Rare Can Be Anywhere

"Alone we are rare, together we are strong"

Poster Abstracts

February 28, 2025

1. DROSHA-related tumor predisposition: a new entity with risk for pineoblastoma and Wilms tumor

   Peter N Fiorica, Lisa Golmard, Jung Kim, Riyue Bao, Frank Y Lin, Angshumoy Roy, Allison Pribnow, Melissa R Perrino, Julien Masliah-Planchon, Sophie Michalak-Provost, Jennifer Wong, Mathilde Filser, Dominique Stoppa-Lyonnet, Franck Bourdeaut, Afane Brahimi, Olivier Ingster, Giselle Saulnier Sholler, Sarah A Jackson, Mark M Sasaki, Trent Fowler, Anita Ng, Ryan J Corbett, Rebecca S Kaufman, Jeremy S Haley, David J Carey, Kuan-lin Huang, Sharon J Diskin, Jo Lynne Rokita, Hussam Al-Kateb, Rose B McGee, Joshua D Schiffman, Kenneth S Chen, Douglas R Stewart, D Williams Parsons, Sharon E Plon, Kris Ann P Schultz, and Kenan Onel.

   Purpose:

   DROSHA, DGCR8, and DICER1 regulate microRNA biogenesis and are commonly mutated in cancer. Whereas DGCR8 and DICER1 germline pathogenic variants (GPVs) cause autosomal dominant tumor predisposition, no association between DROSHA GPVs and clinical phenotypes has been reported.

   Experimental Design:

   After obtaining informed consent, sequencing was performed on germline and tumor samples from all patients. The occurrence of germline DROSHA GPVs was investigated in large pediatric and adult cancer datasets. The population prevalence of DROSHA GPVs was investigated in the UK Biobank and Geisinger DiscovEHR cohorts.

   Results:

   We describe nine children from eight families with heterozygous DROSHA GPVs and a diagnosis of pineoblastoma (n=8) or Wilms tumor (WT, n=1). A somatic second hit in DROSHA was detected in all eight tumors analyzed. All pineoblastoma tumors analyzed were classified as miRNA processing altered-1 (PB-miRNA1) subtype. We estimate the population prevalence of germline DROSHA loss-of-function variants to be 1:3,875-1:4,843, but find no evidence for increased adult cancer risk.

   Conclusions:

   This is the first report of DROSHA-related tumor predisposition. As pineoblastoma and WT are also associated with DICER1 GPVs, our results suggest the tissues-of-origin for these tumors are uniquely tolerant of general microRNA loss. The PB-miRNA1 pineoblastoma subtype is associated with older age of diagnosis and better outcome than other subtypes, suggesting DROSHA GPV status may have important clinical and prognostic significance. We suggest genetic testing for DROSHA GPVs be considered for patients with pineoblastoma, WT, or other DICER1/DGCR8-related conditions and propose surveillance recommendations through research studies for individuals with DROSHA GPVs.

2. Detection of Bilateral Cataracts in Male Fetuses at Routine 20 Week Ultrasound: Always Examine the Mothers!

Lehman JB, Scanga HL, Nischal KK

Abstract

Introduction: Nance-Horan Syndrome (NHS) is a rare X-linked condition characterized by a spectrum of dental and ocular abnormalities, dysmorphic features, and intellectual differences. The most common ocular findings are dense, bilateral, congenital nuclear cataracts in hemizygous males and mild posterior Y-sutural lens opacities in heterozygous females.2 NHS is a monoallelic condition caused by a pathogenic variant in the NHS gene with known variable expressivity between sexes due to lyonization in females.1 Herein, we describe the use of prenatal imaging in the detection of bilateral cataracts and the utility of fetal-maternal phenotyping in the timely diagnosis of NHS.

Methods: A retrospective review of two infant males and four female relatives within a single pedigree was performed. Fetal ultrasounds were reviewed and ophthalmic examinations occurred shortly after birth. NHS analysis was performed at a CLIA-certified laboratory.

Results: Prenatal ultrasonography revealed dense, bilateral cataracts in 2 male fetal cousins. The presence of bilateral congenital cataracts was confirmed in affected male infants postnatally. Female heterozygotes were identified through detection of mild posterior Y-sutural lens opacities on examination. A pathogenic frameshift variant in the NHS gene (c.114dup, p.Gln39Alafs*144) was identified in all affected family members.

Conclusion: The use of prenatal imaging to identify bilateral cataracts and the subsequent intervention by multidisciplinary pediatric ophthalmology and genetics teams are crucial in the early diagnosis of hereditary conditions such as NHS. This case series highlights the value of fetal-maternal phenotyping in the early detection of NHS within previously undiagnosed families.

