Results: Including the index NASA-like proband, we identified 5 patients from 4 unrelated families with bi-allelic, rare variants in *IRAK4* who presented with persistent, severe autoinflammation and without immunodeficiency. Two patients had homozygous variants: one c.333del and the other c.161+892A>G. Another three had compound heterozygous variants one with c.539_540del & c.80A>C and siblings with c.877C>T & c.162-217C>T). All individuals had strongly concordant clinical presentations and neuroimaging features, including an episodic, waxing & waning mental state, visual loss/disturbance, and refractory seizures. With these episodes, neuroimaging showed new areas of transient white matter edema sometimes evolving to gliosis, on a background of often severe calcifications and subsequent brain atrophy. All patients had biomarker evidence of neuroinflammation and anemia. Three of the 5 patients had transient ischemic attacks and infarctions. Median age of onset was 14 years but was highly variable (IQR=14), and patients with later onset had marked psychotic features.
The disease was partially responsive to immune suppressive therapy. Refractory seizures and continued neuroinflammation remained in most cases with overall disease progression.
Conclusion: In these 5 patients, a strongly concordant clinical and radiological phenotype emerges of IRAK4-mediated autoinflammation. This cohort represents both an expansion of the known associated phenotype and of the types of variants causing disease. The severity of neuro- and autoinflammation in these patients requires aggressive immune suppression. Further work is needed to understand the full mechanism of disease and successful treatment strategies.

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P275

Complementary long-read sequencing to identify variants in neurological phenotypes

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Introduction: Short-read (SR) exome (ES) and genome sequencing (GS) have improved molecular diagnosis across rare neurological phenotypes, however long-read (LR) GS offers enhanced resolution for pseudogenes, high homology regions, repeats, and structural variants. We performed LR GS in individuals with undiagnosed neurological phenotypes ranging from nonsyndromic hearing loss to neurodegenerative conditions.
Methods: LR GS was performed to 29 families exhibiting unexplained neurological presentations that had not been resolved by previous SR ES or GS. LR GS was conducted via PacBio instrument and GeneYX software used for the data analysis. Variants were classified according to ACMG/AMP guidelines. Clinical correlation was performed through multidisciplinary review.
Results: Among the 29 families, LR GS identified diagnostic variants in 2 cases (6.9%), previously undetected by SRS. In a case with bilateral sensorineural hearing loss, LR GS identified a homozygous pathogenic c.1030C>T (p.Arg344Ter) variant in the *STRC* gene, confirming autosomal recessive deafness. The *STRC* gene has a pseudogene which has a high sequence homology affecting accurate read mapping with SR GS. In a second case with multiple congenital anomalies and intellectual disability, LR GS identified a homozygous pathogenic n.40C>T variant in the *RNU4ATAC* gene, consistent with a disorder of minor spliceosome function. Previous ES could not detect this variant due to limitations of targeted enrichment.
Conclusion: In this study, we solved 2 out of 29 cases with LR GS previously missed by short-read ES or GS. Utilizing LR GS as a complementary or follow-up tool to SR ES or GS could bridge gaps in current genetic testing workflow. Continued development of LR GS analysis methods can further improve diagnostic yield and variant interpretation.

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P276

Genetic characterization and clinical manifestations in adults with hypophosphatasia in the United States

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Introduction: Hypophosphatasia (HPP) is a rare, progressive metabolic disorder caused by deficient alkaline phosphatase (ALP) activity. This deficiency impairs bone and tooth mineralization and disrupts calcium and phosphate regulation, resulting in a wide range of skeletal and non-skeletal symptoms. Asfotase alfa (AA), an enzyme replacement therapy, is the only FDA-approved treatment for perinatal/infantile- and juvenile-onset HPP.
HPP can be dominant or recessive in inheritance. To date, there are >400 identified *ALPL* pathogenic variants. While most HPP patients have 1 or 2 pathogenic *ALPL* variant(s), many have variants of uncertain significance (VUS), and many patients have no identifiable *ALPL* variant.
Due to the rarity of the disease and the barriers of collecting genetic testing results at a large scale, limited information exists on patients with negative or uncertain genetic testing.
This study aims to describe the genetic classification of adult HPP patients and compare clinical manifestations among those with positive, negative, and VUS genetic test (GT) results.
Methods: This US retrospective observational study analyzed data of adult HPP patients (≥18 years) prescribed AA, prior to treatment initiation. Data were collected to support HPP access to therapy.
GT results were classified as positive (pathogenic/likely pathogenic), negative (benign/likely benign), or VUS, as reported by the testing laboratory. Clinical features, enzyme levels (ALP), and substrate levels (PLP, PEA) were obtained from medical records. For patients with a VUS, identified variant(s) were recorded.
Clinical manifestations and laboratory results were compared across GT categories using chi-square tests and t-tests.

Results: A total of N=748 patients (80.3% female, mean age 46.3 years) met inclusion criteria. Among adult HPP patients initiating AA, 84% had positive GT, 7% negative GT, and 9% VUS. Among patients with VUS results, 44 unique variants were identified; the most common were c.610A>T, c.657G>T, and c.1190G>A.

Clinical data were recorded for N=487 patients. The most frequent symptoms were muscle/joint pain (79%), bone pain (77%), fractures (70%), muscle weakness (59%), and premature/non-traumatic tooth loss [PTL] (53%). Low bone density (44%) and mobility/functional issues, such as, difficulty walking (41%) were also common.

