

February 27, 2026



Rare Disease Day

Diagnose Earlier, Treat Smarter: Innovations in Rare Disease Patient Care

Easel Number	Poster Title	Authors
1	Rapid Whole Genome Sequencing in Neonates: Treatable Diagnoses Beyond the New York State Newborn Screening Panel	Laura Andolina, Robert Rigobello, Xiaonan Zhao
2	Class 9 Myosin Regulation of Epithelial Cell Polarity	Emma C. Murray, Leighton S. Lee, Gillian M. Hodge, Andrew T. Lombardo
3	Cowden Disease with Cerebellar Gangliocytoma Causing Hydrocephalus and Early Papilledema: A Case Report of a Rare Disease	Alyssa Stathopoulos, David J. Rodman
4	Susac Syndrome	Norah S. Lincoff, Marisa Warren
5	In Vitro Neuronal Models Reveal Pathological and Therapeutic Insights in Friedreich's Ataxia	Danielle K. Bailey, Sara Cruz, Daniel J. Kosman
6	Establishing a Time Course for Midbrain-to-Pons Ratio Decline and Behavioral Deficits in a hTau ChAT-Cre Rat Model of Progressive Supranuclear Palsy-Richardson's Syndrome	Kymani Getfield, Aakari Redd, Ryan Dewan, Martin P. K. Leigh, Joseph A. Sperryak, Stewart D. Clark
7	TGF- β superfamily signaling modulation in human neural crest cells and Mowat-Wilson syndrome	Bahun, B. J., Prasad, M. S., Charney, R. M.
8	Developing A Patient-Derived iPSC Endothelial Model to Investigate Mitochondrial Dysfunction in MELAS	Lucas Davis, Karl Swanson, Zahid Manzar, Rita Alevriadou
9	When POTS is the tip of the iceberg: Rare cases of dysautonomia as a possible manifestation of another disorder	Svetlana Blitshteyn, Freshta Masoud
10	Significant Improvement of Postural Orthostatic Tachycardia Syndrome with semaglutide: a case report	Svetlana Blitshteyn, Sanjana Suresh, Lucia M. Lorenzi
11	Beyond behavior: PheWAS identifies ADHD as a risk factor for autonomic nervous system disorders	Morgan Baker, Jamal B. Williams
12	The patient-specific FOXP1 syndrome mouse models with different genetic variation display distinct phenotypes and severities.	Dongjun Shin, Shin Jeon, Jae W. Lee, Soo-Kyung Lee

February 27, 2026

13	FOXG1 in Oligodendrocyte Precursor Cells Regulates Myelination and Mouse Behavior	Soumya Pal, Dongjun Shin, Shin Jeon, Soo K. Lee, Jae W. Lee
14	FOXG1 Missense Variant reveals neuronal circuit dysfunction driving Autism-like behaviors	Liwen Li, Ji-Hwan Moon, Dongjun Shin, Shin Jeon, Jae W. Lee, Soo-Kyung Lee
15	Regulation of FOXG1 expression by cell-type specific enhancers and transcription factors	Varsha Ramachandra Kambar, Shin Jeon, Jae W. Lee, Soo-Kyung Lee
16	Investigating FOXG1 Function in Translational Regulation in FOXG1 Syndrome	Qian He, Shin Jeon, Ji-Hwan Moon, Liwen Li, Francesca Cargnin, Sejal Shukla, Tatsuaki Kurosaki, Jae W. Lee, Soo-Kyung Lee
17	Early Communication Deficits in FOXG1 Mouse Models and AAV9 Rescue	James Oh, Valli Duvvuru, Dongjun Shin, Holly O'Shea, Eunjin Kwak, Shin Shin Jeon, Jae Lee, Soo-Kyung Lee
18	ASO-Mediated Upregulation of FOXG1 via Targeting 5' and 3' UTR Regulatory Elements: A Therapeutic Strategy for FOXG1 Syndrome	Lian Cai, Seon-Ung Hwang, Soumya Pal, Shin Jeon, Jae Lee, Soo-Kyung Lee
19	Convergent Indirect Pathway SPN Dysregulation in FOXG1 Syndrome Models	Valli Duvvuru, Liwen Li, Christine Song, Dongjun Shin, Ji-Hwan Moon, Shin Jeon, Soo-Kyung Lee, Jae W. Lee
20	Characterization of Cortical Neurons Differentiated from FOXG1 W308X Patient-derived Human iPSCs	Seon-Ung Hwang, Lian Cai, Jae W. Lee, Soo-Kyung Lee
21	FOXG1 Syndrome: Characterizing a Large Patient Cohort	Meagan L. Collins Hutchinson, Hanchen Jiang, Justin Cordones, Natalie Phan, Kevin Lin, Lila Bloom, Layla Guy, Jae Lee, Soo-Kyung Lee
22	Phelan-McDermid Syndrome: Clinical Overview and Resources for Patients and Healthcare Providers	Meagan L. Collins Hutchinson, Alexander Kolevzon, Audrey Thurm, Kathy Fiscus, Carla D'Imperio, Lauren Schmitt

February 27, 2026

23	Koolen-de Vries Syndrome: Clinical Overview and Natural History Study	Meagan L. Collins Hutchinson, Ashley Point, Anna C. Pfalzer
24	Syntaxin Binding Protein 1-Related Disorders	STXBP1 Foundation
25	Dravet Syndrome: A Comprehensive Systematic Review: Epidemiology, Genetics, Pathophysiology, Treatment, and Emerging Therapies	Margil Ranpariya, Gurleen Kaur, Amanda Schwandt, Osman Farooq
26	Fatal Community-Acquired Pseudomonas aeruginosa Meningitis in a Previously Healthy 4-Month-Old Infant with Recent Saltwater Pool Exposure.	Peter Habashy, Kashaf Ud Duja, Ahmed Rafay Afzal
27	Pancytopenia in Sepsis: A Missed Window to Evolving B-Cell ALL	Yashita Arora, Mallhi Kanwaldeep
28	Early Vertebral Fragility as a Presentation of Pediatric B-ALL: A Case Highlighting Bone Morbidity Preceding Hematologic Findings	Srilakshmi K. Jayapraksan, David Byrwa
29	Silent in Utero, Severe at Birth: A case of recessive Titinopathy in neonate	Srilakshmi K. Jayapraksan, Sheetal Chepuri
30	Heart Bound by Fibrosis: Understanding Endomyocardial Fibrosis	Aaliyah H., Monay S., Faith M.
31	Short QT Syndrome: A Rare but Lethal Channelopathy	Wing Lam Ho
32	Incomplete Kawasaki Disease in a toddler with T-Cell Lymphopenia and Congenital Heart Defects: Diagnostic Overlap with Atypical DiGeorge Syndrome and Other Hyperinflammatory Conditions	Ahmad Hassan, Vikranth Raja Raja
33	Kienböck Disease as an Early Vasculopathic Manifestation Preceding Systemic Sclerosis: A Case Report	Abira Chowdhury, Sissmol Davis, Ethar Salman, Mahak Khadija
34	Threefold Impact of a Scleroderma-focused Interprofessional Education Event	Hannah Bowen, Amy Gietzen, Lee Shapiro
35	Degosdisease.org: Website Content for an Ultra-Rare Disease and Nature of Inquiries Received	Hannah Bowen, Lee Shapiro
36	Lipoma Arborescens: A Rare Cause of Knee Swelling in an Adolescent Male with Juvenile Idiopathic Arthritis Successfully Treated with Adalimumab	Hend Abd El Baky, Joseph Serghany, Philippe Jaoude, Elias Jaoude, Saif Ibrahim, Ahmad Hassan, Rabheh Abdul-Aziz
37	De Novo KRAS (p.G13C)-Associated Immune Dysregulation Presenting as Refractory Arthritis and Crohn-like Disease	Saif Ibrahim, Ahmad Hassan, Rabheh Abdul- Aziz

February 27, 2026

38	Early Presentation of Familial Mediterranean Fever in a 3-Year-Old Child	Aysenur Danis, Gitanjali Rebello, Rabheh Abdul Aziz
39	Ureaplasma Peritonitis with Severe Systemic Illness in an Immunosuppressed Adolescent with Granulomatous Multi-System Disease	Yuzuguldu B, Lewis D, Euscher L, Habashy P, Grace J, Aziz R
40	Primary Hyperoxaluria Type 2 in Pediatrics: Intrafamilial Genotypic Confirmation and Phenotypic Variability	Sriya Natarajan, Badar Goraya, Xiaoyan Wu
41	Surgical Intervention in PANDAS: Assessing the Benefits of Tonsillectomy	Alicia Loui, Abraham Kassem, Abby Contello, Michele M. Carr
42	Tonsillectomy Outcomes in PFAPA	Abigail Contello, Annabella Nilon, Abraham Kassem, Michele M. Carr
43	Post-tonsillectomy Bleeding in Pediatric Hemophilia Patients	Murilo de Santana Hager, Abraham A. Kassem, Alexandra Corbin, Taylor Ahles, Michele M. Carr
44	Pediatric Thyroid Cancer and Thyroidectomy Incidence Trends During 2005-2023	Annabella Nilon, Abigail Contello, Abraham Kassem, Michele M. Carr
45	Asymptomatic Lingual Osseous Choristoma Following Oral Trauma	Jenna Onetto, Hannah Danziger, Harrison Guigui, Jacob Fried, Michele Carr, Iris Danziger



Poster Abstracts

1. Rapid Whole Genome Sequencing in Neonates: Treatable Diagnoses Beyond the New York State Newborn Screening Panel

Laura Andolina, MS, CGC, Robert Rigobello, MS, CGC, Xiaonan Zhao, PhD, FACMG

Background: Traditional newborn screening (NBS) is a critical public health tool, enabling early detection and treatment of rare disorders which significantly improves health outcomes. However, NBS is limited in scope, capturing only a subset of actionable genetic conditions. Emerging evidence suggests that newborn sequencing, particularly rapid whole genome sequencing (rWGS), may broaden the range of detectable disorders and enhance clinical decision-making in neonatal care. This study evaluated rWGS findings from neonatal patients tested in a clinical laboratory to explore the added value of genomic sequencing alongside routine NBS.

Methods: A retrospective review was conducted on rWGS results from 189 consecutive neonatal patients (≤ 28 days old) referred as inpatients and receiving a positive molecular diagnosis. Clinical indications, implicated genes, variant types, and inheritance patterns were analyzed. Each diagnosed condition was assessed for potential medical interventions. Single-gene findings were also compared against the New York State NBS panel.

Results: Most patients (75.6%) presented with multisystemic clinical features, most commonly cardiac (67.7%), respiratory (56.1%), and neurologic (45.0%). rWGS identified a wide spectrum of genetic disorders associated with diverse variant types, including short tandem repeat expansions and uniparental disomy. Ten patients had at least two distinct molecular diagnoses. Forty-eight patients had diagnoses with specific medical management implications, including medication, surgery, or dietary modification. Among single-gene rWGS findings associated with treatable conditions, 83% would not have been identified by NYS NBS. Average turnaround time for rWGS was 5.5 days.

Conclusions: Rapid WGS in neonatal patients provides substantial diagnostic yield beyond traditional NBS, identifying conditions with meaningful implications for both patient care and family management. Patients may have multiple molecular findings which can be missed by targeted testing approaches. Some variants may be missed by traditional sequencing approaches. Incorporating genomic sequencing alongside conventional NBS may strengthen public health efforts by enabling earlier, more comprehensive detection of genetic disorders.

