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ceRNA Network in Neurodegenerative Disorders

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Abstract

Neurodegenerative diseases are a group of disorders characterized by the progressive degeneration of the structure and function of the nervous system. Although, we know that oxidative stress, mitochondrial dysfunction, excitotoxic amino acids, and inflammations are major pathogenesis involved, the causes of neurodegenerative diseases remain unknown. The competing endogenous RNA (ceRNA) network is a regulatory network that involves various RNA molecules, including messenger RNAs, long non-coding RNAs, and microRNAs (miRNAs). According to the ceRNA hypothesis, RNA-RNA cross-talk via miRNA response elements might build a large-scale regulatory network spanning the transcriptome that includes both coding and non-coding RNAs (ncRNAs). Many genes implicated in neurodegenerative diseases are part of the ceRNA network. By influencing the expression of these genes, ceRNA interactions can impact disease progression. The ceRNA network is highly complex, with multiple interactions occurring simultaneously. This complexity makes it challenging to decipher the precise role of specific ceRNA interactions in neurodegenerative diseases. It is necessary to use computational methods and experimental validation to identify and study relevant ceRNA interactions. Understanding the ceRNA network's role in neurodegenerative diseases may offer potential therapeutic targets. Modulating ceRNA interactions could be a strategy to restore normal gene expression patterns and potentially slow down or halt disease progression. The ceRNA network is an intriguing concept in the context of neurodegenerative diseases. It highlights the intricate interplay among different RNA molecules and their potential contribution to disease pathogenesis. While research in this area is ongoing, it holds promise for uncovering new insights into disease mechanisms and developing novel therapeutic approaches.

Genetics of Hypokinetic Diseases and Genetic Counseling

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Abstract

Hypokinetic diseases, a sub-branch of movement disorders, include a group of neurological conditions characterized by reduced voluntary movements. These diseases usually develop after a genetic disorder. These disorders can be transmitted from the family or may occur uniquely to the individual. A family history of hypokinetic disease may be a strong indicator of a genetic component. Individuals whose close relatives have been diagnosed with these diseases may have a higher risk due to shared genetic factors. Advances in genetic research have led to the investigation of gene therapy as a potential treatment for some hypokinetic diseases. Genetic information can enable the practice of precision medicine by tailoring treatment plans to an individual's genetic makeup. Current genetic diagnostic tests can help identify specific mutations or genetic variations associated with certain hypokinetic diseases. This can provide valuable information for both diagnosis and treatment planning. It is important to note that genetic disorders alone do not determine the development of hypokinetic diseases. To understand and manage these complex neurological disorders, it is necessary to consider both genetic and environmental factors. Environmental factors, such as exposure to toxins or lifestyle choices, can also play an important role in the onset and progression of diseases. Genetic counseling is important in terms of assessing genetic risk after family tree analysis, discussing potential consequences, and providing guidance for patients to make informed decisions about themselves. As a result, genetic approach to hypokinetic diseases; by examining the role of genetics in the pathogenesis of the disease, it aims to identify the relevant genetic factors, understand the personal/familial genetic and clinical risks of these factors and contribute to their management. In this presentation, it is aimed to discuss genetic approach and counseling by providing updated information about hypokinetic diseases and related genetic causes.

Epilepsies and Current Treatment Approaches from the Perspective of a Pediatric Neurologist

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Abstract

Although epilepsy is a historical disease, with the rapid progress of studies in the field of genetics, there is a need for new updates in terms of both definition, classification and treatment. The International League Against Epilepsy defined epilepsy as at least 2 untriggered seizures recurring at intervals longer than 24 hours; a diagnosis of epileptic syndrome, or one untriggered seizure accompanied by >60% probability of recurrence. Epilepsy; affects 5-10 per thousand of children, with the highest incidence in infancy. This rate varies between 8-14 per thousand in Türkiye. Epilepsy syndromes are defined and classified in newborns, infants and children in 2022 by considering certain criteria such as age of onset, family history, neurological examination, possibility of responding to medication, remission, comorbidities, seizure types, electroencephalography features, neuroimaging, genetics, and differential diagnosis. Epilepsy syndromes in newborns and infants were classified as self-limited epilepsies, developmental and epileptic encephalopathies and etiology-specific syndromes. Childhood epilepsies were grouped as self-limiting focal epilepsies of childhood, genetic generalized epilepsies and developmental and/or epileptic encephalopathies of childhood. Knowing the type and etiology of epilepsy and confirming the clinical suspicion of a specific syndrome avoids unnecessary additional tests. Contraindicated medications and ineffective treatment are avoided. Such as avoiding sodium channel blockers in patients with SCN1A-related epilepsy, or preferring these drugs first in channelopathy caused by KCNQ1 mutation in the neonatal period. It allows predicting the prognosis and allowing for information. It helps to personalize treatment based on the etiological gene.

Keywords: Epilepsy, epilepsy syndromes, gene, treatment

The Use of Systems Biology in Treatment of Liver Diseases

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Abstract

To develop novel strategies for prevention and treatment as well as to gain detailed insights about the underlying molecular mechanisms of liver diseases, it is vital to study the biological functions of liver and its interactions with other tissues and gut microbiota. Biological networks can provide a scaffold for studying biological pathways operating in the liver in connection with disease development in a systematic manner. In my presentation, I presented our recent work, where biological networks have been employed to identify the reprogramming in liver physiology in response to fatty liver disease. Based on this mechanistic modelling approach, we identified novel drug targets which may lead to design of targeted and effective treatment for liver diseases. I also presented how we developed number of drug candidates and showed their effect by performing *in vitro* and *in vivo* studies. Our study is a great example for discovery of novel drug targets and development of drug candidates for modulating our drug target.

