AO-01 FUS suppresses RAN translation and neurodegeneration as an RNA chaperone in C9orf72-linked ALS/FTD

Yuzo Fujita1, Morio Ueyama2, Taro Ishiguro3, Daiako Ozawa1, Hayato Inoue4, Asako Murata5, Eiichi Tokuda6, Yoshiaki Furukawa1, Toshiki Mizuno7, Hideki Shimizu8, Kazuhiro Wada9, Kazuyuki Ishikawa9, Osamu Onodera10, Kazuhiro Nakatani11, Hideki Taguchi12, Yoshitaka Naga13

1 Department of Neurology, Keio University Faculty of Medicine, Japan, 2 Department of Neurology, Keto Prefectural Central Hospital, 3 Department of Neurology, Teikyo University School of Medicine, 4 Department of Degenerative Neurological Diseases, National Institute of Neuroscience, 5 Center for Neurology and Psychiatry, 6 Department of Neurology and Neurological Research Center, 7 Kyoto University Graduate School of Medicine, 8 Tokyo University of Life Science, 9 Tokyo Institute of Technology, 10 Department of Regenerative Research, The Institute of Scientific and Industrial Research, 11 Department of Chemical, Kyusyu University, 12 Department of Neurology, Osaka University Graduate School of Medicine, 13 Department of Neurology, Clinical Neuroscience Branch, Brain Research Institute, Nagoya University, Japan

Objective: Abnormal expansion of GGGGCC (G_4C_2) repeat sequence in the noncoding region of the C9orf72 gene is the most common cause of familial amyotrophic lateral sclerosis and frontotemporal lobar dementia (i.e. ALS-FTD). The transcribed G_4C_2 repeat RNA accumulates as RNA foci, queuing various RNA-binding proteins (RBPs). Moreover, the G_4C_2 repeat RNA is also translated into dipeptide repeat proteins (DRPs) by nonsense-mediated unannotated non-AUG (nAUG) translation, which play critical roles in the pathogenesis of ALS-FTD. Herein, we hypothesized that regulating RAN translation may be a potential strategy for C9-ALS/FTD. We selected 15 dipeptide repeat proteins, which showed strong enrichment in our ALS-FTD Drosophila models expressing the expanded G_4C_2 repeat sequence, which showed degenerative phenotype and pathological features including DPR accumulation. We next performed the genetic screening for DRPs targeting G_4C_2 RNA and found that the AML1/MTF4 (RAN) suppressor in tumorigenesis attenuates RAN translation, providing therapeutic insights for ALS-FTD and other RANopathies.

AO-03 A centrally acting connexin hemichannel blocker attenuates multiple system atrophy-coriell-berry type

Masaya Harada1,2, Katsushi Masaki1, Dai Matsue3, Hiroshi Yamaguchi4, Yuji Nishimura5, Eizi Odedomi6, Eigo Tanaka7, Tsutomu Tanaka7, Ryoo Yamashita8, Hideyuki Takeuchi9, Takayuki Taninuki9, Noriko Isobe10, Jun-ichi Kira11

1 Department of Neurology, Neurological Institute, Graduate School of Medical Sciences, Kyushu University, Japan, 2 Division of Neurology, Neurology and Rheumatology, Department of Medicine, Kurume University School of Medicine, Japan, 3 Department of Physical Medicine and Rehabilitation, Rivera Health Science University, Fukashima, Japan, 4 Sumitomo Pharmaceuticals Co., Ltd., Osaka, Japan, 5 Department of Medicine, Medical Course, Neurology and Stroke Medicine Graduate School of Medicine Program, Yokohama City University Medical School, Japan, 6 Graduate School of Life Science and Technology, Tokyo Institute of Technology, Japan, 7 University of Washington School of Medicine, USA, 8 Department of Neurology, Brain and Nerve Center, Fukusha Central Hospital, Japan

Objectives: Multiple system atrophy (MSA) is an intractable neurodegenerative disease characterized by accumulation of dysfunctional α-synuclein in the striatum, progressive autonomic failure, and cerebellar ataxia. Recently, G-quadruplex-targeting RBPs, including G_4C_2 repeat sequence binders, showed promising results in an MSA-C model. In this study, we aimed to validate the potential therapeutic effects of multiple system atrophy-coriell-berry type (MSA-C) in vivo and in vitro models using a centrally acting connexin hemichannel blocker, AO-01-5.

