10th Erciyes Medical Genetics Congress with International Participation

INVITED SPEAKER ABSTRACTS

IS1- Ailevi Akdeniz Ateşi Tanısı için Yenilikçi bir Optik Biyosensör Platformu

Arif E. Cetin[1,2]*
[1]Izmir Biomedicine and Genome Center, Balcova, Izmir 35340, Turkey
[2]Department of Biophysics, Faculty of Medicine, Dokuz Eylul University, Izmir 35340, Turkey
*arifengin.cetin@ibg.edu.tr

Familial Mediterranean Fever (FMF) is a monogenic autoinflammatory disease, particularly prevalent among Mediterranean populations. It arises from mutations in the MEFV gene, which lead to abnormal regulation and overproduction of the pyrin protein—an intracellular sensor involved in innate immune responses. While genetic testing remains the gold standard for FMF diagnosis, it is often limited by high costs, restricted availability, and ambiguous interpretation, especially in heterozygous individuals. To address these limitations, we developed a novel plasmonic biosensing platform that enables direct quantification of pyrin protein levels in biological samples. The sensor integrates gold nanoparticle-functionalized surfaces with anti-pyrin antibodies, forming a selective and label-free detection interface. Coupled with an optofluidic system and visible light spectroscopy, the platform allows real-time monitoring of pyrin concentrations without the need for enzymatic or fluorescent labeling. Our device achieved a detection limit of 0.24 ng/mL and exhibited excellent stability, maintaining consistent signal performance for up to six months. In clinical validation tests, the biosensor successfully distinguished FMF patients from healthy controls with high sensitivity and specificity, demonstrating its capability for early and accurate diagnosis. The portability, rapid analysis time, and cost-effectiveness of the system further support its potential for integration into routine clinical workflows and point-of-care applications. This biosensing approach introduces a paradigm shift in FMF diagnostics, enabling more accessible and definitive testing, particularly in regions with limited access to genetic analysis. It also opens new avenues for protein-based screening of other autoinflammatory diseases.

Keywords: Plasmonics, Label-Free Biosensing, Optofluidics, FMF, Rare-Disease,

Acknowledgements
A.E.C. acknowledges the support of The Scientific and Technological Research Council of Türkiye (TÜBİTAK) through the 1005 – National New Ideas and New Products Research Funding Program (Project No. 119E649). This study was also supported in part by the EU Horizon 2020 ERA Chairs Project RareBoost (Project No. 952346).

IS2- Nadir Solid Tümör Kordomada Ferroptozis Mekanizması

Didem Seven[1]
[1]Yeditepe Üniversitesi Tıp Fakültesi Tıbbi Genetik Anabilim Dalı, İstanbul, Türkiye

Kordoma, embriyonik notokord kalıntılarından köken alan nadir görülen bir kemik tümörüdür. Genellikle omurga hattı boyunca, özellikle kafatası tabanı (klivus) ve sakrum bölgelerinde lokalize olur. Histopatolojik olarak konvansiyonel, kondroid ve dediferansiye olmak üzere üç alt tipe ayrılır. Kordoma tedavisinde temel yaklaşımlar en blok rezeksiyon ve radyoterapi olmakla birlikte, günümüzde hastalık için onaylanmış etkili bir sistemik ilaç tedavisi bulunmamaktadır. Düzenlenmiş hücre ölümlerinin indüklenmesi, hedefe yönelik kanser tedavilerinde önemli bir strateji haline gelmiştir. Bu bağlamda, ferroptozis —demir bağımlı, lipid peroksidasyona dayalı programlanmış bir hücre ölümü türü— özellikle Erastin ve RSL3 gibi ajanlar aracılığıyla tetiklenebilmektedir. Bu çalışmada, kordoma hücrelerinde ferroptozisin etkileri araştırılmıştır.
Yapılan deneylerde, IC50 dozunda uygulanan Erastin sonrası kordoma hücrelerindeki SLC7A11 protein düzeyleri Western blot analizi ile değerlendirilmiştir. Hücre içi reaktif oksijen türleri (ROS) düzeyleri akış sitometrisi yöntemiyle analiz edilmiştir. Ayrıca, hücre proliferasyonunu ve tümöral potansiyeli değerlendirmek amacıyla koloni oluşumu ve tümör küre deneyleri gerçekleştirilmiştir. Bağışıklık kaçış mekanizmalarından biri olan PD-L1 ekspresyon düzeyleri de yine akış sitometrisi ile incelenmiştir.
Çalışmamızda, Erastin uygulanan kordoma hücrelerinde SLC7A11 protein düzeylerinde artış gözlenmiş, buna karşın hücre içi ROS seviyelerinde anlamlı bir değişiklik saptanmamıştır. Erastin tedavisi, hücre proliferasyonunu baskılamış, koloni oluşumunu engellemiş ve tümör küre oluşturma kapasitesini belirgin şekilde azaltmıştır. Ayrıca, Erastin uygulamasıyla birlikte PD-L1 ekspresyonunda artış tespit edilmiştir.
Bu bulgular, Erastin'in hücre ölümünü tetiklediğini ve hücre çoğalmasını engellediğini göstermektedir. PD-L1 düzeyindeki artış, ferroptotik yanıtın kordomada immünoterapi açısından potansiyel bir pencere oluşturabileceğine işaret etmektedir. Öte