February 27, 2026

2. Class 9 Myosin Regulation of Epithelial Cell Polarity

Emma C. Murray, Leighton S. Lee, Gillian M. Hodge, Andrew T. Lombardo

Mutations in the Myo9b gene result in microphthalmia from improper development of the epithelial lens development. Myosin-9b is a single-headed molecular motor that works as a unique actin cytoskeleton regulator protein. It structurally links a myosin force-producing domain to a Rho-GAP signaling domain, which then activates GTP hydrolysis in RhoA GTPases. Knowing that myo9b is found within the microvilli, knockout myo9b expresses more dense microvilli as well as longer microvilli compared to wild type cells. The motor domain function is necessary for myo9b to localize to the microvilli.

3. Cowden Disease with Cerebellar Gangliocytoma Causing Hydrocephalus and Early Papilledema: A Case Report of a Rare Disease

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Abstract: Cowden disease or Cowden syndrome is a rare autosomal dominant entity resulting from mutations in the Phosphatase and Tensin Homolog gene (PTEN). Cowden disease is characterized by multiple benign hamartomas in various organs as well as increased risk of thyroid, breast, and endometrial malignancies. A 23-year-old female patient with newly identified Cowden disease presented to the hospital for neurosurgical evaluation. She reported several months of headaches, increasingly worse in the past 3 weeks and horizontal diplopia. Imaging studies showed a cerebellar gangliocytoma and hydrocephalus. She also had thyroid and breast lesions, along with recurrent cutaneous facial changes. Ophthalmology was consulted to evaluate papilledema. Physical exam showed visual acuity of 20/30 bilaterally with near card, full ductions and versions, minor small angle esotropia via alternating cover test, and a normal anterior segment. Optic nerve exam showed optic atrophy, peripapillary atrophy, and hyperemia in the right eye. There was less atrophy, a similar hyperemia, and an intraretinal flame hemorrhage at 10:00 in the left eye. Ophthalmology determined the patient showed early ophthalmic findings of papilledema due to the appearance of the optic disc bilaterally, known hydrocephalus, presumed increase in intracranial pressure, and peripapillary hemorrhage noted in the left eye. The patient underwent a left stereotactic frameless localization craniotomy. Five weeks after surgery, the patient presented to the hospital with 2 days of headache, blurry vision, nausea, and dizziness. Ophthalmology was consulted to evaluate the blurry vision. Physical exam was notable for slight hyperemia of the optic discs bilaterally. Ophthalmology recommended outpatient neuro-ophthalmology follow-up for her optic disc edema. This case demonstrates a rare but characteristic manifestation of Cowden disease with cerebellar gangliocytoma causing hydrocephalus and papilledema in the setting of pre-existing optic atrophy. Early multidisciplinary diagnosis and neuro-ophthalmology evaluation are important to prevent irreversible optic nerve damage and optimize visual outcomes.

February 27, 2026

4. Susac Syndrome

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Introduction: Susac Syndrome is a microangiopathic disease of the brain, ear and retina. Immune mediated destruction of the microvascular endothelium of vessels lead to classic branch retinal artery occlusions often visible in the retina. We will present an OCT finding that can help in the diagnosis of Susac Syndrome. We will present 4 cases with this stereotypical OCT finding (Peak and Prairie) found on cross sectional cuts of the retina, and discuss the differential diagnosis.

Case Description: Retrospective review of 4 cases of Susac Syndrome followed and treated at one institution, from 1997 to present. OCT and MRI findings in these cases will be discussed as will the differential diagnosis. Stereotypical changes on OCT were found in all four cases. They were found to have a sharp inferior, temporal demarcation on OCT in at least one eye. Localized retinal thinning temporal to the macula was found in all 4 patients which we describe as the "Prairie" beyond the "Peak" of the umbo. This was seen as well in other Susac cases presented in the literature. In the differential diagnosis of this retinal finding, Sickle Cell Disease and large branch retinal occlusions from vascular disease caused similar changes, while the antiphospholipid syndrome and autoimmune states Multiple Sclerosis did not show this finding.

Conclusion: This stereotypical Peak and Prairie OCT finding is very helpful and should be recognized early if found in patients with or without hearing loss or neuropsychiatric changes, who may be suffering from Susac Syndrome. This is especially important, as this syndrome is often diagnosed late in the disease course, leading to severe morbidity in these patients.

February 27, 2026

5. In Vitro Neuronal Models Reveal Pathological and Therapeutic Insights in Friedreich's Ataxia

Danielle K Bailey, Sara Cruz, Daniel J Kosman

Friedreich's ataxia (FA) is a rare, progressive neurodegenerative disease affecting approximately one in every 50,000 people globally and in the United States, and accounts for about 50% of all inherited ataxias. FA has no cure, and effective treatments remain limited. FA is caused by a GAA trinucleotide repeat expansion in the frataxin (FXN) gene encoding a mitochondrial iron chaperone protein, which leads to transcriptional silencing and an average of 5 - 30% residual FXN protein levels in patients. FXN deficiency results in mitochondrial dysfunction, iron accumulation, oxidative stress, and impaired bioenergetics, particularly affecting metabolically active tissues such as the heart, cerebellum, and peripheral nervous system. We have developed two in vitro neuronal models of FA, 1) an shRNA-mediated FXN knockdown in the mouse hippocampal HT22 neuronal cell line and 2) iPSC-derived neurons (iNeurons) from FA patient and matching healthy controls to provide a more representative human model of disease. These neuronal models recapitulate FA pathology, with decreased FXN levels, increased labile iron, decreased mitochondrial membrane potential, and increased lipid peroxidation in the FA cells compared to controls. Using the shFXN HT22 cells, we can more readily investigate the cellular contributions to FA pathology as they relate FXN deficiency, including changes in transcript levels and cellular bioenergetics at baseline and upon treatment with currently available therapeutics. The patient iNeuron model reveals neuron-specific aspects of FA, particularly contributions to neuronal development and maturation. In addition, experiments are ongoing to investigate the role of oxidative protein modifications on neuronal proteins that are essential for proper function and their contribution to progressive neurodegeneration, as well as potential therapeutic effects of drugs tested in the shFXN HT22 model. Together, our findings will further establish the neuron-specific pathology of FA and provide evidence for new therapeutic mechanisms and targets for treatment of the disease.

February 27, 2026

6. Establishing a Time Course for Midbrain-to-Pons Ratio Decline and Behavioral Deficits in a hTau ChAT-Cre Rat Model of Progressive Supranuclear Palsy-Richardson's Syndrome

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Progressive Supranuclear Palsy-Richardson's Syndrome (PSP-RS) is a rare neurodegenerative tauopathy. PSP-RS and Parkinson's Disease (PD) exhibit motor impairments such as bradykinesia, postural instability, and recurrent falls, which frequently result in misdiagnosis. Unlike PD, PSP-RS is characterized by abnormal tau aggregation, midbrain atrophy, and cholinergic neuronal loss in the pedunculopontine nucleus (PPN). In humans, Magnetic Resonance Imaging (MRI) reveals the characteristic "hummingbird sign," a hallmark of midbrain atrophy in PSP-RS. Correspondingly, reduced midbrain-to-pons (MB:P) volume ratios and ventricular enlargement serve as potential quantitative imaging biomarkers distinguishing PSP-RS from PD.

To model this pathology, our lab developed a ChAT-Cre rat model expressing the PSP-relevant 1N4R isoform of human tau (hTau) in PPN cholinergic neurons. An initial 5-month cohort demonstrated significant cholinergic and substantia nigra neuron loss, along with PSP-RS-like behavioral deficits, including impaired acoustic startle reflex (ASR), horizontal ladder deficits, and hindlimb claspings. These preliminary results prompted extended aging of our current cohort (n = 46; 21 males, 25 females; hTau rats and controls - eGFP and Null vectors) to investigate progressive structural and behavioral changes caused by tau accumulation in cholinergic PPN neurons.

MRI was acquired longitudinally at 7, 12, and 17 months, with ex vivo imaging at 23 months using a 4.7T scanner (Paravision 4.0). ASR and motor assessments were conducted at 5 and 17 months. MB:P volume ratios were quantified using Analyze 14.0 with rat brain atlases as anatomical guides. When sexes were combined, significant ventricular enlargement was observed in eGFP and hTau rats. Furthermore, hTau rats showed reduced MB:P ratios, with a significant difference at 12 months (preliminary analysis).

Collectively, these findings support the MB:P ratio as a translational imaging biomarker linking structural degeneration to functional impairment. This research advances identification of MRI biomarkers for early diagnosis, disease monitoring, and therapeutic evaluation in PSP-RS and related tauopathies.

February 27, 2026

7. TGF- β superfamily signaling modulation in human neural crest cells and Mowat-Wilson syndrome

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The neural crest (NC) is a transient, multipotent, and migratory embryonic cell population that contributes to many derivatives such as peripheral neurons and glia, craniofacial bone and cartilage, and odontoblasts. Defects in the NC lineage result in a diverse array of human pathologies known as neurocristopathies. Mutations in ZEB2, a key NC gene, underlie Mowat-Wilson syndrome (MWS). MWS patients exhibit complex phenotypes including Hirschsprung's Disease, seizures, delayed developmental milestones, agenesis of the corpus callosum, craniofacial abnormalities, and dental anomalies. However, the molecular mechanisms disrupted in MWS within the NC lineage are not well understood. Using a model of human NC cell formation, we showed that ZEB2 is an essential factor in the NC gene regulatory network. ZEB2 is a transcriptional repressor and SMAD-interacting co-factor which is thought to negatively regulate TGF- β superfamily signaling. Consistent with this, we identified a dysregulation of BMP ligand and BMP/TGF- β modulator gene expression in mutant ZEB2 human NC cells. Here, we report on the molecular characterization of human NC cell formation using two MWS patient-derived induced pluripotent stem cell lines (iPSCs). Notably, these iPSCs display reduced expression of ZEB2 in NC cells compared to a healthy control. We then identified dynamic gene expression changes of key NC markers during the timecourse of human NC formation, including TGF- β modulators DACH1, BMPER, SOX5, and HIVEP2. Validating the role of ZEB2 in BMP signaling modulation, we observed changes in the total level of phospho-SMAD1/5/9 during NC formation. Together, these findings suggest that dysregulation of BMP signaling is a driver of the MWS phenotype. We are currently addressing the precise role of ZEB2/SMAD in the human NC gene regulatory network, as well as the roles of DACH1, SOX5, and HIVEP2 in TGF- β modulation in NC as factors contributing to molecular mechanisms underlying the MWS phenotype.

