AO-01-1 A centrally-acting BTK inhibitor improves aggressive MSA-C by suppressing proinflammatory microglia

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Aim: We reported a rapidly progressive multiple system atrophy-cerebellar (MSA-C) mouse model. We aimed to identify a microglia subpopulation that exacerbates MSA-C and to develop a microglia-targeted therapy in this model. **Methods:**Single-cell RNA sequencing of CD11b-positive microglia isolated from brainstem/cerebellum and spinal cord of Tg mice was performed to determine microglia clusters. Tolebrutinib and remibrutinib, respectively centrally and peripherally-acting Bruton's tyrosine kinase inhibitors (BTKi), were orally administered to Tg mice 4 times a week from 18 to 26 weeks of age. Their clinical score, rotarod test performance and body weight were compared to vehicle-treated Tg mice. **Results:** Single-cell RNA sequencing revealed a unique microglia cluster that highly expresses Toll-like receptor 2, transglutaminase 2, arginase-1, and various inflammatory cytokines compared to other clusters. These microglia surrounded phosphorylated α-synuclein aggregates, expressing BTK. We named these microglia as α-synucleinopathy-associated microglia (SAM). Tolebrutinib but not remibrutinib ameliorated clinical score and rotarod performance of Tg mice compared to vehicle-treated mice. Immunostaining for BTK showed significant reduction of BTK-positive activated microglia in tolebrutinib-treated mice at 26 weeks compared to vehicle-treated mice. Moreover, BTK-positive microglia were found to be increased in the brainstem and cerebellum from autopsied patients with MSA-C. **Conclusion:** A centrally-acting BTKi could be a novel therapy for rapidly progressive MSA-C by suppressing SAM.

AO-01-2 Amyloid beta plays an important role in the alpha-synuclein pPropagation in Lewy body disease

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Objective: To investigate the effect of amyloid-beta (Aβ) on α-synuclein (α-syn) propagation. **Background:** Braak et al. proposed that the spreading of Lewy pathology occurs via neuronal connection, initially developing in the olfactory bulb (OB) and the lower brainstem, called Braak hypothesis. Prion-like propagation of α-syn has been increasingly recognized as the mechanism underlying Braak hypothesis. Based on this mechanism, α-syn preformed fibril (PFFs) injection into the unilateral OB of wild-type (WT) mice demonstrated sequential α-syn propagation along anatomical connections. However, these mice exhibited no motor or anxiety-related deficits or significant pathological findings in the cortical areas. In this study, we hypothesized that Aβ may function as an additional factor in the progression of α-syn pathology in Lewy body disease (LBD), as more than 50% of patients exhibit coexisting Aβ pathology. **Methods:** α-syn PFFs were injected into the bilateral OB of amyloid precursor protein knock-in mice ($APP^{NL\text{-}G\text{-}F/NL\text{-}G\text{-}F}$) and WT mice at 4 months of age (n=4). Histological examinations were performed 3 months after the injection. **Results:** $APP^{NL\text{-}G\text{-}F/NL\text{-}G\text{-}F}$ mice exhibited extensive and significant propagation of α-syn in widespread brain regions, including the anterior olfactory nucleus, amygdala, hippocampus, dentate gyrus, caudate-putamen, and frontal cortex compared to WT mice. **Conclusions:** Coexistence of Aβ facilitates the propagation of α-synuclein and may contribute to the pathophysiology of Parkinson's disease with dementia and dementia with Lewy bodies.

AO-01-3 Correlation between clinical and neuropathological subtypes of progressive supranuclear palsy

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[Objective] Progressive supranuclear palsy (PSP) is characterized by pathology prominently in the basal ganglia, the tegmentum of the brainstem, and the frontal cortex. However, pathology varies according to clinical features. This study aimed to statistically verify the correspondence between the clinical and pathological subtypes of PSP. [Methods] We identified patients with a pathological diagnosis of PSP (n = 116) and classified the eight clinical subtypes of the Movement Disorders Society criteria for the clinical diagnosis of PSP into the Richardson, Akinesia, and Cognitive groups. We used anti-phosphorylated tau antibody immunostaining to semiquantitatively evaluate neurofibrillary tangles (NFTs) and coiled bodies/threads (CB/Ths) in the globus pallidus, subthalamic nucleus, and midbrain tegmentum. In the frontal cortex, tufted astrocytes (TAs) and CB/Ths were assessed on a 3-point scale. We compared the pathology among the three groups, recorded the phenotypes ranked the second and lower in the multiple allocation extinction rule and examined whether the pathology changed depending on applying each phenotype. [Results] The Richardson group exhibited severe NFTs and CB/Ths in the midbrain tegmentum. The Akinesia group showed severe NFTs in the globus pallidus. The Cognitive group had severe TAs and CB/Ths in the frontal cortex. TAs and CB/Ths in the frontal cortex correspond to behavioral variant frontotemporal dementia, and supranuclear vertical oculomotor palsy. [Conclusions] These clinical symptoms may reflect the distribution of tau pathologies in PSP.

AO-01-4 Revealing the pathogenesis of ALSP/HDLS using Human Induced Pluripotent Stem Cell-Derived Microglia

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[**Introduction**]Adult-onset leukoencephalopathy with axonal spheroids and pigmented glia (ALSP) is known as a primary microgliopathy caused by pathogenic *CSF1R* gene mutations. We aim to clarify how mutant CSF1R impacts microglial phenotype and contributes to the pathology of ALSP. [**Methods**]Microglia-like cells (MGLs) were generated from induced pluripotent stem cells (iPSCs) of 5 healthy controls (HC) and 3 ALSP patients and phenotypic analysis was performed. [**Results**]The transcriptomic analysis revealed alterations in intracellular metabolism-related genes in MGLs derived from ALSP (ALSP-MGLs). Using an extracellular flux analyzer, we found that the proportion of mitochondrial respiration in ATP production was increased in ALSP-MGLs. Additionally, we observed mitochondrial damage and an increase in mitochondrial reactive oxygen species (ROS)/oxidative stress in ALSP-MGLs, known as a hallmark of cellular senescence. ALSP-MGLs expressed other senescence makers such as γH2AX and increased pro-inflammatory secretary phenotype. Co-culture of ALSP-MGLs induced apoptotic marker caspase-3 activation in neurons, which was abrogated by adding ROS scavenger glutathione in the coculture medium. [**Conclusions**]CSF1R signaling dysfunction causes metabolic alteration and promotes senescent phenotype in microglia, leading to the increase of ROS production, which results in neuronal loss in ALSP brain.

