (ACDC) involving joint and arterial calcifications (Fig. 3A) due to biallelic mutations in *NT5E* [7]. This gene encodes CD73, an ectonucleotidase that converts adenosine monophosphate (AMP) to adenosine and inorganic phosphate within vascular endothelial cells (Fig. 3B).

The discovery of ACDC showed that adenosine functions in preventing vascular calcification, and suggested that the purinergic pathway is involved in other disorders, such as pseudoxanthoma elasticum [52] and Mönckeberg arteriosclerosis [53]. In addition, cultured fibroblasts provide an *in vitro* model to investigate therapeutic interventions; based on such studies, a clinical trial of the bisphosphonate etidronate for ACDC is currently being conducted.

2.3.2. Impairment of inner nuclear membrane lamins—A 48-year-old man had nocturnal enuresis and erectile dysfunction at age 40, and back pain, spastic diplegia, leg weakness, poor balance, and dysesthesias of his feet at age 43. He progressed to dysautonomia, impaired cognition, drooling, and inappropriate crying. He needed a wheelchair and had spastic tetraparesis, ataxia, and dysarthria. MRI showed leukodystrophy in the brainstem and middle cerebellar peduncles (Fig. 3C).

SNP array analysis revealed a segmental duplication including *LMNB1* on chromosome 5q23.3–q31.1 (Fig. 3D). Duplications of *LMNB1*, encoding lamin B1, cause autosomal dominant leukodystrophy [19,54].

The lamins (A, B, and C) combine to form cells' inner nuclear membranes. When the ratio of lamins is perturbed, the membrane structure is altered, resulting in seemingly unrelated disorders. *LMNA* mutations cause progeria, lipodystrophy, Charcot-Marie-Tooth disease, limb-girdle muscular dystrophy, and mandibuloacral dysplasia, among other diseases [55,56]. In contrast, *LMNB1* mutations largely affect oligodendrocytes responsible for myelin deposition in the CNS, perturbing nuclear structure and gene expression [57]. Our patient's induced pluripotent stem cells can be differentiated into oligodendrocytes or

neurons to investigate the effects of *LMNB1* mutations on transcription, myelin synthesis, and senescence.

2.4. Practice of precision medicine

Nowhere is the opportunity to practice precision medicine greater than in rare and undiagnosed diseases. Determining the pathogenesis of patients' unique signs and symptoms can point to innovative treatments.

2.4.1. Refractory epilepsy—A 6-year-old boy had refractory seizures starting in infancy, along with axial hypotonia, appendicular hypertonia, hyporeflexia, random multifocal myoclonic movements, and developmental delays [24,27]. Brain MRI showed progressive cerebral atrophy, thin corpus callosum, and hypomyelination of terminal zones and temporal lobes. The electroencephalogram showed a potential right cerebral epileptic focus at 13 months, and exhibited slow disorganized activity with intermittent irregular high amplitude discharges at age 6 years.

Exome sequencing revealed a *de novo* missense variant in *GRIN2A* (c.2434C>A; p.L812M) [27]. After studies in *Xenopus* oocytes showed that this mutant's increased responsiveness to glutamate and glycine was attenuated by memantine (Fig. 4A), the boy underwent a trial of this FDA-approved drug that decreased his seizures (Fig. 4B), stopped all myoclonic jerks, and substantially improved his EEG [24].

Sophisticated *in vitro* studies targeting a single nucleotide mutation can change the course of a disease and associate another gene with a beneficial anti-epileptic [58].

2.4.2. Diagnosis-based therapy for a rare pediatric disorder—A 12-year-old girl had painful metatarsal exostoses and a calcified elbow mass; excisional biopsy showed ectopic calcification. At the NIH, calcified exudate extruded from her right first distal metatarsal bone computerized tomography revealed a 9 mm mid-diaphyseal cortical lesion in the left tibia. Serum calcium, parathormone, osteocalcin, and alkaline phosphatase were normal, but serum phosphorus levels were 6.6–8.1 mg/dL (normal, 3.1–5.5), and the tubular reabsorption of phosphate was 94–97% (normal, 85–95%).