AO-01-5 Development of novel neuropathic pain treatments targeting SEMA-Plexin pathway

Sato Yoshidomi1, Takayuki Fuji1, Hiroki Honda2, Kaoru Kashu3, Yukino Miyachi4, Hidenori Ogata5, Ryoo Yamashita6, Toru Iwaki7, Noriko Isobe8

1 Department of Neurology, Neurological Institute, Graduate School of Medical Sciences, Kyushu University, Japan

Objective: Semaphorins (SEMA) and their receptors, Plexins, are expressed in pain-conducting neurons of dorsal root ganglia (DRG). However, the role of these molecules in neuropathic pain (NP) has not been clarified. Herein, we aimed to clarify the association between NP and SEMA-Plexin pathway. Methodology: We quantified serum SEMA3A, 3E, 3A, 4A, 4D, and 7A in 45 patients with NP and 17 age- and sex-matched healthy controls (HCs) by enzyme-linked immunosorbent assay (ELISA). SEMA expression in DRG and peripheral nerve (PN) tissues of 4 autopsyed NP patients and 2 controls as well as co-treatment with SEMA3E and anti-SEMA3E blocking antibody induced neurite outgrowth. [Conclusions] SEMA3E/Plexin D1 pathway was revealed to be a susceptibility pathway of NP and the blockade of SEMA3E could be a novel NP treatment.

AO-01-6 Long-read sequencing reveals allelic heterogeneity of repeat expansion in OPDM

Nobuyuki Far1,2, Satoru Nochiguchi3, Masashi Ogawara4, Artisotshi Iida1, Shinichiro Hayashi5, Ichizo Nishino6

1 Department of Neurology and Stroke Medicine, Graduate School of Medicine, University of Tokyo, Japan, 2 Department of Neurology, Nara Medical University, Japan, 3 Medical Genome Center, National Center of Neurology and Psychiatry, Japan

Objective: The pathogenesis of non-coding repeat expansion disorders is not fully understood, although toxicities of the expanded RNAs or repeat-associated non-AUG (RAN) translated proteins have been suggested. To elucidate the pathomechanism of OPDM, we aimed to perform a long-read sequencing of individual samples to compare the allelic heterogeneity of C9orf72 GGGGCC repeats within the expanded alleles in 5UTR of LRPI, GIPC1, NOTCH2NL and KLF11, using long-read sequencing (LRS) at a single molecular level. [Methods] LRPSR/Casp-Targeted LRs were performed on RRMS samples by cutting with designed guide RNAs to isolate C9-exons expanded in the above 4 genes. Basecalling and sequence alignment were carried on GapPy and Minimap2. Genetically confirmed 8 OPDM patients (LRPSR > 40, GIPC1 n=4, NOTCH2NL n=5) were analyzed. [Results] We successfully got a certain number of reads regardless of expansion (17±14 / sample) with 100% of sensitivity and specificity. The number of expanded reads in affected genes was about half of the total reads (47±13%), indicating heterozygosity in OPDM. Interestingly, even within the individual patient, the repeat length differed from allele to allele. Also, the expanded reads frequently had insertions and deletions, indicating that the reading frame in RAN-translated product would not be maintained. [Conclusion] We have established a diagnostical method for OPDM with high accuracy. The heterogeneity in the size and composition of expanded alleles suggests pathomechanism of OPDM is not so simple as toxicities of the homogenous expanded RNAs or RAN translation product a simple cause of OPDM.