February 27, 2026

8. Developing A Patient-Derived iPSC Endothelial Model to Investigate Mitochondrial Dysfunction in MELAS

Lucas Davis, Karl Swanson, Zahid Manzar, Rita Alevriadou

Mitochondrial encephalomyopathy, lactic acidosis, and stroke-like episodes (MELAS) is the most common mitochondrial disease and is characterized by recurrent stroke-like episodes (SLE) in children and young adults. These episodes cause progressive neurological disability and are the strongest predictor of reduced life expectancy. Despite identification of the causative mitochondrial DNA mutation, there are currently no disease-modifying therapies. One major barrier to therapeutic development is the lack of reliable human vascular models to study how mitochondrial dysfunction leads to SLE. Endothelial cells, which line all blood vessels, are increasingly implicated in MELAS pathogenesis. Mitochondrial defects in these cells are thought to impair energy production, increase reactive oxygen species, reduce nitric oxide availability, and promote inflammation, all as hallmarks of endothelial dysfunction that may precipitate SLE. However, this hypothesis remains insufficiently tested due to the absence of robust human models. This project seeks to establish a patient-specific vascular model of MELAS using induced pluripotent stem cell (iPSC) technology. Skin-derived iPSCs from healthy individuals have successfully been differentiated into induced endothelial cells (iECs) using a rapid 4-day protocol and validated by endothelial marker expression and functional flow alignment. Building on this foundation, MELAS patient-derived iPSCs will be converted into MELAS-iECs and examined for mitochondrial and endothelial abnormalities. MELAS-iECs will be assessed for ATP production, reactive oxygen species generation, nitric oxide bioavailability, and inflammatory activation. Demonstrating that MELAS-iECs recapitulate mitochondrial and endothelial dysfunction would establish one of the first human vascular platforms to directly study SLE mechanisms. This model will provide a critical foundation for mechanistic discovery and future therapeutic testing in a disease that currently has none.

February 27, 2026

9. When POTS is the tip of the iceberg: Rare cases of dysautonomia as a possible manifestation of another disorder

Svetlana Blitshteyn, MD and Freshta Masoud

Background: Postural tachycardia syndrome (POTS) is a heterogenous disorder of the autonomic nervous system that is commonly associated with small fiber neuropathy, Ehlers-Danlos Syndrome and autoimmune disorders, but association with rare conditions may also occur.

Methods: Reported here are clinical features, diagnostic tests and treatment outcomes of 6 unique patients who presented with POTS and were subsequently diagnosed with Fabry disease, McArdle disease, Complex V mitochondrial disease, carcinoid tumor, Hodgkin's lymphoma and chemotherapy-induced neuropathy.

Results: All patients (age range 15-57 years, 3 females, 3 males) presented with orthostatic intolerance of at least 6 months duration, and all patients had co-morbid small fiber neuropathy. Five patients presented with symptoms of POTS months to years before the underlying or associated medical condition was discovered, and three out of six patients experienced either complete resolution or significant improvement of POTS after treatment of the underlying or associated medical condition.

Conclusion: In rare cases, POTS can present as a possible manifestation of genetic, neoplastic or neurotoxic disorders. Unusual clinical features that fall outside of the typical spectrum of dysautonomia can point toward the presence of another disorder and help guide further diagnostic investigation.

February 27, 2026

10. Significant Improvement of Postural Orthostatic Tachycardia Syndrome with Semaglutide: A Case Report

Svetlana Blitshteyn, MD, Sanjana Suresh, Lucia M. Lorenzi

Introduction: Postural orthostatic tachycardia syndrome (POTS) is a chronic autonomic disorder characterized by orthostatic intolerance and a sustained heart rate increase of ≥ 30 bpm upon standing without hypotension. Many patients experience significant functional impairment, and treatment options remain limited, particularly in those with comorbid conditions such as hypermobile Ehlers-Danlos syndrome (hEDS), a heritable rare connective tissue disorder, and mast cell activation syndrome (MCAS). Glucagon-like peptide-1 receptor agonists (GLP-1 RAs), such as semaglutide, are approved for diabetes and obesity but may have central autonomic and anti-inflammatory effects relevant to POTS.

Case Presentation: A 38-year-old woman with POTS, hEDS, MCAS, chronic migraine, irritable bowel syndrome, asthma, cholinergic urticaria, and ADHD had persistent orthostatic intolerance despite multiple prior treatments. Baseline Composite Autonomic Symptom Score (COMPASS-31) was 51, indicating severe autonomic dysfunction. A 10-minute stand test demonstrated a heart rate increase of 40 bpm. The average daily step count was 1,728. Semaglutide was initiated at 0.25 mg weekly and titrated to 0.5 mg weekly. Within days, the patient reported reduced fatigue, lightheadedness, and improved cognition. After 8 months, COMPASS-31 decreased to 18 (65% reduction), heart rate change on standing decreased from 40 to 19 bpm (53% reduction), and daily step count increased to 3,274. These improvements occurred without significant weight loss or changes in fasting glucose. Symptoms worsened after discontinuation due to cost, with COMPASS-31 increasing to 44.

Conclusion: Semaglutide therapy was followed by notable improvement in autonomic symptoms and orthostatic tachycardia in this patient. Improvements appeared independent of metabolic effects. These findings support further evaluation of GLP-1 receptor agonists as a potential therapeutic option for POTS. This case highlights the need for expanded treatment strategies for patients with POTS and hypermobile Ehlers-Danlos syndrome.

February 27, 2026

11. Beyond behavior: PheWAS identifies ADHD as a risk factor for autonomic nervous system disorders

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ADHD is a common neurodevelopmental disorder frequently defined by its observable behavioral characteristics: inattention, hyperactivity, and impulsivity. Beyond behavior, previous studies have identified millions of genetic variants associated with ADHD, implicating the autonomic nervous system (heart rate, blood pressure, modulation of stress response), inflammatory pathways, sensorimotor processing, and other cross-system biological pathways in ADHD pathophysiology. Consistent with previous observations, we demonstrate that ADHD is associated with multiple conditions involving significant ANS dysfunction. Specifically, phenome-wide association study (PheWAS) using the NIH All of Us dataset identified increased prevalence of postural orthostatic tachycardia syndrome (POTS), orthostatic hypotension, syncope, Raynaud's syndrome, Sjogren's disease, familial dysautonomia (Riley-Day syndrome), and long COVID, among others, in individuals diagnosed with ADHD ($n = 7,183$) compared to individuals without an ADHD diagnosis ($n = 28,732$, odds ratios 2.39 to 5.14 across conditions).

We hypothesize that the diversity in ADHD-ANS comorbidity phenotypes results from the simultaneous effects of polygenicity/pleiotropy in neurodevelopmental disorders and gene-environment interaction in the neuro-immune axis, where shared genetic and epigenetic architecture may predispose individuals with ADHD to ANS dysregulation and disease. Many of the comorbidities identified are underrecognized and chronic in nature, with limited access to quality, evidence-based care. Individuals with ADHD and comorbid autonomic disorders are therefore at risk of increased disease burden which healthcare systems may be ill-equipped to manage. Our preliminary findings contribute to the growing body of evidence suggesting that inattention, impulsivity, and hyperactivity may only be the tip of the ADHD iceberg.

February 27, 2026

12. The patient-specific FOYG1 syndrome mouse models with different genetic variation display distinct phenotypes and severities.

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FOYG1 is a critical transcription factor involved in forebrain development. Mutations in the FOYG1 gene cause a severe neurodevelopmental disorder known as FOYG1 syndrome (FS). FS patients exhibit a range of structural and developmental abnormalities in brain and behavioral deficits. The most common symptoms are microcephaly, corpus callosum agenesis, sitting and walking difficulty, mental retardation, difficulties in fine motor control, higher anxiety and deficit in social abilities, with severity varying depending on the specific type of mutation. To study the correlation of this phenotypic variability with the *FOYG1* gene mutations, we generated mouse models carrying patient-specific *Foxg1* mutations. These mouse models recapitulated the most common structural brain abnormalities observed in FS patients, such as corpus callosum agenesis and microcephaly, although the severity varied among different models.

Behavioral phenotypes also appeared with some variations within the mouse models. Muscle strengths measured in wire hanging test showed decreased muscle strength in all four mouse models. However, locomotor activity in open field test and sociability in 3-chamber sociability test appeared to be different based on the types of the mutation in *Foxg1* the mouse carry. The differences observed across the mouse models suggest that the location and the type of mutation play a critical role in shaping the resulting phenotypes highlighting the importance of mutation-specific approaches in the study of FS.

February 27, 2026

13. FOXC1 in Oligodendrocyte Precursor Cells Regulates Myelination and Mouse Behavior

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FOXC1 Syndrome (FS) is a devastating neurodevelopmental disorder characterised by the presence of one functional copy of the transcription factor Forkhead Box G1 (FOXC1). FOXC1 is a vital regulator of forebrain development, and its haploinsufficiency leads to reduced FOXC1 protein expression, resulting in neuronal agenesis and structural brain abnormalities that manifest as intellectual disability and epilepsy. While the neuronal roles of FOXC1 are well established, its contribution to glial dysfunction, particularly within the oligodendrocyte lineage, remains unclear. Notably, FOXC1 expression is enriched in oligodendrocyte precursor cells (OPCs) and reduced in fully differentiated oligodendrocytes, implying a critical role at defined stages of oligodendrocyte lineage progression.

To investigate the cell-autonomous function of FOXC1 in oligodendrocyte development, we generated a conditional knockout model in which *Foxg1* is selectively deleted from oligodendrocyte lineage cells starting at the onset of active oligodendrogenesis and continuing through maturation. Oligodendrocyte development and myelination are essential for neuronal function and network integrity; therefore, perturbing FOXC1 in this lineage provides a mechanistic link between glial dysfunction and FS-relevant phenotypes. Behavioral analyses of adult conditional mutants revealed increased anxiety-like behavior, hypoactivity, altered sociability, and constipation, indicating widespread circuit and potential autonomic dysregulation. Immunohistochemical analyses demonstrated reduced myelin basic protein (MBP) volume and complexity and an increased number of OLIG2-positive oligodendrocyte lineage cells. Together, these findings suggest that FOXC1 loss in OPCs impairs oligodendrocyte maturation and myelination, driving circuit-level and behavioral abnormalities and establishing glial dysfunction as a key component of FOXC1 Syndrome.

February 27, 2026

14. FOXG1 Missense Variant reveals neuronal circuit dysfunction driving Autism-like behaviors

Liwen Li, Ji-Hwan Moon, Dongjun Shin, Shin Jeon, Jae W. Lee, Soo-Kyung Lee

FOXG1 missense mutations are frequently associated with Autism Spectrum Disorder (ASD), yet the underlying pathogenic mechanisms remain poorly understood. Here, we characterize a novel *FOXG1* G216S knock-in mouse model to investigate these mechanisms. Unlike homozygous loss-of-function mutants, G216S mice survive to adulthood and exhibit largely preserved forebrain morphology, but display profound defects in cortico-cortical and cortico-thalamic connectivity. Cut&Run analysis revealed that genomic regions bound by *FOXG1*-G216S significantly overlap with high-risk ASD genes curated by SFARI. Strikingly, we uncovered selective defects in prefrontal and thalamic inputs to striatal striosome and matrix compartments, revealing a previously unrecognized vulnerability of corticostriatal and thalamostriatal circuits. Together, these data suggest that synaptic and circuit-level dysfunctions underlie the shared features of *FOXG1* syndrome and ASD.