Decoding Diseases in 3D: AI-powered Cell Level Imaging and Omics

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Abstract

Our research integrates cell-level imaging by tissue clearing and omics methods via deep learning to accelerate drug development. We focus on visualizing complex biological systems at the single-cell level, including whole mouse bodies and centimeter-size human tissues. We combine this 3D-imaging data with proteomics to characterize pathologies and therapeutic effects including toxicity and efficacy. Unbiased 3D cell-level imaging on complex biological systems leads to quicker discoveries for diseases such as neurodegeneration, cancer, and diabetes. Exemplary applications of cell level assessment in whole mouse body, organoids, and large monkey and human tissues.

Modeling Neurodevelopmental Disorders in *Drosophila melanogaster*

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Abstract

Drosophila melanogaster (fruit fly) is a powerful model organism in the study of neurodevelopmental disorders (NDDs). NDDs have a global impact, affecting over 15% of children and covering a broad spectrum of early-onset syndromes that alter the development of the central nervous system. The severity of these disorders ranges widely and includes conditions such as intellectual disability, developmental delay, and autism spectrum disorder, among others. The mechanisms leading to NDD involve nervous system development, ubiquitination, chromatin modification and transcription regulation, signal transduction, synaptic function, metabolism, cytoskeletal dynamics, and Rho GTPase signaling. My presentation will focus on the *RNFT2* gene, which has not yet been linked to any disease. A missense mutation in RNFT2 (c.1150T>C, resulting in p.C384R) was investigated for its role in intellectual disability. This mutation affects zinc ion binding and alters protein stability. We show that the *Drosophila* homolog of RNFT2, CG13605, is expressed in the mushroom bodies, which are crucial for learning and memory. Our study utilized CRISPR/Cas9 technology to create CG13605 mutants, revealing significant morphological problems in mushroom body structure and a shorter lifespan. Negative geotaxis and courtship behavior tests were conducted to assess the mutants' behavioral aspects. Interestingly, human RNFT2 was shown to rescue the defects in CG13605 mutants, suggesting functional conservation and potential therapeutic avenues. This research demonstrates the efficacy of *Drosophila* as a model for understanding the genetic and molecular underpinnings of neurodevelopmental disorders, paving the way for future medical genomics applications in diagnosing and treating these conditions.

Keywords: *Drosophila melanogaster*, neurodevelopmental disorders, RNFT2

Genetics of Epilepsy and Genetic Counseling

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Abstract

Epilepsy, a neurological disorder characterized by recurrent seizures, manifests as a heterogeneous group of conditions, with genetic factors emerging as pivotal contributors to its pathogenesis. Various genes have been implicated in elevating susceptibility to epilepsy, offering crucial insights into the disorder's underlying mechanisms. These genes, influencing key aspects of brain function such as ion channel regulation, neurotransmitter release, and neuronal excitability, when mutated, disrupt the delicate balance of neuronal activity, culminating in abnormal electrical discharges and seizure manifestation. Genetic testing assumes a crucial role in the diagnostic process, facilitating the identification of causative mutations. As our comprehension of the genetic architecture of epilepsy evolves, genetic testing becomes increasingly integral in informing clinical decision-making. Treatment modalities for genetic epilepsy encompass a spectrum including antiepileptic drugs, ketogenic diets, and, in certain cases, surgical interventions. Ongoing research endeavors focus on unraveling intricate genetic interactions contributing to epilepsy, holding promise for novel therapeutic targets. Within the comprehensive management of epilepsy, genetic counseling provides indispensable information and support to affected individuals and their families. Precision medicine, leveraging unique genetic profiles, holds potential for more individualized treatment strategies. Advancements in gene-editing technologies further offer prospects for targeted correction of pathogenic mutations, introducing a potential curative dimension to the management of genetic epilepsy. In sum, the integration of genetic insights into diagnosis, treatment, and counseling underscores a transformative paradigm in addressing the complexities of epilepsy.

Keywords: Epilepsy, genetic counseling, neurogenetic disease

Identifying the Route from Mutation to Function from the Perspective of Elucidating Neurodevelopmental Disorders

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Abstract

Neurodevelopmental disorders (NDDs) with a heterogeneous etiology are characterized by impairment in cognition, communication, adaptive behavior and psychomotor skills. NDDs include autism spectrum disorder, impaired cognition and epilepsy. Considering that the diagnosis period of single gene disorders varies between 5-30 years, molecular basis of gene-disease relations needed to be determined. Microcephalic Primordial Dwarfism (MPD) is a group of rare diseases consists of four different subgroups of syndromes named Seckel syndrome, Meier-Gorlin syndrome, Microcephalic Osteodysplastic Primordial Dwarfism Type II (MOPDII) and Type I/III (MOPDI/III). Common characteristics of MPD include severe prenatal and postnatal growth retardation, skeletal dysplasias, agenesis of the corpus callosum, impaired development of the cerebral cortex (pachygyria/agiri), microcephaly, ıntellectual disabilitiy and epileptic seizures. We evaluated three different family affected from Renpenning syndrome, Seckel syndrome and MOPDI/III. In all three families, genome-wide homozygosity mapping and exome/DNA sequencing analyses identified the genes responsible for the disease. We identified *PLK4* as a new *Candidate* gene in the patient affected by Seckel syndrome and demonstrated by functional studies that it plays a role in response to DNA damage. Third family was linked to MPD, where we identified a gene of unknown function by genome-wide homozygosity mapping-exome sequencing. In this context, we cloned the *Candidate* gene and delivered it into HEK293 cell line by stable transfection. We identified its interaction partners by Immunoprecipitation and Mass Spectrometry analysis. Immunofluorescence staining was also used for identification of cellular localization of protein of interest which may partly give information about its cellular processes.

