Peripheral Auditory Nerve Impairment in a Mouse Model of Syndromic Autism

McChesney et al.

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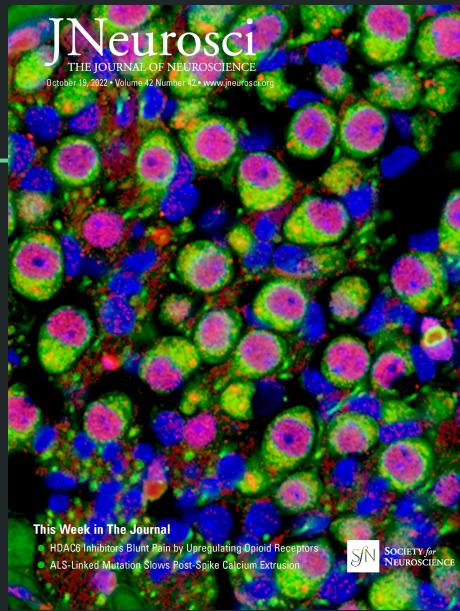


Background

- Autism Spectrum Disorder (ASD) is a neurodevelopmental disorder associated with communication deficiencies, repetitive interests, and other behaviors that affect quality of life
- Hearing impairment could contribute to ASD symptoms, including peripheral auditory nerve dysfunction and other auditory system related abnormalities (Kancherla et al., 2013; Do et al., 2017)
- Myocyte enhancer factor 2C (MEF2C) gene regulates neuronal cell differentiation and synapse density during development; mutations have been associated with MCHS, a disorder similar to ASD and intellectual disability
- Mutated Mef2c-Het mice show social deficits, repetitive behaviors, and other ASD-like symptoms

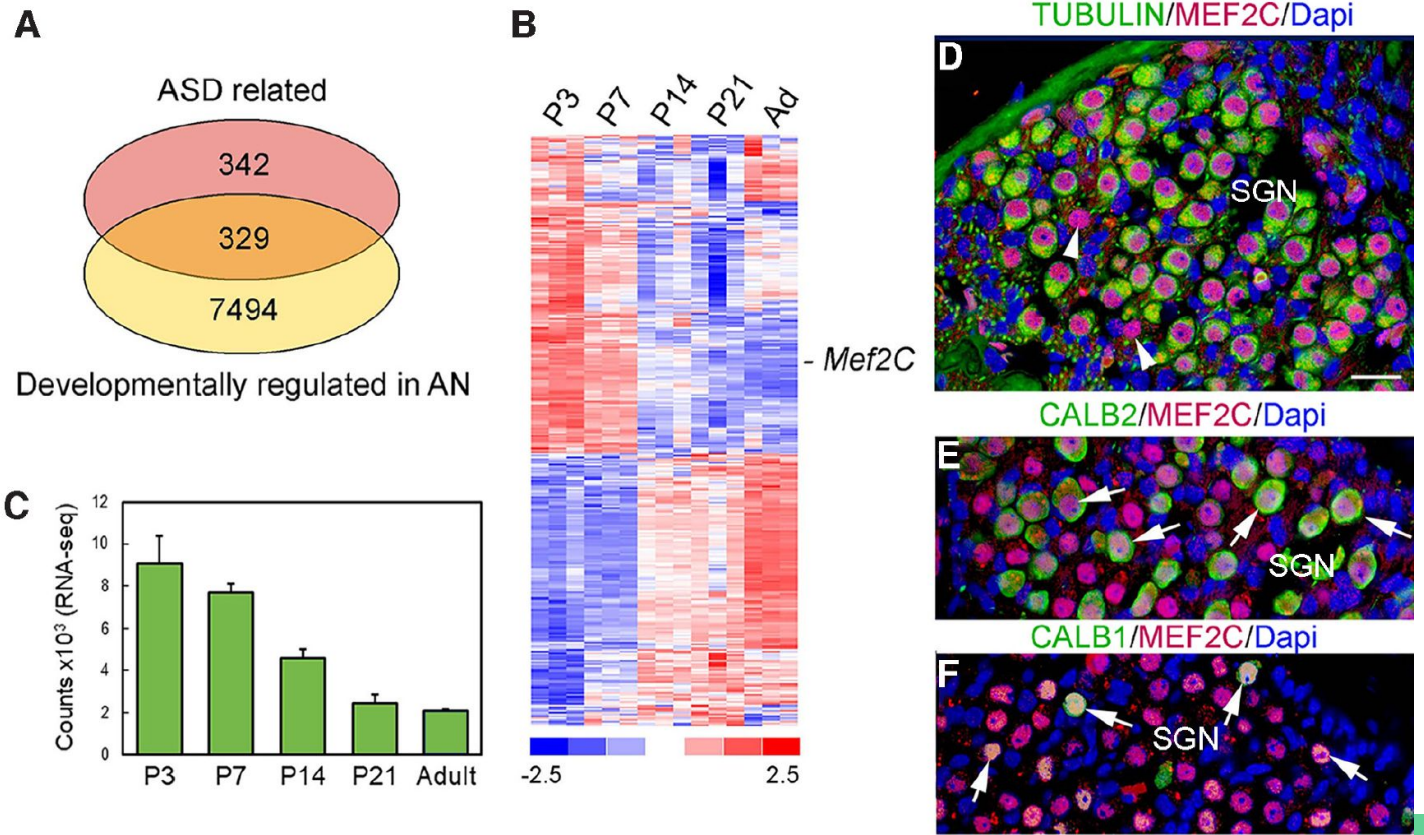
What is the direct impact of peripheral auditory system abnormalities on ASD symptoms?

How do myocyte enhancer factor 2 (MEF2C) mutations affect peripheral auditory nerve dysfunction and ASD associated symptoms?