AO-01-7 Tim3 critically regulates microglial function and accelerates Alzheimer’s disease pathology

Kimitoshi Kimura1, Aghshwarya Subramanian2, Zhouran Yin3, Oleg Butovsky3,4, Vijay Kuchroo1

1 Ann Romney Center for Neurologic Diseases, Brigham and Women’s Hospital and Harvard Medical School, USA, 2 Evergreen Center for Integrative Neurology, Brigham and Women’s Hospital, USA

Objective: Microglia (MG) get activated (M1/MG2 phenotype) in Alzheimer’s disease (AD) and phagocytose / clear neurotoxic amyloid beta (Aβ). Haverz encoding a receptor known for its role in neuroinflammation and phagocytosis has been recently found as a susceptibility gene in AD. We aim to find its as-yet-unknown role in AD. [Methods] MG-specific Tim3-deficient (Haverz+/−) mice were crossed to an AD model, 3XFAD (n=5). Behavior test, immunohistochemistry, and single cell RNA sequencing were performed. Intracellular mechanism was further explored with molecular analyses including IP-MS screening. [Results] Tim3 expression was strikingly high in MG. Tim3-deficient MG showed enhanced neurodegenerative capacity in vitro and ex vivo. The increased expression of Tim3 correlated with decreased expression of TGF-β signaling-deficient MG. Consistently, Haverz+/− Xfox3 deficient mice showed no cognitive impairment, with less Aβ plaque load (525% reduction) and less neuronal death. [Conclusion] Aβ dependent microglia activation was found in Tim3-deficient MG subset. IP-MS screening and confirmatory IP-WB showed that Tim3 binds Smad2, indicating heterozygosity in OPDM. Interestingly, even within the individual patient, the repeat length differed from allele to allele. Also, the expanded reads frequently had insertions and deletions, indicating that the reading frame in RAN-translated product would not be maintained. [Conclusion] We have established a diagnostical method for OPDM with high accuracy. The heterogeneity in the size and composition of expanded alleles suggests pathomechanism of OPDM is not so simple as toxicities of the homogenous expanded RNAs or RAN translation product a simple cause of OPDM.

AO-01-8 Progressive MS patients-derived gut bacteria induce neuronal inflammation via flagella-Th17 axis

Daiki Takewaki1, Hiroaki Masukawa2, Yuya Kiguchi3, Wakiro Sato4, Wataru Sud4, Takashi Yamamura5

1 National Center of Neurology and Psychiatry, Department of Immunology, Japan, 2 RIKEN Laboratory for Meta-Brain Sciences, Japan

Objective: To identify the specific gut bacterial species associated with multiple sclerosis (MS) progression from RRMS to SPMS and reveal the mechanism which exacerbates neuronal inflammation. [Methods/Results] We analyzed the composition of microbial communities between 62 RRMS patients, and 15 SPMS patients based on the metagenomic sequencing data. We identified bacteria X whose abundance was significantly enriched in SPMS and positively correlated with clinical scores and rotarod. Then, we isolated bacteria X from the fecal samples of SPMS and PRMS patients and conducted in vivo analysis to verify the functional significance of them. Mono-culture of germ-free mice with SPMS-derived bacteria X (n=13) caused severe neurological disability (p=0.00067) after immunization with significantly increased T helper 17 (Th17) cells in the central nervous system and large intestine lamina propia compared with germ free mice (n=13) or RRMS-derived bacteria X mono-cultured mice (n=13). In the genome comparison among various bacteria X strains, the genome of SPMS-derived bacteria X specifically included flagellar genes. The presence of flagella in SPMS-derived bacteria X was confirmed by electron microscopic images and in vitro co-culture experiments. A specific type of flagella is reported to be a selective agonist of toll-like receptor 5 and potentially induces Th17 cells via the secretion of interleukin-6. In conclusion, the functional assessment of bacterial X enriched in the gut of SPMS patients might exacerbate neuronal inflammation via flagella-Th17 axis.
【目的】慢性炎症性脱髄性多発神経炎（CIDP）の発症機序や病態は依然として不明である。我々は、CIDP患者の血清で検出したサブタイプ特有のセリニン結合型糖鎖、酸性複合型糖鎖の変動を評価することで、これらの変動が初回副腎皮質ホルモン治療（IVIg）に対する反応性を予測する新たなバイオマーカーとなる可能性を考察した。近藤葉子、内村卓也、今野久美子