Keywords: *Candidate* gene identification, DNA sequencing, genetic mapping, protein-protein interaction

Comparative Analysis of Familial Exome Analysis Tools: Finding Low Frequency Rare Variants in Familial Multiple Sclerosis

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Abstract

Analyzing familial exome data involves various steps, can be complex, requiring a combination of different tools to process and interpret the genetic information effectively. Among the publicly available tools like Exomiser, famFHAT, and pVAAST, Exomiser focuses on phenotype associations, while famFHAT integrates pedigrees and covariates such as severity scores. However, linear models bypass gene functionality and pathway nuances, whereas knowledge-based methods might miss genetic variations. We employed linear methods famFHAT, pVAAST, burden tests and relatedness enriched RandomForest model, alongside knowledge graph-based techniques Exomiser and g:Profiler for enrichment analysis in Turkish Familial MS cohort consisting of 45 multiply affected families. Exomiser's top 50 genes for each family were integrated based on interfamily sharing and ranked by subgraph occurrence. Known MS-associated genes in the top 100 rankings were assessed for validation. Also, segregation pattern of variants in families was investigated with the full-likelihood bayes factor algorithm. In the famFHAT analysis of the top 100 genes, five were linked to MS with p-values ranging from 0.000450 to 0.004880, while the pVAAST analysis revealed four genes associated with MS, with p-values between 0.0 and 0.04. Likewise, the Exomiser analysis identified four MS-associated genes with p-values ranging from 0.0001 to 0.01. Functional enrichment analysis focusing on blood-brain barrier, cell adhesion and immune pathways, multiple pathogenic rare variations found in genes such as *LAMA5*, *LAMB4*, *LAMB1*, *LAMA2*, *LAMA1*, *TJP1*, *OCLN*, and *TNFRSF21* among affected individuals. Our findings provide a novel perspective on the genetic landscape of familial MS. Project was supported by GeleceğiMSin Project (2022).

Keywords: Multiple sclerosis, exome analysis, laminin genes

Genetic Basis of Hydrocephalus and Modeling Congenital Hydrocephalus Genes in the Xenopus Model System

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Abstract

Congenital hydrocephalus (CH), the pathological expansion of the cerebral ventricles due to cerebrospinal fluid (CSF) accumulation, is a common birth defect affecting 1 in every 700 births. Unfortunately, the genetic basis of CH impedes our understanding of CH pathogenesis. Although sequencing technologies enable *CH* gene discovery, we do not have a tractable animal model to test the impact of gene dysfunction on CSF circulation and CH pathogenesis. For this purpose, we developed the frog *Xenopus* as a rapid animal model to study CH pathogenesis. *Xenopus* has many advantages. Hundreds of synchronized embryos can be manipulated from the cleavage stages after in vitro fertilization. In addition, *CRISPR/CAS9* gene editing technology works well in *Xenopus,* producing biallelic gene modifications in F0 embryos, enabling rapid modeling of disease phenotypes in F0 embryos. Specifically for studying hydrocephalus, the *Xenopus* tadpole brain is semi-transparent, enabling optical coherence tomography imaging to detect 3D CSF flow throughout the entire ventricular system in living tadpoles. Using this system, we showed the visualization of a whole ventricular CSF flow network, enabling us to analyze better the interactions between the candidate human *CH* genes, ventricular development, and brain patterning. A currently held view is that CH forms due to excessive fluid/pressure in the ventricles due to obstruction or loss of CSF flow, requiring neurosurgical shunting to relieve the accumulation of this fluid. However, when we modeled candidate human genes in *Xenopus*, we showed earlier developmental defects leading to late hydrocephalus phenotype, including changes in neural cell fate.

Keywords: Hydrocephalus, *Xenopus*, optical coherence tomography

Genetic and Phenotypic Analysis of Patients with Mucopolysaccharidosis type IIIB Co-morbid with Autism Spectrum Disorder

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Abstract

Mucopolysaccharidosis type IIIB (MPS IIIB) is an autosomal recessive lysosomal disorder caused by mutations in the α-N-acetylglucosaminidase (*NAGLU*) gene. Our WES and standard Sanger sequencing effort on 220 consanguineous families, in children diagnosed with ASD, identified two recurrent damaging biallelic p.D312N and p.R234G variants in the *NAGLU* gene in seven cases of four families. All affected individuals' enzymatic assay in leukocytes clearly showed that α-N-acetylglucosaminidase was completely inactive. Structure modeling of these mutations suggested that each mutation affects the stability of the enzyme and results in a loss of activity. knn-DREMI analysis of scRNAseq data of the developing human brain identified that several genes implicated in neurodegenerative disorders are positively regulated with *NAGLU* expression. Among these genes, mutations in *CLN5* and *ZBTB20* were linked to neurodevelopmental disorders including autism. Our findings suggest that molecular and cellular mechanisms controlled by the genes positively regulated with *NAGLU* expression have promise to develop the potential treatment for neurodevelopment and neurodegeneration in patients with MPS IIIB and autism.

Keywords: NAGLU, MPS IIIB, autism spectrum disorder, lysosomal enzyme, α-N-acetylglucosaminidase, scRNAseq

Autism Spectrum Disorder and Genetic Counseling

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Abstract

Neurodevelopmental disorders are characterized by developmental deficits in cognition, language, behavior, and/or motor skills that result in impairments in personal, social, academic, and/or occupational functioning. Among chronic diseases in the pediatric age period (between 3-17 years of age), the most common reason for applying to primary healthcare services is neurodevelopmental disorders. Autism spectrum disorder (ASD) is one of them. Copy number variations (CNVs) are recommended as the first-line genetic test for ASD in guidelines. When the data of 11 studies examining CNVs are examined, it has a diagnostic rate of 1.5-20.5% (average 8.1%) in the diagnosis of ASD. Among these CNVs, variants of uncertain significance are most challenging conditions. In this case, it should be evaluated whether the detected variant relevantly associated with phenotype, whether there are previously reported cases involving a similar region, whether the breakpoints match, whether it is *de novo*/familial, whether it is related to SNVs in the same gene. In a meta-analysis study investigating the Exome Sequencing method, which included ASD cases, the diagnosis rate was found to be 8-26% (average 15%). As a conclusion genetic tests and genetic counseling providing information about the risk of other individuals in the family, risk of recurrence, preimplantation genetic diagnosis and prenatal diagnosis is important for family planning.