AO-01-5 Allele selective silencing of polyQ proteins by SNA-modified siRNA targeting CAG expansions in mice

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[Objective] Polyglutamine (polyQ) diseases are inherited neurological disorders caused by expansions of CAG repeat in each causative gene. Reduction of polyQ protein level is promising therapeutic approach in polyQ diseases, but concomitant silencing of the corresponding protein from the wild-type allele with normal CAG repeats might result in neuronal dysfunction. The objective of this study is to develop a novel serinol nucleic acid (SNA)-modified siRNA selectively targeting CAG expansions and to evaluate the efficacy of the siRNA in mouse models of spinal and bulbar muscular atrophy (SBMA) and spinocerebellar ataxias type 3 (SCA3). [Methods] Based on screening results of the siRNAs using a reporter assay, we tested the potency and allele selectivity of promising candidates in SBMA and SCA3 patients' derived fibroblasts. We then injected a candidate siRNA into SBMA and SCA3 model mice. [Results] The reporter assay and fibroblast experiments identified the optimal sequence and chemistry of the siRNA. The siRNA injected intracerebroventricularly was widely distributed throughout the central nervous system, exerting selective silencing of polyQ proteins and a reduction of intranuclear aggregation of polyQ proteins in SBMA and SCA3 mice (n = 3 mice/group). Furthermore, the siRNA attenuated neuromuscular degeneration and motor dysfunction in SBMA mice compared to vehicle-injected mice (n = 13 mice/group). [Conclusions] These findings indicate that SNA-modified siRNAs targeting CAG repeats are a promising approach commonly available for the treatment of polyQ diseases.

AO-01-6 Association between the pathogenesis of OPDM and G4 structure suggested by single nucleus RNA-seq

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[Objective] Oculopharyngodistal myopathy (OPDM) is a hereditary myopathy caused by CGG repeat expansion. However, the pathogenesis is unknown. The purpose of our study is to elucidate the pathogenesis of OPDM based on single nucleus RNA-seq (snRNA-seq) data. [Methods] We performed snRNA-seq on muscles of OPDM patients with myofiber atrophy and rimmed vacuoles. We combined immunohistochemical staining of patient's muscles to evaluate the features of myofibers, which express each gene signature indicated by snRNA-seq. [Results] On pseudo-time trajectory analysis, two distinct pathogenic pathways were identified. In the two terminal clusters, distinct genes were upregulated, *COL19A1* or *NCAM1*. Pathologically, COL19A1 was expressed in the extremely atrophic and clustered fibers. NCAM1 was expressed in small angular fibers, some of which had rimmed vacuoles. At the midpoint of the pathway to *COL19A1* positive cluster, denervation related genes were upregulated. On the other hand, at the midpoint towards the *NCAM1*-positive cluster, the genes encoding guanin quadruplex (G4) binding proteins were upregulated. G4 RNAs were seen in the cytosol of the patient's myofibers and co-localized with repeated CGG RNA and RNA binding proteins. [Conclusions] We assume that G4 structure with CGG-expanded RNA may be the beginning of OPDM. In the neurogenic pathway, G4 structure may cause denervation. In the myogenic pathway, G4 structure may form a condensate with various RNA binding proteins. It can be the seeds for protein aggregates which may lead to form rimmed vacuoles as myofiber degeneration.

AO-02-1 A Phase 1 Study of NS-035 in Patients with Fukuyama Congenital Muscular Dystrophy

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[**Objective**] Fukuyama congenital muscular dystrophy (FCMD) is an autosomal recessive disease that affects the skeletal muscles, brain, and eyes. FCMD is caused by a 3-kb retrotransposal insertion mutation in the *fukutin* gene, resulting in aberrant mRNA splicing (exon-trapping). We discovered an antisense oligonucleotide, NS-035, that prevented exon-trapping and recovered normal *fukutin* mRNA expression and protein function *in vitro* and *in vivo*. We initiated an investigator-initiated first-in-human phase 1 study of NS-035 for regulatory approval. [**Methods**] This was a two-center, open-label, uncontrolled, dose-escalation clinical trial comprising four cohorts. Twelve patients with FCMD were included, with three patients in each cohort. Simultaneous doses of NS-035 and D-mannitol were administered intravenously once a week for 12 weeks. The dose of NS-035 was increased stepwise from cohorts 1 to 4. The primary endpoint was safety. The secondary endpoints were pharmacokinetics and efficacy, including exon-trapping inhibition efficiency, glycosylation of alpha-dystroglycan, changes in blood creatine kinase (CK) values, and gross motor function. [**Results**] There were no cases of withdrawal after the administration of the study drug. Inhibition of exon-trapping of *fukutin* mRNA and clinical findings suggestive of its efficacy, including improved CK values and motor function, were observed. The comprehensive results will be presented at the congress. [**Conclusions**] The NS-035 was generally safe and improved CK values and motor function. A Phase 2 study is currently being prepared.

AO-02-2 Clinical features and acute treatment in 100 patients with anti-NMDA receptor encephalitis in Japan

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【目的】本邦における抗NMDAR脳炎の臨床像および急性期治療の現状を報告する。【方法】2007年1月～2024年11月の間に神経表面抗体を測定した781例のうち、NMDAR抗体陽性と判明した100例（全国47施設に入院した患者）を対象に、臨床症候、画像・髄液所見、治療および予後を検討した。予後は発症1年後と最終受診時のmRSで評価し、mRS 0-2を良好とした。各値はmedian（IQR）で示した。【結果】女性71例、発症年齢は29.5歳（21-38歳）、44例に腫瘍（卵巣奇形腫82%、癌14%）を認めた。45歳以降に発症した遅発性成人発症は20例（男性60%、癌30%）であった。MS1例、Post-HSE4例、PERM1例を除外した94例における初発症状は精神症状が52%、痙攣発作が21%、記銘力障害が12%の順で多く、急性期には精神行動異常・記銘力障害を98%で認め、55%に人工呼吸管理を要した。不全型は27%であった。髄液細胞数増加は89%、OCBは59%、頭部MRI異常所見を47%（8%で脱髄病変）に認めた。4例は発症10ヶ月（5-16ヶ月）で死亡した（うち2例は癌）。予後良好は発症1年後で65%、最終受診時である発症22ヶ月（12-49ヶ月）後で74%であった。第1選択薬は95%、第2/第3選択薬は52%に投与され、それぞれ発症9日（5-21日）後と48 日（29-90日）後に投与開始された。第1選択薬無効例では、発症8週以内に第2/第3選択薬を投与された症例で、投与されなかった症例より1年後の予後良好を示す割合が高かった（P=0.0324）。【結論】本邦における抗NMDAR脳炎の臨床的特徴と急性期治療の現状が明らかになった。脱髄疾患やHSEに続発する症例があること、27%が不全型を呈すること、遅発性成人発症は男性に多く癌合併率が高いこと、26%は予後不良、死亡率は4%であることが示された。約半数で第2/第3選択薬が使用されていた。第1選択薬無効例で、発症8週以内に投与された第2/第3選択薬の１年後の予後に対する有効性が示されたことから、これら治療薬の早期の保険適応取得が望まれる。

AO-02-3 Delineating three distinct spatiotemporal patterns of brain atrophy in Parkinson's disease