Symptom burden was similar across GT groups. For example, muscle/joint pain prevalence were similar across GT (positive:79%, negative:81%, VUS:78%; p=0.96). Bone pain trended nominally higher in the negative GT group (positive:79%, negative:88%, VUS:74%; p=0.41). Fractures trended nominally higher in the VUS GT group (positive:72%, negative:69%, VUS:85%, p=0.31). Statistically significant differences were observed only in dental findings: poor dentition (positive:40%, negative:65%, VUS:33%; p=0.03) and PTL (positive:55%, negative:54%, VUS:30%; p=0.04).

On average, patients experienced 6-7 HPP symptoms, with no difference across GT categories (positive:6.8, negative:6.9, VUS:6.1; p=0.51). The majority of patients had low ALP and elevated substrates: 98% with low or borderline-low ALP, 82% with elevated B6/PLP, and 85% with elevated PEA. The proportion of patients with low ALP (≤40 IU/L in adults) was also similar (positive:94%, negative:89%, VUS:94%; p=0.12).

Conclusion: Clinical manifestations of HPP are remarkably consistent across patients with positive, negative, or VUS genetic results, confirming that disease burden does not depend on the GT category.

Importantly, many HPP patients are diagnosed and treated for HPP despite negative or uncertain GT results. While early reports estimated GT sensitivity at 95%, our analysis suggests that this is an overestimate, indicating that a larger proportion of patients with HPP may have negative or VUS results.

Although the majority of patients had a pathogenic or likely pathogenic GT, a substantial proportion had either negative GT or VUS, supporting the notion that GT is informative, but not mandatory for either making the diagnosis or treatment decisions.

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P277

Underrecognized late-onset forms of vascular Ehlers–Danlos syndrome: Insights from a community hospital case series

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Introduction: Vascular Ehlers Danlos Syndrome (vEDS) is a severe, autosomal dominant form of Ehlers Danlos Syndrome (EDS) caused by variants in the COL3A1 gene. vEDS is characterized by tissue fragility and increases the risk of major clinical complications such as aortic dissections, colonic perforations, and uterine ruptures, leading to reduced lifespan. There are known genotype–phenotype correlations in COL3A1 with loss-of-function variants leading to delayed disease onset, yet milder or late-onset presentations of vascular Ehlers–Danlos syndrome remain underrecognized. As genetic testing has become more accessible, the historical perception of vEDS as an early-onset and almost uniformly severe disorder is being challenged. Ascertainment bias - where testing was previously limited to the most severely affected - has likely obscured the true phenotypic spectrum. This is exemplified by three recent families identified at our community hospital, in whom genetic testing confirmed new diagnoses of vEDS in multiple individuals in their seventh to ninth decades of life.

Methods: This study is a retrospective case series describing three families diagnosed with vEDS at a community hospital.

Results: The probands of the families were in their 4th, 6th, and 7th decades of life at diagnosis. The youngest proband is a woman with a history of spontaneous pneumothoraces, multiple dental surgeries, and a uterine rupture during her second pregnancy, leading to her diagnosis of vEDS. Genetic testing identified a heterozygous likely pathogenic COL3A1 variant (c.3275G>C (p.Gly1092Ala)). Cascade testing confirmed the variant in her 74-year-old mother with a history of severe scoliosis, iliac artery dissections, and a thoracic aortic aneurysm for which the patient underwent elective repair after the diagnosis was established.

The second proband was a 53-year-old man referred to genetics due to a celiac artery dissection. Genetic testing identified a heterozygous, pathogenic COL3A1 variant (c.4184C>A (p.Ser1395*)). The proband's 56-year-old brother was also diagnosed at our center and had a normal head-to-pelvis MRA, and has a history of hip replacement. The variant was also identified in the proband's 82-year-old mother, making her the oldest new diagnosis in this series. She had spontaneous colonic perforation in her 50's and no other known findings.

The eldest proband is a 62-year-old man who presented with a Type-A thoracic aortic dissection. He had a known 4.2cm ascending aortic aneurysm at the time of his dissection and history of aortic disease in multiple relatives in their 6th and 7th decades. Genetic testing revealed a heterozygous, pathogenic variant in COL3A1 (c.3325C>T (p.Arg1109*)). His brother also received a diagnosis of vEDS at the age of 66 years with a history of aortic disease and iliac artery dissection. He underwent elective valve-sparing aortic root and hemi-arch replacement.

Conclusion: This case series highlights the broad phenotypic variability and often underrecognized late-onset presentations of vascular vEDS. Historically, vEDS has been defined by early and catastrophic events, but increasing use of genetic testing is revealing that some individuals may experience a much milder disease course extending into older adulthood. Although milder or atypical presentations have been described in the literature, awareness of these presentations remains limited within the medical community, leading to missed or delayed diagnoses. The individuals described here, many diagnosed in their sixth to ninth decades, demonstrate that vEDS can still remain undiagnosed well into older adulthood. Genetic testing in the past was limited to severely affected patients, likely leading to underdiagnosis of families with attenuated forms of the condition. By documenting these late and variable presentations, case series such as this study can help to increase awareness of the true phenotypic spectrum of vEDS, improve recognition of milder disease, and guide more inclusive approaches to genetic evaluation, counseling and surveillance of affected individuals and their families.

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