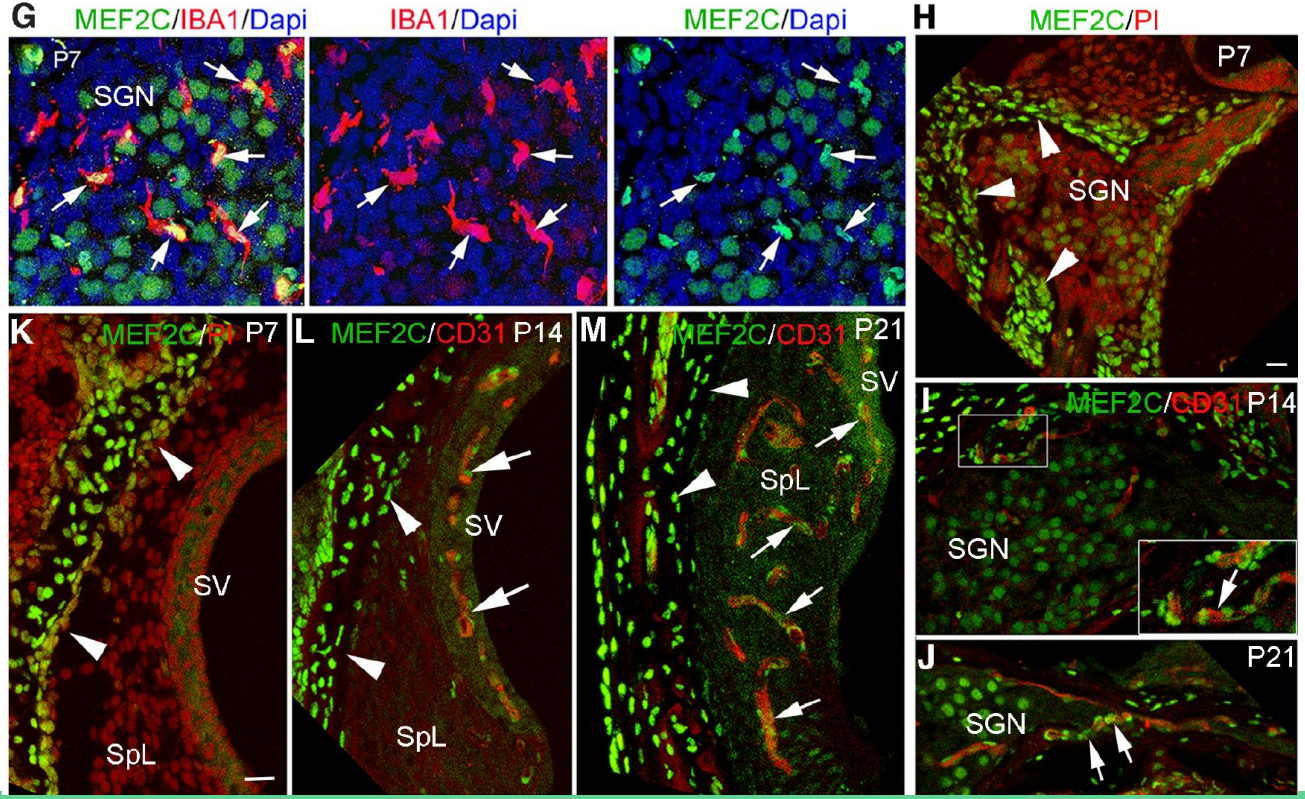
Methods

- Mouse model of ASD with MEF2C haploinsufficiency syndrome has communication deficits
- Measured cochlear and auditory nerve function using the cochlear microphonic (CM) and auditory brainstem response (ABR)
    - CM measures mouse cochlear health, as it is sensitive to endocochlear potential and hair cell loss
        - Active electrode in ear, inverting electrode in scalp, ground electrode at hindlimb
    - ABR for overall AN function, estimates for neural synchrony
        - Same ABR electrode placements as CM
- Staining was done with antibodies conjugated with fluorescent avidin or primary antibodies conjugated to Alexa Fluor Dyes
- Analyzed blood vessel system in mouse stria vascularis
- Classifications of abnormality:
    - Myelin sheaths were abnormal if at least two areas were degenerative
    - Mitochondria were abnormal if they had disrupted cristae
    - Spiral ganglion neuron were abnormal if their cell bodies exhibited aging-like features

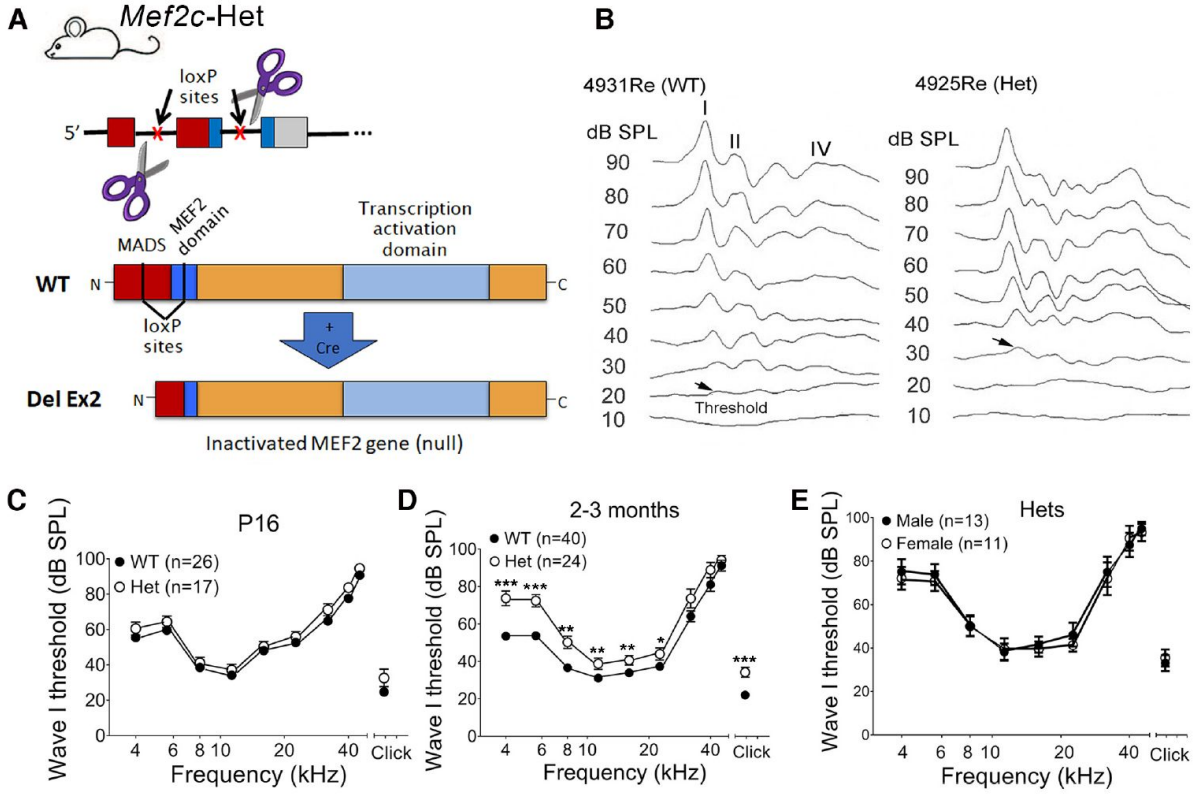
Multiple ASD risk genes including Mef2C are expressed during mouse peripheral Auditory Nerve development



