59th Annual Diagnostic Slide Session 2018

Case 10

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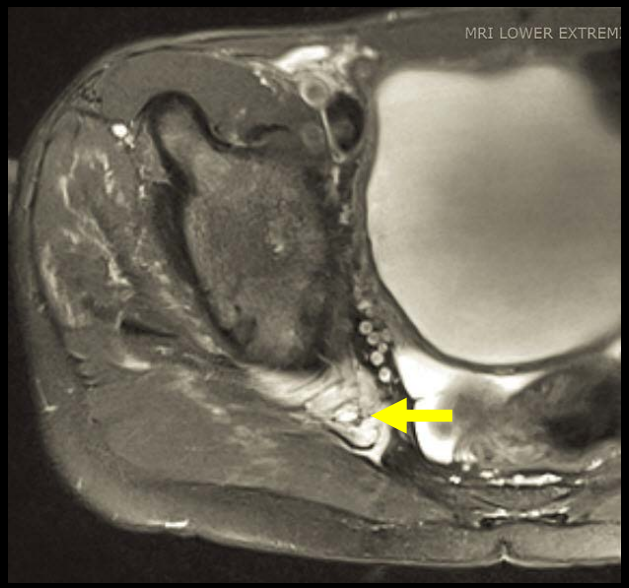