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[Objective] The heterogeneity of clinical course of Parkinson's disease (PD) suggests that PD can be classified into distinct subtypes, whose pathological basis has not been fully elucidated. This study aimed to unveil the distinct spatiotemporal trajectories of neurodegeneration of PD. [Methods] 504 PD patients and 279 healthy controls underwent 3-Tesla structural MRI scan. Subtype and Stage Inference (SuStaIn), an unsupervised machine learning algorithm that combined disease progression modelling with clustering methods, was applied to the volume of cortical and subcortical structures. Longitudinal MRI data were collected for 178 patients at 2-year follow-up and 140 patients at 4-year follow-up. [Results] The SuStaIn analysis revealed three subtypes with distinct trajectories of brain atrophy: neocortical, limbic, and brainstem. The neocortical subtype showed diffuse cortical atrophy with earliest involvement in frontal and parietal cortex. The limbic subtype showed the atrophy of amygdala and striatum followed by temporal cortex. The brainstem subtype showed gradual rostral progression of the atrophy from brainstem. Longitudinal MRI data confirmed that 77.8% (2-year follow-up) and 84.0% (4-year follow-up) of patients were assigned to subtypes consistent with the baseline classification. [Conclusions] This study revealed three subtypes of PD with distinct atrophy pattern: neocortical, limbic, and brainstem. This classification was robust in longitudinal follow-up. These subtypes aligned with the neuropathological consensus criteria for patients with Lewy pathology.

AO-02-4 Long-read sequencing to diagnose unresolved familial Parkinson's disease

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[Background] PRKN and PINK1 are the most common genes linked to autosomal recessive Parkinson's disease (ARPD) and early-onset Parkinson's disease (EOPD). While biallelic variants in these genes are well-established causes, the role of heterozygous variants remains controversial. Notably, some Parkinson's disease (PD) patients exhibit a typical EOPD phenotype, despite having only a single PRKN or PINK1 variant identified. A recent breakthrough using long-read sequencing uncovered a 7.4 Mb inversion in PRKN in a genetically undiagnosed EOPD family, highlighting the potential of structural variants. [Methods] We studied early-onset PD patients with a single pathogenic PRKN or PINK1 variant identified via short-read sequencing and multiplex ligation-dependent probe amplification. To identify potential second structural variants, we applied Oxford Nanopore long-read sequencing to analyze DNA samples from these patients. [Results] In a Japanese cohort (PRKN: n=23, PINK1: n=12), long-read sequencing identified second variants in over 20% of PRKN heterozygous carriers but none in PINK1 heterozygous carriers. Newly identified PRKN variants included complex inversions, duplication-normal-duplication/inversion, overlapping copy number variants within the same allele, and exon deletions on different alleles. Screening of additional populations (European, African, and others, n=35) is ongoing. [Conclusions] This study shows the complexity of PRKN structural variants undetected by short-read sequencing and highlights the utility of long-read sequencing in accurately diagnosing ARPD.

AO-02-5 Longitudinal analysis of high-risk cohort of Lewy body disease

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【目的】我々は、2017年より複数のレビー小体病プロドローマル症状を有するハイリスク者コホート研究を実施している。本研究では、ハイリスク者の認知機能・運動機能の経時的変化を検討する。【方法】50歳以上の健診受診者に対し、SCOPA-AUT、SAOQ、RBDSQの各質問紙を用いて、自律神経障害、嗅覚障害、レム睡眠行動異常のうち複数のプロドローマル症状を有するハイリスク群と、1つも有しないローリスク群とに分類した。両群に対し、認知機能、運動機能、嗅覚機能、DaT-SPECT、MIBG心筋シンチグラフィを1年毎に評価し、認知機能、運動機能等の経時的変化に影響を与える要因について線形混合効果モデルを用いて解析した。【結果】ハイリスク群87名（平均64.6［7.5］歳）を最長6年（平均3.1［1.5］年）、ローリスク群33名（平均64.1［5.1］歳）を最長4年（平均2.6［0.8］年）縦断的に評価した。両群に年齢・性別の有意差を認めず、ベースラインのMoCA-Jは同様のスコアで（26.7［2.8］vs 27.0［2.6］, p = 0.541）、MDS-UPDRS IIIはハイリスク群でわずかに高値であった（4.2［3.3］vs 2.2［2.6］, p = 0.002）。縦断的解析において、ハイリスク群はローリスク群と比較してMoCA-Jの低下速度が有意に速く（-0.52［0.16］, p = 0.001）、ベースライン時のMIBG画像異常例は非異常例と比較してMoCA-J、MDS-UPDRS III、OSIT-Jの悪化が有意に速く（-0.66［0.23］, p = 0.038; 0.99［0.33］, p = 0.003; -0.44［0.18］, p = 0.014）、DaT異常例では非異常例と比較してMoCA-J、OSIT-Jの悪化が有意に速かった（-0.40［0.17］, p = 0.019; 0.99［0.33］, p = 0.003; -0.27［0.13］, p = 0.049）。【結論】アンケートに基づいたリスク分類は認知機能の経時的低下と関連していた。また、ベースラインのDaT・MIBG異常は認知機能・嗅覚機能の経時的低下と関連し、MIBG異常は運動機能の経時的低下とも関連していた。

AO-02-6 Plasma exosome miR30c-2 correlates with neuronal damage and glial activation in Alzheimer's disease

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Aim: We reported that blood exosome (Ex) microRNA (miR) 203 increase and miR30c-2 decrease in Alzheimer' disease (AD) by a mouse model and a retrospective human study. By a multicenter prospective cohort study, we aimed to further elucidate plasma Ex-miR markers useful for early diagnosis and monitor of AD. **Methods:** This study prospectively enrolled 51 patients with AD, 35 with mild cognitive impairment (MCI) and 34 aged healthy controls (HC). Ex-RNA was extracted from plasma and miR203 and 30c-2 were measured by qPCR. Plasma levels of neurofilament L (NfL), glial fibrillary acidic protein (GFAP), Aβ42, Aβ40 and total tau (t-tau) were measured by single molecule array. **Results:** Ex-miR203 was higher in AD than MCI and HC, and in MCI than HC (p<0.01) and negatively correlated with MMSE (p<0.01). In contrast, Ex-miR30c-2 was lower in AD than MCI and HC, and in MCI than HC (p<0.01) and positively correlated with MMSE (p<0.01). ROC analysis of miR30c-2 revealed that AUC between AD+MCI vs. HC was 0.95, and the sensitivity/specificity determined by the Youden Index were 91.2/89.5%. miR30c-2 negatively correlated with plasma NfL and GFAP (p<0.01) and positively correlated with plasma Aβ42/Aβ40 ratio (p<0.01) while Ex-miR203 weakly positively correlated with GFAP (p<0.04) but not NfL. **Conclusion:** We discovered that Ex-miR30c-2 successively decreases from early to late stage of AD, correlating with neuronal damage and glial activation markers. As brain miR30c-2 was reported to decrease responding to Aβ accumulation, plasma Ex-miR30c-2 is useful for early diagnosis and monitoring of AD.