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15. Regulation of FOXP1 expression by cell-type specific enhancers and transcription factors

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FOXP1 syndrome is a rare neurodevelopmental disorder caused by mutations in a single copy of the *FOXP1* gene, which encodes a Forkhead box transcription factor essential for forebrain development and function. Proper FOXP1 expression levels and patterns are critical for cortical organization, neuronal connectivity, and brain maturation. While the role of FOXP1 in neurodevelopment is well established, the spatiotemporal regulation of its expression by upstream enhancers and transcription factors remains poorly understood. In this project, we investigate how cis-regulatory DNA elements called enhancers, together with transcription factors, regulate FOXP1 expression across distinct regions and cell types of the developing forebrain. Enhancers act as regulatory elements that integrate transcription factor inputs to regulate gene expression in a context-dependent manner. Using integrative genomic datasets, we identified multiple candidate FOXP1 enhancers and tested their activity in vivo using mouse models. By delivering AAV vectors expressing enhancer-driven hFOXP1 to the neonatal brain, we assess region-specific enhancer activity across forebrain regions including the cortex, hippocampus, and striatum. Published transcriptomic studies have established that endogenous FOXP1 is expressed across multiple forebrain cell types, including neural progenitors, neurons, astrocytes, and oligodendrocyte progenitor cells, highlighting the importance of understanding how region-specific regulatory elements control FOXP1 expression across these diverse cell populations. We also examine the role of FOXP2, a closely related Forkhead family transcription factor expressed in overlapping forebrain regions and independently associated with neurodevelopmental disorders, to determine whether it modulates the activity of a subset of FOXP1 enhancers. This work addresses a fundamental question of how FOXP1 expression is controlled by enhancers and transcription factors such as FOXP2 is essential for defining the regulatory mechanisms that govern its region- and cell-type-specific expression during brain development.

February 27, 2026

16. Investigating FOXP1 Function in Translational Regulation in FOXP1 Syndrome

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FOXP1 syndrome (FS) is a severe neurodevelopmental disorder caused by heterozygous mutations in the transcription factor FOXP1, a critical regulator of forebrain development that is highly expressed in the cortex, hippocampus, and striatum. Although FOXP1 is best known for its nuclear transcriptional functions, emerging evidence suggests that it also has important cytoplasmic roles. We generated a patient-specific W300X mouse model harboring a truncating FOXP1 mutation to investigate its pathogenic mechanisms. We found that the truncated FOXP1 protein in W300X-heterozygous (W300X-Het) mice was shown to be less abundant in the cytoplasm compared to the full-length protein. In addition, our transcriptomic profiling of W300X-Het mice revealed that downregulated genes were strongly enriched for pathways related to cytoplasmic translation and ribosome biogenesis, suggesting altered subcellular distribution that may impair cytoplasmic function, particularly in translation. Consistently, we recently found that global translation was reduced in W300X mice relative to wild-type controls via polysome profiling, accompanied by a marked decrease in the monosome peak. As monosomes have been implicated in the preferential translation of neurophil-localized synaptic transcripts, and our data indicated broad dysregulation of synaptic genes in W300X-Het mice, these observations raise the possibility that FOXP1 mutations may dysregulate synaptic protein translation. Intriguingly, our proteomic analyses revealed that FOXP1 associated with ribosomal proteins and multiple components of the translation machinery. We further verified FOXP1 interacts with the translation initiation factor DDX3X and the translational repressor FMRP using co-immunoprecipitation assays. Combined with the cytosolic localization of FOXP1 in neurons, these findings support a previously unappreciated role for FOXP1 in translational regulation. Ongoing studies aim to define the molecular mechanisms by which FOXP1 modulates protein synthesis and to determine whether translational dysregulation represents a convergent pathogenic mechanism across diverse FOXP1 variants in FS.

February 27, 2026

17. Early Communication Deficits in FOYG1 Mouse Models and AAV9 Rescue

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FOYG1 is a transcription factor essential for forebrain development and is highly expressed in the cortex, hippocampus, and striatum. Heterozygous mutations in FOYG1 cause FOYG1 syndrome (FS), a severe neurodevelopmental disorder characterized by motor, cognitive, and social communication impairments, including profound deficits in expressive language. Notably, approximately 79% of individuals with FS lack expressive language. Ultrasonic vocalizations (USVs) emitted by mouse pups provide one of the earliest measurements of communication and neurodevelopmental circuit integrity. In this study, we analyzed isolation-induced USVs at post-natal day 7 in multiple *Foxg1* mutant mouse models (Q84Pfs/+ and G161Gfs/+) and assessed the effects of AAV9-mediated FOYG1 gene delivery. We observed genotype-dependent alterations in USV frequency and call duration, with conditional *Foxg1* heterozygous pups exhibiting significant communication deficits. High-dose AAV9 treatment partially rescued specific USV parameters, emphasizing the importance of FOYG1's role in early communication circuitry and highlighting the therapeutic potential of gene delivery strategies.

February 27, 2026

18. ASO-Mediated Upregulation of FOXC1 via Targeting 5' and 3' UTR Regulatory Elements: A Therapeutic Strategy for FOXC1 Syndrome

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FOXC1 syndrome is a severe neurodevelopmental disorder caused by pathogenic variants in the FOXC1 gene and characterized by profound cognitive and motor impairments. Many disease-associated variants result in reduced FOXC1 protein expression, supporting haploinsufficiency as a key pathogenic mechanism. Therapeutic strategies that restore endogenous FOXC1 expression may therefore offer clinical benefit.

MicroRNAs (miRNAs) repress gene expression by binding to complementary sequences within the 3' untranslated region (3'UTR) of target mRNAs, while regulatory elements within the 5' untranslated region (5'UTR) can also influence mRNA stability and translational efficiency. We hypothesized that antisense oligonucleotides (ASOs) targeting regulatory regions within both the 5' and 3'UTRs of FOXC1 could relieve post-transcriptional repression and enhance FOXC1 protein production.

Using *in silico* prediction and prioritization based on binding affinity, target accessibility, CpG content, and predicted safety, we designed 25-mer ASOs targeting candidate regulatory sites within the FOXC1 5' and 3'UTRs. Thirty-six top-ranked ASOs were selected for functional screening. Human iPSC-derived cortical neurons from FOXC1 wild-type and K15X heterozygous (haploinsufficient) lines were used to evaluate therapeutic potential. Both lines carry an N-terminal HiBiT tag, enabling quantitative measurement of endogenous FOXC1 protein levels. ASOs were delivered at differentiation day 10, and FOXC1 expression was assessed at day 21 via luminescence-based detection. Among the candidates, ASO#22 and ASO#23 demonstrated the most robust increase in FOXC1 protein expression. Ongoing studies aim to determine whether ASO-mediated FOXC1 upregulation rescues molecular and functional deficits associated with haploinsufficiency and to define the specific regulatory mechanisms involved. These findings support a targeted post-transcriptional therapeutic strategy for FOXC1 syndrome.

February 27, 2026

19. Convergent Indirect Pathway SPN Dysregulation in FOXG1 Syndrome Models

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Heterozygous mutations in FOXG1 cause FOXG1 syndrome, a severe neurodevelopmental disorder characterized by intellectual disability, motor impairment, and structural brain abnormalities. FOXG1 encodes a transcription factor that regulates telencephalic patterning, progenitor proliferation, and neuronal differentiation; however, how patient-specific variants impact striatal development remains incompletely understood. To define cell-type-specific consequences of Foxg1 dysfunction, we characterized two patient-derived mouse models: a homozygous G216S missense mutant and a Q84Pfs/+ frameshift model. MRI analysis of adult brains revealed reduced relative striatal volume in mutant genotypes compared to controls, indicating structural alterations associated with patient-relevant Foxg1 variants. To investigate early cellular mechanisms underlying these changes, we performed single-cell RNA sequencing of postnatal day 9 (P9) striatum. Neuronal subtype analysis revealed genotype-specific shifts within spiny projection neuron (SPN) populations. In G216S homozygotes, indirect pathway SPNs (iSPNs) displayed increased expression of synaptic vesicle cycling, neuronal projection remodeling, and ion transport programs, accompanied by reduced expression of translation, ribosome biogenesis, and metabolic pathways. In contrast, Q84Pfs/+ iSPNs were enriched for synapse organization, neuronal differentiation, and cell adhesion programs, with decreased expression of genes involved in axon development and guidance. These data demonstrate variant-specific yet partially overlapping transcriptional remodeling within developing SPNs. To assess cell-autonomous requirements for Foxg1 in iSPNs, we generated a *Drd2-cre;Foxg1* conditional knockout. RNAscope confirmed reduced *Drd2* mRNA expression, validating effective targeting, and immunohistochemical analysis at P9 revealed increased Sox2-positive progenitors and altered neuronal organization, consistent with impaired differentiation. Collectively, these findings integrate structural MRI abnormalities with cell-type-resolved transcriptional remodeling and implicate disrupted SPN maturation as a mechanistic contributor to striatal pathology in FOXG1 syndrome.

February 27, 2026

20. Characterization of Cortical Neurons Differentiated from FOXG1 W308X Patient-derived Human iPSCs

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FOXG1 Syndrome is caused by a single gene, FOXG1, which comprises a single exon. The FOXG1 gene plays a crucial role in the development of the telencephalon, responsible for generating the cerebrum, during embryonic development. Patients with FOXG1 Syndrome exhibit a wide range of mutations (such as W308X, Q86Pfs, G224S, E154G, N232S, etc.) identified in each individual, and the severity of symptoms varies accordingly. Therefore, there is a need for an in vitro model that accurately reflects the genetic characteristics of individual patients. In this study, we aimed to differentiate W308X patient-derived iPSCs into cortical neurons and analyze the characteristics of those neurons. W308X patient-derived iPSCs successfully differentiate into cortical neurons. Expression of FOXG1 protein was reduced in W308X neurons. About neurite formation, dendrite length and complexity were reduced in W308X group compared to the control group. The number of synaptophysin vesicles, a synaptic marker, was significantly decreased. In W308X group, the number of moving mitochondria was decreased, and the length of mitochondria was shortened compared to the control group. In conclusion, FOXG1 is thought to be directly associated with the microtubule network, which may contribute to defects in dendrite development and movement of mitochondria and synaptic vesicles within dendrites in FOXG1 W308X patients. The characteristics of the W308X patient's neurons revealed in this study are expected to help understand the patient's symptoms and develop treatments.

February 27, 2026

21. FOXG1 Syndrome: Characterizing A Large Patient Cohort

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FOXG1 syndrome (OMIM 613454) is a rare genetic neurodevelopmental disorder caused by pathogenic variants in the FOXG1 gene. The estimated incidence of FOXG1 syndrome is 2.8-3.5 per 100,000 live births. We know of approximately 1,200 individuals with FOXG1 syndrome worldwide. Some core clinical features include developmental delay, epilepsy, movement disorders, and communication impairment. However, substantial variability in presentation and severity exists across affected individuals. In this study, we analyzed clinical, genetic, and medication data from 112 individuals with FOXG1 syndrome enrolled in Citizen Health, a real-world patient database. Clinical features were systematically curated using Systematized Nomenclature of Medicine Clinical Terms (SNOMED CT) codes. Genetic variants were categorized by variant type and location and were classified by the American College of Medical Genetics and Genomics (ACMG) standards and guidelines using Franklin by Genoox (Qiagen). Reported medication names were reviewed by RxNorm identifiers. Continued integration of standardized clinical data may inform prognosis, clinical management, and future therapeutic development for individuals with FOXG1 syndrome.