References

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[2]Reches A, Yaron Y, Burdon K, et al. Prenatal detection of congenital bilateral cataract leading to the diagnosis of Nance-Horan syndrome in the extended family. Prenat Diagn. 2007;27(7):662-664. doi:10.1002/pd.1734

NOTE: this poster is to be presented at AAPOS meeting 3/6/25, received clearance from AAPOS to submit to this event

3. Title: Primary Orbital Burkitt-like Lymphoma with 11q Aberration

Authors: Sinan Ersan, Charles Zhang, Andrew L. Reynolds

Orbital lymphomas, while rare, represent a significant form of orbital disease in adults and can present with a range of symptoms mirroring other orbital disorders, including abnormal extraocular movements, double vision, and proptosis. We present a case of primary orbital Burkitt-like lymphoma with 11q aberration in a 22-year-old male, an exceptionally rare occurrence that has only been reported once prior in literature. The patient initially presented to the hospital with a complaint of left eye pain that was more prominent in abduction. Physical examination revealed noticeable deficits in extraocular movements (-1.5 adduction, -1.5 abduction, -3 supraduction), eyelid edema, moderate proptosis and hypoglobus of the left eye. Additionally, a 4cm lymph node was palpated in the left supraclavicular chain. Visual acuity was 20/20 in both eyes and the remainder of the physical exam was unremarkable. The patient did not report any significant past medical history, but family history was significant for a lymphoma in his mother who had recently passed. Appropriate imaging was obtained and the patient was sent for a surgical biopsy with immunohistochemical analysis. After the results were obtained, the patient was referred to ocular oncology for an urgent evaluation. However, 3 days later, before the patient was able to attend his appointment, his condition acutely worsened. He developed worsening pain, severe proptosis and decreased visual acuity in the left eye, consistent with compression of the optic nerve. As a result, the patient was immediately admitted to a specialized cancer institution that very day, where he received intravenous prednisone and began his first round of Hyper-Cyclophosphamide, Vincristine, Adriamycin, and Dexamethasone (CVAD) chemotherapy. After 6 cycles of treatment, the patient was cured. This case demonstrates the importance of diagnostic precision in healthcare, as it paves the way for delivery of the most effective therapies.

4. Pemphigus and Hypertrophic/Keloidal Scarring: A Potential Role for Th2-Driven Inflammation

Justin Baroukhian, Kristina Seiffert-Sinha, Animesh A. Sinha

The existence of a hypertrophic form of pemphigus, Pemphigus vegetans, has been long appreciated. Moreover, multiple case reports spanning nearly three decades have documented instances of hypertrophic and/or keloidal scarring ("excessive scarring") in individuals with pemphigus. Emerging evidence has implicated the Th2 pathway-long linked to pemphigus pathogenesis-in the development of excessive scarring.

Despite these suggestive links and a plausible Th2-mediated mechanism, population-level evidence on an association between pemphigus and excessive scarring is lacking. To address this gap, we conducted a retrospective cohort study using TriNetX's Global Collaborative Network. Our pemphigus cohort (cohort-1) included individuals with ICD-10 codes for any subtype of pemphigus (L10) while excluding those with bullous pemphigoid (L12.0) to reduce misclassification. Control cohorts were identified by the absence of pemphigus and pemphigoid codes and the presence of ICD-10 codes for psoriasis (cohort-2A, a non-Th2 inflammatory disease), atopic dermatitis (AD) (cohort-2B, a Th2-mediated disease), and healthy individuals (cohort-2C, identified by routine health examination codes in order to minimize potential detection bias from differential healthcare utilization). Comparisons were propensity score-matched for age, gender, race, and ethnicity. The outcome of interest was the ICD-10 code L91.0, indicating excessive scarring.

Among over 12,000 pemphigus patients and >36,000 matched controls, pemphigus patients consistently showed significantly increased odds of excessive scarring. Compared to psoriasis, pemphigus was associated with higher odds of excessive scarring (OR=1.645, 95% CI 1.213-2.231). Compared to AD-a known risk factor for excessive scarring-the odds were also elevated (OR=1.506, 95% CI 1.119-2.026). Pemphigus patients demonstrated a threefold increased odds of excessive scarring compared to healthy controls (OR=3.172, 95% CI 2.155-4.67).

These findings may inform future treatment considerations regarding more targeted, mechanistically-informed, immune therapies which may provide dual benefit in appropriate cases, e.g. individuals with pemphigus and a known or predicted risk for excessive scarring.

5. Allergic and Atopic Comorbidities in Pemphigus: A Data-Driven Investigation of Th2 Immune Associations

Justin Baroukhian, Rebekah R. Schwartz, Kristina Seiffert-Sinha, Animesh A. Sinha

Pemphigus vulgaris (PV) and Pemphigus foliaceus (PF) are autoimmune blistering diseases driven by Th2-mediated immune responses. Given the shared Th2 involvement in allergic and atopic diseases, understanding the comorbidities between pemphigus and these conditions is crucial for optimizing treatment strategies, especially with emerging therapies such as dupilumab, which targets IL-4 and IL-13 signaling. This study investigates the prevalence of allergic and atopic conditions in pemphigus patients to provide insights into their comorbidity and potential therapeutic implications.