【結果】個別の糖鎖では、α2,3結合型シアル酸含有糖鎖の値を用いることで、IVIg治療中の反応性を経時的に反映する可能性が示唆された。また、α2,6結合型シアル酸含有糖鎖の値は、IVIg治療中で有意に変動しなかった。

【結論】典型CIDPではN結合型糖鎖および酸性複合型糖鎖量は健常者と比較し、有意に低下しており、個別の糖鎖では、α2,3結合型シアル酸含有糖鎖の値を用いることで、IVIg治療中の反応性を経時的に反映する可能性が示唆された。
AP-01-1 A new strategy for DMD exon skipping with RNA-DNA hetero-G4 structure inducing ASOs

Ryo Iwase, Taro Ishiguro, Juri Hasegawa, Rintaro Iwata Hara, Tetsuya Nagata, Takanori Yokota

Department of Neurology and Neurosceince, Tokyo Medical and Dental University, Japan

Objective: Duchenne muscular dystrophy (DMD) is a fatal X-linked disorder caused by nonsense or frameshift mutations in the DMD gene, resulting in a loss of normal dystrophin production. Therapies by antisense oligonucleotides (ASOs) have been developed and showed promising results in animal models and clinical trials. Recently, we identified a new mechanism of ASOs: ASOs mediated exon skipping and correcting a shift of the amino acid are the leading approach for restoring dystrophin expression. However, these therapies still have only limited effects in DMD patients. Our aim is to develop novel strategies for treating DMD by modulating the secondary RNA structure with ASOs. Herein, we report newly designed guanine-rich ASO (G-ASOs) for exon skipping, which introduce the formation of an RNA-DNA hetero-G4 quadruplex (G4) structure in pre-mRNA. These G4 structures inhibit RNA splicing by splicing enzyme and enhance exon skipping in vitro and in vivo. Methods: To determine whether G-ASO induce G4 in RNA template comprising G tracts, in vitro stop assay for RTase activity and TH binding assay for G4 structures were performed. In addition, we have newly developed a RFP-based reporter assay system to detect fluorescence only when skipping of mdx-type exon 23 is induced by ASOs. Finally, we evaluated the effects of exon skipping in the mdx mice treated with G-ASO by intramuscular injection.

Conclusion: We confirmed the exon 23 skipping by the formation of G4 and the restoration of dystrophin expression level with the administration of the G-ASOs. Our data highlight the potential for exon skipping using G-ASOs and allow us to propose a novel therapeutic approach for neuromuscular diseases.

AP-01-3 Igratimid blocks IL-6 production and TH17 migration in a progressive multiple sclerosis model

Satoshi Nagata, Ryo Yamasaki, Ezgi Ozdemir, Kaoru Kashu, Eriko Matsuo, Hiroo Yamaguchi, Mitsuji Watanabe, Katsushika Miura, Fumichi Kira and Tetsu Ishii

1 Department of Neurology, Neurological Institute, Graduate School of Medical Science of Aging, Aichi Medical University, Japan, 2 Department of Neurology, Faculty of Rehabilitation, Reiwa Health Science University, Fukuoka, Japan, 3 Department of Neurology, Neurological Institute, Graduate School of Medical Science of Aging, Aichi Medical University, Japan

Objective: We report a novel secondary progressive multiple sclerosis (SPMS) model experimental autoimmune encephalomyelitis (EAE) in splenectomized-spleen Gáf/Luda congenic knockout (Gáf/Luda) mice. As we reported the efficacy of gatifloxacin (GAT), an anti-bacterial drug, on acute EAE, we aimed to elucidate the effects of GAT on the SPMS model. Methods: Gáf/Luda mice were immunized with MOG35-55 to induce EAE. EAE was evaluated using clinical scores from 0-10 and was continuously evaluated until 70 days post immunization. We were treated in vitro stimulated mixed cell culture and measured cytokine levels in the culture supernatant after stimulation. Flow cytometric analyses of CNS tissues revealed that migrated Th17 cells were decreased by IGU. Results: We confirmed the protective effect of IGU by intramuscular injection.