February 27, 2026

22. Phelan-McDermid Syndrome: Clinical Overview and Resources for Patients and Healthcare Providers

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Phelan-McDermid syndrome (OMIM 606232) is a rare genetic condition caused by 22q13.3 deletions or pathogenic variants in the *SHANK3* gene. The predicted incidence of Phelan-McDermid syndrome is 1 in 10,000 births. Symptoms of Phelan-McDermid syndrome encompass a wide variety of biological systems, including hypotonia, gastrointestinal manifestations, developmental delay, intellectual disability, sleep disturbances, and neurobehavioral characteristics. Regression or loss of skills, seizures, and gait changes can also occur. Additionally, individuals with Phelan-McDermid syndrome are at increased risk for developing severe neuropsychiatric illnesses such as catatonia. To address the complex neuropsychiatric needs of this population, the Phelan-McDermid Syndrome Foundation (PMSF) has partnered with the Seaver Autism Center for Research and Treatment at the Icahn School of Medicine at Mount Sinai to establish the Phelan-McDermid Syndrome Neuropsychiatric Consultation Group. This program provides specialized consultation to clinicians managing patients with significant behavioral and psychiatric symptoms. To date, 95 consultations have been completed, alongside ongoing research efforts aimed at improving evidence-based clinical care. Currently, management of Phelan-McDermid syndrome remains symptomatic, as no FDA-approved disease-modifying therapies are available. To accelerate research and improve evidence-based patient care, Phelan-McDermid Syndrome Foundation has developed an online DataHub platform to systematically collect longitudinal patient data. More than 800 individuals are currently enrolled, creating one of the largest centralized datasets available and providing an essential resource for research, clinical care optimization, and ongoing clinical trial development.

February 27, 2026

23. Koolen-de Vries Syndrome: Clinical Overview and Natural History Study

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Koolen-de Vries syndrome (OMIM 610443) is a rare genetic disorder caused by heterozygous microdeletions at chromosome 17q21.31 or intragenic pathogenic variants in *KANSL1* (OMIM 612452). The estimated prevalence ranges from approximately 1 in 16,000 to 1 in 55,000 individuals. Clinical features commonly include developmental delay, intellectual disability, speech and language impairment, hypotonia, epilepsy, characteristic dysmorphic features, and congenital malformations. To better understand the clinical priorities of affected families, the Koolen-de Vries Syndrome Foundation asked caregivers to identify the most burdensome symptom. Caregivers identified cognitive and communication deficits as well as neurological manifestations and behavioral/emotional challenges as the top concerns. In response, the Koolen-de Vries Syndrome Foundation initiated a multi-year natural history study (NHS) to systematically characterize symptoms, progression and variability over time. To date, more than 75 individuals with Koolen-de Vries syndrome and 35 parent and sibling controls have been enrolled.

24. Syntaxin Binding Protein 1-Related Disorders

STXBP1 Foundation

Syntaxin-binding protein 1 related disorder (STXBP1-RD) is a rare neurologic disorder associated with global neurodevelopmental delay, intellectual disability, early onset epilepsy, motor abnormalities disorders, and autism. The underlying pathophysiology stems from a de novo mutation in the STXBP1 gene, which codes for the STXBP1 protein. The STXBP1 protein is involved in synaptic vesicle fusion and neurotransmitter release. Pathogenic variants in the STXBP1 gene generally result in haploinsufficiency, an impairment in neurotransmitter release, and subsequent dysfunction in neuronal communication. Current interventions are multidisciplinary and consist of symptomatic treatment of seizures, and therapies (behavioral, physical, occupational, and speech) to address functional problems; unfortunately, these interventions are minimally effective.

February 27, 2026

25. Dravet Syndrome: A Comprehensive Systematic Review: Epidemiology, Genetics, Pathophysiology, Treatment, and Emerging Therapies

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Background: Dravet syndrome (DS) is a rare, severe developmental and epileptic encephalopathy predominantly caused by de novo loss-of-function mutations in the SCN1A gene. First described by Charlotte Dravet in 1978, DS represents one of the most challenging pediatric epilepsy syndromes, characterized by drug-resistant seizures, neurodevelopmental impairment, and elevated mortality risk. This systematic review synthesizes the published evidence on DS spanning epidemiology, genetics, pathophysiology, clinical management, treatment outcomes, and emerging therapeutic strategies.

Methods: A systematic literature search was conducted according to PRISMA guidelines across MEDLINE, Embase, PsychINFO, Cochrane Database of Systematic Reviews, and Epistemonikos from inception through December 2025. Studies were selected based on predefined inclusion criteria encompassing epidemiological data, genetic characterization, clinical trial results, and long-term outcome assessments. Two independent reviewers screened records. Data extraction followed standardized protocols, and narrative synthesis with descriptive statistical analysis was performed.

Results: After screening 2,172 deduplicated records, 91 studies met inclusion criteria. The incidence of DS ranges from 1:15,500 to 1:40,900 live births, with prevalence estimates of 1.2 to 6.5 per 100,000 individuals. SCN1A pathogenic variants are identified in over 80% of cases. The mortality rate is estimated at 15.84 per 1,000 person-years, with SUDEP accounting for 49-61% of deaths. Three FDA-approved therapies—stiripentol, cannabidiol, and fenfluramine—demonstrate ≥50% responder rates of 43-71%, 43-49%, and 54-68%, respectively, in pivotal phase III trials. Emerging disease-modifying therapies, including the antisense oligonucleotide zorevunersen (STK-001) and gene regulation therapy ETX101, have entered clinical trials with encouraging preliminary data showing seizure reductions exceeding 85% and neurodevelopmental improvements.

Conclusions: DS remains a severe lifelong condition with substantial morbidity and mortality. While approved anti-seizure medications have expanded the treatment armamentarium, the therapeutic landscape is undergoing transformation with the advent of precision genetic therapies that target the underlying SCN1A haploinsufficiency. Longitudinal data collection, standardized diagnostic criteria, and continued investment in disease-modifying interventions are essential to improve outcomes for affected individuals and their families.

February 27, 2026

26. Fatal Community-Acquired *Pseudomonas aeruginosa* Meningitis in a Previously Healthy 4-Month-Old Infant with Recent Saltwater Pool Exposure.

Peter Habashy, MD; Kashaf Ud Duja, MBBS; Ahmed Rafay Afzal, MBBS

Bacterial meningitis in infancy remains life-threatening, with diagnosis often complicated by nonspecific presentations and rapid deterioration [1]. Although vaccination and advances in critical care have reduced overall incidence and mortality, gram-negative meningitis continues to carry a poor prognosis [2]. While *P. aeruginosa* is a recognized nosocomial pathogen, community-acquired infection in immunocompetent infants without healthcare exposure is exceptionally rare [3,4]. We report a four-month-old infant who presented with fever, altered mental status, and seizures after exposure to a saltwater swimming pool, requiring emergent seizure management, airway stabilization, and intensive care admission. Initial laboratory evaluation revealed severe hyponatremia, leukopenia with neutropenia, and elevated inflammatory markers. Cerebrospinal fluid Gram stain showed gram-negative bacilli, and blood and CSF cultures grew *Pseudomonas aeruginosa*; therapy was escalated to CNS-penetrant antipseudomonal coverage once identified. Neuroimaging demonstrated global restricted diffusion consistent with severe meningoencephalitis, dural venous sinus thrombosis, and secondary hemorrhage. Continuous EEG showed progression to profound encephalopathy without ongoing electrographic seizures within 24 hours of presentation. Despite broad-spectrum antimicrobials, hyperosmolar therapy, and maximal supportive care, the patient experienced rapid neurologic deterioration and underwent brain death testing. Following multidisciplinary discussion and family counseling, life-sustaining therapies were withdrawn before the second brain death test. The patient's twin sibling, who had the same exposure, remained asymptomatic. This case illustrates the devastating potential of rare gram-negative meningitis in infancy and underscores the diagnostic complexity of meningitis in young infants, who often lack classic meningeal signs. The patient was previously healthy without evidence of immunocompromise. Although rare, *Pseudomonas* meningitis should be considered in critically ill infants presenting with seizures and signs of severe systemic infection. Early recognition, rapid diagnostic evaluation, and timely pathogen-directed antimicrobial escalation are essential once culture data become available. In two pediatric case series, 70-90% of pediatric patients had prior neurosurgical procedures and/or leukemia [5,6]. Community-acquired *P. aeruginosa* meningitis in otherwise healthy children is exceedingly rare, with only isolated reports [7,8]. Anticipatory guidance in infancy should incorporate AAP Red Book recommendations, including avoidance of swimming pools until 6 months of age and hygiene measures with avoidance of poorly maintained warm-water venues [9].

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February 27, 2026

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February 27, 2026

27. Pancytopenia in Sepsis: A Missed Window to Evolving B-Cell ALL

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Introduction: Severe bacterial sepsis can cause profound transient bone marrow suppression and immune dysregulation that closely mimics hematologic malignancy. Infection-related reactive bone marrow changes may obscure detection of preleukemic clonal hematopoiesis during single timepoint evaluations. Children may appear to recover while underlying disease evolves, creating prolonged diagnostic uncertainty and necessitating repeated evaluations. Recognizing this scenario underscores the importance of longitudinal surveillance.

Case Presentation: A previously healthy adolescent female was hospitalized for two weeks with methicillin-susceptible *Staphylococcus aureus* bacteremia complicated by toxic shock syndrome and septic shock requiring ICU care. She developed profound pancytopenia warranting bone marrow aspirate/biopsy evaluations which revealed a markedly hypercellular marrow with erythroid and megakaryocytic hyperplasia and left-shifted myeloid hypoplasia, without diagnostic evidence of leukemia, despite a small abnormal B-lymphoblast population on flow cytometry. Chest imaging demonstrated bilateral pulmonary nodules and pleural effusions attributed to septic emboli; plasma microbial cell-free DNA sequencing confirmed MSSA. Immunologic studies showed transient lymphopenia and hypogammaglobulinemia. She improved with antimicrobial therapy, but one week later was readmitted with a moderate-to-large pleural effusion; cultures and immunologic testing remained nondiagnostic. Serial CBC evaluations revealed resolution of her pancytopenia with appropriate antibiotic treatment. After eight months of apparent stability, she presented with recurrent pancytopenia, fevers and fatigue. Repeat peripheral blood flow cytometry demonstrated 16.4% abnormal B-lymphoblasts, and bone marrow biopsy confirmed B-cell acute lymphoblastic leukemia with ~80% morphologic marrow involvement and 26% flow cytometric involvement.

Conclusion: Reactive hypercellular marrow during critical illness does not exclude evolving malignancy, and small populations of atypical blasts may represent preleukemic clonal hematopoiesis below diagnostic thresholds. This case highlights the importance of repeated, longitudinal evaluation in children with unexplained or recurrent cytopenias.

February 27, 2026

28. Early Vertebral Fragility as a Presentation of Pediatric B-ALL: A Case Highlighting Bone Morbidity Preceding Hematologic Findings

Srilakshmi K. Jayaprakasan and David Byrwa

Acute lymphoblastic leukemia (ALL) is the most common pediatric malignancy, with overall survival surpassing 90% [1]. Bone morbidity with reduced bone density is a recognized comorbidity at diagnosis, attributed to leukemic marrow infiltration, increased osteoclast activity, and cytokine-mediated osteopenia [1–2]. Nontraumatic vertebral fractures are reported in up to 16% of newly diagnosed children, with a four-year cumulative incidence of approximately 26% [1–3]. A low lumbar spine bone mineral density (BMD) Z-score (≤ -2.0) at diagnosis correlates with increased risk of subsequent fractures. Importantly, skeletal manifestations may precede overt hematologic abnormalities and can mimic benign metabolic bone disease, delaying diagnosis [1]. We present an 8-year-old previously healthy girl who developed persistent right-sided abdominal and later back pain after a minor fall. Initial evaluation, including laboratory studies and imaging, was unremarkable aside from significant stool burden. Symptoms were attributed to constipation, and she received bowel cleanout and analgesics. Two weeks later, she returned to ED with worsening back pain and cross-sectional imaging was obtained which revealed multilevel thoracic and lumbar vertebral wedging. Her mobility declined as pain intensified. Spine radiographs demonstrated diffuse thoracolumbar demineralization with multiple wedge-shaped compression deformities without evidence of healing. Due to concern for an underlying endocrine disorder, she was started on calcium and vitamin D supplementation and received zoledronic acid for low BMD (DEXA Z-score < -2). At that time, no hematologic abnormality was detected. Six weeks later, she returned with escalating back pain, reduced activity, and lethargy. Repeat labs showed pancytopenia, and examination revealed hepatosplenomegaly along with previously detected vertebral changes which overall now was concerning for underlying malignant process. Peripheral blood flow cytometry demonstrated an abnormal B-lymphoblast population consistent with B-cell acute lymphoblastic leukemia (ALL). Bone marrow biopsy confirmed B-ALL with iAMP21 positivity; cerebrospinal fluid was negative. She began induction chemotherapy per COG AALL1732 including dexamethasone, calaspargase, vincristine, daunorubicin, and intrathecal cytarabine. This case underscores the need to consider malignant marrow processes in progressive pediatric vertebral fractures without a clear benign cause, as skeletal fragility may precede hematologic evidence of ALL.