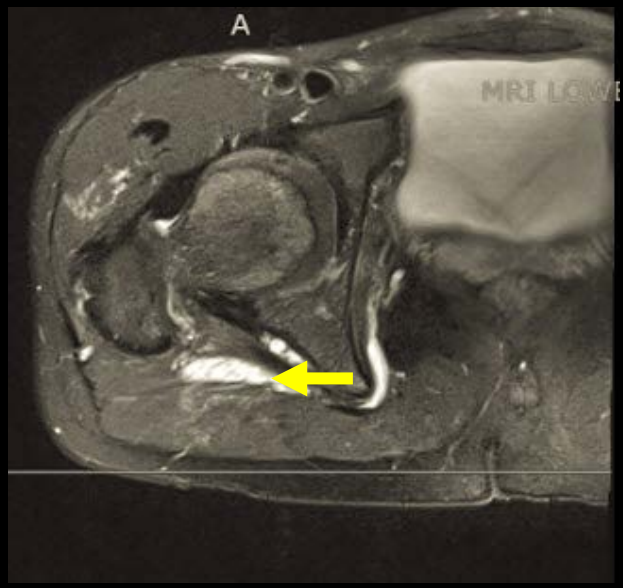
No financial disclosures

Case 10
Clinical summary

- 11-year-old boy
  - One year with right leg length discrepancy