AP-01-1 Cell-type- and disease-specific effect of the neuromyelitis optica spectrum disorder-related variant

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[Objective] Neuromyelitis optica spectrum disorder (NMOSD) is a rare autoimmune disease, characterized by optic neuritis and transverse myelitis. The genetic backgrounds of NMOSD have not been elucidated in detail due to the low prevalence. We attempted to find risk genes of NMOSD using genome-wide association study (GWAS) and to perform the functional analysis. [Methods] We conducted a GWAS meta-analysis of NMOSD in Japanese (240 patients and 50,578 controls). We applied human leukocyte antigen (HLA) imputation to fine-map the risk HLA variants. To elucidate the cell-type-specific expression profile of the putative target gene, we performed single-cell RNA sequencing (scRNA-seq) in peripheral blood cells from 25 NMOSD patients and 101 controls. [Results] Our GWAS meta-analysis identified NMOSD risks at the HLA region and *CCR6* (rs12193698; $P = 1.8 \times 10^{-8}$, odds ratio [OR] = 1.73), a novel associated gene. HLA fine-mapping showed the strongest association at HLA-DRβ1 amino acid position 11 with NMOSD. In the scRNA-seq analysis, the risk variant at *CCR6* showed the disease-specific expression quantitative trait loci (eQTL) effects in CD4 memory T cells, especially in T helper 17 (Th17) cells. [Conclusions] We found Japanese NMOSD-related variants NMOSD using GWAS meta-analysis. The cell-type-specific eQTL analysis enabled us to functionally interpret the GWAS result and demonstrated genetic regulation underlying the pathogenic role of Th17 cells in NMOSD.

AP-01-2 Exitron-Splicing-Derived Isoforms Fine-tune TDP-43 Protein Dynamics

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Objectives: We aim to explore how sTDPs, generated through alternative splicing in TDP-43's autoregulatory process that removes the "exitron" encoding its intrinsically disordered region (IDR), influence ALS/FTD pathophysiology. This study examines the roles of these isoforms in TDP-43 aggregation, homeostasis, and mitigating dysfunction from TDP-43 excess. **Methods:** We investigated sTDP's effects on TDP-43 aggregation using in vitro assays and cell models. We also analyzed sTDP's role in TDP-43 clearance. To assess in vivo effects, we introduced sTDP via AAV vectors into *TARDBP* transgenic mice. Using 84 mice, we evaluated RNA metabolic changes and phenotypes caused by TDP-43 overexpression, including survival outcomes. **Results:** In vitro, sTDP suppressed TDP-43 aggregation. In cell models, sTDP reduced IDR proximity, decreasing aggregation. sTDP promoted TDP-43 degradation through direct interaction with HSPA8, facilitating chaperone-mediated autophagy. In vivo, RNA-seq analysis showed that sTDP mitigated TDP-43-induced transcription shifts. Survival analysis revealed that homozygous females expressing sTDP showed improved survival compared to controls (AAV n=9, Control n=15). **Conclusions:** sTDP interacts with TDP-43 to suppress aggregation and promote its degradation via HSPA8-mediated autophagy, reducing excess TDP-43. In TDP-43 overexpression mice, sTDP counteracted abnormalities associated with TDP-43 excess. These findings demonstrate that sTDPs mediate a protein-level autoregulatory mechanism of TDP-43, which could be leveraged to mitigate its proteinopathy.

AP-01-3 Altered TDP-43 expression and synapse formation in ALS patient iPSC-derived motor neurons

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[Objective] TAR DNA-binding protein 43 (TDP-43) is an RNA-binding protein that forms phosphorylated aggregates in ALS patients. It is not yet fully understood which RNA interactions with TDP-43 contribute to ALS development. To explore the relationship between TDP-43 and RNA in ALS, we focused on the early phenotypes of TDP-43-ALS using ALS patient induced pluripotent stem cells (iPSC)-derived motor neuron. [Methods] We used CRISPR/Cas9 to generate isogenic control lines from immortalized lymphocytes of ALS patients with I383V mutation. We then differentiated these mutant and corrected isogenic lines into iPSC-derived motor neurons. Motor neurons (N = 3 each from mutant and corrected isogenic lines) were analyzed by immunostaining to compare the nuclear and cytoplasmic amounts of TDP-43 in each cell line. Synaptic morphology was evaluated using immunostaining. [Results] In TDP-43 I383V mutant motor neurons, TDP-43 expression was increased in both the nucleus and cytoplasm compared to isogenic controls. In addition, more synaptic particles stained with anti-synaptophysin antibodies were observed along MAP2-positive neurites in mutant motor neurons. [Conclusions] Our findings show that TDP-43 expression is elevated in both the nucleus and cytoplasm of iPSC-derived motor neurons with TDP-43 mutation, along with an increase in the number of presynaptic particles. These results may provide insight into early-stage ALS pathogenesis.

AP-01-4 Elucidation of RAN translation regulators using C9orf72-linked ALS/FTD fly models

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[**Objective**] Abnormal expansion of short tandem repeats in the genome causes over 50 neuromuscular diseases, collectively termed repeat expansion diseases. These expanded repeats can undergo noncanonical repeat-associated non-AUG (RAN) translation, producing toxic repeat polypeptides. In *C9orf72*-linked amyotrophic lateral sclerosis and frontotemporal dementia (C9-ALS/FTD), the most common genetic cause of these conditions, expanded intronic GGGGCC repeats are RAN-translated into dipeptide repeat proteins, contributing to neurodegeneration. While recent genome-wide screening in human cells has identified potential regulators of RAN translation, their roles *in vivo* remain unclear. This study aims to identify genes regulating RAN translation and neurodegeneration *in vivo*, using C9-ALS/FTD fly models. [**Methods and Results**] From 221 genes identified in prior cellular screening, we selected 49 candidates involved in RNA metabolism or binding GGGGCC repeat RNA. Using fly models expressing expanded GGGGCC repeats in compound eyes, we performed genetic screenings and identified 7 genes as *in vivo* modifiers of neurodegeneration. Notably, knockdown of *translation factor 1* (*TF1*), essential for AUG-dependent translation, enhanced RAN translation and eye degeneration whereas *TF1* overexpression suppressed RAN translation and degeneration. [**Conclusion**] We identified TF1 as a novel regulator of RAN translation, suggesting its opposing roles in AUG-dependent and RAN translation. These findings advance our understanding of RAN translation mechanisms widely underlying repeat expansion diseases.