yandan, SLC7A11 ekspresyonundaki artış, klasik ferroptozis mekanizmasının ötesinde, yeni tanımlanan düzenlenmiş hücre ölüm türlerinden biri olan disülfidoptozisin de bu süreçte rol oynayabileceğini düşündürmektedir. Bu nedenle, kordomada disülfidoptozisin araştırılması ileri çalışmalarda önemli bir odak noktası olabilir.

IS3- Diagnostic Power of Third-Generation Sequencing Technologies in Rare Genetic Disorders

Dr. Irem Kalay, MD – Ümraniye Training and Research Hospital, Department of Medical Genetics

Rare diseases constitute a significant health burden both individually and globally. Over 80% of these disorders are of genetic origin, with the majority presenting in childhood. Despite advances in genetic testing, many patients remain undiagnosed for years, leading to a frustrating and often exhausting diagnostic odyssey for families and clinicians alike.

Short-read sequencing technologies, while effective in identifying many types of genetic variation, have notable limitations in detecting repetitive sequences, large structural variants, phasing, and deep intronic mutations. These constraints hinder the diagnostic yield in complex or unsolved genetic cases.

Third-generation sequencing technologies offer a transformative approach by enabling the continuous reading of long DNA molecules. Their advantages include real-time sequencing, PCR-free library preparation, simultaneous detection of epigenetic modifications, and the ability to resolve repetitive and structurally complex genomic regions. These capabilities make them especially powerful in addressing previously undiagnosable cases.

This presentation highlights the diagnostic contributions of long-read sequencing in rare disease cohorts, particularly in neurological and developmental disorders. Key applications discussed include structural variant analysis, detection of tandem repeat expansions, and variant phasing, where long-read sequencing technologies demonstrate clear technical superiority over traditional methods.

In conclusion, third-generation sequencing represents a critical advancement in the molecular diagnosis of rare diseases. Its integration into clinical workflows can significantly improve diagnostic rates, reduce time to diagnosis, and support the implementation of individualized medicine strategies.

IS4- Current Status of Gene Editing Therapies in Hematological Diseases

Pınar ATA
Marmara University School of Medicine
Genetic Diseases Evaluation Center

Gene editing has revolutionized the treatment landscape for hematological disorders, offering unprecedented precision in correcting underlying genetic defects. This rapidly evolving field is moving from experimental stages to approved clinical applications, transforming the lives of patients with previously intractable conditions. Gene Editing Technologies include TALENs (Transcription Activator-Like Effector Nucleases) and ZFNs (Zinc Finger Nucleases), which also enable targeted DNA modifications. More recent innovations like base editing and prime editing offer even greater precision, allowing for single-nucleotide changes or small insertions/deletions without inducing double-strand breaks, potentially reducing off-target effects.The cornerstone of these advancements lies in powerful gene editing tools. CRISPR-Cas9 (Clustered Regularly Interspaced Short Palindromic Repeats-CRISPR-associated protein 9) is the most prominent, known for its efficiency and relative ease of use in making precise cuts in DNA.

Delivery Methods and Challenges; Effective delivery of gene editing components to target cells remains a critical challenge. Common strategies include: Ex vivo editing:Hematopoietic stem cells are harvested from the patient, edited in the lab, and then reinfused. This method is highly controlled but invasive. In vivo editing: Gene editing components are delivered directly into the patient's body, often using viral vectors(e.g., adeno-associated viruses - AAV) or lipid nanoparticles (LNPs). This approach is less invasive but faces challenges with targeting specificity and potential immunogenicity.