Keywords: Autism spectrum disorder, genetics, counselling

When should We do which Test?

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Abstract

Genetic diagnostic and screening tests are used to analyze an individual's genetic material to detect genetic changes that may cause diseases or to identify potential genetic diseases. Genetic testing is usually considered when there is a family history of genetic diseases or problems with the individual's own health. These tests are also used to screen for common diseases in the populations. The main criteria for test selection can be summarized as the purpose of the test, the type of genetic variation causing the genetic disease, age of onset and hereditary or acquired status. These tests show a wide range of methodological diversity, from chromosome analysis to whole genome analysis, and have different coverage areas. Since the sensitivity of the methods and the size and nature of the variations detected vary, the etiology of the diseases must be taken into account when selecting the tests. For this, clinical prediagnosis/diagnosis should be considered as a requirement for test selection (forwards genetics). Sometimes, in cases that cannot be diagnosed clinically, a diagnosis can be made by utilizing laboratory diagnosis (reverse genetics), but for this, the clinical evaluation of the patient should be performed before the analysis. The appropriate timing of genetic testing depends on specific periods in an individual's life. For example, pre-marital or preconception screening/diagnostic tests may be followed by preimplantation genetic diagnosis and/or prenatal diagnosis, if necessary. In the postnatal period; genetic testing for a genetic disease can be done at any stage of life, from newborn to adulthood.

Keyword: Genetic testing

Autism Spectrum Disorders from a Psychiatrist's Perspective

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Abstract

Autism symptoms can range from mild to severe forms. Since the symptoms vary from case to case, the term autism spectrum disorder (ASD) was included diagnostic manuals. This term includes Autism, Asperger Disorder and Atypical Autism. Family studies show that after the older child is diagnosed with ASD, 7-20% of subsequent children have ASD. This prevalence increases in children with two older siblings with ASD. ASD has a important health burden on families and population. With early diagnosis, problems in the developmental process can be prevented. Patients' communication skills can be improved. Awareness of the increasing prevalence of ASD; It is important to direct the interventions of society and decision makers. Genetic studies are extremely important in terms of better understanding of this disease, follow-up of cases and family planning.

Keywords: Autism spectrum disorder, child and adolescent psychiatry, follow-up, neurodevelopmental disorder

What does a Geneticist Expect from a Neurologist?

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Abstract

Genetic evaluation and genetic tests play an important role in the diagnosis, classification, follow-up and treatment of neurological diseases. For this reason, a geneticist is involved in the evaluation of the patient and selection of appropriate tests beside the neurologist. In the diagnostic process, the geneticist needs to see and evaluate the patient to obtain detailed information about the patient and his/her family, to draw a pedigree and to have information about neurological findings and other system findings and complaints. In addition, it is important to get information from the patient's neurologist about the prediagnosis and differential diagnoses. In this way, it will be determined which test will be ordered first in the test ordering algorithm of neurologic diseases, which are a genetically very heterogeneous group. In this way, the diagnosis process of diseases with specific inheritance patterns will not be prolonged and financial losses will be prevented. In fact, in order to accelerate this process, it would be very efficient for neurology and medical genetics clinics to hold regular meetings and evaluate patients together.

Genetics and Genetic Counseling of Hyperkinetic Diseases

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Abstract

Hyperkinetic movement disorders are neurological syndromes characterized by excessive movement in voluntary and automatic movements without loss of strength or spasticity. It occurs as a result of the basal ganglia being affected. The most common types are chorea, ballismus, dystonia, athetosis, myoclonus, tic, and tremor. It is divided into many subgroups. It is a heterogeneous group of diseases, each with a different pathophysiology, etiology, diagnosis, and treatment. Clinical findings are variable. Genetic counseling is also different for each individual. It is named according to the nature of the abnormal or involuntary movement that dominates the clinical picture. It is crucial to diagnose movement disorders to give accurate info and advice to patients and their at-risk relatives about genetic causes, consequences, risks, precautions, and treatment options. Early identification of at-risk individuals is vital for patients who can benefit from effective medical intervention. Predictive genetic testing is inappropriate for adult-onset conditions or asymptomatic young children at risk but should be considered if clinical findings are present. The best time to identify genetic risks and evaluate the availability of prenatal or preimplantation genetic testing is before pregnancy. Families with a known disease may consider preimplantation genetic testing an option. Due to the possibility of preventable causes in the etiology, taking preventive measures will reduce the incidence of these diseases. The best way to deal with a disease is to prevent it from occurring. The possibility of effective treatment and protection of future generations depends on accurate and early diagnosis.

Keywords: Genetics, genetic counseling, hyperkinetic, movement disorders

Functional Analysis of Autism Genes in Zebrafish Identifies Convergence in Dopaminergic and Neuroimmune Pathways and Pharmacological Candidates

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Abstract

A central challenge in the genetics of autism spectrum disorders (ASDs) is advancing from gene discovery to the identification of actionable biological mechanisms. To investigate the function of ten genes that are strongly associated with ASD in the developing vertebrate brain, we performed behavioral, whole-brain structural, circuit, cellular and molecular analyses in zebrafish mutants of ASD genes. First, we identified both unique and overlapping effects of gene loss of function on basic sensory processing and arousal behaviors. Next, we identified the forebrain as the most significant contributor to brain size differences, while brain regions involved in sensory motor control, particularly dopaminergic regions, are associated with altered baseline brain activity. Third, using whole-brain RNA sequencing in zebrafish mutants of *SCN2A* and *DYRK1A*, we identified conservation of dysregulated pathways associated with *ASD* gene loss of function in zebrafish and mammals. Using hypothesis-driven gene set

enrichment analysis, we found that dopaminergic genes are significantly enriched among downregulated genes in both mutants, while microglial genes are significantly enriched among upregulated genes. Finally, we show that both mutants display a significant increase in microglia throughout the brain, with *DYRK1A* mutants exhibiting a nearly two-fold increase in microglia. Therefore, our study implicates neuroimmune dysfunction as an important pathway downstream of select ASD genes. As a next step, we are using pharmaco-behavioral profiling to identify pharmacological suppressors of mutant behavioral phenotypes. Together, this study demonstrates the power of *in vivo* functional analyses in zebrafish to identify biologically relevant pathways downstream of ASD genes.