AP-01-5 Exogenous macropharges proliferate in the putamen in patients of Multiple System Atrophy

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Introduction Multiple system atrophy (MSA) is a progressive neurodegenative disease characterized by parkinsonism, cerebellar ataxia, and autonomic dysfunction. Recently, it has been reported that some macrophages and T cells significantly increase in the putamen and substantia nigra of MSA patients, which might be involved in the pathogenesis of MSA. However, the pathological features have not been studied in detail. **Objective** In this report, we compared the pathological picture of macrophages in the putamen with MSA patients and control patients. **Methods** We conducted immunostaining of postmortem brains of 9 patients with MSA patients and 7 age-matched control patients.The two primary antibodies used in this study were as follows : chemokine receptor 2 (CCR2) for exogenous macropharge staining and tranmembrane protein 119 (TMEM119) for endogenous macropharge staining. **Results** In the putamen, the mean density of CCR2 positive macropharges in MSA cases were significantly increased, wheares TMEM1119 staining did not differ between MSA cases and control cases. **Conclusions** Hypothetically, the disruption of the blood brain barrier in the putamen triggers the infiltration of exogenous macrophages into the brain, which might be related to pathogenesis of MSA.

AP-01-6 Parkinson's disease-linked PSAP gene mutation affects progranulin trafficking and GCase activity

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[Objective] Mutations in the saposin D domain of *PSAP* are linked to autosomal dominant familial Parkinson's disease (PD). This domain is essential for the intracellular lysosomal trafficking of prosaposin (PSAP), which acts as a precursor for four sphingolipid activator proteins and binds progranulin (PGRN). However, the effect of saposin D domain mutations on PGRN trafficking remains unclear. We investigated whether these mutations alter PGRN trafficking. [Methods] Isogenic induced pluripotent stem cells (iPSCs) carrying pathogenic *PSAP* p.C412Y mutation were generated and differentiated into dopaminergic neurons (iPSC-DAs). These iPSC-DAs were analyzed by immunofluorescence and subcellular fractionation, followed by GCase enzyme activity assays. Statistical analyses were performed using one-way ANOVA with post hoc tests. [Results] Immunofluorescence revealed reduced lysosomal localization of PSAP, PGRN, and GCase in *PSAP*-mutated iPSC-DAs ($p < 0.001$). Total GCase activity in whole-cell lysates was unchanged between wild-type (WT) and *PSAP*-mutated iPSC-DAs. However, GCase activity was significantly lower in the lysosomal fraction and higher in the microsomal fraction of *PSAP*-mutated iPSC-DAs ($p < 0.001$). [Conclusion] PGRN has recently been associated with GCase activity. Our findings suggest that saposin D mutant PSAP disrupts the trafficking of PGRN and GCase. Further studies are needed to clarify the role of the PSAP/PGRN/GCase network in the pathomechanisms of FPD.

AP-01-7 Transcriptome change of peripheral immunity after thymectomy in anti-AChR antibody positive patients

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[Object] Myasthenia gravis (MG) is frequently associated with thymoma, which induces various autoimmune responses. Although thymectomy has been empirically recognized as an effective treatment for MG associated with thymoma, comprehensive changes in immune system following thymectomy remains unclear. In this study, we aimed to elucidate the immune response changes induced by thymectomy in anti-AChR antibody positive patients without apparent symptoms of MG. [Methods] Two patients positive for anti-AChR antibody without apparent symptoms of MG were enrolled in this study, and peripheral blood mononuclear cells (PBMCs) were collected both preoperatively and postoperatively. scRNA-seq was performed on each sample, and data analysis was conducted using Loupe Browser, Bbrowser, and Seurat R package for annotation, DEG, and pathway analyses.[Result] The percentage of B cells decreased in both cases after thymectomy (from 1.8% to 1.1%, and from 2.7% to 1.0%, respectively). Additionally, in CD14-positive monocytes, changes in specific immune pathways were observed. [Conclusion] Transcriptome analysis elucidated peripheral immune changes after thymectomy.

AP-02-1 Clinical features of 175 cases of anti-MAG neuropathy

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【目的】2021年の全国調査では，本邦の抗MAG（myelin-associated glycoprotein）ニューロパチーの患者数は353人，有病率は10万人あたり0.28人と推定されており，稀な疾患である．当院で血清抗MAG抗体を測定し，陽性を確認した抗MAGニューロパチー症例について検討を行った．【方法】2012年3月から2024年9月までに当院で血清抗MAG抗体を測定（Western blot，一部でELISAを併用），陽性の175例を対象とし，臨床像について検討した．【結果】診断時年齢は70.0±8.8歳（35-89歳）で，男性133例，女性42例であった．診断時の神経学的所見は152例で確認でき，脳神経異常は3例（2%），筋力低下は92例（61%），腱反射減弱-消失は125例（82%），異常感覚は116例（76%），表在感覚障害は93例（61%），深部感覚障害は126例（83%），振戦は16例（11%）で認めた．診断時点で造血器腫瘍の精査が為され，併存が確認された15例はいずれもlymphoplasmacytic lymphoma/Waldenström's macroglobulinemia（LPL/WM）であった．診断時の血清IgM値は135例で確認でき，709.7±658.6 mg/dL（68-5000 mg/dL）であった．診断時の血清IgM型M蛋白陽性は136例で確認でき，L鎖クラスを確認できた112例ではλ型が19例，κ型が93例であった．診断時の脳脊髄液検査所見は79例で確認でき，細胞数は2.1±4.0 /μL，蛋白は99.6±66.9 mg/dLであった．【結論】本研究において，抗MAGニューロパチーは高齢男性に好発し，神経学的所見では腱反射減弱-消失や深部感覚障害の頻度が特に高かった．血清IgM型M蛋白はκ型が多く，併存する造血器腫瘍はLPL/WMが多かった．脳脊髄液検査では，細胞数は正常で，蛋白は上昇する蛋白細胞解離を認める傾向があった．血清IgM値について多数例で検討した報告はなく，今回の検討では診断時の血清IgM値は必ずしも高値であるとは限らず，ばらつきが大きいことが示され，診断に際して留意すべき点と考えられた．

AP-02-2 SOMAscan proteomics identifies novel plasma biomarkers for spinal and bulbar muscular atrophy

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[Objective] Spinal and bulbar muscular atrophy (SBMA) is an inherited neuromuscular disease characterized by gradually progressive muscle weakness and atrophy. The aim of this study is to identify potential biomarkers associated with the pathogenesis of SBMA using plasma from SBMA patients. [Methods] Plasma samples were collected from 30 SBMA patients and 10 controls, and analyzed using the SomaScan® proteomics platform. Various multivariate analysis techniques, including differential expression analysis, principal component analysis (PCA), and significance analysis of microarray (SAM) were employed to thoroughly investigate the differences between the groups. Correlations between top candidate proteins and CAG repeats, testosterone levels, and other clinical findings were examined. [Results] We quantified a total of 7,323 proteins in the plasma of two groups. A number of molecular pathways showed significant alterations in SBMA patients compared to controls, with notable changes in pathways related to skeletal muscle function. Among the 32 proteins identified as significant by SAM, APOBEC2 and INHBA, which had higher correlation coefficients with CAG repeats, were selected for further analysis. The involvement of these molecules in the pathogenesis of SBMA was confirmed using cellular models of SBMA. [Conclusions] This study suggests profound changes in protein levels and molecular pathways in the plasma of patients with SBMA, which were consistent with the putative mechanism of the disease. APOBEC2 and INHBA potentially serve as biomarkers for SBMA.