We conducted a large-scale, retrospective analysis of over 140 million electronic medical records from the Global Collaborative Network TriNetX database. Cases of pemphigus were identified using ICD-10 codes, and propensity score matching (1:1) was employed to match pemphigus patients with controls based on age, gender, race, and ethnicity. Multivariable logistic regression was used to assess the odds of developing allergic and atopic conditions in patients vs. controls.

Our results showed significantly increased odds of prurigo nodularis (OR 3.71, CI 1.854-6.127), atopic dermatitis (OR 2.399, CI 1.738-3.311), eosinophilia (OR 2.318, CI 1.289-4.171), pruritus (OR 1.936, CI 1.638-2.289), and urticaria (OR 1.514, CI 1.166-1.966) in pemphigus patients. Surprisingly, pemphigus was associated with significantly decreased odds of asthma (OR 0.774, CI 0.679-0.882) and allergic rhinitis (OR 0.578, CI 0.512-0.654). No significant differences were observed for allergic contact dermatitis, angioedema, or allergic conjunctivitis.

These findings provide novel insights into the comorbidities of pemphigus, highlighting both expected and unexpected novel associations. These results may help to guide therapeutic decisions, particularly regarding the use of Th2-targeted therapies in pemphigus patients.

6. Title: The role of age and otitis media in hearing loss patterns in mucopolysaccharidosis

Authors:
Murilo de Santana Hager BS, Gaayathri Varavenkataraman MA, Michele M Carr DDS MD PhD

Introduction
Mucopolysaccharidosis (MPS) is a group of inherited metabolic disorders causing glycosaminoglycan accumulation, resulting in skeletal, neurological, and auditory impairments. Despite the known risk of hearing loss (HL) in MPS, data on specific types of HL and the role otitis media (OM) plays are limited. This retrospective cohort study analyzed HL prevalence in MPS patients, stratified by age, and examined the impact of OM on outcomes.

Methods
Data from the TriNetX US Network identified MPS patients (ICD-10 E76) from 1/1/2006 to 12/31/2024. HL prevalence was stratified by age group, and HL types were categorized as conductive (CHL; ICD-10 H90.0, H90.1, H90.2, H90.A1), sensorineural (SNHL; ICD-10 H90.3, H90.4, H90.5, H90.A2), and mixed (MHL; ICD-10 H90.6, H90.7, H90.8, H90.A3). MPS patients with/without a history of OM (ICD-10 H65, H66, H67) were propensity score matched by demographics, and HL outcomes were analyzed. HL outcomes were also compared between matched OM patients with/without MPS.

Results
Among 3,288 MPS patients (mean age=26.5 years, SD=25.5) 1,600 (48.7%) male, 1,429 (43.5%) female, and 259 (7.8%) unknown, SNHL was the most common type of HL affecting 433 (13.2%) patients, followed by CHL 229 (7.0%) and MHL 177 (5.4%). Peak CHL occurred at 6-10 years (N=47, 15.8%), SNHL at 11-15 years (N=80, 21.6%), and MHL at 16-20 years (N=43, 11.6%). Assessing the impact of OM on HL, MPS patients with a history of OM (N=569) had higher HL rates compared to those without OM: CHL (21.4% vs. 3.2%; OR=8.4, p<.001), SNHL (29.7% vs. 9.3%; OR=4.1, p<.001), and MHL (16.9% vs. 2.5%; OR=8.0, p<.001) when compared with patients without OM. Assessing the impact of MPS on HL, MPS patients with OM (N=586) had elevated HL risks compared to non-MPS patients with OM: CHL (22.2% vs. 6.7%, OR=4.0, p<.001), SNHL (30.7% vs. 3.2%, OR=13.2, p<.001), and MHL (17.7% vs. 1.7%, OR=12.4, p<.001) when compared to non-MPS patients.

Conclusions
OM significantly increases the risk for all types of HL in MPS patients, highlighting the need for routine auditory monitoring and proactive OM management to optimize patient outcomes in this group.