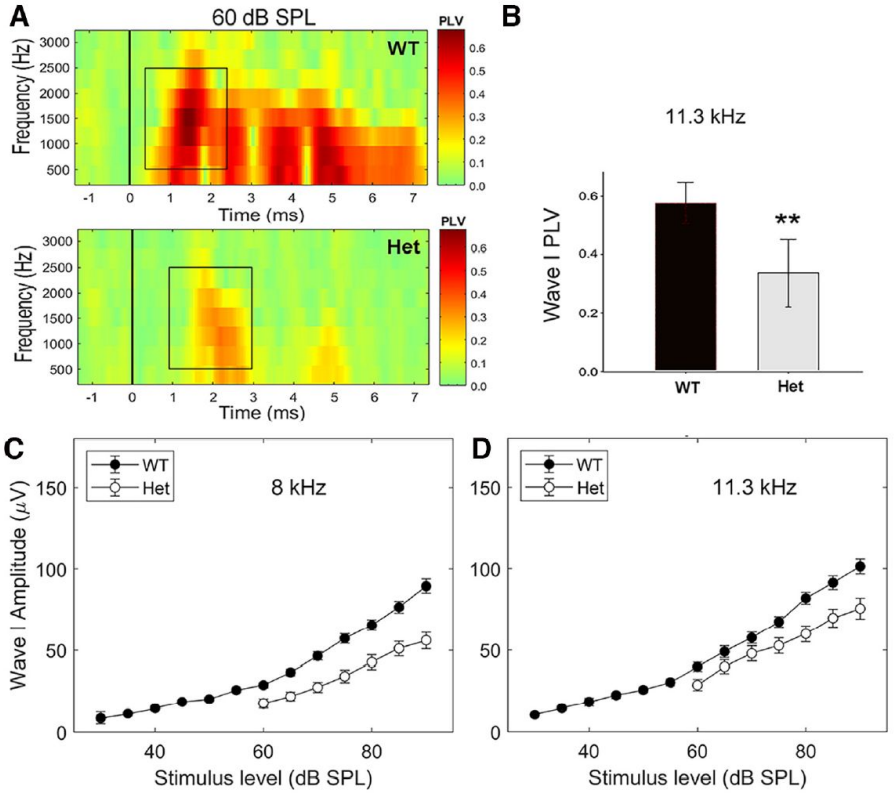
Immunostaining for Mef2C reveals multiple cell types expressed in the developing Auditory Nerve



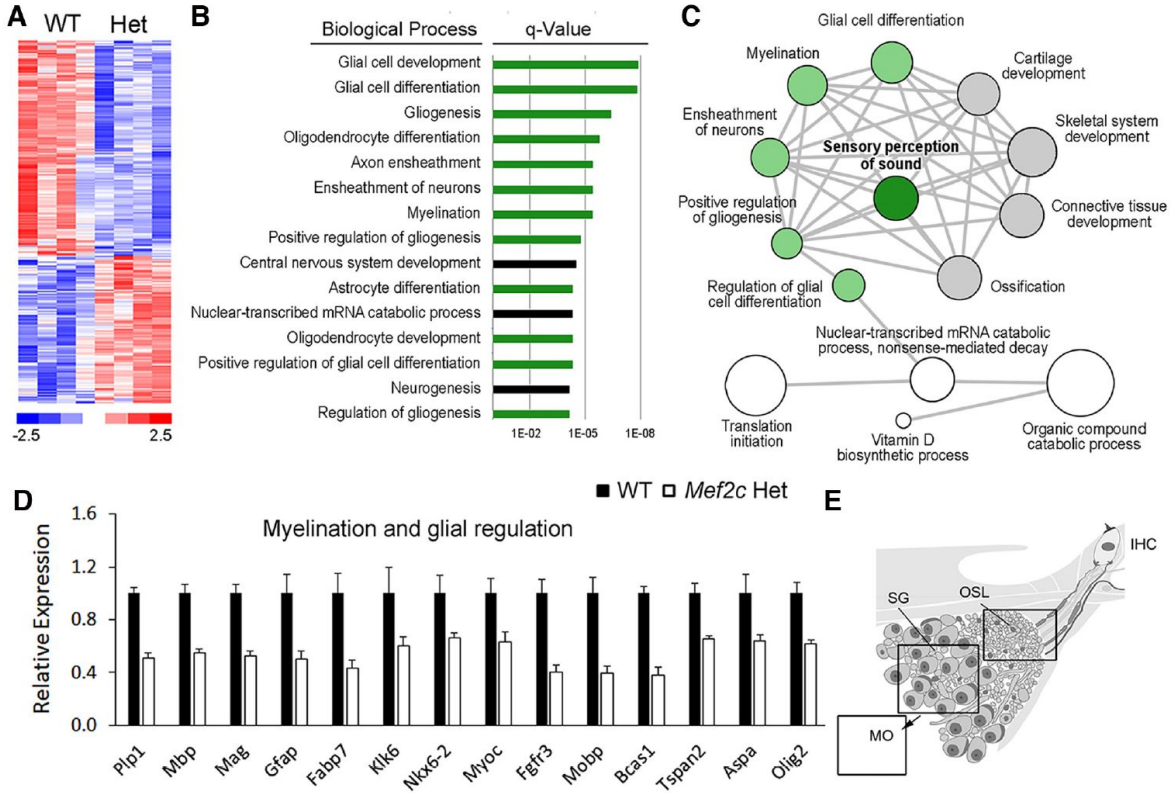
Mef2c deficiency results in a reduction of hearing sensitivity in young adult animals