Conclusion: IGU mitigates SPMS model severity by reducing the migration of Th17 cells and IL-6 production. IGU may be a potential therapeutic agent for SPMS.

AP-01-4 Vitamin B12 may inhibit the neurotoxicity of Amyloid beta oligomers and protect memory function

Atsushi Kimura, Toru Yasumoto, Yukiko Morii, Yutaro Momma, Tetsutsubo Nobuhara, Akikuni Futamura, Takashi Kuroda, Hideyoshi Kasai, Ryuta Kimmo, Sotaro Hida, David Temple, Mayumi Taniguchi, Yuki Kichi, Hisashi Shimada, Hidetomo Murakami, Kenjiro Ono

1 Showa University Clinical Research Institute for Clinical Pathology and Therapeutics, Japan, 2 Institute of Biomedical Research, National Institute, Japan, 3 Department of Internal Medicine, Division of Medicine, Showa University, Japan, 4 Department of Neurology, School of the University of California-Los Angeles, USA, 5 Department of Neurology, Los Angeles, CA, USA, 6 Showa University Pharmacological Research Center, Japan, 7 Department of Neurology and Neurology of Aging, Kanazawa University, Japan

Objective: Amyloid beta oligomers (AβO) play the primary role in Alzheimer’s disease (AD). Recently, we have reported that vitamin B12 (VB12) may present therapeutic potential for AD, however, its effect on AβO neurotoxicity is not well understood. We examined the effects of VB12 on the non-cytotoxic AβO, and investigate the protection of brain microstructures in AD.

Conclusion: We found that VB12 reduced AβO-induced cell injury by its strong antioxidant effect, suggesting that VB12 may be helpful for the protection of brain microstructures in AD.
AP-01-7  眠や異常がAMNに伴う脳の萎縮を示す

【目的】 副腎白質ジストロフィー(ALD)はABCD1遺伝子変異によるX連鎖性遺伝性疾患で、中枢神経系の萎縮をきたし、進行性の運動障害を呈する。本研究では、ALDの磁気共鳴断層像（MRI）と電気生理学的検査（ERG・ABR）を用いて、ALDの臨床像を調べ、ALDと皮質下の病変の関連性について検討した。

【方法】 2006年~2022年の診断例で、小脳・脳幹型ALDの臨床像を呈した症例を対象とした。MRI、ERG、ABR、EMG、LTEなどの検査を用いて症例の臨床像を評価した。さらに、HSCT施行例の経過観察期間を含む症例の臨床経過、検査所見、治療効果について、後ろ向きに検討を行った。

【結果】 症例は7例で、平均発症年齢29歳（18-39歳）、平均経過観察期間4.8年（1.1-6.8年）であった。2例がAMN、5例が小脳型であった。本症候群の成因は、もともと全対性の遺伝であり、(md)を含む症例では小さいが、現在は約200例に成長している。ALDの臨床像を調べた結果、HSCT施行例の予後は良好であった。ALDの臨床像を評価する上で、MRI、ERG、ABR、EMG、LTEなどの検査が有用であることが示された。

【結論】 小脳・脳幹型ALDの臨床像を呈する症例の臨床経過、検査所見、治療効果について、後ろ向きに検討を行った。ALDの臨床像を評価する上で、MRI、ERG、ABR、EMG、LTEなどの検査が有用であることが示された。
Genetical and clinical features in a cohort of Japanese patients with dystonia