7. Title: Synthetic Modulator Rescues Gating Deficits in GluN1 Y647 Disease-Related NMDA Receptor Variants

   Authors: Samantha R. Schwarz, Jamie A. Abbott, and Gabriela K. Popescu

   Abstract: N-methyl-D-aspartate (NMDA) receptors are glutamate-gated channels that mediate a substantial portion of excitatory transmission in the central nervous system and are essential for brain development and cognitive function. They assemble as heterotetramers of homologous GluN1 and GluN2 subunits. Disease-related variations at GluN1 Y647, which lies within the agonist-controlled gate, have altered biophysical properties and cause neurodevelopmental pathologies. GNE-9278, a novel NMDA receptor positive allosteric modulator (PAM), binds at the extracellular surface of the transmembrane domain and potentiates macroscopic receptor currents. We hypothesize that single-channel parameters and gating kinetics of these patient-derived variants can be recovered with application of GNE-9278. To investigate this hypothesis, we co-expressed NMDA receptor subunits containing patient-derived GluN1-1a variants (Y647C, H, and S) and wild-type (WT) GluN2A subunits in HEK 293 cells and recorded activity from individual channels trapped within a cell-attached membrane patch with or without GNE-9278 (50 μM). Results showed a robust increase in open probability for all three variants: 14-, 30-, and 35-fold increase for Y/C (n = 3), H (n = 3), and S (n = 6), respectively, thus approaching WT receptor levels (0.48 ± 0.14, n = 8). Kinetic analyses and modeling of these data allow us to propose a quantitative mechanism by which GNE-9278 restores gating and conductance deficits in the variants we examined. Results also suggest that GNE-9278 may represent a promising therapeutic approach for patients who carry these variants.

8. 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, Rabheh Abdul-Aziz
   Department of Pediatrics, Oishei Children's Hospital, University at Buffalo
   Abstract
   Lipoma arborescens (LA) is a rare intra-articular benign tumor characterized by hyperplastic proliferation and replacement of subsynovium by mature fat cells, forming villous projections in the joint space. It usually affects the knee joint and manifests unilaterally. Treatment is based on surgical or arthroscopic synovectomy aimed at removing proliferative adipose tissue and restoring joint function. There is lack of data on the use of anti-inflammatory therapy and most authors are doubtful about the success of anti-inflammatory therapy in management of LA. We report a13 year old male patient with juvenile idiopathic arthritis and lipoma arborscens of the left knee who was successfully treated with Adalimumab.

9. Clear Cell Carcinoma Arising from Endometriosis in a Cesarean Section Scar: A Case Report with Literature Review

Martha Chavez, MD; Frank Chen, MD, PhD, MBA; Mohamed Desouki, MD, PhD

Background: Endometriosis is a frequent benign disorder. Malignancy arising in association with endometriosis mainly includes endometrioid carcinoma (70%), sarcoma (25%), and clear cell carcinoma (5%). The incidence rate of abdominal surgical scar endometriosis is between 0.03% and 1.08% of women undergoing pelvic surgery. Malignant transformation arising in the background of scar endometriosis is extremely rare. Here, we report a case of clear cell carcinoma arising from endometriosis in a cesarean section scar of a 48-year-old woman. Previously reported similar cases will also be reviewed and discussed.
Clinical Presentation: A 48-year-old female presented to the emergency department with a palpable abdominal mass and constipation. A CT scan revealed a mass in the infraumbilical suprapubic rectus abdominis muscle region at the site of a cesarean section scar. A biopsy of this mass revealed an epithelioid neoplasm with papillary features which was positive for AE1/AE3, PAX-8, and Napsin, suspicious for malignancy of gynecologic or upper urinary tract origin. The patient underwent an exploratory laparotomy, abdominal wall resection and reconstruction, and total abdominal hysterectomy with bilateral salpingo-oophorectomy. The resulting specimen included a 13.7 x 10.0 x 7.0 cm portion of red-yellow muscle and adipose tissue from the abdominal wall.
Results: Microscopic examination showed clear cell carcinoma arising from endometriosis in a cesarean section scar. ER, PR, and FOLR1 were all negative, compatible with the diagnosis. There was also metastasis to 6 out of 14 total lymph nodes submitted. The omentum, appendix, uterus, ovaries, fallopian tubes, and cervix were all benign, with the uterus containing a disordered and proliferative endometrium.
Conclusion: Although clear cell carcinoma arising from malignant transformation of endometriosis in the abdominal wall after a cesarean section is extremely rare, for a female patient with a history of gynecologic or obstetric surgery developing an abdominal wall mass, the possibility of a primary malignancy arising from endometriosis should be considered in the differential diagnosis. A tissue biopsy with histological evaluation and ancillary studies should be performed to ensure early detection of malignancy with proper next step treatment.

10. Title: Conjunctival Amyloidosis: A Case Report of a Rare Progressive Disease Over Thirteen-Years

Authors: Eric A. Lovett Jr., MBA, BS; Thomas M. Catapano, MD; Carol L. Shields, MD

Abstract:
Introduction
Conjunctival amyloidosis is a rare, benign condition characterized by localized amyloid deposition in the conjunctiva. Unlike systemic amyloidosis, it typically remains confined to the eye, though progression can affect vision. Only a few dozen cases have been reported in the literature, underscoring its rarity and the limited knowledge surrounding its pathophysiology and treatment options. Currently, the most aggressive treatment available is surgical excision; however, due to a high recurrence rate, management is often conservative.