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February 27, 2026

29. Silent in Utero, Severe at Birth: A case of recessive Titinopathy in neonate

Srilakshmi K. Jayapraksan, Sheetal Chepuri

Titin, encoded by the TTN gene, is the largest known human protein. It plays a critical role in sarcomere assembly and structural stability of skeletal and cardiac muscles. Pathogenic TTN variants cause a heterogeneous group of skeletal and cardiac muscle disorders termed titinopathies, inherited in autosomal dominant or recessive patterns. Recessive titinopathies represent a rare, underrecognized cause of congenital myopathy. Prenatal manifestations are often nonspecific, ranging from decreased fetal movements and contractures to cardiomyopathy. Severe neonatal presentations are typically associated with biallelic loss-of-function TTN variants and include muscle weakness, respiratory insufficiency, and multisystem involvement, making early diagnosis challenging.

We report a late preterm female infant born at 36+1 weeks' gestation to a multigravida mother with three healthy children following routine prenatal care. Pregnancy was complicated by fetal growth restriction, bilateral clubfeet and scoliosis. Fetal echocardiography raised concern for hypoplastic left heart with right ventricular dilation; amniocentesis was declined. Delivery occurred via cesarean section for frank breech presentation, and the infant required intubation and surfactant at birth for respiratory failure.

Postnatal examination demonstrated micrognathia, hypertelorism, scoliosis, lower extremity contractures, externally rotated hips, clubfeet, and clenched fists. Imaging revealed right diaphragmatic eventration. Echocardiography showed reduced left ventricular ejection fraction, dilated right ventricle, and impaired systolic and diastolic function. The course was complicated by persistent ventilator dependence with multiple failed extubation attempts and pathologic fractures of the right forearm and left femur and tibia.

Karyotyping and chromosomal microarray were normal. Whole exome sequencing identified biallelic pathogenic TTN variants, confirming congenital autosomal recessive titinopathy. Serial echocardiograms demonstrated improved ventricular function, and fluoroscopy confirmed right diaphragmatic paresis. The infant remains ventilator-dependent but hemodynamically stable, with healing fractures. Following multidisciplinary counseling, tracheostomy is under consideration.

This case presents a phenotypic spectrum of recessive titinopathy and highlights the importance of early genomic testing in neonates presenting with arthrogryposis and respiratory insufficiency.

February 27, 2026

30. Heart Bound by Fibrosis: Understanding Endomyocardial Fibrosis

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Endomyocardial fibrosis was first described in 1947 by Jack N. P. Davies in Uganda. Endomyocardial fibrosis is a rare disease characterized by fibrous buildup in the endocardium of the heart's ventricles. Dense scar tissue forms along the inner lining, restricting ventricular filling and leading to heart failure. Symptoms vary depending on which ventricle is affected. The right ventricle is most involved, causing ascites, an enlarged liver, and distended neck veins. When the left ventricle is affected, patients experience shortness of breath, fatigue, and pulmonary congestion. Additional symptoms include peripheral edema, heart murmurs, arrhythmias, and thromboembolic complications.

Endomyocardial fibrosis is often described as a disease of poverty and is most prevalent in tropical regions of Africa, Asia, and South America, with the highest prevalence reported in Uganda. Cases have also been documented in Mozambique, West Africa, Congo, Malawi, Kerala State in India, Brazil, and Colombia. Although the disease is considered idiopathic, evidence suggests that nutritional, environmental, infectious, and socioeconomic factors contribute to damage of the endomyocardium, resulting in scarring.

Studies show that EMF accounts for up to 20% of heart failure hospitalizations in some African countries. Management includes medical therapy to relieve symptoms and surgical interventions such as endocardectomy and valve repair or replacement; however, limited access to advanced surgical care in endemic regions contributes to poor outcomes.

February 27, 2026

31. Short QT Syndrome: A Rare but Lethal Channelopathy

Wing Lam Ho, MD

Short QT syndrome (SQTS) is a rare inherited cardiac channelopathy characterized by abnormally shortened ventricular repolarization and an increased risk of atrial and ventricular arrhythmias, including sudden cardiac death. The condition is primarily caused by genetic mutations affecting cardiac potassium and calcium channels, leading to accelerated myocardial repolarization. SQTS can present at any age, ranging from early childhood to adulthood, and clinical manifestations include syncope, palpitations, atrial fibrillation, and sudden cardiac arrest, while some individuals remain asymptomatic. Due to its low prevalence, diagnosis is often challenging and relies on electrocardiographic findings, clinical history, family history, and genetic testing. Currently, there is no definitive cure for SQTS; however, early recognition allows for appropriate risk stratification and management. Standard treatment includes implantable cardioverter-defibrillator therapy for high-risk patients and pharmacological agents such as quinidine to prolong the QT interval and reduce arrhythmic events. In recent years, advances in genetic testing and improved understanding of molecular mechanisms have enhanced diagnostic accuracy and therapeutic approaches. Despite these developments, significant challenges remain in establishing standardized risk assessment models and evidence-based treatment guidelines, particularly due to limited large-scale studies. Further research is necessary to improve long-term outcomes and optimize care for patients with this potentially life-threatening condition.

February 27, 2026

32. Incomplete Kawasaki Disease in a toddler With T-Cell Lymphopenia and Congenital Heart Defects: Diagnostic Overlap with Atypical DiGeorge Syndrome and Other Hyperinflammatory Conditions

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Background: Kawasaki disease (KD) is an immune-mediated vasculitis and a leading cause of acquired heart disease in developed countries. In patients with baseline immune dysregulation, presentation may be incomplete/atypical, making timely recognition more difficult. Delayed recognition increases the risk of coronary artery complications and long-term cardiovascular morbidity.

Case Presentation: We describe a 16-month-old toddler with congenital cardiac defects (partial atrioventricular canal defect, ventricular septal defect, cleft mitral valve), chronic hypocalcemia with low parathyroid hormone levels, and persistent T-cell lymphopenia, features concerning for an atypical DiGeorge syndrome phenotype despite negative 22q11.2 testing. She developed prolonged fever following respiratory syncytial virus infection and a presumed urinary tract infection. Her course was marked by polymorphic rash, mucocutaneous changes, acral desquamation, anemia, progressive thrombocytosis, and persistently elevated inflammatory markers. Initial echocardiography showed normal coronary arteries. Despite initial improvement with antimicrobial therapy, fever recurred with rising inflammatory markers. Based on evolving clinical and laboratory findings, incomplete KD was diagnosed. Treatment with intravenous immunoglobulin (IVIG) and high-dose aspirin resulted in rapid defervescence and subsequent improvement in inflammatory markers.

Discussion: This case illustrates incomplete KD in a child with features suggestive of atypical DiGeorge syndrome, highlighting how immune dysregulation can confound assessment of fever and inflammation. Concurrent infections and transient clinical improvement with antibiotics delayed diagnostic clarity. Importantly, normal early echocardiography did not exclude KD. Serial laboratory trends particularly marked reactive thrombocytosis, anemia, and persistently elevated C-reactive protein were pivotal in identifying an evolving vasculitic process. The rapid clinical response to IVIG further supported the diagnosis and argued against infection as the primary source of inflammation.

Conclusion: Incomplete KD should remain a key diagnostic consideration in children with persistent or recrudescent fever and systemic inflammation, even in medically complex patients with plausible alternative diagnoses. Early recognition and timely immunomodulatory therapy are critical to preventing long-term cardiovascular complications.

February 27, 2026

33. Kienböck Disease as an Early Vasculopathic Manifestation Preceding Systemic Sclerosis: A Case Report

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Background: Kienböck disease, or avascular necrosis of the lunate, is a rare condition of uncertain etiology. While traditionally considered idiopathic, emerging evidence suggests that lunate osteonecrosis may be an under-recognized manifestation of systemic sclerosis (SSc), potentially linked to disease-associated vasculopathy [1]. We present a patient in whom Kienböck disease preceded the onset of RNA polymerase III antibody-positive systemic sclerosis.

Case Presentation: A 69-year-old woman presented with right wrist swelling, mild pain, and limited mobility. MRI confirmed avascular necrosis of the right lunate consistent with Kienböck disease. One year later, she developed progressive right-sided facial skin tightening, prominent Raynaud's phenomenon (upper and lower extremities, right > left), inflammatory joint stiffness, and facial and chest telangiectasias.

Serology revealed ANA 1:1280 with a nucleolar pattern, positive anti-RNA polymerase III antibodies, and anti-La 1.8. Anti-Scl-70, anticentromere, anti-RNP, rheumatoid factor, anti-CCP, and HLA-B27 were negative. Echocardiography showed mild pulmonary hypertension. Based on these findings, she was diagnosed with systemic sclerosis and started on mycophenolate mofetil and calcium channel blockers, with good symptomatic improvement.



Discussion: This case illustrates Kienböck disease as a potential early vasculopathic manifestation preceding classical SSc features by one year. A case series of nine patients with SSc and MRI-confirmed lunate osteonecrosis suggests that this may be an under-recognized consequence of SSc-related microvascular dysfunction [1]. The unilateral presentation and gradual progression in our patient are consistent with previous reports. Anti-RNA polymerase III positivity carries prognostic implications, including increased risk of diffuse cutaneous involvement, scleroderma renal crisis,

February 27, 2026

cardiopulmonary complications, and malignancy [2,3]. Recognition of this association is clinically important, as management of osteonecrosis differs from that of inflammatory wrist arthritis in SSc.

Conclusion: Kienböck disease may serve as an early musculoskeletal marker of systemic sclerosis. Clinicians should consider screening for underlying connective tissue diseases, particularly systemic sclerosis, in patients presenting with lunate osteonecrosis, particularly in patients without other identifiable risk factors.

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February 27, 2026

34. Threefold Impact of a Scleroderma-focused Interprofessional Education Event

Hannah Bowen, MS; Amy Gietzen; and Lee Shapiro, MD

Scleroderma is a complex chronic disease that impacts several organ systems. A team of health-care specialists from different disciplines is required for optimal treatment. A scleroderma-focused Interprofessional Education Event (IPE) was created in 2018 and has educated over 1,200 students to date. The IPE event increases self-reported knowledge and awareness of scleroderma among rising health professional students, develops patient confidence in conveying their lived experiences, and emphasizes the importance of a coordinated care team.