Keywords: Autism spectrum disorder, genetics, zebrafish, dopamine, microglia

SMA Genetics and Genetic Counseling

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Abstract

Spinal muscular atrhopy (SMA) is a rare autosomal recessive neuromuscular, where one out of each 10,000 live births can be affected by this syndrome. The atrophy is caused by the gradual loss of alpha motor neurons, either within the ventral spinal cord or motor nuclei within the lower brainstem. In this study, we aimed to evaluate the carrier frequency of *SMN1* mutation causing SMA in Turkish and Turkish Cypriot populations. This is the first study to evaluate the *SMN1* deletion mutations in Turkish Cypriot population. We compare our results with the Turkish Ministry of Health and will be presented at the conference. Our findings revealed that the carrier frequency of mutation in the *SMN1* gene for exon 7 is 2% and exon 8 is 2% in Turkish population and 4% in Turkish Cypriot for both exon 7 and exon 8 deletions. In conclusion, health precautions must be taken due to the high frequency of SMA linked to the deletion of the *SMN1* gene. Carrier testing as a technique for genetic counselling may be advantageous for individuals with a positive family history. To this population, we strongly recommend premarital testing.

Keywords: SMA, genetic counselling, carrier status, exon 7, exon 8

Clinical Aspects of Multiple Sclerosis

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Abstract

Multiple sclerosis (MS) is the second most disabling disease of young adults in their reproductive ages after accidents. In my talk, “Clinical Aspects of MS”, I will try to concentrate on the changes in the terminology of clinical phenotypes of MS and also I will address the relation of clinical and genetical findings. Classically 4 types of MS were defined in 1996: Relapsing-remitting (RR) (85% of all MS patients), secondary progressive (SP), primary progressive (10-20% of all MS patients), and progressive relapsing. If left untreated, most of the patients with RRMS are expected to become SP at the end of 19 years. Clinical isolated syndrome, RRMS, PPMS, SPMS were the accepted clinical MS phenotypes according to the 2013 revision. MS may be claasifed according to age of onset of MS as childhood (<18 year), adult (18-50 years), late adult (>50 years) or very late onset (>60 years). During relapsing phase, clinical attacks or radiological new forming or gadolinium enhancing lesions serve as markers of MS. In progressive phase, disability worsens in dependent of attacks. Vision loss, diplopia, defects in visual field, sensory findings (most frequent initial finding), motor deficits, cerebellar/brain stem/spinal cord/bowel and urinary system/sexual/cognitive dysfunctions, neuropsyhiatric sypmtoms, seizures, sleep difficulties, pain, MS-associated fatigue, extrapyramidal findings or paroxysmal symptoms like Lhermitte’s sign, Uhfhoff’s phenomenon may be present alone or in different combinations as MS suggesting signs and symptoms.

Keywords: Multiple sclerosis, clinical phenotypes, relapsing, progressive

Hyperkinetic Movement Disorders and Current Treatments from the Perspective of Neurologist

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Abstract

The term movement disorders (MD) basically describes neurological conditions characterized by excessive or excessive movement in voluntary and automatic movements without loss of strength or spasticity. Lack of movement is defined as hypokinesia (decrease in movement amplitude), bradykinesia (slowing of movement) and akinesia (loss of movement). Excessive movement is expressed as hyperkinesis (increased movements) and dyskinesia (abnormal movements) or "abnormal involuntary movements". The main hyperkinetic MDs are: dystonia, tremor, chorea and myoclonus. There are significant difficulties with the clinical diagnosis of dystonia. Great progress has been made in recent years regarding its etiological basis. It is possible to reach the correct diagnosis with the differential diagnosis list created after a good clinical evaluation and genetic analysis performed by an experienced team-laboratory. Symptomatic treatment of focal dystonia; botulinum neurotoxin, oral medications and rehabilitation. Therapeutic indications and potential stimulation targets for deep brain stimulation (DBS) continue to expand. Pathogenesis-based treatments, including gene therapy, may be possible in the near future. Tremor is a common hyperkinetic MD. Oral medication options are limited and also its systemic side effects could be seen. DBS and MRg-focused ultrasound are effective treatment methods forr tremor. After careful patient selection by the MD specialist neurologist, then the appropriate DBS target is selected. Many studies continue to be carried out regarding the treatment of chorea, especially Huntington's disease, with an increasing number in recent years. Myoclonus is seen with many etiological causes and a heterogeneous clinical picture. Therefore, treatment studies that include only patients with isolated myoclonus are limited. There is increasing evidence that DBS is particularly effective in DYT 11 myoclonus dystonia.