○ Konoka Tachibana1, Ryosuke Miyamoto, Hiroyuki Morino1, Tatsuya Fukumoto, Shinichi Matsumoto1, Takahiro Megaki1, Kyoico Hoshino, Kotoro Asamuma2, Takashi Sakamoto, Ryuji Kaji1, Yuushin Izumi3, Japan Dystonia Consortium

1Department of Neurology, Tokushima University, Japan, 2Department of Medical Genetics, Tokushima University Graduate School of Biomedical Sciences, Japan, 3Department of Neurology, Osaka Neuropsychiatric Institute, Japan, 4Department of Neurology, Sakakibara Hakuho Hospital, Japan, 5Department of Pediatric Neurology, Segawa Memorial Neurological Clinic for Children, Japan, 6Department of Neurology, Toyohashi University of Health Sciences, Japan, 7Department of Neurology, National Center of Neurology and Psychiatry, Japan, 8National Hospital Organization Utano Hospital, Japan

【目的】 本邦におけるジストニアの遺伝的・臨床的特徴を明らかにする。【方法】 Japan Dystonia Consortiumで集積したデータ・サンプルのうち、ジストニアが主徴であり、かつエクソーム解析を行った414例（全て発端者）からなる部分コホートを解析した。エクソーム解析では、DYTナンバーを持つものと、NBIAなどのジストニアを主徴とする疾患の原因遺伝子に存在する病原性の高いバリエントを検索した。検索対象遺伝子: TOR1A, IFCA, TUBBA, GCH1, THAP1, MEI, PRRT2, SGC, ATP1A3, FK506, SUZLI, CEBH, ANOS1, OAR, KCTD7, COX3, KMT2B, VPS16, AOPEP2, VPS1, TIL, ADCT, CN2, AUBP, MDC1, MEH, ORC2L, ATX, TIMMA, KAFB17, REPS1, CRAT, COASTY, CHIBR1, TUL, PANK2, PLAS6, WHSC1L1【結果】ジストニアの罹患部位は、focal:169例、segmental:58例、multifocal:10例、hemidystonia:10例、generalized:125例、unknown/unspecified:27例であった。またこのことから、ジストニアは遺伝子異常を含む、多様な表現型をもつ疾患であることが示唆された。【結論】 今回解析した部分コホートの大部分は、臨床情報からターゲットシークエンスを行ったが診断が確定しなかった例である。GCH1, PRRT2, SGC, ATP1A3, ANOS1, OAR, CN2, MEH, AREP2, MIT, AUBP, TIL, ADCT, CN2, AUBP, MDC1, MEH, ORC2L, ATX, TIMMA, KAFB17, REPS1, CRAT, COASTY, CHIBR1, TUL, PANK2, PLAS6, WHSC1L1異常は、ジストニアの原因遺伝子を示すものとされる。
Amelioration of HD-associated Phenotypes by Chemical Interference of SUPT4H/SUPT5H Complex Formation

Yun-yun Wu, Ning Deng, Yanan Feng, Wen-chih Huich, Jen-shin Song, Yu-shuian Lin, Ya-hsien Tseng, Wan-jhu Liu, Yi-fan Chu, Yu-cheng Lin, Ein-cheng Chang, Chia-yung Liu, Shih-yi Sheu, Ming-tsan Su, Hung-chih Kuo, Stanley N. Cohen, Tao-hao Cheng

Institute of Biochemistry and Molecular Biology, National Yang Ming Chiao Tung University, Taipei, Taiwan, Taiwan International Graduate Program in Molecular Medicine, National Yang Ming Chiao Tung University and Academia Sinica, Taipei, Taiwan, Department of Genetics, Stanford University School of Medicine, Stanford, CA, USA, Institute of Biotechnology and Pharmaceutical Research, National Health Research Institutes, Zhunan, Taiwan, Department of Life Science and Institute of Genome Sciences, National Yang Ming Chiao Tung University, Taipei, Taiwan, Institute of Neuroinformatics, National Yang Ming Chiao Tung University, Taipei, Taiwan, Department of Life Science, National Taiwan Normal University, Taipei, Taiwan, Institute of Cellular and Organismic Biology, Academia Sinica, Taipei, Taiwan, Institute for Brain Research Center, National Yang Ming Chiao Tung University, Taipei, Taiwan