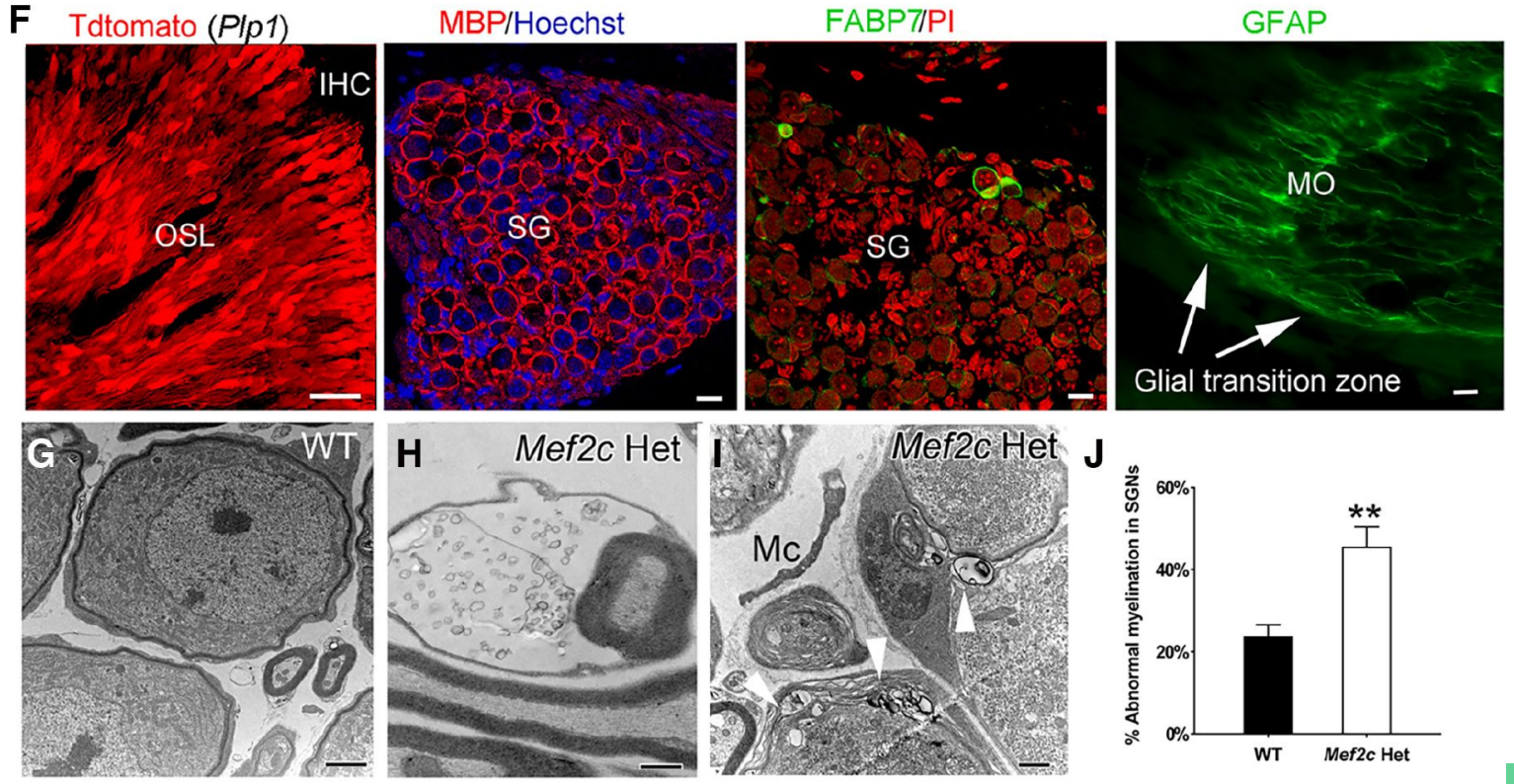
MEF2C deficiency results in reduced neural synchrony and Auditory Nerve activity



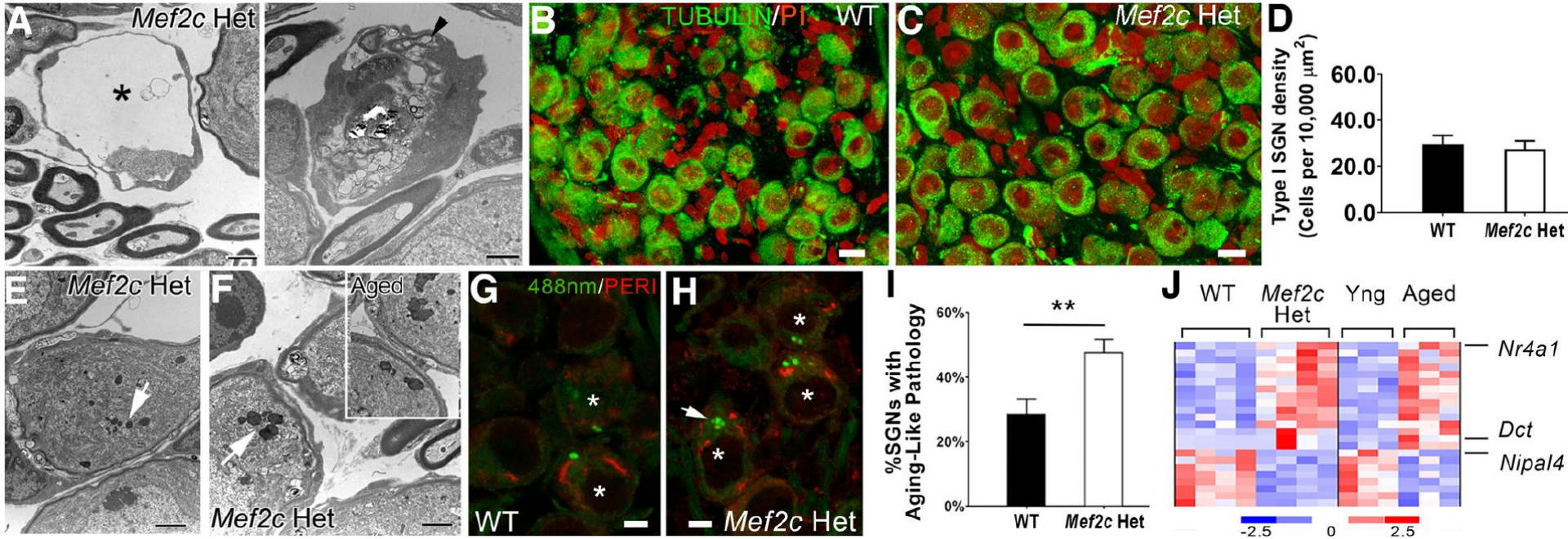
MEF2C deficiency leads to glial dysfunction in Auditory Nerve of young adult animals



