Literature Review: Wild Card

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Disclosures and Goals

• Disclosures: None

• Goals:
  • new and interesting publications, that did not overlap with the other basic science topics were reviewed and the focus was decided to be genetics and mitochondria, inflammation and immunity, and wild cards
Genetics and Mitochondria

• Take Home Messages

• Are there risk alleles for cognitive dysfunction in PSP?
  • Still not sure, but the study design is a bit flawed

• Recessive mutations in the mitochondrial quinone oxidoreductase may cause optic atrophy but also may cause extensive neurologic consequences that depend on the specific mutation

• Dominant mutations in DNM1L may cause isolated optic atrophy ---
  • This is interesting because there is increased mitochondrial fusion, in contrast to excess mitochondrial fission seen in OPA1 mutations

• Mitochondrial dysfunction in oligodendrocytes may enhance demyelination in experimental autoimmune encephalomyelitis (EAE)
  • May mimic chronic or progressive demyelination as a new animal model
Genetic influences on cognition in progressive supranuclear palsy

• PSP: ~ half of patients develop early stage cognitive dysfunction
  • GWAS autopsy study of PSP revealed single nucleotide polymorphisms as risk alleles in multiple genes…
    • Including microtubule associated protein tau (MAPT) rs8070723 and rs242557 (MAPT) which has 2 haplotypes, H1 and H2
    • H1 is strongly linked to PSP and may be associated with progression from mild cognitive impairment (MCI) to dementia in Parkinson’s disease
  • In this paper they describe a cohort of 350 PSP patients from 15 sites who (mini-mental state examination ≥ 24), 305 had genetic samples and extensive neuropsychological evaluation
    • 20 patients underwent autopsy, 18 of which had PSP and 2 had a different tauopathy

Genetic influences on cognition in progressive supranuclear palsy

• Other than MAPT, there were no other statistically significant effects of the other tested genes, including APOE (different from patients with Alzheimer’s)

• MAPT effect on neurocognitive performance
  • Carriers of the H1c-specific rs242557/A MAPT alleles actually had better cognitive functioning
    • However they excluded patients with dementia, who may have been key to determining genetic associations

• TAKE HOME: read the study, does the design make sense?
Neurologic Phenotypes Associated With Mutations in RTN4IP1 (OPA10) in Children and Young Adults

• Mutations identified in RTN4IP1 previously reported in 3 families with recessive OA, and 3 sisters from another family with OA and cerebellar ataxia, seizures, and mild intellectual disability
  • Encodes a mitochondrial targeted protein with a quinone oxidoreductase activity, previously thought to result in a mild deficit in complex I and complex IV enzymatic activities

• The authors screened 300 patients who were suspected to have inherited OA but were negative for OPA1 and 3 major LHON mutations. 11 new families are reported with mutations in RTN4IP1 resulting in a spectrum of phenotypes ranging from OA to encephalopathies

Neurologic Phenotypes Associated With Mutations in RTN4IP1 (OPA10) in Children and Young Adults

• New pathogenic mutations identified with early-onset encephalopathy and OA
  • All had mutations that were likely to destabilize the protein or impair function
  • Some cases had the absence of the protein and these showed fragmentation of mitochondrial network in fibroblasts

• Take home: genetics are increasingly complex and reveal the spectrum of diseases that result from different mutations of the same gene

Mutations in DNM1L, as in OPA1, result in dominant optic atrophy despite opposite effects on mitochondrial fusion and fission

- Genes control the mechanisms of fusion and fission of the outer and inner mitochondrial membranes
  - OPA1 and MFN1/2 (Charcot-Marie-Tooth type 2A in MFN2) helps the membranes in fusion
  - DNM1L/DRP1 (encephalopathy) and DNM2 (Charcot-Marie-Tooth type 2M) helps the membranes to pinch and undergo fission

- Inherited dominant optic atrophy had previously been identified with mutations in OPA1, OPA3, MFN2, and AFG3L2; and recessive optic atrophy has been associated with mutations in TMEM126A, ACO2, RTN4IP1, and NDUFS2.
  - However, only 50-60% of individuals with an inherited optic atrophy are identified to have a specific mutation

Mutations in DNM1L, as in OPA1, result in dominant optic atrophy despite opposite effects on mitochondrial fusion and fission

- Next gen sequencing identified new mutations associated with isolated dominant optic atrophy
- 3 families identified with mutations in DNM1L
  - Excess mitochondrial fusion (which led to a syndrome indistinguishable clinically from the excess mitochondrial fission seen in OPA1): elongation of mitochondria