Case Presentation
With few cases of conjunctival amyloidosis reported in the literature, we present a 71-year-old healthy male who presented to Wills Eye Hospital with intermittent nasal redness in his right eye (OD) for ten years. Examination revealed best-corrected visual acuity (BCVA) of 20/25 in both eyes (OU). Slit lamp examination demonstrated an elevated, yellow-pink conjunctival lesion OD with intrinsic vascularity and hemorrhage; the left eye was unaffected. Biopsy confirmed subconjunctival amyloidosis with equal staining for kappa and lambda light chains. Given the indolent nature of the disease and the lack of effective interventions, conservative management was pursued. Over thirteen years of follow-up, the patient's conjunctival amyloid deposits progressed, eventually extending 360 degrees overhanging the cornea OU. At his last visit, he remained asymptomatic with a BCVA of 20/50 OU. Systemic workup, including annual serum protein electrophoresis (SPEP), has remained negative. Given the high recurrence rate after surgical debulking, conservative management with annual monitoring continues to be advised.

Conclusion
This case highlights the slow but progressive nature of conjunctival amyloidosis and the need for more effective treatment strategies. While most patients maintain functional vision, extensive conjunctival involvement can lead to secondary ocular complications like keratoconjunctivitis sicca and subconjunctival hemorrhage. Further research is necessary to develop targeted therapies to slow or halt disease progression.

11. Title: 14 and 6 Hz Positive Spikes: A Rare Benign EEG Variant More Prevalent in Children with Benign Rolandic Epilepsy

Authors: Margil Ranpariya, Osman Farooq

Abstract:

Objective: This study investigates the novel association between 14 and 6 Hz positive spikes, a rare benign EEG variant, and its prevalence in patients with Benign Focal Epileptiform Discharges of Childhood (BFEDCh). It aims to characterize its topographic distribution, sleep-stage predominance, and age of onset, contextualizing findings within existing literature on benign EEG variants in pediatric populations.

Methods: Retrospective analysis of EEG data from 10 BFEDCh patients was conducted to identify 14 and 6 Hz positive spikes. The study evaluated topographic localization, sleep-stage specificity, and demographic characteristics, comparing findings with existing studies on benign EEG variants such as 6 Hz spike-and-wave patterns and 14 Hz bursts. (1,2)

Results: The 14 and 6 Hz positive spikes were commonly observed in BFEDCh patients, contrary to their classification as rare. They were predominantly localized to the right central-temporal region (100% of cases) and were most frequent during stage 2 (60%) and REM sleep (40%). The 14 Hz component was significantly more prevalent than the 6 Hz component, consistent with prior reports. (3) Onset occurred around age 3, aligning with BFEDCh presentation. (4) These findings support prior studies on lateralized and sleep-stage-specific patterns in pediatric EEG variants. (5)

Conclusion: This study establishes a novel association between 14 and 6 Hz positive spikes and BFEDCh, highlighting its right central-temporal predominance and occurrence during stage 2 and REM sleep. The 14 Hz component is dominant, and onset around age 3 aligns with BFEDCh's natural history. These findings are crucial to recognize and interpret as a benign variant rather than epileptiform discharges, contributing to the understanding of benign EEG variants and their clinical significance in pediatric epilepsy. (6,7)

12. Slow Rise in Platelet Count as a Predictor of GCA in Patients with or Without PMR

    Norah Lincoff MD, Lindsey Dressler BS, Linda Burns DO, Michael Freitas MD

    Thrombocytosis is often seen or described as an acute phase reaction in GCA; in reality it is usually a gradual increase over 6 months to a year, often culminating in profound visual loss in one or both eyes. Mild anemia also develops over the same time period. This criss-cross in lab values is a useful tool to predict GCA, especially in patients with or without PMR who present with minimally elevated ESR or CRP levels.

13. Exploring the death and signaling of Galactosylceramidase-deficient oligodendrocytes

    Meghana Kushwaha, Anjali Bhagavatula, Jacob Favret, and Daesung Shin

    Krabbe disease (KD) is a progressive and fatal neurodegenerative lysosomal storage disorder due to autosomal recessive mutations in the galactosylceramidase (GALC) gene, resulting in demyelination, neuroinflammation, and degeneration in both the central and peripheral nervous systems. Myelin-forming cells, such as oligodendrocytes (OLs), are primarily affected by GALC deficiency in KD. However, the specific processes by which the GALC-deficient OLs die and how degenerating OLs interact with other neuronal cells are unknown. To determine the primary cell death mechanism in GALC deficiency in OLs, we have investigated multiple cell death pathways including apoptosis, necroptosis, ferroptosis, parthanatos, and autophagic death in primary OLs from Galc-null KD mice. Our findings revealed that necroptosis is the primary cell death mechanism for GALC-deficient OLs. Clinical observation of KD samples revealed that glial cells such as astrocytes and microglia are rapidly activated before demyelination. We hypothesized that glial cells engage in direct physical interactions with diseased OLs promoting cell death. Therefore, we screened membrane proteins that are uniquely expressed in GALC-deficient OLs compared to healthy OLs. Our results revealed a significant disparity in the expression of Glycoprotein α-Subunit of Glucosidase II (GANAB) in mutant OLs. GANAB has been identified as a key regulator of the unfolded protein stress response. Therefore, we are further characterizing if GANAB is involved in the induction of cell survival in Galc-null oligodendrocytes and if its suppression promotes cell death. We anticipate that further understanding the key molecules triggering the progression of KD will allow for novel therapeutic interventions.