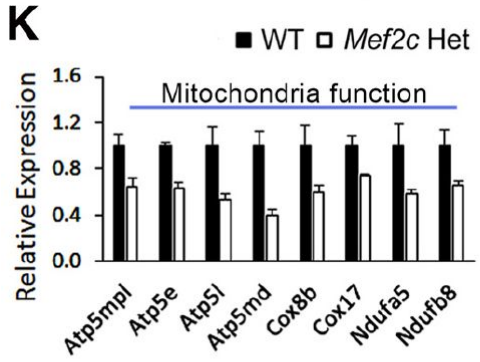
Glial cell dysfunction and abnormal myelination observed in the Auditory Nerve of Mef2c-Het mice

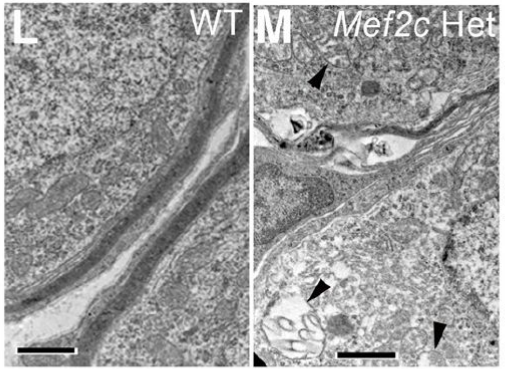


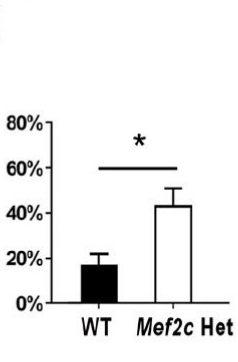
MEF2C deficiency causes aging-like changes in neurons in young adult AN

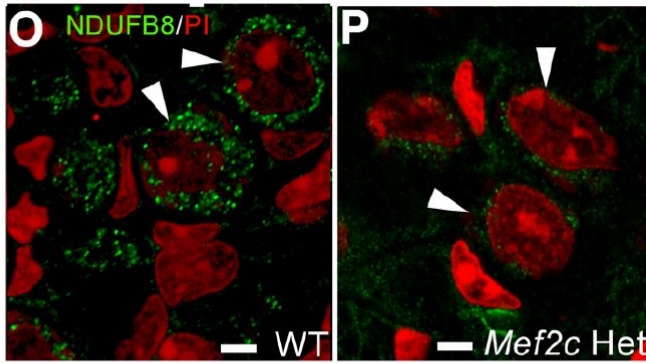


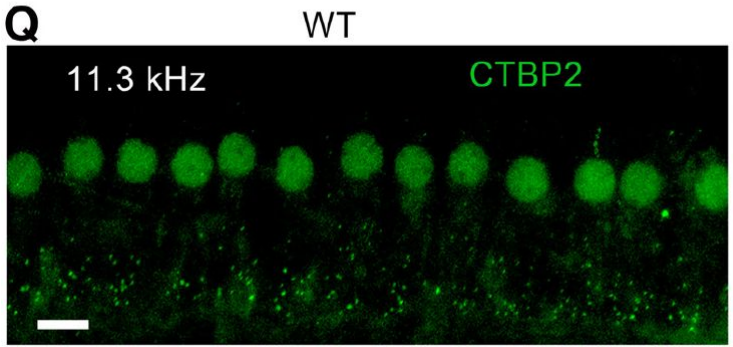
MEF2C deficiency causes aging-like changes in mitochondria in young adult AN