AP-02-3 Determining the pathological thresholds for CAG repeat units in CACNA1A

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[Objective] Spinocerebellar ataxia type 6 (SCA6) is caused by expansion of CAG repeat units (RUs) in *CACNA1A*. While the pathological threshold has been considered to be 20 or 21 RUs, the lower limit remains controversial. This study aimed to clarify the pathological significance of RUs in SCA6, including the role of opposite alleles (OAs). [Methods] We included 2768 cases in which spinocerebellar degeneration was suspected, and genetic testing for SCA6 was performed. We analyzed the relationship between *CACNA1A* RUs and age at onset (AAO). Family history positivity rates were examined for different RUs of the expanded allele (EA). [Results] Family history positivity rates increased progressively above 19 RUs and plateaued at ≧23 RUs. Regression analysis of cases with ≧23 RUs showed that 96.20% of cases with ≧23 RUs, 90.67% of cases with 22 RUs, 91.15% of cases with 21 RUs, 61.54% of cases with 20 RUs, and 33.33% of cases with 19 RUs fell within the 95% prediction interval for AAO. However, no patients with ≦18 RUs were included. In the 21-22 RU group, OA significantly influenced AAO. For ≧23 RUs, no significant OA effect was observed. Cases with 19-20 RUs showed a higher prevalence of OA with ≧19 RUs compared to cases with ≧23 RUs. [Conclusions] The 19-20 RU range represents an intermediate zone where OA may influence disease likelihood. For 21-22 RUs, OA significantly affects AAO, indicating a complex interplay between EA and OA. ≧23 RUs appear sufficient to cause disease onset within a typical lifespan, regardless of OA.

AP-02-4 Brain volume in the prodromal stage of Parkinson's disease

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【目的】パーキンソン病（PD）の早期診断と疾患修飾薬の開発のために、運動症状出現前の臨床病期の早期発見が注目されている。prodromal PD（pPD）と脳容積の関係を明らかにすることでPD発症の病態解明および早期発見へ貢献することを目的とする。【方法】前向きコホートであるYahaba Active Aging and Healthy Brain（YAHABA）studyに登録された65歳以上の地域在住高齢者962名を登録した。MDS（International Parkinson and Movement Disorder Society）のpPD基準に基づいた自記式質問票を用いた。MDSの研究運営方針宣言に従いpPD probability 0.3以上をpPDと定義した。T1強調画像はSynthSegとFree-Surfer（ver7.4）を用いてスキャンした。頭蓋内容積に対する各関心領域の比率をpPD群と対照群で単変量解析した。【結果】最終的に691人（男性313人、女性378人）から質問票への回答とMRI画像を得ることができた。参加者の平均年齢は72.6±6.1歳（65〜93歳）であった。性別では有意差はなかったが（p=0.453）、年齢では有意差があった（p=0.013）。半球別の頭蓋内容積比は、pPD群では小脳白質（p＝0.013、0.043）、小脳皮質（p＝0.000、0.004）、淡蒼球（p＝0.026、0.016）、側頭極（p＝0.045、0.025）の両側で有意に低かった。側脳室はpPD群で高かった（p=0.003, 0.007）。視床、尾状核、被殻については、pPD群と対照群との間に差はなかった。両側合わせた頭蓋内体積比では、pPD群では全脳（p=0.015）、灰白質（p=0.014）、側頭（p=0.017）、海馬（p=0.030）、扁桃体（p=0.025）、楔状突起（p=0.015）、側頭極（p=0.006）が有意に低かった。第三脳室（p=0.024）と脳脊髄液（p=0.013）は高かった。【結論】灰白質全体、側頭葉、小脳、海馬、扁桃体の萎縮と脳室の拡大が観察された。pPDではすでに形態学的変化が始まっている可能性が示唆され、これらの結果は、疾患修飾薬の開発やPDの発症を明らかにするための早期発見における画像診断技術の重要性を支持するものである。

AP-02-5 PET imaging of AMPA receptors on Angelman syndrome patients

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【目的】AMPA受容体は興奮性シナプス伝達を担う重要な分子の1つであり、記憶・学習に伴う神経細胞同士の機能的な接続を強化・弱化する（Derkach et al., 2007）。AMPA受容体はUBE3Aを原因遺伝子とするAngelman症候群の病態に関与すると考えられている（Greer et al., 2010; Kühnle et al., 2013; Mabb et al., 2014; Pastuzyn & Shepherd, 2017）。近年、ヒト生体脳で神経細胞表面におけるAMPA受容体の分布・密度を定量できるPETプローブ[^{11}C]K-2が開発された（Miyazaki et al., 2020; Arisawa et al., 2020）。本研究では、Angelman症候群患者で、[^{11}C]K-2を用いたPETイメージング（AMPA-PET）を行い、AMPA受容体密度分布・密度の特性を明らかにすることを目的とした。【方法】遺伝的にAngelman症候群と診断された患者（n = 10）に対し、代諾者から文書同意を得たのち、麻酔鎮静下でAMPA-PETを行い、年齢対照健常成人画像（n = 33）と脳内のAMPA受容体の分布・密度を比較した。【結果】Angelman症候群患者群は年齢対照健常成人群と比較して、小脳及び尾状核でのみ著明なAMPA受容体密度低下を認めたが、大脳皮質の広範な領域でAMPA受容体密度の低下は認めなかった。【結論】原因遺伝子としてUBE3Aが特定されている本疾患では脳全体でAMPA受容体発現変化が予想された。しかし、AMPA-PET画像からはAngelman症候群において脳領域特異的なAMPA受容体発現密度変化が生じており、病態には遺伝子異常だけでなく発達段階における回路変化も関わっていると推察された。

AP-02-6 A novel heterozygous STUB1 mutation causes facial onset sensory and motor neuronopathy (FOSMN)

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[Objective] Facial-onset sensory and motor neuronopathy (FOSMN) is accepted as a type of TDP-43 proteinopathy. This study reports an autopsy case of FOSMN with pathological features distinct from TDP-43 proteinopathy. [Methods] A pathological diagnosis was made in the pathology department, and additional immunohistological analyses were performed on brain tissues. Whole exome sequencing was conducted using the patient's blood DNA. The identified gene mutation was introduced into HEK293 cells for functional evaluation. [Results] A 59-year-old woman presented with a 7-year history of left-sided facial numbness. Over the following years, she developed progressive facial hypoesthesia, facial muscle atrophy, and dysarthria, which were later accompanied by cerebellar ataxia affecting the left extremities. A diagnosis of FOSMN was rendered. Her condition continued to worsen, with progressive respiratory muscle involvement, ultimately resulting in death from respiratory failure at the age of 61. Immunohistological analysis of the autopsied brain revealed a reduction in the number of neurons in the sensory-motor nuclei of the brainstem and a decrease in cerebellar Purkinje cells, without ubiquitin-positive inclusions. Genetic analysis identified a novel heterozygous T110C mutation in the *STUB1* gene. Functional assays using HEK293 cells demonstrated that this mutation impaired the interaction between STUB1 and HSC70. [Conclusions] The T110C mutation in *STUB1* impairs its interaction with HSC70, potentially disrupting the ubiquitin-proteasome system and leading to neuronal cell death.