14. FDXR-related disease is a complex mitochondrial disorder with distinct effects on neurological function, iron metabolism, and steroid hormone regulation

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Iron-sulfur (Fe-S) clusters, synthesized in mitochondria, are essential co-factors for the cell. A variety of human disorders have been associated with impaired Fe-S cluster synthesis, including neurodegenerative disorders (e.g. Parkinson's disease and Friedreich's ataxia) and myopathy with lactic acidosis. Ferredoxin reductase (FDXR) is a flavoprotein that functions in both Fe-S cluster biogenesis and steroid biosynthesis pathways in the mitochondria. Not surprisingly, loss of FDXR function causes severe mitochondrial disease in humans. Optic atrophy, movement disorder, and developmental delay are frequent findings. Mortality is high, with 18% of patients (often infants) passing from complications. Notably, approximately 25% of cases are homozygous or compound heterozygous for a 'hotspot' variant (p.Arg386Trp), with a carrier frequency estimated to be as high as 1/185 in the Mexican population. Here, we describe a comprehensive investigation of the pathogenic mechanisms underlying FDXR-related disease (FRD), using a combination of in vitro and in vivo approaches spanning patient cells as well as a "human-like" mouse model carrying a knock-in allele identical to the human "hotspot" variant. These studies point to ferroptosis (iron-related cell death) and adrenal insufficiency as significant contributors to the pathologies observed in FDXR-related disease. In the future, we hope to leverage these results to begin exploring possible therapeutic strategies that may benefit individuals affected by FDXR-related disease as well as other Fe-S cluster disorders.

15. Title: Chronic brain edema and acid-base transport: A novel disease-causing mutation in the sodium-bicarbonate cotransporter NBCe1

Authors: Richard A. Pasternack together with the laboratories of Mark D. Parker, PhD, Rogier Min, PhD, and Marjo van der Knaap, MD, PhD.

Abstract: The sodium-bicarbonate cotransporter NBCe1 contributes to the intracellular pH regulation of many organs and tissues, including astrocytes in the central nervous system. Dysfunction of NBCe1 has been associated with a variety of clinical phenotypes, primarily affecting the renal, neurological, and visual systems. A novel heterozygous mutation in NBCe1 has been identified in three unrelated pediatric patients who present with progressive brain edema and evidence of abnormal hypertrophy of the cerebral white matter in MRI studies. We hypothesized that the cause of the observed clinical phenotype is the result of an alteration or pathological gain of function in NBCe1 activity of the mutant transporter in cells.

cRNA encoding for the mutant NBCe1 protein was injected into Xenopus laevis oocytes with and without IRBIT, a soluble protein binding partner that potentiates the activity of NBCe1 in astrocytes. Whole-cell conductance was measured in solutions where bicarbonate was either present or absent via 2-electrode voltage clamp. Oocytes injected with the mutant NBCe1 protein lacked the typical bicarbonate-dependent increase in conductance seen in the wild-type protein, which could not be rescued by the presence of IRBIT. Voltage clamp data showed the presence of a depolarizing ion leak compared to controls that was dampened with IRBIT co-expression. Subsequent biotinylation studies showed a substantial decline in surface expression of the mutant compared to the wild-type protein.

The results demonstrate a significant defect in ion-permeability and membrane trafficking in the NBCe1 mutant, which provides a reasonable explanation to the pathological edema seen in the patients identified in this study. If the behavior of the mutant in oocytes is predictive of its behavior in astrocytes, the mutation could disrupt astrocyte ion and therefore fluid balance, resulting in a clinical phenotype of brain edema.

16. Ancestral Differences in Genetic Architecture of Rare and Ultra-Rare Variants in Children with ADHD

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Attention-Deficit/Hyperactivity Disorder (ADHD) is a highly heritable neurodevelopmental disorder, its underlying etiology is multifactorial where genetics, environment and development of central Nervous system play key roles. Our study observes the burden of protein-truncating variants (PTVs), missense, and synonymous variants in potentially constraint genes in ADHD cases and controls across African and European ancestries using whole-genome sequencing (WGS) data from the Adolescent Brain Cognitive Development Study (ABCD) study.

We categorized the rare variants (minor allele frequency (MAF) < 0.01) and ultra-rare variants (MAF < 0.001) to evaluate their enrichment across the four groups: African cases, African controls, European cases, and European controls. We further explored the variant burden in highly constrained genes using different parameters such as LOEUF (Loss-offunction
Observed/Expected Upper-bound Fraction) and pLI (probability of Loss-offunction Intolerance) scores to identify intolerance of loss of function in genes to
damaging mutations.