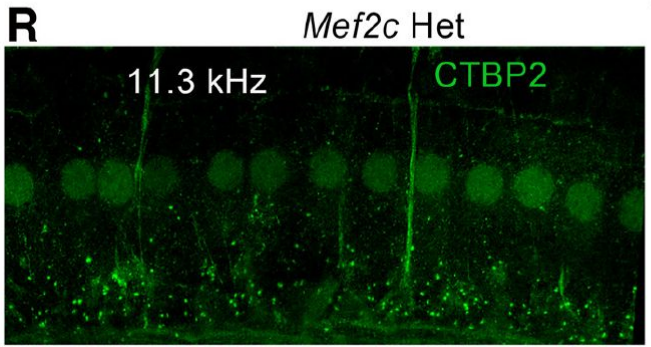


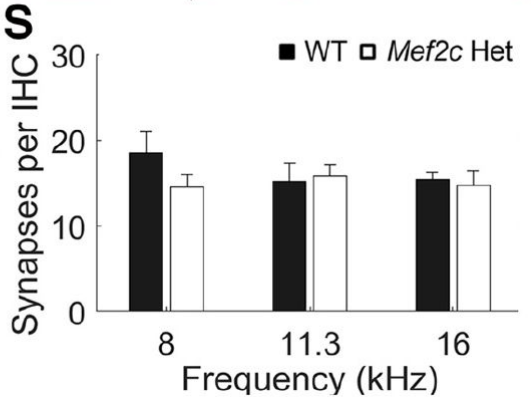




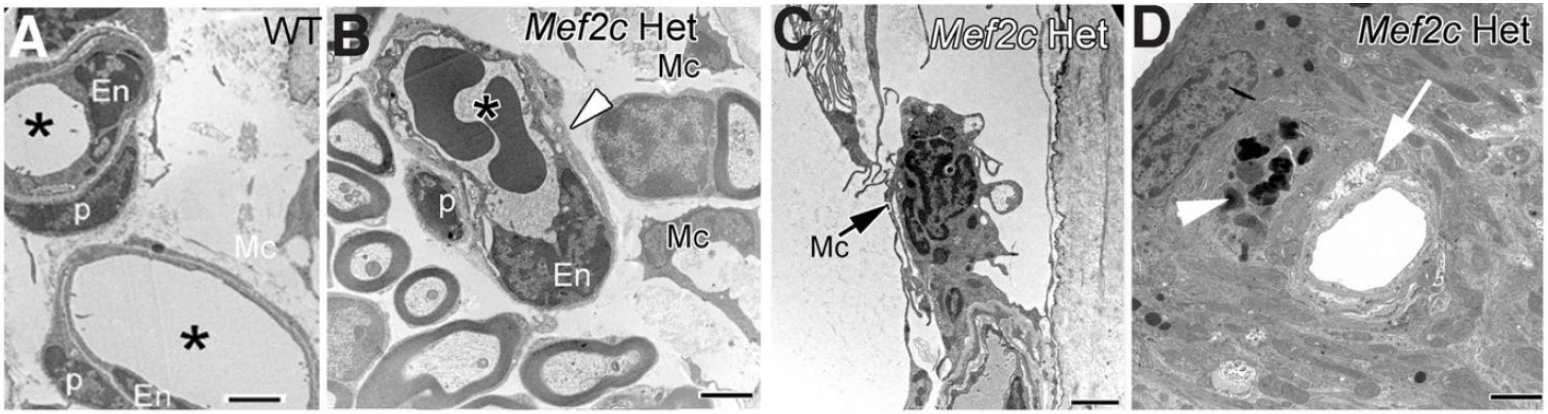


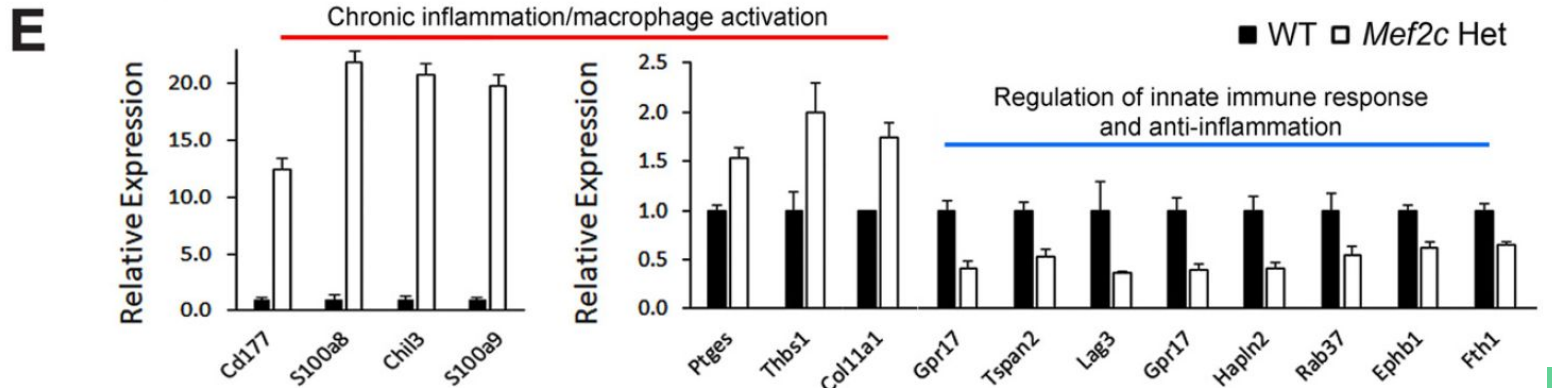






MEF2c-Het Mice exhibit increased inflammation and macrophage activation in AN and stria vascularis