Objective: Huntington’s disease is an autosomal dominant neurodegenerative disorder caused by CAG repeat expansion in the coding sequence of huntingtin gene. As monogenic disorder, the abundance of mutant gene product is the primary determinant for the onset and progression of HD. Accumulated evidence also suggest that mutant HTT suppression could mitigate or prevent the HD pathological development. Our earlier studies showed that SUPT4H/SUPT5H protein complex is required for RNA polymerase II transcribing over DNA region containing a long stretch of CAG repeats. Also, genetic knockdown of SUPT4H results in a decrease of mHTT expression and an alleviation of motor function deficits in a HD mouse model. Using two independent cell-based reporter assays, we have identified a nucleoside compound enabling to interfere with SUPT4H/SUPT5H complex formation of SUPT4H/SUPT5H.

Method: We demonstrated the compound can inhibit the expression of mHTT gene in a variety of HD cultured cell models, including proliferative murine striatal neuronal cells and terminally differentiated GABAergic neurons. On top of this, in GABAergic neurons, an increased sensitivity to oxidative stress caused by mHTT is reversed by the nucleoside compound. Moreover, alleviation of HD neurodegenerative phenotypes is observed in a Drosophila model of HD. Our findings suggest that the SUPT4H/SUPT5H protein complex is a potential therapeutic target to lower mutant HTT expression and prevent HD progression.

Results: We demonstrated the compound can inhibit the expression of mHTT gene in a variety of HD cultured cell models, including proliferative murine striatal neuronal cells and terminally differentiated GABAergic neurons. On top of this, in GABAergic neurons, an increased sensitivity to oxidative stress caused by mHTT is reversed by the nucleoside compound. Moreover, alleviation of HD neurodegenerative phenotypes is observed in a Drosophila model of HD. Our findings suggest that the SUPT4H/SUPT5H protein complex is a potential therapeutic target to lower mutant HTT expression and prevent HD progression.

Conclusion: Our findings suggest that the SUPT4H/SUPT5H protein complex is a potential therapeutic target to lower mutant HTT expression and prevent HD progression.
Objective: Autosomal dominant cerebral arteriopathy with subcortical infarcts and leukoencephalopathy (CADASIL) is an inherited cerebral small vessel disease caused by Notch3 mutation. Though hyperintensities trisecting the pons lead to the 'Mercedes-Benz' sign (MBs) and a quadrisection of the pons can lead to a 'hot cross bun' sign (HCBs). We explored the expression of HCBs and MBs in CADASIL and its relationship with the ischemic damage of the middle cerebellar peduncle (MCP). Materials and methods: The clinical data of 106 patients with CADASIL confirmed by genetic examination were collected. All patients underwent head MRI. T1 mean, axial T2 and 3D T2 flair were performed on the pons. Diffusion tensor image (DTI) fiber tracking was performed in 18 CADASIL patients and 10 normal controls. Results: MRI of 106 patients showed 12 cases had bilateral MCP lesion and among them, 2 cases had HCBs and 2 cases had Mercedes-Benz sign. The average age of onset of patients with bilateral MCP lesions was 43 years. The median course of disease at the time of MRI examination was 4.5 years. The main clinical manifestations included paralysis, vertigo, neuropsychological disorder, gait disorder and bulbar symptoms. DTI results showed that the mean, radial and axial diffusion ratio of MCP in patients with MCP damage were significantly higher than those in normal controls. Conclusion: Our study confirms for the first time that vascular HCBs and MBs can occur in cerebral small vessel disease, and further confirms that the ischemic damage of bilateral MCP is related to its formation.