The Molecular Landscape of ALS in Türkiye

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Abstract

Amyotrophic Lateral Sclerosis (ALS) is a neurological disease characterized by the degeneration and subsequent loss of the upper and lower motor neurons. The list of ALS genes continues to expand, with up to 20% of ALS heritability linked to genetic variants. In addition to these genetic associations, cumulative environmental exposures and epigenetic modifications appear likely to promote an individual across the disease-onset threshold. Thus, neurodegeneration in ALS reflects a complex interplay between genetic factors and the environment, with consequent dysfunction of molecular pathways and network circuitry. Here we present our results over a cohort of 2320 ALS patients, consisting of 501 fALS and 1819 sALS cases. The four major ALS genes C9ORF72, SOD1, TARDBP and FUS solved 35% of familial and 6% of apparently sporadic cases in our cohort. Further investigation of the remaining samples with Whole Exome Analysis increased the diagnostic rate to 45% in fALS and to 10% in sALS. Understanding the genetic contributions to disease is crucial in illuminating the major molecular pathways disrupted in ALS. Most importantly, under the surface of the seemingly disparate clinical, syndromic and diagnostic classification, not only shared genes and phenotypes, but also common mechanisms and pathways may be hidden. In the new era of translational medicine, diagnoses and potential therapies are based on genetic mutations and genetic screening, and counselling gain significance.

Keywords: Amyotrophic lateral sclerosis, ALS, genetic counselling, neurogenetics, genetic screening

Neuromuscular Diseases from a Pathologist's Perspective

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Abstract

The accurate histopathological evaluation of neuromuscular diseases requires a robust clinico-pathological collaboration. Neuromuscular diseases involve a wide range of healthcare professionals, starting from those dealing with newborns in delivery rooms to various specialists at different levels of expertise. The histopathological assessment of these diseases largely relies on morphological findings, with only a small portion of these findings being disease-specific. To achieve the best evaluation, pathology laboratories specific to these diseases, rather than general pathology

laboratories where all procedures are performed, should be established. The most crucial sources of data in neuromuscular diseases are biopsies of striated muscle and peripheral nerves. The preferred method for muscle biopsy is incisional biopsy, while needle biopsies can be used in compulsory situations. Biopsies must be evaluated alongside sufficient and appropriate clinical and laboratory data. The accurate selection of the muscle to be biopsied and the biopsy site is of utmost importance. In ideal conditions, hematoxylin and eosin stains, histochemical examinations, enzyme histochemistry, and, when necessary, immunohistochemical examinations are applied to muscle biopsies in the laboratory. Electron microscopic evaluation is required for the diagnosis of some diseases. Biopsies should be of a quantity and quality sufficient for these examinations. Nerve biopsy is a less commonly used histopathological examination method due to the necessity of sacrificing the nerve being biopsied. Peripheral nerve biopsy may be considered in peripheral neuropathies and certain muscle diseases. Sural nerve biopsy is most commonly performed due to the inability of the biopsied nerve to function. Motor nerves are not subjected to biopsy. To obtain a healthy result, the physician who examines the patient should collaborate with the pathologist before performing the biopsy and should continue this collaboration throughout the biopsy examination process.

Keywords: Neuromuscular disease, histopathology

Genetics and Genetic Counseling in Spinocerebellar Ataxias

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Abstract

Spinocerebellar ataxias (SCA) are a group of neurodegenerative diseases occurring usually at the age of 30-40 years or older with a slow progression and autosomal dominant inheritance. In almost all patients, cerebellar atrophy accompanies to gait ataxia, dysarthria, and visual impairment. More than 50 loci and genes have been identified (https://neuromuscular.wustl.edu/ataxia/domatax.html). Disease-causing mutations are often the expansion of tandem repeats within the disease gene and are most commonly seen as polyglutamine (CAG) defects. Other mutations are point mutations, deletions, insertions, duplications in related genes. Disease mechanisms of SCAs include gain of toxic RNA function, mitochondrial dysfunction, channelopathies, autophagy and transcription-dysregulation. While CAG expansions responsible for SCA1, SCA2, SCA3, SCA6, SCA7, SCA17, DRPLA and SCA12, there are different expansions in SCA8, SCA10, SCA27B, SCA31, SCA36 and SCA37. It has been reported 28 genes in which are identified non-repeat mutations. Diagnostic tests for expansions sequences are fragment analysis, triplet primed polymerase chain reaction and long read sequencing. For other mutations, targeted next generation sequencing panels and whole exome sequencing are preferred. SCA, which is inherited as an autosomal dominant disorder, has a 50% risk of recurrence in the next generation. Asymptomatic individuals, can be detected in types with a known gene. Since there is no cure yet, genetic counseling should be provided with psychiatric support.

Keywords: Spinocerebellar ataxias, tandem repeat expansions

Muscular Dystrophies and Genetic Counseling

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Abstract

Muscular dystrophy (MD) is a group of inherited genetic diseases in which muscles weaken and degenerate over time as a result of hereditary deficiencies in the muscle membrane or accessory proteins. Genetic counseling is the process that includes providing information to individuals who carry or are at risk of carrying a genetic disease and their family members about the prognosis of the disease, its treatment, if there is a possibility of recurrence, as well as which tests should be performed at what periods and their results. Muscular dystrophies can be single gene diseases as well as multigenic. In order to understand the genetic etiology in this disease group that shows genetic heterogeneity, it is necessary to know the terms of locus heterogeneity and allelic heterogeneity. Duchenne muscular dystrophy and Becker muscular dystrophy are the best known muscular dystrophies which approximately 60% are caused due deletion, 30% due point mutation and 10% by duplication. Other diseases with well-known genetic etiologies are Limb Gİrdle, facioscapulohumeral and myotonic dystrophies. It is necessary to choose the diagnostic test method according to the type of mutation in the etiology and to provide genetic counseling both before and after the genetic testing.