The current structure consists of a patient as keynote speaker, a segment for the students on the art of interviewing, a panel led by scleroderma experts from various disciplines, and "virtual" breakout rooms with two scleroderma patients and 8 to 10 health care students in each. The patients share their experiences living with the disease with students in the following disciplines: medicine, pharmacy, dentistry, nutrition, psychology/social work, physical therapy, occupational therapy, and nursing.

Results of pre- and post-event surveys indicate that the students' self-report rating of level of knowledge score was significantly higher after attending the event, $z = -8.093$, $p < .001$. The median score on a 5-point Likert scale item was 4 after attending the IPE event compared to 1 pre-event. Awareness also increased as 63.8% reported having not heard of scleroderma prior to the event. Patients reported a mean score of 4.50 regarding their confidence in conveying their lived experiences after participation in the Art of Advocacy patient training (1-5 scale, 5=very confident). In open response questions, nearly 100% of students reported appreciation of the importance of collaboration and a team approach in the care of individuals with scleroderma.

The IPE Event bridges the gap between textbook knowledge and the realities of living with a chronic, multi-system disease.

February 27, 2026

35. Degosdisease.org: Website Content for an Ultra-Rare Disease and Nature of Inquiries Received

Hannah Bowen, MS and Lee Shapiro, MD

Degos disease is an ultra-rare disease that presents with highly characteristic skin lesions but often progresses to systemic disease called "malignant atrophic papulosis." There are fewer than 300 cases of systemic Degos reported in the literature. Up until 15 years ago all papers on systemic Degos were reports with fatal outcomes, with none describing prolonged survival. This has since changed with recent treatment advances, which have provided the means to achieve dramatic improvements in patient status. However, speedy diagnosis, recognition of evidence of systemic disease, and prompt access to therapy are all critical if such positive results are to be obtained.

To help achieve these better outcomes the Degos Disease Foundation provides a website to share the most up-to-date information, improve diagnosis awareness, increase accessibility to physicians who have experience with the disease, and invite patients and physicians to make inquiries. The website includes the following sections: Path to Diagnosis, Differential Diagnosis, Timely Diagnostic Testing, Treatments and Care, Physician Support Network Research Articles, Patients, Families, and Caregivers, Patients Stories, NIH Resources, and more. These sections allow for easy navigation to locate needed information quickly. We have also worked to improve search engine optimization, so the site is one of the first choices following a web search.

The Foundation receives inquiries via email and through the website. We track information on the source of the inquiry (country and state), who is inquiring (physician, caregiver, student, patient), and the nature of the inquiry. Website content such as resources, physicians, student research, and foundation events is updated monthly. Our goal is to reach a global audience, and we are working to address the issue of language translation.

February 27, 2026

36. Lipoma Arborescens: A Rare Cause of Knee Swelling in an Adolescent Male with Juvenile Idiopathic Arthritis Successfully Treated with Adalimumab

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Background: Lipoma arborescens (LA) is a rare benign intra-articular lesion characterized by villous lipomatous proliferation of the synovium, most commonly affecting the knee joint. It typically presents in adults, with no gender predilection. LA may occur as a primary idiopathic condition or as a secondary process related to chronic synovial irritation from trauma, degenerative disease, or inflammatory arthritis. MRI is the preferred diagnostic imaging modality, while definitive diagnosis is established by histopathology. Management is traditionally surgical, with arthroscopic or open synovectomy considered standard, as medical therapy is generally regarded as ineffective, with only limited reports of biologic treatment success

Case Presentation: A 13-year-old male presented with intermittent bilateral knee swelling and activity-related pain, without fever, morning stiffness, or limitation of movement. Examination revealed hypermobility, periocular eczematous rash, mild swelling of the right third PIP joint, significant left knee effusion, enthesitis, and a large Baker's cyst. MRI of the left knee demonstrated diffuse synovial hypertrophy with characteristic fat-signal villous projections consistent with lipoma arborescens, inflammatory synovitis, and a complex multiloculated Baker's cyst. Laboratory studies showed mild inflammatory marker elevation with negative autoimmune and infectious serologies. The patient met ACR criteria for juvenile idiopathic arthritis (JIA). Initial treatment with intra-articular corticosteroid injection and NSAIDs led to transient improvement, followed by recurrence. Methotrexate produced minimal clinical and radiographic response. Escalation to adalimumab resulted in marked and sustained clinical improvement, resolution of effusion, and significant radiographic regression of synovial inflammation and LA features.

Discussion: Differential diagnoses included JIA, arthritis associated with celiac disease or inflammatory bowel disease, psoriatic arthritis, and pigmented villonodular synovitis. These were systematically excluded through serologic testing, dermatologic evaluation, joint aspirate analysis, and MRI findings. This case supports secondary LA arising from chronic inflammatory synovial stimulation and demonstrates responsiveness to biologic immune modulation.

Conclusion: LA should be considered in pediatric patients with persistent knee swelling and synovitis, particularly in inflammatory arthritis. TNF- α inhibition may represent a viable non-surgical treatment option in selected inflammatory-associated cases, emphasizing the importance of etiologic diagnosis and individualized management.

February 27, 2026

37. De Novo KRAS (p.G13C)-Associated Immune Dysregulation Presenting as Refractory Arthritis and Crohn-like Disease

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Background: Ras-associated autoimmune leukoproliferative disorder (RALD) is a rare monogenic immune-dysregulatory syndrome caused by somatic gain-of-function RAS pathway variants, most commonly NRAS or KRAS. It is characterized by monocytosis, splenomegaly, hypergammaglobulinemia, autoimmune cytopenias, antiphospholipid antibodies, marrow abnormalities, and variable enteropathy, with heterogeneous phenotypes that frequently overlap with rheumatologic and gastrointestinal diseases, leading to diagnostic delay. KRAS p.G13C and other G13 variants have been repeatedly reported and may be mosaic, influencing tissue distribution and clinical penetrance. Because RAS variants are oncogenic in other contexts, concern exists for elevated malignancy risk. Management is individualized, with immunomodulation as the cornerstone; sirolimus is a well-supported steroid-sparing therapy for lymphoproliferation and autoimmune cytopenias. TNF inhibitors may be used for refractory inflammatory disease or enteropathy, requiring careful risk-benefit assessment and structured monitoring.

Case Presentation: We report a 13-year-old male with a 1-year history of intermittent finger swelling, progressive inflammatory polyarthritis (knees, wrists, PIPs, ankles), morning stiffness, failure to thrive, recurrent infections, intermittent rashes, abdominal pain, and easy bruising. Examination revealed livedo reticularis, splenomegaly, scoliosis, leg-length discrepancy, and active arthritis. Investigations showed monocytosis, hypergammaglobulinemia (IgG, IgA, IgM), elevated ESR/CRP, positive antiphospholipid antibodies, atypical p-ANCA, marrow hypercellularity with myeloid hyperplasia and megakaryocytic atypia, attenuated small-bowel villi on endoscopy, and splenomegaly on ultrasound. Genetic testing identified a de novo pathogenic KRAS p.G13C mutation, confirming RALD. He had a complex course including methotrexate-responsive arthritis, Crohn-like enteropathy, cytopenias, and progressive systemic immune dysregulation. Treatment with sirolimus led to initial improvement; infliximab was discontinued due to high anti-drug antibodies, and adalimumab resulted in significant clinical and laboratory remission, with subsequent relapse prompting reassessment.

Discussion: Differentials included RF-negative polyarticular juvenile idiopathic arthritis, Crohn disease, and KRAS-associated RASopathy spectrum disorders (Noonan/CFC), but the constellation of monocytosis, hypergammaglobulinemia, splenomegaly, marrow atypia, enteropathy, and KRAS mutation supported RALD. This case highlights the phenotypic overlap between immune dysregulation syndromes and rheumatologic/gastrointestinal diseases, and the importance of genomic testing in refractory multisystem disease.

Conclusion: KRAS-driven RALD should be considered in children with inflammatory arthritis, enteropathy, cytopenias, and systemic immune abnormalities. Early molecular diagnosis enables targeted immunomodulation, coordinated multidisciplinary care, and longitudinal surveillance for immune complications and malignancy risk.

February 27, 2026

38. Early Presentation of Familial Mediterranean Fever in a 3-Year-Old Child

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Familial Mediterranean Fever (FMF) is a genetic autoinflammatory disorder that can present diagnostic challenges in pediatric patients. Early manifestations often resemble surgical or infectious conditions, which may delay recognition.

We report a 3-year-old boy of Egyptian and Syrian descent who developed recurrent high fevers and severe abdominal pain beginning at 28 months of age. Initial evaluations, including imaging to rule out intussusception, were unrevealing. At 30 months, he developed fever and right knee swelling concerning for septic arthritis; synovial fluid analysis showed inflammatory findings with sterile cultures. One month later, he was hospitalized with persistent fever, vomiting, diarrhea, and abdominal pain. CT imaging was concerning for an inverted Meckel's diverticulum, and laparoscopy with appendectomy was performed. Operative findings demonstrated serous free fluid and mild small bowel thickening without appendiceal inflammation.

Given recurrent sterile inflammatory episodes, targeted next-generation sequencing was performed and identified pathogenic variants in the MEFV gene, confirming FMF. Colchicine therapy was initiated, after which the patient has had no further attacks. Family screening demonstrated carrier status in the father and siblings.

FMF should be considered in young children of Mediterranean ancestry presenting with recurrent febrile abdominal pain and sterile inflammatory findings. Early recognition may prevent unnecessary surgical intervention and prolonged diagnostic evaluation.

February 27, 2026

39. Ureaplasma Peritonitis With Severe Systemic Illness in an Immunosuppressed Adolescent With Granulomatous Multi-System Disease

Yuzuguldu B, Lewis D, Euscher L, Habashy P, Grace J, Aziz R

Background: Ureaplasma spp. are uncommon causes of invasive disease outside the genitourinary tract and can be diagnostically elusive, particularly in immunocompromised hosts. We describe a prolonged hospitalization for suspected Ureaplasma peritonitis identified only after extensive testing in a patient with complex granulomatous disease requiring long-term immunosuppression.

Case/Clinical Course: A 14-year-old female with a multi-year history most consistent with sarcoidosis versus an atypical granulomatous lymphocytic interstitial lung disease phenotype presented with fever, headache, abdominal pain, and diarrhea. Her course had been complicated by hepatosplenomegaly, diffuse lymphadenopathy with non-necrotizing granulomas, chronic cytopenias, restrictive lung disease, and anterior uveitis. Prior therapy included prolonged corticosteroids with adverse effects and biologics, later transitioning to rituximab maintenance, on which she remained in remission for four years.

She required a 28-day hospitalization with extensive infectious and abdominal evaluation. Imaging showed moderate ascites concerning for peritonitis and enterocolitis, hepatosplenomegaly, intraperitoneal adenopathy, and a persistent mediastinal lymph node. Ascitic fluid demonstrated an inflammatory, lymphocyte-predominant effusion. Conventional extensive microbiologic testing was unrevealing. Plasma microbial cell-free DNA sequencing detected Ureaplasma, and she was treated for presumed Ureaplasma peritonitis. Therapy was narrowed to doxycycline, after which she became symptom-free with normalization of inflammatory markers and cytopenias.

Her course was complicated by acute hypoxic respiratory failure requiring PICU admission and intubation, attributed to pulmonary edema. She ultimately stabilized and completed therapy.