  - Subtle café-au-lait spots
  - X-rays ⟶ multiple stress fractures


MRI LOWER EXTREM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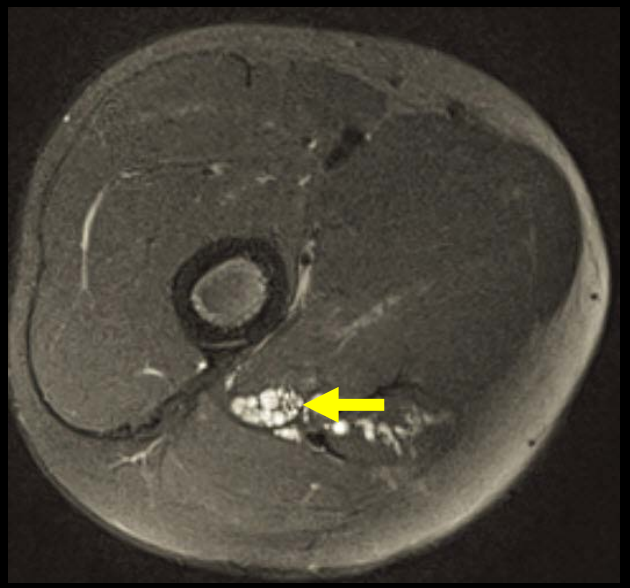