Major challenges that are actively being addressed include:

Off-target effects:Unintended edits at non-target sites can lead to safety concerns.Delivery efficiency and specificity:Ensuring the editing machinery reaches the correct cells in sufficient quantities. Immunogenicity: The body's immune response to gene editing components or delivery vectors. Long-term efficacy and safety: Understanding the durability of the edits and potential long-term complications. Cost and accessibility: Gene editing therapies are currently very expensive, limiting their widespread availability.

The applications in hematological diseases are Gene editing therapies that are being explored and developed for a wide range of hematological disorders: **Sickle Cell Disease (SCD) and Beta-Thalassemia**:These are among the most advanced areas. Gene editing aims to reactivate fetal hemoglobin (HbF) production (e.g., by targeting the BCL11A gene) or to directly correct the disease-causing mutations in the beta-globin gene. Several clinical trials have shown promising results, with some patients achieving transfusion independence and significant symptom improvement.**Severe Combined Immunodeficiency (SCID):** Gene editing can correct the genetic defects in hematopoietic stem cells, restoring a functional immune system in patients with various forms of SCID, such as ADA-SCID. **Hemophilia:**While gene therapy (gene addition) has seen success, gene editing approaches are being explored to achieve more durable and potentially curative solutions by correcting the faulty coagulation factor genes directly in hepatocytes. **Fanconi Anemia (FA):**This rare genetic disorder leads to bone marrow failure. Gene editing holds promise for correcting the defective genes in hematopoietic stem cells to prevent progressive

bone marrow failure and reduce cancer risk. **Acute Myeloid Leukemia (AML) and Lymphoma:** Beyond correcting genetic defects, gene editing is also being used to enhance CAR T-cell therapy. By editing the T-cells themselves (e.g., to remove PD-1 or other inhibitory receptors, or to insert specific chimeric antigen receptors), their anti-cancer efficacy and persistence can be significantly improved. Future Therapies; The field of gene editing for hematological diseases is rapidly advancing. With ongoing research, improved delivery systems, and enhanced specificity of editing tools, it is anticipated that more gene-edited therapies will gain regulatory approval. The focus is shifting towards making these curative treatments safer, more accessible, and applicable to a broader range of genetic blood disorders, ultimately offering new hope for patients worldwide.

IS5- Unveiling the role of a deSUMOylating isopeptidase in a new ALS like syndrome

Nasrinsadat Nabavizadeh[1,2], Seyide Ecesu Uygur[1,2], Şahin Avcı[3], Yunus Akkoc[2,4], Devrim Gozuacik[2,4], Hulya Kayserili[3], Zehra Piraye Oflazer[5,6], Henry Houlden[7], Ehsan Ghayoor Karimiani[7], Reza Maroofian[7], Nathalie Escande-Beillard[1,2*]

[1] Functional Genomics Laboratory, Medical Genetics Department, Koç University School of Medicine (KUSoM), Istanbul, Türkiye.

[2] Koç University Research Center for Translational Medicine (KUTTAM), Koç University Hospital M-4th floor, Istanbul, Türkiye

[3] Genetic Diseases Evaluation Center, Medical Genetics Department, Koç University Hospital, Istanbul, Türkiye

[4] Medical Biology Department, Koç University School of Medicine (KUSoM), Istanbul, Türkiye.

[5] Muscle Center, Koç University Hospital, Istanbul, Türkiye.

[6]Neuromuscular Disease Unit, Neurology Department, Koç University School of Medicine (KUSoM), Istanbul, Türkiye.

[7] Department of Neuromuscular Diseases, Queen Square, Institute of Neurology, University College London, London, United Kingdom.

Background: Amyotrophic Lateral Sclerosis (ALS) is a devastating neurodegenerative syndrome primarily affecting the motor neuron system and is undoubtedly associated with genetic predisposition. Despite the identification of over 40 ALS-related genes, many patients remain without a genetic diagnosis, highlighting the complexity of its underlying pathogenesis. Identifying novel genetic variants is essential for improving diagnostics and developing targeted treatments.

Materials and Methods: Whole Exome Sequencing (WES) was employed to investigate genetically undiagnosed ALS-like cases, leading to the identification of two distinct recessive mutations in *DESI1*, a deSUMOylase enzyme, in two unrelated families. Functional studies including cloning, immunoblotting, immunofluorescence staining, and co-immunoprecipitation, were conducted using *DESI1* mutant patient-derived fibroblast and CRISPRi knockdown in SH-SY5Y neuroblastoma cells to investigate molecular pathomechanisms.