Our findings reveal a significant burden of PTVs and damaging missense variants in ADHD cases compared to controls, with distinct enrichment patterns across ancestral groups. African cases exhibit a higher burden of ultra-rare PTVs in highly constrained genes compared to African controls, whereas European cases show an increased burden of damaging missense variants with high MPC (Missense badness, PolyPhen, and Constraint) scores. Genes such as ANK2, DST, CACNA1C, and NRXN3 emerged as highly constrained loci with elevated variant burden, suggesting their potential role in ADHD pathogenesis.

Additionally, we assessed copy number variation (CNV) burden, highlighting an increased frequency of large deletions in cases, particularly in genes with brain-expressed developmental trajectories. These findings emphasize the importance of ultra-rare and damaging variants in ADHD risk and underscore the need for ancestry-specific analyses to elucidate genetic contributors to neurodevelopmental disorders.

Our study provides novel insights into the rare variant architecture of ADHD, contributing to a deeper understanding of its genetic basis and potential targets for future therapeutic interventions.

17. The Exclusion of Non-Muscle Myosin-2 is required for Microvilli Actin Maintenance in Human Cells

Leighton S. Lee*, Emma C. Murray*, Andrew T. Lombardo

Abstract
Microvilli Inclusion Disease is a rare neonatal enteropathy that results from genetic defects in proteins that regulate epithelial cell polarity and trafficking. It is defined in part by the aberrant formation of microvilli at internal vesicular inclusions. Microvilli are 'finger' like projections that increase the surface area of cells in the gut, kidney, and placenta. The biogenesis of microvilli involves signaling of the actin cytoskeleton to form microvilli at the correct cellular location at the correct time. The location of different actin-based structures is largely regulated by Rho GTPases through specific effectors. We use the apical aspect of epithelial cells as a model system to investigate how RhoA is locally regulated to contribute to two distinct adjacent actin-based structures. Assembly of the non-muscle myosin-2 filaments in the terminal web is dependent on RhoA activity, and assembly of the microvilli also requires active RhoA for phosphorylation and activation of ezrin. We show the RhoGAP, ARHGAP18, is localized by binding active microvillar ezrin, and this interaction enhances ARHGAP18's RhoGAP activity. We present a model where ezrin-ARHGAP18 acts as a negative autoregulatory module to locally reduce RhoA activity in microvilli. Consistent with this model, loss of ARHGAP18 results in disruption of the distinction between microvilli and the terminal web including aberrant assembly of myosin-2 filaments forming inside microvilli. Thus, ARHGAP18, through its recruitment and activation by ezrin, fine-tunes the local level of RhoA to allow for the appropriate distribution of actin-based structures between the microvilli and terminal web. As RhoGAPs vastly out-number Rho GTPases, this may represent a general mechanism whereby individual Rho effectors drive specific actin-based structures.
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18. Iron Metabolism in Astrocytes: Implications for Myelination and Remyelination of the Central Nervous System

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Multiple sclerosis (MS) is an autoimmune disease affecting more than five million people worldwide, according to WHO. It's a neurodegenerative disorder that impairs vision, motor coordination, and normal cognitive functions and eventually decreases life expectancy. In MS, the immune system attacks the myelin sheath present on neurons in the central nervous system (CNS). Oligodendrocytes make the myelin sheath, using iron as a cofactor for various enzymes involved in this process. Reduced iron leads to demyelinated neurons. Astrocytes take iron from the blood, package it in several safe, transferrable forms, and distribute it to oligodendrocytes in the brain with the help of Ceruloplasmin (Cp). Ceruloplasmin is a key player, as it converts toxic iron into its non-toxic transferrable form. This project specifically focuses on understanding the effects of Cp, or the lack thereof, in astrocytes. We are studying how the absence of this protein affects demyelination, neuroinflammation, and the progression of the disease in a mouse model of MS. To this aim, we conditionally knock out Cp in astrocytes (Cp KO) and induce experimental autoimmune encephalomyelitis (EAE), an autoimmune-mediated model of demyelination. Immunohistochemical analysis is performed on the central nervous system to understand cellular-level dynamics. Cp ablation in astrocytes increased the severity of disease in both the acute and chronic phases. The day of onset, peak disease severity, and cumulative clinical score were all significantly increased in Cp KO animals. Furthermore, the spinal cord of Cp KO mice displays increased numbers of reactive astrocytes, activated microglia, and infiltrating lymphocytes. Correspondingly, oxidative stress was increased in the CNS of Cp KO subjects, particularly in white matter regions of the spinal cord. The cerebellum, which was the second most affected, also showed increased infiltration of immune cells, leading to a higher number of active lesions in the tissue. The same pattern was observed in the Corpus Callosum region of the cerebrum. Thus, deleting Cp in astrocytes increased neuroinflammation and oxidative stress in EAE animals. How the absence of Cp in astrocytes affects these animals' brains and spinal cords will help improve our understanding of the disease pathophysiology and explore new treatment options.