AP-02-7 Effect of the Midnolin gene on the Parkinson's disease phenotype: a study in Yamagata, Japan

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【目的】Midnolin（*MIDN*）遺伝子の欠失はParkinson病（PD）のリスク因子とされ，山形県の孤発性PD患者の10.5%，英国では6.55%に見られた．山形で修正オッズ比24.6，英国でオッズ比4.35であった．*MIDN*遺伝子の欠失とPDの表現型についての知見は乏しく，これを検討した．【方法】2022年10月から2024年8月に山形県内の9施設に通院あるいは入院したPD患者で，MDS診断基準で「臨床的に確実なパーキンソン病」あるいは「臨床的にほぼ確実なパーキンソン病」を満たす157症例を対象とし，発症年齢，評価時年齢，罹病期間，運動および非運動症状，脳形態画像，核医学検査，治療内容，MDS-UPDRSスコア，*MIDN*遺伝子などを評価した．遺伝子解析はdigital PCRを用い，Zinc finger protein 266（ZNF266）をコントロールとしてMIDN/ZNF266が0.725以下を欠失，1.5以上を増幅とした．統計はt検定，重回帰分析を行った．【結果】*MIDN*増幅の2例，欠損値のある6例は解析から除外した．対象を*MIDN*欠失群18例，*MIDN*正常群131例の2群に分けた．*MIDN*欠失群でPD家族歴は見られなかった．t検定でMDS-UPDRS Part III総スコアは*MIDN*欠失群39.7±15.9で，*MIDN*正常群31.6±14.3と比較し有意に高値であった（p=0.029）．MDS-UPDRS part III総スコアを目的変数，評価時年齢，罹病期間，L-ドパ換算用量相当量，性別，*MIDN*遺伝子（正常0，欠失1のダミー変数として解析した）を説明変数として，重回帰分析を行った．MDS-UPDRS Part III総スコアに対して評価時年齢（β=0.276，p<0.001），罹病期間（β=0.220，p=0.006），*MIDN* 遺伝子（β=0.181，p=0.019）が有意に関連した（p<0.001）．【結論】MDS-UPDRS Part III総スコアは年齢や罹病期間に加えて*MIDN* 遺伝子の欠失が関与している可能性があり，*MIDN*遺伝子のコピー数を測定することは有用である．また，*MIDN*遺伝子の欠失は発症のみならず，運動症状進行に関与している可能性が示唆された．

APe-01-1 The genetic architecture of the human hypothalamus and its involvement in neuropsychiatric disorders

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Objective: The objective of this study was to uncover the genetic architecture of the human hypothalamus and its involvement in neuropsychiatric behaviours and disorders. **Methods**: We conducted multivariate genome-wide association studies (GWAS) on hypothalamic imaging data from 32,956 individuals. An automated segmentation tool based on deep convolutional neural networks was used to acquire the largest imaging samples of the hypothalamus and its 6 subregions. **Results**: The study identified 23 significant genomic loci associated with the hypothalamus, with functional enrichment for genes involved in intracellular trafficking systems and metabolic processes of steroid-related compounds. Substantial genetic associations were observed between the hypothalamus and limbic system structures, as well as neuropsychiatric traits including chronotype, risky behaviour, cognition, satiety, and autonomic activity. Genetic overlaps between the hypothalamus and neuropsychiatric disorders were recognized for schizophrenia, Parkinson's disease, stroke, etc. The strongest signal in the primary GWAS, the *ADAMTS8* locus, was replicated in three independent datasets (N = 1,685-4,321) and was strengthened after meta-analysis. Mendelian randomization suggested a causal effect of lower ADAMTS8 expression on larger hypothalamic volumes. **Conclusions**: This study advances our understanding of the complex structure-function relationships of the hypothalamus. The findings highlight the potential of ADAMTS8 as a key genetic factor influencing hypothalamic structures.

APe-01-2 Unveiling the tDCS effects on premotor cortex and primary motor cortex and the role of EEG markers

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Objective: Combining transcranial direct current stimulation (tDCS) with mirror therapy (MT) has shown promise for stroke rehabilitation. However, the effectiveness of tDCS targeting different brain regions (premotor cortex, PMC vs. primary motor cortex, M1) is unclear. This presentation evaluates the effects of tDCS-MT on motor function in chronic stroke patients and explores underlying therapeutic mechanism by correlation alpha oscillations with clinical outcomes. **Methods**: In a double-blinded, randomized controlled trial, 36 chronic stroke patients were assigned to PMC tDCS-MT, M1 tDCS-MT, or Sham tDCS-MT. They received 90-minute sessions, 3-5 days/week, totaling 20 sessions. tDCS was applied using a StarStim device at 2 mA for 20 minutes. Motor function was assessed pre-treatment, post-treatment, and 3 months later. EEG was recorded during a simple directional task. **Results**: Post-treatment, significant differences were found in Wolf Motor Function Test-time (p=0.02) and alpha power (p=0.02). Sustained improvements were seen in Fugl-Meyer upper extremity scores (p=0.04), especially in the PMC group (p<0.01). Alpha power in the temporal lobes correlated with FMA-UE scores in the PMC group (ρ= 0.65, p=0.04). Alpha power in central and temporal regions predicted FMA-UE improvement at 3 months (R^2 = 0.23, p=0.03). **Conclusions**: tDCS particularly applied to the PMC, enhances upper extremity recovery in stroke patients. Temporal alpha power was strongly linked to motor recovery, suggesting it may play a role in inhibiting non-motor information from the temporal lobe.