Results: *DESI1* variants cause protein truncation and instability, resulting in degradation and likely loss-of-function. Remarkably, DESI1 interacts with ALS-associated proteostasis regulators, including UBQLN1, 2, and 4, highlighting its potential role in ALS pathogenesis. The UBQLN4-DESI1 complex mediates the nuclear export of polyubiquitinated proteins to the cytosol. Notably, *DESI1* mutant cells exhibited defective nuclear export, leading to the aberrant accumulation of polyubiquitinated proteins, a well-known hallmark of ALS.

Conclusion: Our findings establish *DESI1* as a novel genetic cause of ALS-like syndrome and suggest that physicians should consider this gene as a potential candidate in genetically undiagnosed cases. DESI1, sharing the same pathogenic pathways with known ALS-associated proteins, is a promising target for developing neuroprotective treatments strategies in a broader range of ALS patients.

Grants: This work is funded by TÜBİTAK-ARDEB 1001 (Türkiye) to NEB and supported by an AFM-Telethon Postdoctoral Fellowship (France) to NN.

References

1. Mead RJ, Shan N, Reiser HJ, Marshall F, Shaw PJ. Amyotrophic lateral sclerosis: a neurodegenerative disorder poised for successful therapeutic translation. Nature Reviews Drug Discovery. 2023 Mar;22(3):185-212.
2. Wang H, Guan L, Deng M. Recent progress of the genetics of amyotrophic lateral sclerosis and challenges of gene therapy. Frontiers in neuroscience. 2023 May 12;17:1170996.
3. Hirayama S, Sugihara M, Morito D, Iemura SI, Natsume T, Murata S, Nagata K. Nuclear export of ubiquitinated proteins via the UBIN-POST system. Proceedings of the National Academy of Sciences. 2018 May 1;115(18):E4199-208.
4. González-Pérez P, Lu Y, Chian RJ, Sapp PC, Tanzi RE, Bertram L, McKenna-Yasek D, Gao FB, Brown Jr RH. Association of UBQLN1 mutation with Brown–Vialetto–Van Laere syndrome but not typical ALS. Neurobiology of disease. 2012 Dec 1;48(3):391-8.
5. Deng HX, Chen W, Hong ST, Boycott KM, Gorrie GH, Siddique N, Yang Y, Fecto F, Shi Y, Zhai H, Jiang H. Mutations in UBQLN2 cause dominant X-linked juvenile and adult-onset ALS and ALS/dementia. Nature. 2011 Sep 8;477(7363):211-5.
6. Edens BM, Yan J, Miller N, Deng HX, Siddique T, Ma YC. A novel ALS-associated variant in UBQLN4 regulates motor axon morphogenesis. Elife. 2017 May 2;6:e25453.

IS6- Genetic etiopathogenesis of Charcot-Marie-Tooth disease and emerging novel treatment options

Şahin Avcı
Koç Üniversitesi Hastanesi
Genetik Hastalıklar Değerlendirme Merkezi

Zeytinburnu-Topkapı / İstanbul.
e-mail: saavci@kuh.ku.edu.tr

Charcot-Marie-Tooth (CMT) disease is characterized by progressive motor and sensory nerve dysfunction leading to distal muscle weakness and atrophy and is one of the most common hereditary neuromuscular disorders with a prevalence of 1:2500. The most common form is CMT1a and it is related to *PMP22* duplications leading to overexpression. The other common associated genes are *GJB1*, *MFN2*, *MPZ*, *SH3TC2* and *SORD*. There are no curative treatments for CMTs yet. However, there are promising results by in vitro and in vivo preclinical studies including RNA, antisense oligonucleotides or CRISPR/Cas9 mediated downregulation of *PMP22* expression in mice models as well as lentiviral or AAV-mediated gene therapies for the other common CMT forms. There are also some significant pathways targeted for the treatments of specific CMT types such as *SARM1* pathway for axonal CMTs and unfolded protein response (UPR) pathway for CMT1B. The most probable novel treatments expected in the near future are aldose reductase inhibitors for *SORD*-related CMT forms due to their promising results in the ongoing phase III clinical study. The other expected novel treatments for which phase I / II clinical studies are going on are sephin-1 targeting UPR pathway, and AAV-mediated neurotrophin-3 gene therapy which is crucial for Schwann cell autocrine survival and regeneration.
Key words: Charcot-Marie-Tooth disease; inherited neuropathy; *PMP22*; gene therapy; aldose reductase inhibitors