Keywords: Muscular dystrophy, genetic counseling, heterogeneity

Genetics for All: Basic Principles, Family History, and Inheritance Patterns of Neurogenetic Diseases

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Abstract

A detailed clinical investigation is essential to assess the inheritance model of the disease afflicting a family, considering also possible clinical variability. Investigator notes any parental consanguinity and any natural abortions. We are most familiar with monogenic diseases with Mendelian inheritance, but many diseases exhibit complex inheritance, the best-known of which is decreased penetrance that can range from 0.99 to <0.01 per cent. Very low penetrance is considered susceptibility instead. Reduced penetrance as well as variable expressivity is due to a modifier variant in some other gene. Such modifiers either manifest a severer phenotype or hinder development of the disease. Mutations in a gene can lead to different diseases with no clinical overlap and different inheritance patterns, as in *TBC1D24*. Mutations in the same gene can cause a disease involving a single trait such as polydactyly or a syndrome with neurological findings when the mutation burden of the individual is high, as in Bardet-Biedl syndrome. Lastly, gonadal mosaicism is possible in diseases in single sibships, as in Duchenne muscular dystrophy. Many cases have been solved by exome sequencing of parent and sibs to detect such *de novo* mutations, which are not rare for genes responsible for dominant diseases. Almost all cases with dominant diseases that hinder reproduction in any way are due *de novo* mutations, and others due to somatic mosaicism. Mutations of mitochondrial DNA leading to severe disease are often due to gonadal mosaicism, mimicking recessive inheritance. All these phenomena need to be taken into consideration in assessing the pattern of inheritance.

Keywords: Complex inheritance, pedigree

New Generation Treatments for Epilepsis

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Abstract

Epilepsy is a disease historically associated with evil spirits and mystery. The long history of epilepsy dates back to a 4000-year-old Akkadian tablet found in Mesopotamia; It depicts a person “with his neck turned to the left, his hands and feet tense, his eyes wide open, and foam flowing from his mouth without him realizing it”. About a thousand years later, Late Babylonians wrote a diagnostic manual called Sakikku, which included texts describing epilepsy. Documentation on epilepsy also dates back to about B.C. It is also found in Chinese texts dated to 770-221. A group of physicians published the Yellow Emperor’s Classic of Internal Medicine, the Huang Di Nei Ching, which outlined generalized seizures. The spiritually based pathophysiology of epilepsy dates back to 3000 BC, when the Hippocratic School in Greece suggested that the brain might be the root cause of epilepsy. It remained largely unchallenged until the 5th century. Aristotle, an important philosopher of the 4th century BC, suggested that epilepsy and sleep arise from similar mechanisms. The Hippocratic idea that epilepsy was a brain disease finally gained traction in Europe from the 17th century onwards and continued throughout the millennium. Samuel Tissot (1728-1797), a prominent Swiss physician, published Traité de l’épilepsie in 1770. John Hughlings Jackson (1835-1911) laid the scientific foundation of epileptology and studied the localization of lesions that could cause seizures. He published the influential text “The Study of Convulsion”, which was the culmination of his scientific findings. The current focus of gene therapy strategies for epilepsy is primarily on neuropeptide Y, galanin, etc. It aims to reduce neuronal excitability through overexpression of neuromodulatory peptides, such as, or through genetic modification of astrocytes, for example, to suppress adenosine kinase expression.

Keywords: Epilepsy, antiepileptic treatment, gene therapy, seizure

Application of High-Throughput Sequencing Technologies in Development of Neurogenetic Disorders

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Abstract

NGS technology is speeding up neurogenetics research, helping to unravel the intricacies associated with it. Neurological disorders are not predictable in the early-stage and different people show different responses to treatment. This difference can be caused by molecular pathways

or environmental effects. Therefore, as a first step selecting a correct genetic test for diagnosis is important, which should be customized to fit the disorder. Microarray, single gene analysis and repeat expansion disorders could be used as rapid first-level tests to address these issues. If the associated results are negative, NGS methods such as whole exome sequencing (WES) and whole genome sequencing (WGS) can be considered as second-level testing platforms. WES is most commonly used due to its low associated cost and turnaround time, compared with WGS. However, the overall diagnosis rate remains low, primarily due to challenges associated with the detection of pathogenic mutations, which may be classified as a variant of insignificance. So interpretation of variants as a pathogenic or non-pathogenic become challenging as many variants are unknown or not reported previously. Another issue is that many variants may lie into non-coding regions which comprises 90% of the genome and they can't be captured by short sequencing read technologies. However, over the last decades third generation sequencing emerges to overcome some shortcomings of NGS. Specifically, long read technologies have the potential to identify molecular mechanisms associated with the neurological disorders that are caused by expansion repeats such as Friedreich ataxia, spinocerebellar ataxias, Alzheimer's disease.

Keywords: NGS technology, neurogenetics research, challenges

SMA Treatment Innovations

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Abstract

Spinal muscular atrophy (SMA) is an autosomal recessive genetic associated with the survival motor neuron 1 gene (SMN1), leading to reduced levels of the survival motor neuron (SMN) protein, results in the death of motor neurons in the anterior horn (apoptosis). The deficiency of SMN protein contributes to motor neuron loss and disease progression. Currently, there are three approved treatment methods for SMA: Onasemnogene abeparvovec (Zolgensma®), Nusinersen, and Risdiplam, all of which aim to increase SMN protein levels and alter the disease's course. Onasemnogene abeparvovec utilizes an adenovirus-associated vector serotype 9 to modify the human SMN1 gene, aiming to express SMN protein in motor neuron cells via a single-dose intravenous application. Nusinersen, when administered intrathecally, regulates the maturation of SMN2 mRNA, thereby increasing SMN protein synthesis in the central nervous system. Risdiplam operates similarly but shows efficacy not only in the central but also the peripheral nervous system, administered orally. Studies continue to explore combination therapies, high-dose applications, sequential treatments, and long-term efficacy and side effect profiles, with the aim of better understanding the advantages of each treatment option. Additionally, gene therapy, such as recombinant adeno-associated virus serotype 9 gene therapy, has shown promise in the treatment of SMA. The therapeutic sdevelopments for the treatment of SMA are focused on restoring SMN expression, which is crucial in addressing the underlying cause of the disease. In this presentation, the current treatment options for SMA were discussed. Case studies were presented.