Conclusion: In immunosuppressed adolescents with granulomatous multi-system disease, invasive Ureaplasma infection may present as prolonged febrile abdominal illness with ascites and nondiagnostic conventional testing. This case highlights the importance of considering atypical organisms and nontraditional diagnostics in high-risk hosts.

February 27, 2026

40. Primary Hyperoxaluria Type 2 in Pediatrics: Intrafamilial Genotypic Confirmation and Phenotypic Variability

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Introduction: Primary hyperoxalurias are rare autosomal recessive metabolic disorders characterized by elevated oxalate production and recurrent nephrolithiasis. Primary hyperoxaluria type 2 (PH2) is one of the rarest subtypes. PH2 results from pathogenic variants in the GRHPR gene¹ and is generally less common than primary hyperoxaluria type 1². Compared to PH1, PH2 may demonstrate greater variability in clinical severity. We describe the clinical, biochemical, and genetic findings among biological siblings with genetically confirmed PH2 within a single family.

Methods: We retrospectively reviewed clinical data from five siblings who underwent genetic testing after recurrent nephrolithiasis was identified in the oldest child. Urinary oxalate excretion, renal function, nephrolithiasis burden, and clinical outcomes were analyzed.

Results: Three siblings were homozygous for a pathogenic GRHPR variant, one was heterozygous (carrier), and one was wild type. Among the homozygous siblings, clinical severity varied markedly despite similarly elevated 24-hour urinary oxalate levels. The degree of nephrolithiasis and need for surgical intervention differed substantially among affected individuals. Treatment strategies included optimization of fluid intake, crystallization inhibitors, and discussion of emerging RNA interference-based therapies targeting hepatic oxalate production.

Conclusion: These cases demonstrate significant intrafamilial phenotypic variability in PH2 despite identical homozygous GRHPR variants and marked hyperoxaluria. Biochemical severity did not consistently predict clinical trajectory. Early cascade genetic screening enabled timely identification and surveillance, and management decisions - including consideration of emerging RNA interference therapies - must be individualized according to disease expression and shared decision-making.

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February 27, 2026

41. Surgical Intervention in PANDAS: Assessing the Benefits of Tonsillectomy

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Introduction: Evidence supporting tonsillectomy for Pediatric Autoimmune Neuropsychiatric Disorders Associated with Streptococcal infections (PANDAS) remains limited. We investigated whether tonsillectomy reduces persistent PANDAS diagnoses.

Methods: A retrospective cohort study from 2015 to 2024 using the TriNetX Research Network was conducted, with identification of pediatric patients (≤ 18 years) with PANDAS (ICD-10-CM code D89.9) and stratification by tonsillectomy status. 1:1 propensity score matching utilized age, sex, race, ethnicity, and presence of comorbid conditions, including obstructive sleep apnea (G47.33), gastroesophageal reflux disease (K21), allergic rhinitis (J30.9), asthma (J45), streptococcal pharyngitis (J02.0), and streptococcal tonsillitis (J03.0). Outcomes were assessed between 3 and 12 months following the index.

Results: Before matching, 210 patients underwent tonsillectomy and 2,248 did not. The tonsillectomy group was younger, more often White, and had higher rates of acute tonsillitis and obstructive sleep apnea. After 1:1 propensity matching, 206 patients remained in each cohort with balanced baseline characteristics. Between 3-12 months, persistent D89.9 diagnoses occurred in 36.4% of the tonsillectomy group vs 33.5% of controls (RR 1.09, 95% CI 0.84-1.42; $p=.535$). Streptococcal pharyngitis rates were similar (10.2% vs 13.1%; $p=.357$). Fever-related diagnoses were less frequent in the tonsillectomy cohort (4.9% vs 11.7%; RR 0.42, 95% CI 0.20-0.85; $p=.012$).

Conclusion: Tonsillectomy was not associated with a significant reduction in short-term persistence of PANDAS diagnoses and should not be considered a primary intervention for this condition. Surgical decisions in this population should be guided by established clinical indications rather than presumed disease-modifying effects on PANDAS.

February 27, 2026

42. Tonsillectomy Outcomes in PFAPA

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Introduction: Periodic fever, aphthous stomatitis, pharyngitis, and adenitis (PFAPA) syndrome is characterized by recurring high fevers every 2-8 weeks, typically appearing before 5 years old. We investigated whether post-tonsillectomy outcomes, including inpatient admissions, bleeding, emergency department (ED) visits within 30 days, and postoperative fever rates differ in children with PFAPA versus matched controls.

Methods: A retrospective cohort study from 2015 to 2024 used the TriNetX Research Network to identify patients ≤ 18 years with PFAPA and stratified groups by tonsillectomy status. One-to-one propensity score matching included age, sex, race, ethnicity, streptococcal pharyngitis, asthma, obstructive sleep apnea, gastroesophageal reflux disease, and allergic rhinitis. Primary outcomes were fever and persistent PFAPA diagnosis. Secondary analyses compared postoperative complications.

Results: Among 890 matched PFAPA patients, those with tonsillectomy had lower fever rates at 6-12 months (46 [5.2%] vs. 96 [10.8%]; Relative Risk [RR]=0.48, $p < .0001$) and reduced persistent PFAPA diagnosis (69 [7.8%] vs. 183 [20.6%]; RR=0.38, 95%, $p < .0001$) compared to those without tonsillectomy. In secondary analysis of 931 matched PFAPA and non-PFAPA tonsillectomy patients, PFAPA was associated with higher 30-day inpatient admission (78 [8.4%] vs 55 [5.9%]; RR=1.42; $p = .039$) and postoperative bleeding (56 [6.0%] vs. 34 [3.7%]; RR 1.65; $p = .017$), while ED visits were similar (49 [5.3%] vs. 58 [6.2%]; RR=0.85; $p = .37$). PFAPA patients also demonstrated higher postoperative fever from 30 days to 1 year (99 [10.6%] vs 45 [4.8%]; RR=2.20; $p < .0001$), and higher rates of fever within 30 days of surgery (142 [15.3%] vs 13 [1.4%]; RR 10.92; $p < .0001$).

Conclusion: Tonsillectomy is associated with significant reduction in PFAPA disease activity, but patients experience more frequent early post-tonsillectomy complications, which may inform perioperative management and anticipatory guidance.

February 27, 2026

43. Post-tonsillectomy Bleeding in Pediatric Hemophilia Patients

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Introduction: Post-tonsillectomy hemorrhage is the most concerning complication after pediatric tonsillectomy/adenotonsillectomy (TA). The risk of post-tonsillectomy bleeding in children with hemophilia is not well described. We compared the incidence of post-tonsillectomy bleeding in children with hereditary hemophilia versus matched controls.

Methods: We conducted a retrospective cohort study from 2015-2024 using the TriNetX U.S. Collaborative Network to identify pediatric patients (≤ 18 years) who underwent TA. Patients with hemophilia were identified using ICD-10-CM codes D66 and D67 and compared to patients without hemophilia. Propensity score matching was performed 1:1 based on age, sex, race, and ethnicity. The primary outcome was postoperative bleeding identified using ICD10 codes.

Results: Pre-match, 258 hemophilia and 342,303 control patients underwent TA. Hemophilia patients more often received hemostatic agents (aminocaproic acid 32.4%, N=81 vs 0.18%, N=588; factor VIII 17.6%, N=44 vs 0.04, N=140; tranexamic acid 10.4%, N=26 vs 0.23%, N=744; desmopressin 4.8%, N=12 vs 0.13%, N=436) and received less NSAID prescriptions (12.4%, N=31 vs 56.5%, N=186,947) (all $p < .0001$). After matching (N=245/group; mean age 9.21 ± 5.31 vs 9.00 ± 4.84 years), bleeding occurred in 4.9% (N=12) in both groups (RR 1.00, 95% CI 0.46-2.18). Events requiring operative control of hemorrhage were below the database's threshold for detection following matching.

Conclusion: These findings suggest that current perioperative management of children with hemophilia undergoing TA can result in postoperative bleeding outcomes comparable to unaffected peers. Further work incorporating medication dose/timing may refine best practices for this high-risk population.

February 27, 2026

44. Pediatric Thyroid Cancer and Thyroidectomy Incidence Trends During 2005-2023

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Introduction: The rising incidence of pediatric thyroid cancer has important implications for clinical management and surgical decision-making. This study assessed recent trends in pediatric thyroid cancer incidence alongside thyroidectomy rates.

Methods: A retrospective observational study was conducted using the TriNetX Research Network to evaluate temporal trends in thyroid cancer diagnoses and thyroidectomy procedures among patients aged ≤ 18 years from 2005 to 2023. Thyroid cancer was identified using ICD-10-CM code C73, and thyroidectomy was identified using SNOMED CT and CPT codes corresponding to partial and total thyroidectomy. Annual incidence proportions and counts were calculated using the Incidence and Prevalence function with first occurrence per patient per calendar year. Temporal trends were assessed using linear regression and Spearman correlation. Annual percent change (APC) was estimated using log-linear regression models. Trend analyses were restricted to years with complete data capture.

Results: From 2005 to 2023, the incidence proportion of thyroid cancer increased from 0.001% to 0.016%. Over the same period, the incidence proportion of thyroidectomy increased from 0.001% to 0.01%. APC analysis showed significant annual increases for thyroid cancer (34.46% per year; 95% CI, 30.48-38.56; $p < .001$) and thyroidectomy (35.84% per year; 95% CI, 32.01-39.78; $p < .001$). Among patients with thyroid cancer, the proportion undergoing thyroidectomy increased from 6.13% (19/310) in 2005 to 16.48% (326/1,978) in 2023.

Conclusion: The sustained upward trend in thyroid cancer and thyroidectomy suggests a changing public health landscape that may reflect increased detection or evolving risk factors. Identifying the forces behind this rise is critical to inform screening and treatment practices.

February 27, 2026

45. Asymptomatic Lingual Osseous Choristoma Following Oral Trauma

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Background: Osseous choristomas are rare benign lesions composed of mature bone tissue arising in anatomically abnormal locations. In the oral cavity, they most commonly occur on the posterior third of the tongue, near the foramen cecum. Fewer than 100 cases of lingual osseous choristomas have been reported worldwide, leading to debate over their pathogenesis.

Case Report: A 44-year-old woman presented with a slowly enlarging, asymptomatic midline posterior tongue mass. She reported a history of thermal trauma to the posterior tongue preceding lesion development. Physical examination revealed a 10 x 5 mm tan mass adjacent to the foramen cecum. Flexible laryngoscopy excluded ectopic lingual thyroid tissue. The lesion was completely excised. Histopathologic evaluation demonstrated squamous epithelium with acute inflammation overlying mature bone with regenerative changes, consistent with a lingual osseous choristoma. No malignancy was identified, and there was no evidence of recurrence at follow-up.

Conclusion: Lingual osseous choristomas should be considered as a possible differential diagnosis in asymptomatic patients presenting with posterior tongue masses, particularly in women between the second and fifth decades of life. Although often asymptomatic, patients may present with globus sensation, dysphagia, vomiting, nausea or sore throat. The only definitive diagnosis is through biopsy, with histology showing the appearance of mature lamellar bone tissue covered in mucosal tissue without osteoblastic or osteoclastic activity. Surgical excision is curative, with rare recurrence and no reported malignant transformation. This case supports existing demographic trends and contributes to the understanding of the possible pathogenesis of lingual osseous choristomas within the pre-existing framework of the reactive theory, hypothesizing that pluripotent or ectopic mesenchymal cells undergo reactive ossification after exposure to trauma or chronic irritation.