Drs. Michael Collins and Rachel Gafni suspected tumoral calcinosis due to deficiency of fibroblast growth factor 23 (FGF23) and mutations in *GALNT3*, the gene that encodes polypeptide N-acetyl-galactosaminyltransferase 3 (GALNT3), an enzyme that protects FGF23 from degradation [59]. The patient was compound heterozygous for two *GALNT3* splice site variants, c.516-2A>T and c.1525+5G>A. The intact FGF23 level was 38 pg/mL (normal, 10–50), but the C-terminal FGF23 level was 892 RU/mL (normal, 20–100). FGF23 acts at the FGFR-1- α Klotho receptor complex to inhibit the action of transporters that reabsorb phosphate; FGF23 also inhibits the formation of 1,25-OH₂-vitamin D. Without GALNT3, poorly glycosylated FGF23 is cleaved to inactive fragments, which may compete with intact FGF23, increasing renal phosphate retention and vitamin D-mediated gastrointestinal absorption of calcium and phosphate.

The patient received a low phosphate diet, non-calcium containing phosphate binders, acetazolamide, and probenecid to promote phosphate excretion. The elbow lesion resolved. In this case, targeted sequencing rather than exome sequencing yielded the molecular diagnosis.

3. Conclusions

Nowhere in medicine have technological advances in diagnostics been as revolutionary as in genetics, where the resolution of human genetic information has increased steadily from the level of chromosomes (karyotyping) to the level of molecules (DNA sequencing). Genomic sequencing now provides vast insights into the individual genetic variations that interact with each person's environment to create health or disease.

Indeed, targeted and agnostic sequencing constitute a huge component of the modern geneticist's armamentarium [60]. Half of the UDP's diagnoses were made by exome sequencing combined with SNP analysis. Many diagnoses, however, were made *without* agnostic sequencing, and all diagnoses required thorough clinical evaluations, specialized medical expertise, and collaborative consultations.

The benefits of discovery seem profound. For 16 of the 20 UDP patients diagnosed and discussed here, the interval from onset of first symptoms or signs to diagnosis ranged from 2 to 54 years (mean and median, 10 years). A molecular genetic diagnosis in the probands permitted diagnoses of at least seven relatives, genetic counseling in the families, and reassurance of low recurrence risk in some couples. The discovery of a role for adenosine in ectopic calcification led to a therapeutic trial of bisphosphonates. One girl's progressive calcification was reversed by vigorous manipulation of phosphate excretion. Because fibroblasts of the boy with homozygous *TOP1MT* mutations responded to EPI-743, he became eligible for a clinical trial of that experimental anti-oxidant.

The UDP also provided insights of broad genetic and medical importance. Rare and novel monogenic disorders described here reflect mechanisms and pathways that are likely to be operational in the pathogenesis of common and complex diseases and that could be targets for therapeutic interventions, although none has yet reached fruition. In addition, the UDP cases expanded the clinical spectrum of several syndromes, *e.g.*, Brown-Vialetto-van Laere syndrome 2 and MOGS-CDG. Other cases provided functional studies critical in establishing the relationship of genes and specific variants to disease. Finally, the clinical utility of exhaustive sequence evaluation and whole genome sequencing was highlighted by two disease-causing mutations found in introns. The UDP also provided the hope embodied in the concept of precision medicine to desperate patients with nearly unique disorders and private mutations.

A national network, the UDN, now offers phenotyping, genotyping, environmental exposure analysis, functional studies, model system investigations, and broad data sharing to undiagnosed patients, bringing customized diagnostics closer to home [5]. With at least one other published program in the US [60] and international expansion already underway [61],

the UDN paradigm should allow additional patients, some on a diagnostic road longer than that of Odysseus himself, to find answers.

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Fig. 1.

Understanding common and complex diseases. (A) Gracile, osteoporotic tibia and fibula. (B) Polyamine synthetic pathway. Addition of a propylamine moiety from decarboxylated *S*-adenosylmethionine to putrescine produces spermidine. A second propylamine moiety is added to spermidine by spermine synthase, producing spermine. Spermine synthase is deficient in boys with Snyder-Robinson syndrome. Spermidine and spermine are polyamines whose ratio is crucial for cell processes including transcription and translation [39]. (C) Pathway defective in Congenital Disorder of Glycosylation IIb. Glucosidase I, deficient in the disorder, catalyzes the first step in the conversion of high mannose glycoproteins to complex glycoproteins, as part of the endoplasmic reticulum protein quality control process, also known as the unfolded protein response. (D) Viral infections in patient cells. Glycosylated viruses such as HIV can infect these cells, but the cells produce viruses that contain an abnormally glycosylated coat, making them less infective. No differences in terms of infectivity were noted when non-glycosylated viruses were tested. (Courtesy of Dr. Sergio D. Rosenzweig.)