APe-01-3 Identifying causal genes for stroke via integrating proteome and transcriptome from brain and blood

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Objective: Genome-wide association studies (GWAS) have revealed numerous loci associated with stroke. However, the underlying mechanisms at these loci in the pathogenesis of stroke and effective stroke drug targets are elusive. Therefore, we aimed to identify causal genes in the pathogenesis of stroke and its subtypes. **Methods:** By integrating the brain and blood protein and expression quantitative trait loci (QTL) data with GWAS summary data for stroke and its subtypes, we integrated proteome-wide association study (PWAS), transcriptome-wide association study (TWAS), Mendelian randomization (MR), and Bayesian colocalization analysis to prioritize genes that contribute to stroke and its subtypes risk via affecting their expression and protein abundance in brain and blood. **Results:** Our integrative analysis revealed that *ICA1L* was associated with small-vessel stroke (SVS), according to robust evidence at both protein and transcriptional levels based on brain-derived data. We also identified *NBEAL1* that was causally related to SVS via its cis-regulated brain expression level. In blood, we identified 5 candidate genes (*MMP12, SCARF1, ABO, F11*, and *CKAP2*) that had causal relationships with stroke and stroke subtypes. **Conclusions:** Together, via using an integrative analysis to deal with multidimensional data, we prioritized causal genes in the pathogenesis of SVS, which offered hints for future biological studies as well as prioritize potential drug targets.

APe-01-4 Intermittent Theta-Burst Stimulation Effects on Cognition and Glymphatic Activity in MCI and AD

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Objective: To evaluate the effects of intermittent theta-burst stimulation (iTBS) on cognitive function and glymphatic activity in individuals with amnestic mild cognitive impairment (MCI) or very mild Alzheimer's disease (AD). **Methods:** In this double-blind, randomized, sham-controlled trial, 52 participants underwent 10 iTBS sessions over two weeks, targeting the left dorsolateral prefrontal cortex. Cognitive and glymphatic assessments using diffusion tensor image analysis along the perivascular space (DTI-ALPS) were conducted at baseline, week 2, and week 6. Of the 52 participants, 28 received active iTBS, while 24 underwent sham stimulation before transitioning to active iTBS. **Results:** Significant cognitive improvements were observed at week 6 in the iTBS group, indicating delayed cognitive enhancement. However, no immediate changes in cognition or glymphatic system activity (measured by the ALPS index) were found. No adverse events were reported. **Conclusions:** These findings suggest that iTBS may lead to delayed cognitive enhancement in individuals with amnestic MCI and very mild AD, while its impact on glymphatic activity remains uncertain and warrants further investigation. **Trial registration:** Clinicaltrials.gov (NCT04555941)

APe-01-5 Role of Nurr1-miR-30e-NLRP3 axis in inflammation-mediated neurodegeneration of Parkinson's disease

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Objective Nuclear receptor related-1 (Nurr1), a ligand-activated transcription factor, is considered a potential susceptibility gene for Parkinson's disease (PD). The present study is to investigated the molecular mechanism of Nurr1 in PD-related inflammation. **Methods** Nurr1-dependent miRNA and its target gene were identified through the miRNA-sequencing, bioinformatics and verification in PBMC from a cohort of 450 individuals. The involvement of Nurr1-related pathway in PD was investigated by developing a mouse model conditionally knocking out Nurr1 in Cd11b-expressing cells ($Nurr1^{cKO}$). The interactions among Nurr1-related pathway were confirmed by chromatin immunoprecipitation and dual-luciferase reporter assays. **Results** (1) We identified a significant change of a Nurr1-dependent miRNA miR-30e in PD patients compared to healthy controls (HC). PD patients exhibited an elevated plasma IL-1β level and an increased expression of NLRP3 in PBMC as compared to HC. (2) Investigations in $Nurr1^{cKO}$ mice unveiled significant dopaminergic neurodegeneration. Nurr1 deficiency triggered the activation of NLRP3 inflammasome, resulting in increased IL-1β secretion. (3) MiR-30e level was significantly decreased in microglia of $Nurr1^{cKO}$ mice when compared to the controls. (4) *In vitro* experiments demonstrated that miR-30e specifically targeted NLRP3. In Nurr1-knockdown microglia, NLRP3 expression was upregulated via miR-30e. **Conclusions** Our findings highlight the involvement of Nurr1-miR-30e-NLRP3 axis in the inflammation-mediated neurodegeneration in PD.

APe-01-6 Metabolomics in Parkinson's Disease: From Biomarkers to Pathogenic Mechanisms

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Objectives: Parkinson's disease (PD) is a common neurodegenerative disease, with unknown causes and no definitive diagnostic markers. Emerging evidence indicated that metabolic dysregulations might precede and contribute to neurodegeneration. This study mainly introduced the use of metabolomics to discover reliable biomarkers and elucidate the pathogenesis of PD. **Methods:** Plasma from PD patients, healthy controls and PD-unrelated neurological disease controls (n=460) were collected for metabolomics analysis. Multiple statistical analyses were performed to identify the most promising metabolite panel for the discrimination of PD. Besides, by transplanting the fecal microbiota from PD patients into mice, we further investigated the impacts of fecal delivery on the fecal microbiota, metabolism and pathophysiology in recipient mice. **Results:** We identified a metabolite panel (FFA 10:0, FFA 12:0, indolelactic acid, phenylacetyl-glutamine) that effectively discriminates between PD and controls. The fecal microbiota from PD patients increased intestinal inflammation, intensified microglia and astrocyte activation, abnormal deposition of α-Synuclein, and dopaminergic neuronal loss in the brains of A53T mice. Besides, we found that transplantation of fecal microbiota from PD patients altered both the composition of the gut microbiota and the fecal metabolic profile of the recipient mice. **Conclusions:** This study offers novel approaches for the clinical diagnosis of PD and highlights the pivotal role of gut microbiome dysbiosis and its associated dysfunctions in the pathogenesis of PD.

APe-01-7 An Atlas of Plasma Metabolites Uncovers Neurological Disease Pathways and Early Metabolic Signatures

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Objective: This study aims to unveil an atlas of plasma metabolites correlated with neurological diseases, quantify the metabolomic shifts preceding disease onset, and clarify potential causal relationships between metabolites and diseases. Methods: We present an extensive atlas that includes 313 plasma metabolites linked to 50 neurological disorders, scrutinized across a cohort of 274,241 individuals. A nested case-control study was conducted to delineate the temporal trajectories of neurological diseases 15 years before onset. Utilizing whole-genome sequencing data from our study cohort, we conducted Mendelian randomization to elucidate potential causal relationships between metabolites and neurological disease endpoints from FinnGen. Results: Our atlas revealed 1,701 associations between metabolites and neurological diseases. We identified that over half (57.5%) of the metabolite changes occurred more than a decade before disease onset. Diseases were grouped into 13 clusters based on their temporal trajectories. Notably, creatinine, glucose/sphingomyelins, and linoleic acid emerged as key markers in predicting neurological diseases. Through Mendelian randomization, 30 significant metabolite-disease associations were pinpointed, with particular emphasis on the causal role of eight metabolites on all-cause dementia. Conclusions: This atlas provides critical insights into the pathophysiology, early diagnosis, prediction, and therapeutic strategies for neurological diseases. It serves as a comprehensive resource for the implementation of precision medicine in clinical settings.