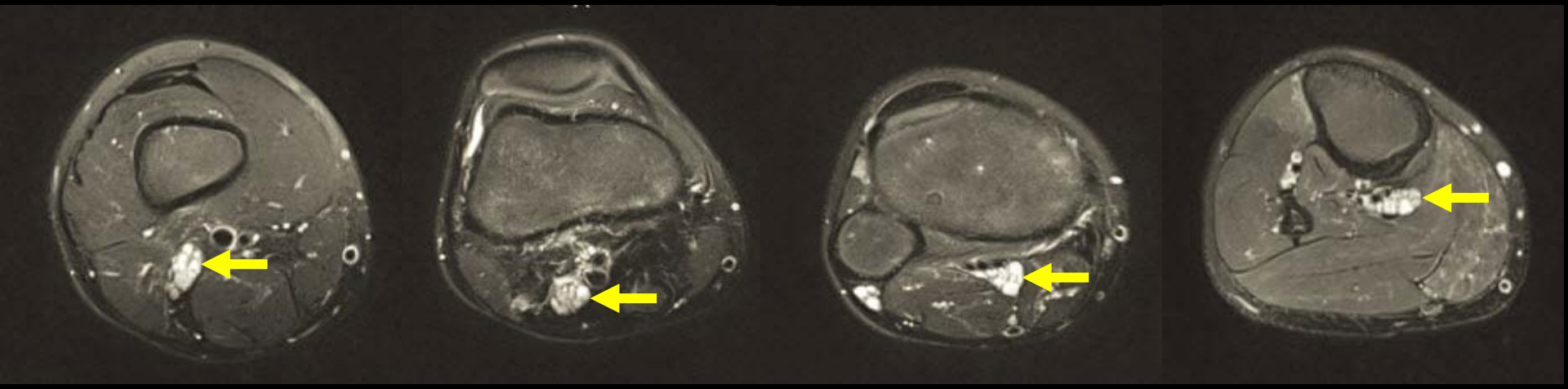
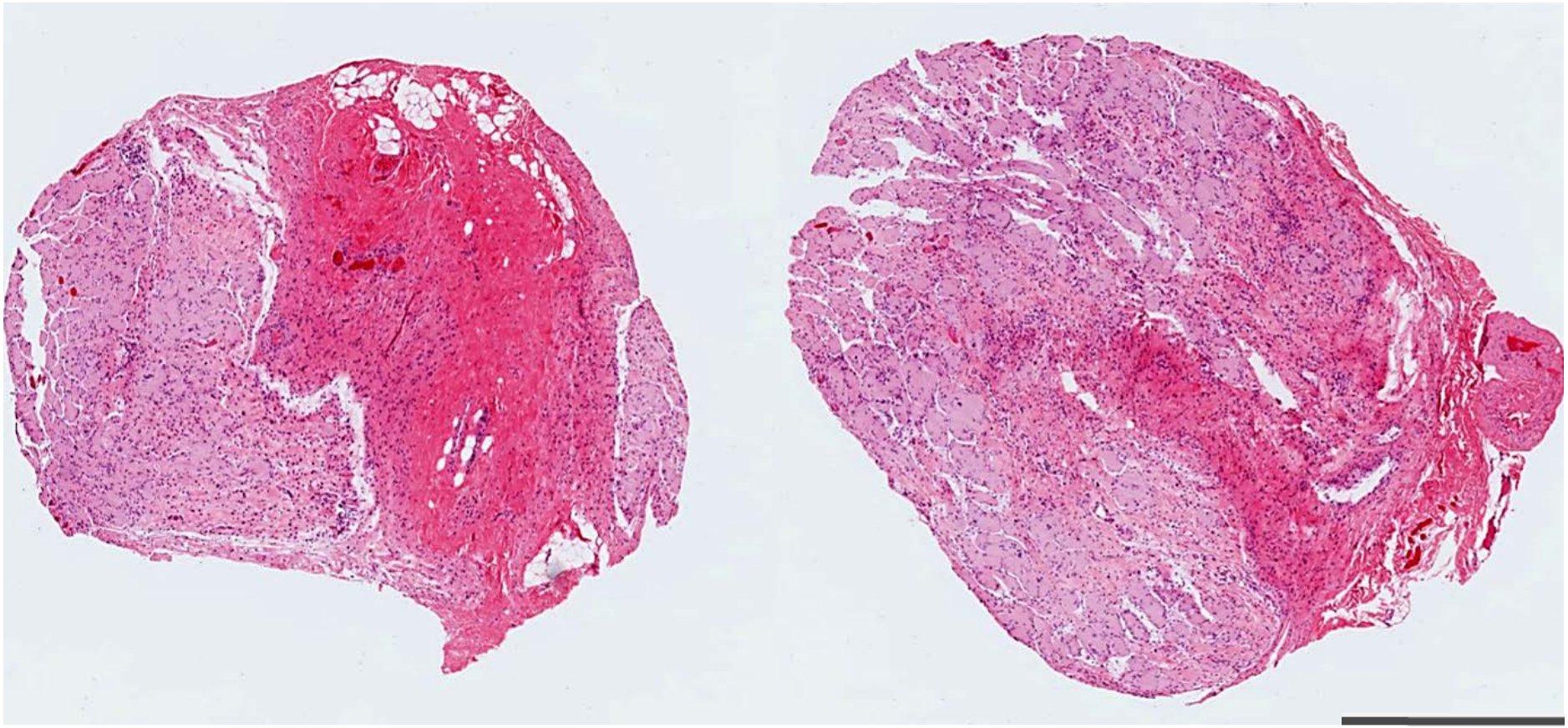




Case 10
Clinical summary

- Underwent orthopedic surgery with