- Take home:
  - Mitochondrial fission is important for function and pathologic consequences of defects in mitochondrial fusion OR fission result in RGC death

Mitochondrial DNA Double-Strand Breaks in Oligodendrocytes Cause Demyelination, Axonal Injury, and CNS Inflammation

- Can mitochondrial dysregulation in oligodendrocytes be associated with MS or other demyelination?
- Creates a mouse model in which double-strand breaks are induced in mitochondrial DNA in oligodendrocytes
  - Express a specific endonuclease starting at 3 weeks of age
  - Demyelinating disease
    - Spontaneous demyelination
    - More sensitive to induced EAE and develop features of chronicity or progression, which was not previously robust in existing animal models
- Take Home:
  - New animal model
  - Could potentially be used in remyelination also

Inflammation and Immunity

• Take Home Messages

  • TLR4 signaling in the microglia may be critically important in controlling infarcts and outcomes in cortical injury
    • This is potentially important in developing new approaches to limit the impact of brain injury
  
  • An autoimmune rat model of myasthenia gravis has been developed using sequences from the human acetylcholine receptor and antigen specific immune adsorption was successful in removing antibodies with specificity for their target antigen
    • This could potentially be useful in future therapies to selectively remove antibodies that recognize specific epitopes
TLR4 signal ablation attenuated neurological deficits by regulating microglial M1/M2 phenotype after traumatic brain injury in mice

- Toll-like receptor family: TLR4 recognizes damage-associated molecular patterns, like HSP90 and HMGB1, may initiate the inflammatory cascade
- TLR4: highly expressed in microglia and may be activated in brain injury

- Mice, WT and TLR4-/-, were subjected to a controlled cortical impact
  - MRI was used to assess infarct volume
  - Behavioral testing was done

- TLR4-/- after controlled injury, as compared to WT injured animals
  - Had less brain edema and less infarct volume
  - Had improved recovery of learning and memory
  - Microglial effects included polarization toward an M2 phenotype, increased migration around the injury, and promote cytokines that promote tissue repair

TLR4 signal ablation attenuated neurological deficits by regulating microglial M1/M2 phenotype after traumatic brain injury in mice

• Take Home: Could limiting TLR4 expression or targeting a downstream pathway help preserve neuronal function after traumatic brain injury?

Specific removal of autoantibodies by extracorporeal immunoadsorption ameliorates experimental autoimmune myasthenia gravis

• MG model
  • Rats immunized with extracellular domains of recombinant human AChR subunits
    • α subunit was most pathogenic despite antibody titers against all subunits
    • Disease scores, EMG, and quantitation of muscle AChR evaluated

• Treatment
  • Immunized animals received femoral vein catheterization by which blood was removed, passed through a sepharose column with either the antigen or control protein, and returned to the animal. About 15 ml was passed through each session and the animals received 3 sessions per week.

Specific removal of autoantibodies by extracorporeal immunoadsorption ameliorates experimental autoimmune myasthenia gravis

- Decrease in antibody titer was to ~5% of the original titer after 3 weeks of treatment

- Significant improvement in clinical score was observed

- Take Home: selective immunoabsorption can be used ex vivo on blood and can improve clinical disease in experimental MG


Wild Card #1: Lateral geniculate neurons projecting to primary visual cortex show ocular dominance plasticity in adult mice

- Experience dependent plasticity is believed to be cortical
  - This paper suggests that ocular dominance shifts after monocular deprivation in adult mice may reflect plasticity of eye-specific inputs onto the lateral geniculate neurons

- Most dorsal lateral geniculate nucleus (dLGN) cell boutons are monocular during normal vision (~86%)
  - After monocular deprivation in adult mice, there was a loss in responsiveness to the deprived eye and gain in responsiveness to the non-deprived eye
    - Achieved through single cell analysis over time
  - Eye-specific cortical changes to the dLGN were blocked through cortical inactivation

Wild Card #2: Selective attention within the foveola

- Shifts in covert attention is a way to improve and enhance processing
  - Technique allows for improved localization and retinal stabilization to help adjust for fixational movement
  - Used stimuli that appear within the foveola, only a few arcminutes away from center (1 arcmin = 1/60 of a degree)
  - Used spatial cueing discrimination to determine that microscopic shifts of attention play a role in high-acuity vision
  - “fine spatial vision cannot be regarded as a purely sensory accomplishment, but as the outcome of a complex visuomotor interaction in which precise control of covert attention plays a critical role”

• Mahalo!