19. Title: Food Impaction as an Early Sign of Eosinophilic Esophagitis

Authors: Erin M. Gawel, Alex Bogosian BS, Hardeep S. Tiwana BS, Gaayathri Varavenkataraman MA, Amanda Baanante MS, Grace Maley BS, Michele M. Carr DDS MD PhD

Abstract

Introduction: Eosinophilic Esophagitis (EoE) is a chronic, immune-mediated disorder that leads to eosinophilic infiltration of the esophageal epithelium, often causing dysphagia and food impaction. This study explores the link between food impaction and subsequent EoE diagnosis in pediatric patients, while assessing the role of atopic comorbidities.

Methods: A retrospective analysis was conducted from 2016 to 2024 using the TriNetX US Collaborative Network. Pediatric patients (<21 years) with a diagnosis of food impaction (ICD-10 T18.12) and an outpatient visit (CPT 1013626) were identified. A comparison group was formed by excluding patients with food impaction. Propensity score matching was performed based on age, sex, race, ethnicity, and gastroesophageal reflux (GER). The primary outcome, EoE diagnosis (ICD-10 K20.0), was analyzed.

Results: A total of 2,415 food impaction patients were matched with an equal number of controls. The mean age was 10.0 years (SD=5.4). Patients with food impaction were 102 times more likely to receive an EoE diagnosis compared to those without (33.8% vs. 0.5%; OR=102.2, 95% CI=57.6-181.3, p<.001). Common comorbidities in food impaction patients with EoE included asthma (28.4%), allergic rhinitis (27.1%), GER (23.7%), dermatitis/eczema (19.7%), and food allergies (18.0%), all significantly higher than in controls (p<.001).

Conclusion: Pediatric patients presenting with food impaction should be evaluated for EoE to ensure early diagnosis and management. The strong association between EoE and atopic comorbidities underscores the importance of considering these conditions in clinical assessments.

20. Identification of Immunogenic Cardiac Peptides Driving T-Cell Activation in ICI-Induced Myocarditis

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Objective. Immune Checkpoint Inhibitor (ICI) therapy enhances anti-tumor immunity but increases the risk of immune-related adverse events, including myocarditis, the most severe complication. The mechanisms underlying ICI-induced myocarditis remain unclear, and no effective treatments exist that mitigate myocarditis without compromising cancer therapy. This study aims to identify immunogenic cardiac proteins that contribute to myocarditis using Raji (antigen-presenting) and Jurkat (T-cell) human cell lines.
Hypothesis. We hypothesize that ICI-induced myocarditis results from T-cell activation against cardiac proteins, triggering myocardial inflammation.
Methods. Six cardiac troponin and myosin peptides were identified using the Immune Epitope Database (IEDB) based on IC50 scores, peptide length, and allele predictions with NetMHCpan 4.1 for MHC-I and MHC-II tetramers, targeting CD8+ and CD4+ T-cells. Immunological assays, including luciferase assays, will be performed using the most antigenic immunized and deimmunized peptides from cardiac troponin I (cTnI) and cardiac myosin.
Results. We anticipate that the immunized peptide will induce robust T-cell activation, leading to higher luciferase activity, whereas the deimmunized peptide will show reduced activity due to diminished TCR recognition. This contrast will demonstrate the impact of deimmunization on T-cell activation.
Conclusion. Identified cardiac peptides may trigger a strong T-cell response, revealing a mechanism of ICI-induced myocarditis. Selective T-cell activation, particularly with PD-1 antibody treatment, suggests a potential pathway for myocarditis. These findings could inform targeted strategies to prevent ICI-induced myocarditis while preserving immunotherapy's anti-cancer efficacy.

21. Title: Understanding Duchenne Muscular Dystrophy (DMD): Pathophysiology and emerging therapies.

Author(s): Kylie A. Limback, Yuan Zhou, Victoria Brown.

Abstract: Duchenne Muscular Dystrophy (DMD) is a severe X-linked genetic disorder caused by a mutation leading to a deficiency of the dystrophin protein, a protein crucial for muscle operation. The disease primarily affects boys as symptoms are seen in early childhood between the ages of 2 and 3 and in some rare cases pre-adolescence. This neuromuscular disease causes muscle weakness, delayed motor milestones and eventual loss of ambulation. Currently, there is no cure for DMD, but early diagnosis through genetic testing allows for improved disease management. Standard treatment involves corticosteroids to decrease muscle degeneration along with physical therapy to maintain mobility. In recent years, Advanced genetic testing such as novel gene and exon skipping therapies offer promising avenues for slowing disease progression. Despite these advancements, challenges remain in ensuring accessibility and efficiency, especially in low income and third world countries.