Pathophysiology of Multiple Sclerosis

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Abstract

Multiple sclerosis (MS) is an autoimmune and degenerative disease of the central nervous system. Characterized by both inflammatory and neurodegenerative components, this condition is the most common non-traumatic disabling neurological disorder among young adults. Women are approximately three times more likely to be affected by this disease compared to men. The tissue damage in MS results from a complex and dynamic interplay among the immune system, glial cells (including myelin-producing oligodendrocytes and their precursors, microglia, and astrocytes), and neurons. Although the exact cause of this autoimmune response remains elusive, it is thought to involve a combination of genetic, environmental, and immunological factors. T-lymphocytes play a significant role in the immunopathogenesis of MS, operating through various T-cell subtypes. Th1 cells contribute to the autoimmune response in the central nervous system by secreting pro-inflammatory cytokines (interferon-γ and tumor necrosis factor-α). Th17 cells can initiate neuronal damage by producing interleukin-17. Regulatory T-cells (Tregs) play a crucial role in suppressing the autoimmune response, and their dysregulation is implicated in the pathogenesis of MS. B lymphocytes are also influential in MS pathogenesis through their role in antibody production. In individuals with MS, B-cells contribute to lesion development and disease progression. T-cells assist in activating B-cells and triggering their antibody production, while B-cells also influence T-cells by presenting antigens and enhancing T-cell activation. Innate immune system cells are essential in the pathogenesis of MS. Well-known environmental risk factors for the development of MS include low vitamin D levels, Epstein-Barr virus infection, and smoking. In conclusion, MS is an autoimmune-mediated demyelinating and neurodegenerative disease that emerges under the influence of environmental factors in genetically predisposed individuals. T-lymphocyte autoimmunity forms the

basis of its pathophysiology, with various immune system elements contributing to autoimmune-mediated central nervous system damage. The cause of autoimmunity is not definitively known. Reducing the effects of modifiable risk factors is of significant importance. Immunomodulatory treatments targeting multiple stages of pathophysiology are being used and developed. Personalizing pathophysiological understanding and treatment in MS care is among the future objectives of therapy.

Keywords: Multiple sclerosis, pathophysiology, autoimmunity, demyelination

ALS and New Treatments

Necdet Karlı

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Abstract

Motor neuron diseases (MND) are classified according to their clinical presentation as;

1. Amyptrophic Lateral Sclerosisi
2. Primary Lateral Sclerosis
3. Progressive Muscular Atrophy
4. Progressive Bulbar Palsy
5. Pseudobulbar Palsy
6. Monomelic Amyotrophy

Classical ALS is the most frequent MND making about 70% of all MND. It's clinical presentation comes with first and second motor neuron findings. Cramps and fasciculations, extremity weakness, bulbar signs (dysarthria, dysphagia, choking) may be the presenting symptoms or may be seen during the evolution of the disease. ALS is a multifactorial diseases based on a genetic mutation. 10% of ALS cases are familial. More than 40 genetic mutations have been associated with ALS. The most frequent ones being; C9ORF72, SOD1, FUS, TARDBP mutations. Diagnosis is based on neurologic examination and EMG. Treatment options are limited, all are slowing but neither curing nor stopping the disease. Riluzole, Edaravone, Sodium phenylbutyrate + tauroursodiol and tofersen are the choices for the treatment of ALS. Sodium phenylbutyrate + tauroursodiol and tofersen are recently approved treatment by FDA. Studies showed both were more promising, rate of slowing was higher than the previous treatments.

Inovations in Muscular Dystrophy Treatment: Hopes and Challenges

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Abstract

In this speech, it is privileged to share insights into the revolutionary advancements in muscular dystrophy (MD) treatment, a field witnessing remarkable strides in genetic therapy and personalized medicine. MDs, characterized by progressive muscle weakening, encompass a variety of genetic disorders. The most common, Duchenne muscular dystrophy (DMD), results from mutations in the dystrophin gene, essential for muscle function and stability. The recent surge in biomedical innovations has ushered in gene-based therapies, offering new hope. Gene replacement therapy, using Adeno-Associated virus vectors, introduces functional dystrophin genes into affected cells. Meanwhile, gene editing, particularly CRISPR/Cas9, promises to correct mutations at the DNA level. However, challenges in precision and safety persist. Exon skipping, another innovative approach, uses antisense oligonucleotides to bypass mutated gene sections, facilitating the production of a functional dystrophin protein. This technique has led to specific therapies like Eteplirsen for certain DMD mutations. In parallel, symptom management remains vital. Corticosteroids, the current standard, improve muscle strength, while emerging drugs target inflammation and fibrosis, key factors in MD progression. Looking ahead, the future of MD treatment lies in tailoring therapies to individual genetic profiles, enhancing effectiveness while minimizing side effects. Research continues to evolve, with combination therapies targeting multiple disease facets promising a more holistic approach. Our journey towards effective MD treatment is challenging but filled with potential. Through continued innovation and dedication, we aspire not just to treat MD but to transform the lives of those affected.

Keywords: Muscular dystrophy, gene therapy, gene editing, duchenne

Developing Dynamic Structure-based Pharmacophore and ML-based QSAR Models for the Discovery of New Anti-Cancer Therapeutics: Computational Drug Repurposing Efforts

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Abstract

RET holds paramount importance. Small molecules exhibit potential as inhibitors, binding to the kinase domain of RET and hindering its enzymatic activity. Nevertheless, the emergence of resistance, attributed to single amino acid changes, presents a formidable challenge. In this talk, a structure-based, dynamic pharmacophore-driven approach that utilizes E-pharmacophore modeling derived from molecular dynamics trajectories will be introduced. The objective is to identify hypotheses with low-energy favorability, employing machine learning-trained QSAR models to predict pIC_{50} values for compounds. To achieve this, a comprehensive screening of extensive small molecule libraries was conducted using developed ligand-based models. The outcome suggests potent compounds with the capability to inhibit RET activation.