Fig. 2. Coincidental rare Mendelian diseases: Dulling Occam’s razor. (A) Brother (left) and sister (right) with Brown-Vialetto-van Laere syndrome type 2, distal renal tubular acidosis, hearing loss, and mitochondrial topoisomerase 1 deficiency. (B) The family pedigree; double line indicates consanguinity. There were seven previous spontaneous abortions. Below each patient symbol is a list of that individual’s pertinent gene variants. The table lists the genes and the family’s associated diseases, all recessive disorders. Abbreviations: cmpd het = compound heterozygous; homo = homozygous; SAB = spontaneous abortions. (C) Response of the proband’s cultured fibroblasts to EPI-743 compared with inactive compound (RS-743) in the presence of oxidizing agents. The patient’s fibroblasts have increased sensitivity to oxidizing compounds, and EPI-743 rescues cell viability. (Courtesy of Edison Pharmaceuticals, Inc.) (D) Pedigree of a non-consanguineous family with multiple disorders; asterisks denote allele pairs causing disease.

Fig. 3.

Newly recognized mechanisms of disease. (A) Plain radiograph of a patient showing extensive, irregular calcification and dilatation of the femoral and popliteal arteries [7]. (B) Purinergic pathway at the surface of vascular endothelial cells. Normally, CD73 (encoded by *NT5E*, defective in ACDC) converts adenosine monophosphate to adenosine and inorganic phosphate (Pi). Adenosine binds to the adenosine receptor, trophically inhibiting alkaline phosphatase (APL) expression. When CD73 is absent, ALP is increased and converts pyrophosphate (PPI, an inhibitor of calcification) to Pi (a stimulator of calcification). *In vitro* studies showed that *NT5E* mutant fibroblasts calcified under osteogenic conditions, and the calcification could be reversed by adenosine or an APL inhibitor. (Courtesy of Shira Ziegler, Johns Hopkins University School of Medicine.) (C) Brain MRI showing leukodystrophy in brainstem and middle cerebellar peduncles of a patient with duplication of *LMNB1*. (D) Log R ratios of fluorescent intensity of SNPs on chromosome 5q. A contiguous group of SNPs has higher intensity, reflecting a duplication, *i.e.*, three total copies rather than two. The gene annotation of the region indicates that *LMNB1* is encompassed by the duplication.

Fig. 4.

Precision medicine: Treatment based on variant function studies. (A) Patch clamp results showing maximal response to glutamate and glycine in *Xenopus* oocytes transfected with the normal and mutant *GRIN2A*. Both the wild type and the mutant receptors were responsive to memantine inhibition. (Courtesy of Drs. Hongjie Yuan and Stephen F. Traynelis.) (B) Seizure frequency of the patient in response to various anti-epileptic medications. Note pronounced decrease in seizures on memantine. (Courtesy of Dr. Tyler Pierson.)

Table 1

UDP publications on rare and new diseases, ordered by increasing PMID number.