concurrent biopsy of the tibial nerve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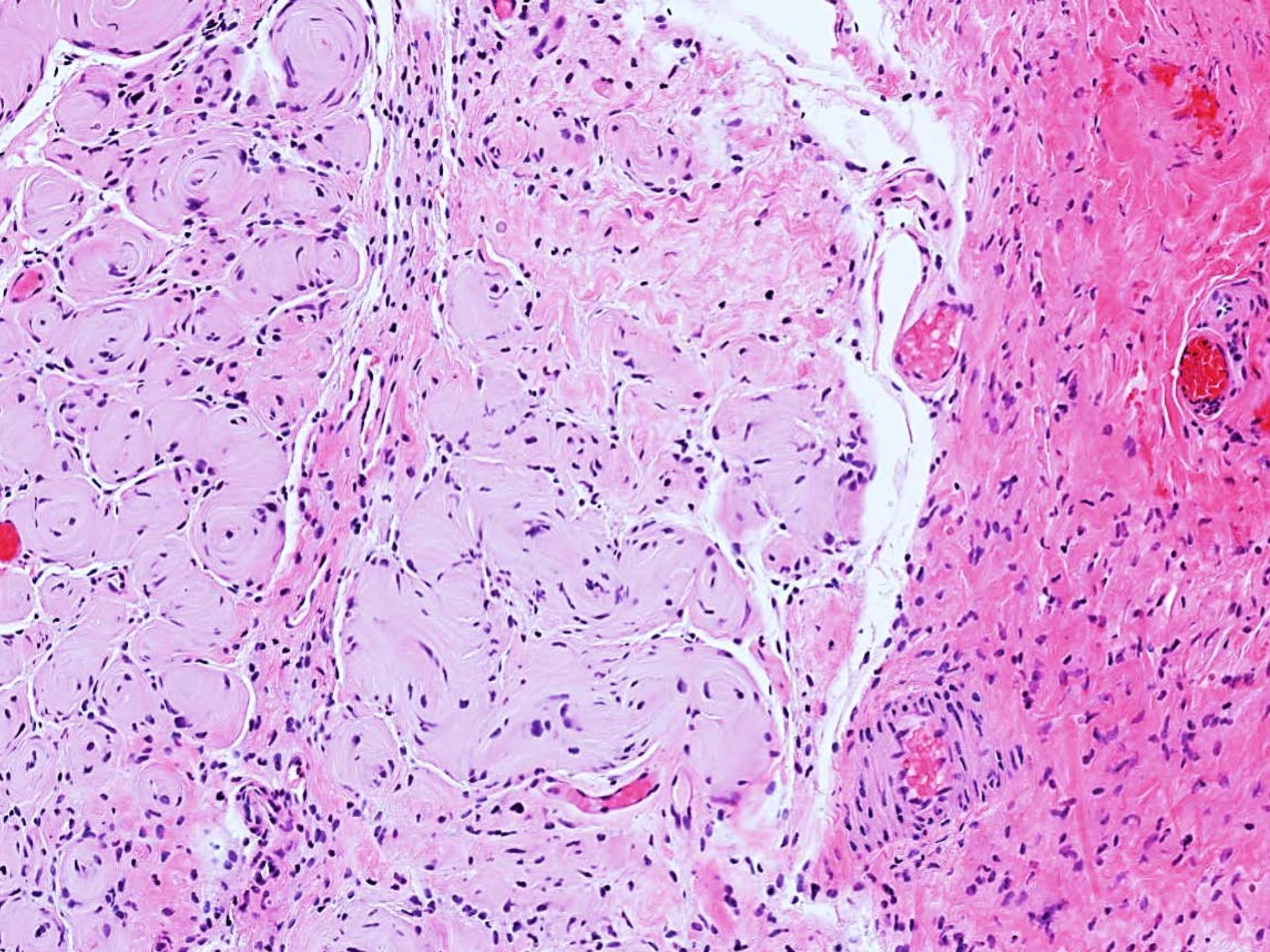
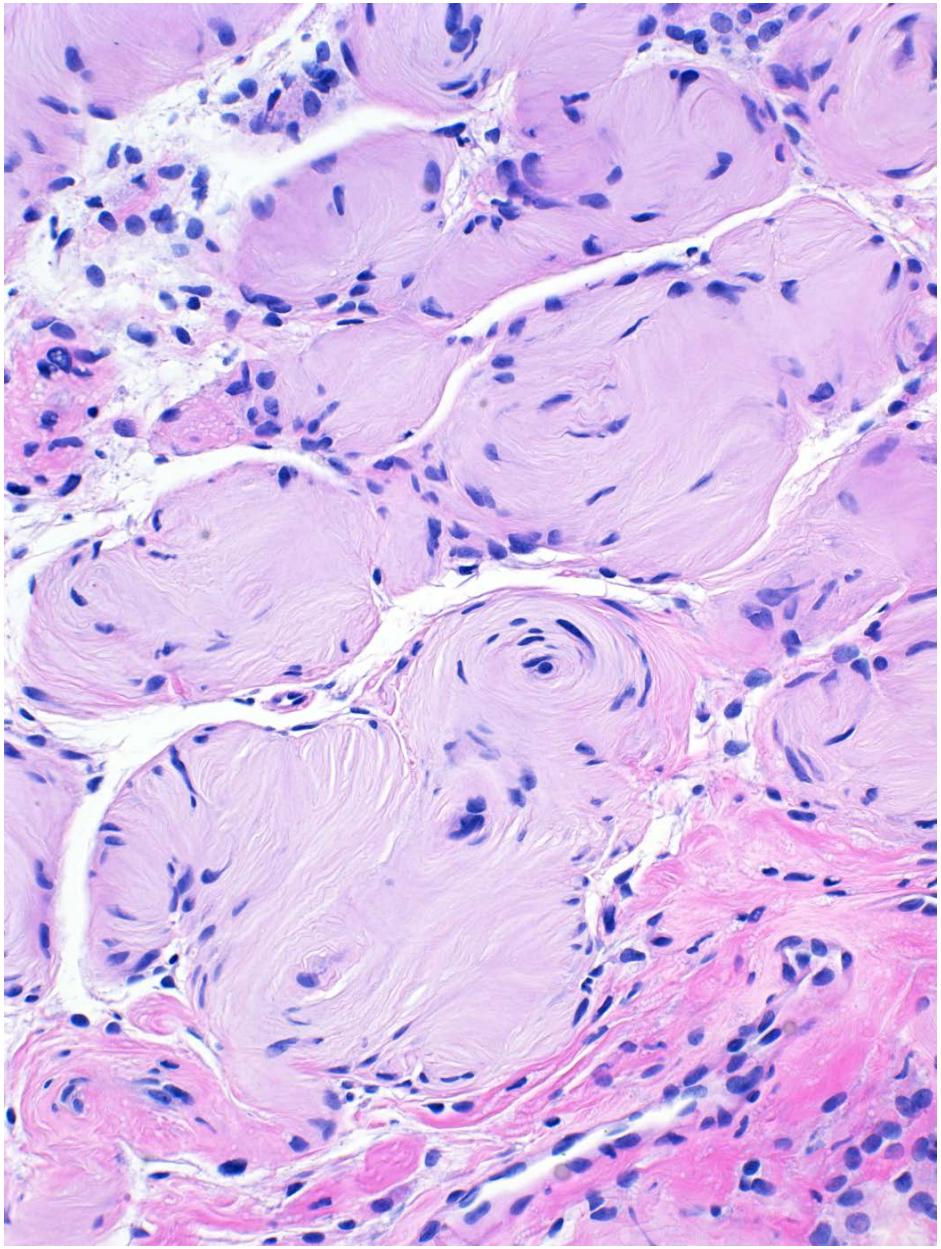