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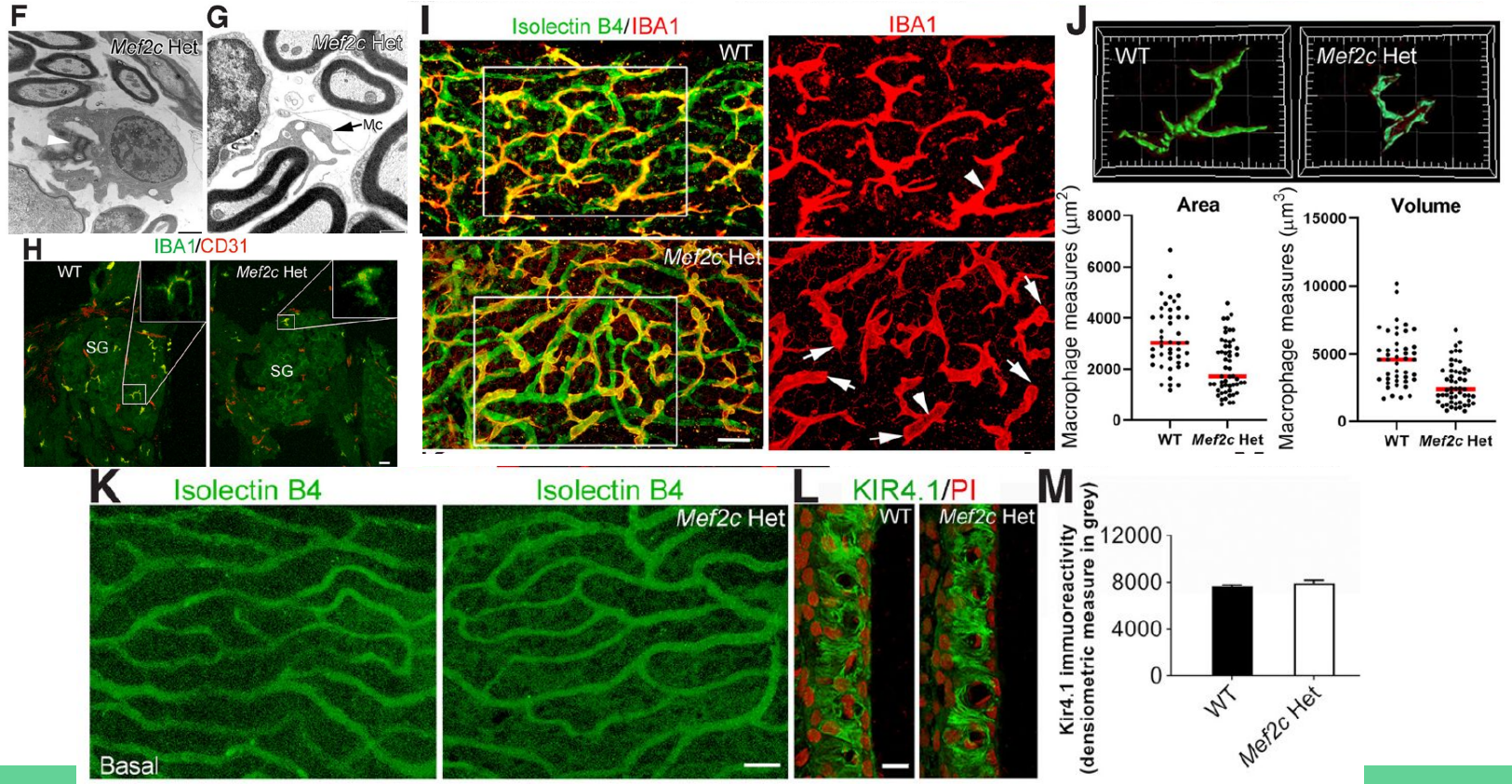
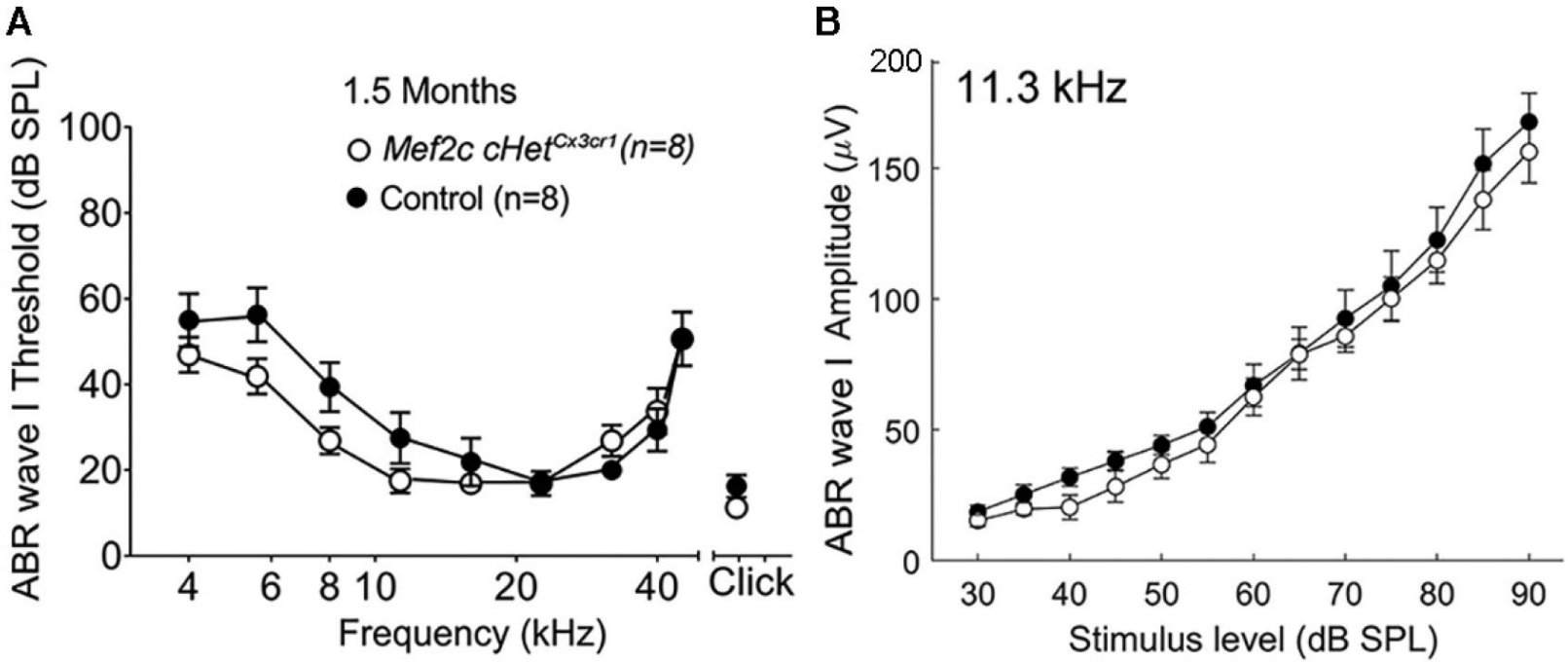
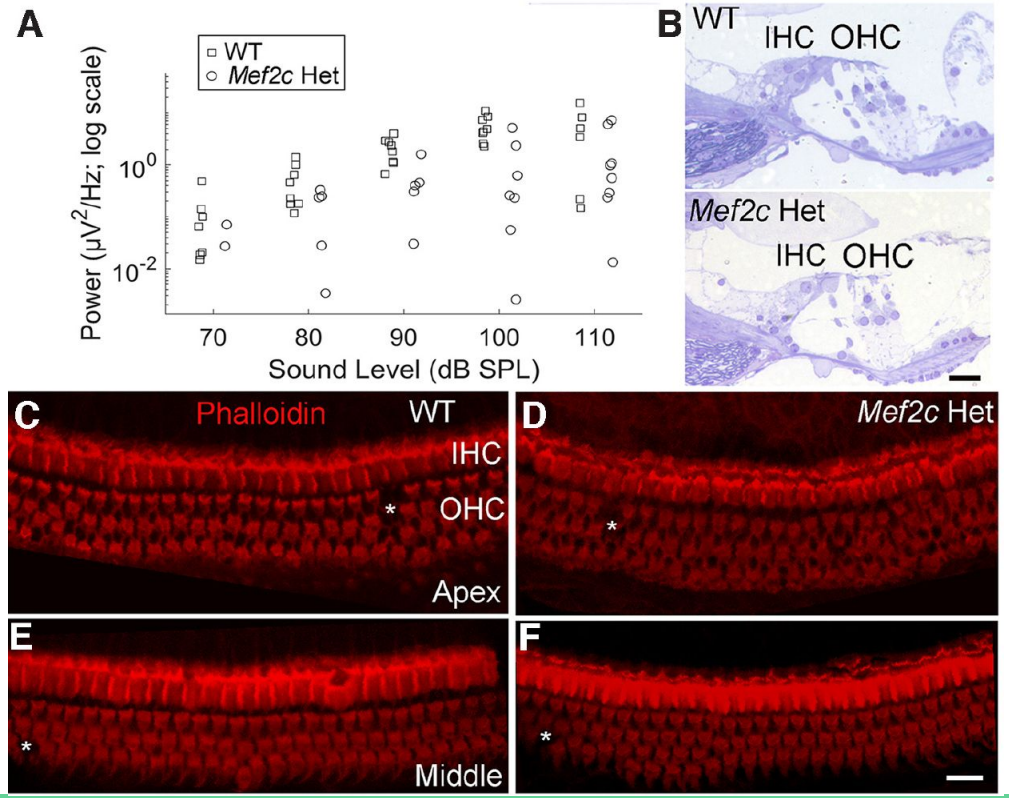