Reference	Vignette number ^c	PMID number	Diagnosis	Phenotype OMIM number	Gene name abbreviation	Gene OMIM number	Inheritance ^b	Frequency
7 ^c	2.3.1	21288095	Calcification of joint and arteries	211800	<i>NTSE</i>	129190	AR	17 patients
8		21353777	Spinal muscular atrophy, distal, autosomal recessive, 1	604320	<i>IGHMBP2</i>	600502	AR	60 patients
9		22022284	Spastic ataxia 5, autosomal recessive and neuropathy	614487	<i>AFC3L2</i>	604581	AR	4 patients
10		22146942	Spastic paraplegia 35, autosomal recessive	612319	<i>FA2H</i>	611026	AR	18 patients
11		22252885	IgG4-related sclerosing mastoiditis	604360	Somatic?		None	~200 patients
12		22675082	GM1-gangliosidosis, juvenile	230600	<i>GLB1</i>	611458	AR	1/300,000
13		22749184	Spastic paraplegia, autosomal recessive	604360	<i>SPG11</i>	610844	AR	1/100,000
14 ^c	2.1.2	23293122	Nephrolithiasis	143880 and 52 others	<i>CYP24A1</i>	126065	AR	Up to 1/1000
15		23420719	Kearns-Sayre syndrome with growth failure	530000	Mitochondrial DNA deletion		Mitochondrial	1/100,000
16		23443029	Recurrent subacute post-viral ataxia	?variant of 603553	<i>PRF1</i>	170280	AR	2 sisters (plus 4 with different phenotype)
17		23453856	Myopathy, areflexia, respiratory distress, dysphagia, early-onset (EMARDD)	614399	<i>MEGF10</i>	612453	AR	14 patients in 7 families
18		23465863	Anyloid myopathy	Not in OMIM	Somatic		None	15/year in U.S.
19 ^c	2.3.2	23649844	Leukodystrophy, demyelinating, adult-onset, autosomal dominant	169500	<i>LMNB1</i>	150340	AD	148 patients in 33 families
20		23661660	Mucopolysaccharidosis IIIB	252920	<i>NAGLU</i>	609701	AR	1/100,000
21		23857908	Hereditary spastic paraplegia type 43	615043	<i>C19orf12</i>	614297	AR	53 patients
22		23968566	Neurodegeneration with brain iron accumulation 1	234200	<i>PANK2</i>	606157	AR	1–3/1,000,000
23		24006476	Cutaneous skeletal-hypophosphatemia syndrome()	Not in OMIM	<i>NRAS</i> and <i>HRAS</i>		Somatic, AD	5 patients
24 ^c , 27 ^c	2.4.1	24504326 24839611	Epilepsy, focal, with speech disorder	245570	<i>GRIN2A</i>	138253	AD	124 patients
25		24686847	Aicardi-Goutières syndrome 7	615846	<i>IFIH1</i>	606951	AD	14 patients
26 ^c	2.1.3	24716661	Congenital disorder of glycosylation IIb (MOGS-CDG)	606056	<i>MOGS</i>	601336	AR	3 patients
28 ^c	2.2.2	24863970	Phosphoenolpyruvate carboxylate deficiency, cytosolic	182290	<i>PCK1</i>	614168	AR	First report
			Smith-Magenis syndrome	613970	<i>RAI1</i>	607642	AD	1/15,000
			Cognitive defects, autosomal dominant 6	261680	<i>GRIN2B</i>	138252	AD	37 pathogenic variants

Mol Genet Metab. Author manuscript; available in PMC 2017 August 17.

Reference	Vignette number ^c	PMID number	Diagnosis	Phenotype OMIM number	Gene name abbreviation	Gene OMIM number	Inheritance ^b	Frequency
29		25251875	Brain hypomyelination	8 OMIM entries	<i>ERCC6</i>	609413	AR	25 patients
30		25527264	Cockayne syndrome B	133540				
31		25577287	Hypomyelination with brainstem and spinal cord involvement and leg spasticity	615281	<i>DARS</i>	603084	AR	13 patients
32		25678555	Stormorken (York platelet) syndrome	185070	<i>STIM1</i>	605921	AD	22 patients
33		25817015	Congenital disorder of glycosylation Ia	616457	<i>CAD</i>	114010	AR	First report
34		25845469	Epileptic encephalopathy, early infantile, 29	616339	<i>AARS</i>	601065	AR	First report: 3 patients
35 ^c	2.1.1		Cognitive impairment, autosomal recessive 18	614249	<i>MED23</i>	605042	AR	7 patients in 2 families
36		25888122	Cognitive impairment, syndromic, Snyder-Robinson type	309583	<i>SMS</i>	300105	X-linked	20 patients
37		25943031	Multiple congenital anomalies-hypotonia-seizures syndrome 3	615398	<i>PIGT</i>	610272	AR	7 patients
38		26119818	Ablepharon macrostomia syndrome	200110	<i>TWIST2</i>	607556	AD	59 patients
		26373698	Barber-Say syndrome	209885				
			Musculocontractural type of Ehlers-Danlos syndrome	601776	<i>CHST14</i>	608429	AR	39 patients

^aOMIM, Online Mendelian Inheritance in Man.

^bAR, autosomal recessive; AD, autosomal dominant.

^cIllustrative patient vignettes in text, in section number given in second column.