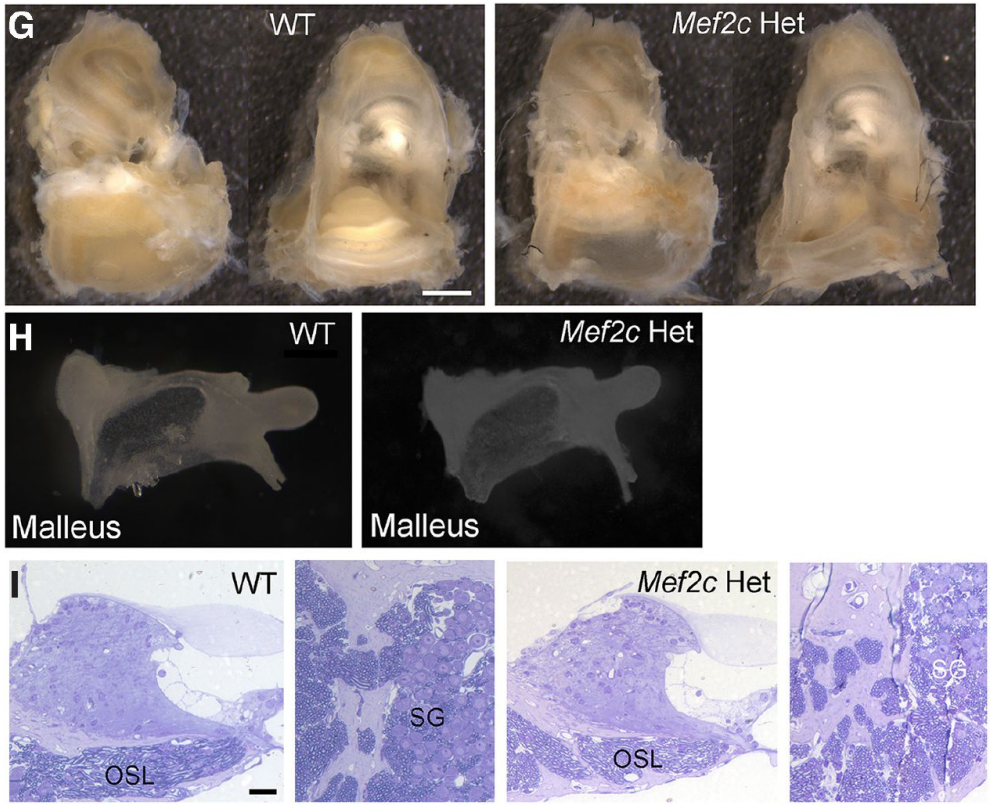
Mef2C deficiency in immune cells alone does not lead to cochlear and Auditory Nerve decline



Mef2C deficiency has no effect on hair cell function



Mef2C deficiency has no effect on cochlear bone formation



Results Summarized

- MEF2c-Het mice exhibit functional impairment of the peripheral auditory nerve
  - Reduction in hearing sensitivity
- MEF2C is expressed during development in different AN and cochlear cell types
- Abnormal myelination observed in Mef2c-Het
- Neuronal degeneration, mitochondria dysfunction
- Increased macrophage activation, cochlear inflammation
- Microglia/macrophages may contribute to AN dysfunction and ASD -related symptoms
- No major change in hair cell function or cochlear bone formation

Significance and Future Plans

- Links a ASD-related mouse model with an impairment in peripheral auditory nerve structure and function
- May explain a new role of Mef2C in peripheral auditory nerve development
- Can lead to clinical test of suprathreshold peripheral auditory nerve function as an indicator of ASD-related disorders
- Further studies needed to address specific relationships and whether inhibition of macrophage activation can be a potential treatment strategy for auditory nerve function/improving ASD-related communication impairments

Limitations

- Uses a mouse model which is not a perfect representation of human symptoms or complex autism-like symptoms
- Most figures show only one example image
- MEF2C mutations are not directly related to Autism; associated with Mef2C haploinsufficiency syndrome which has ASD- like symptoms
- Only focuses on the role of auditory impairment on ASD-related symptoms

Thank you for listening!