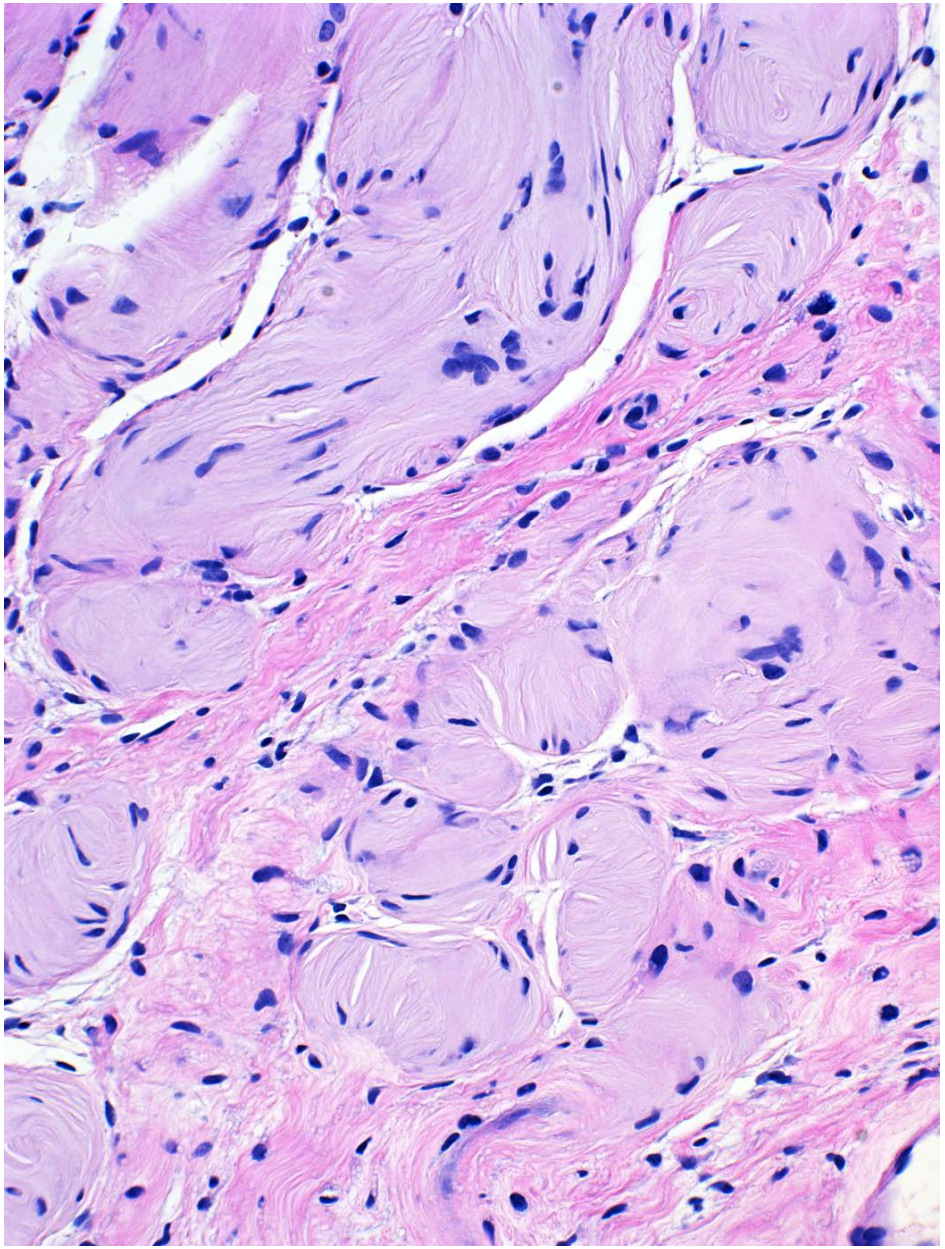
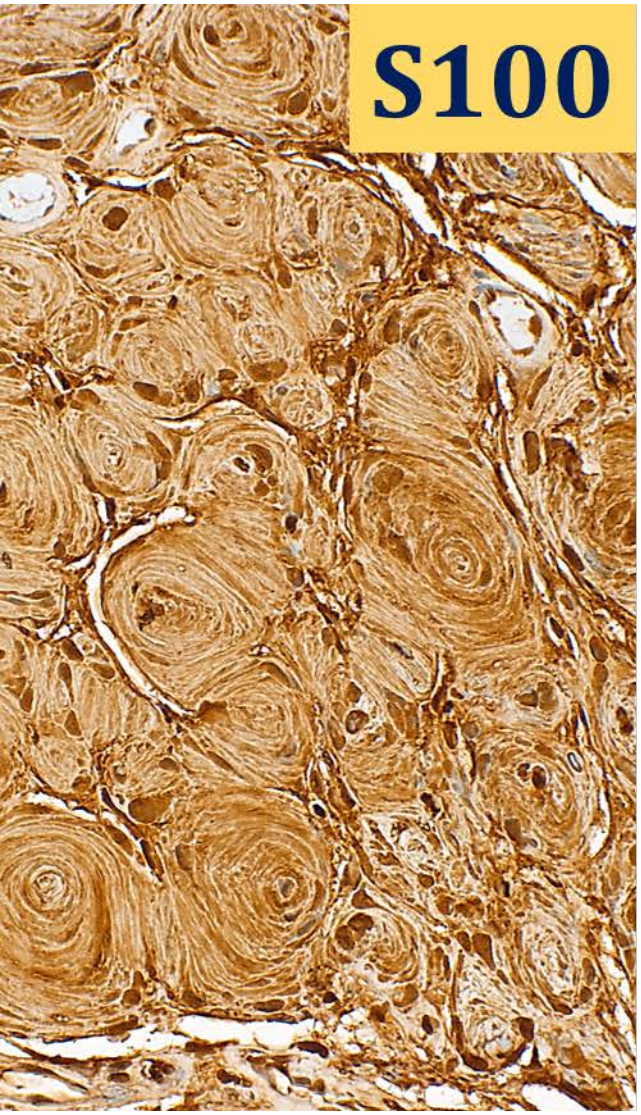


Diagnosis ?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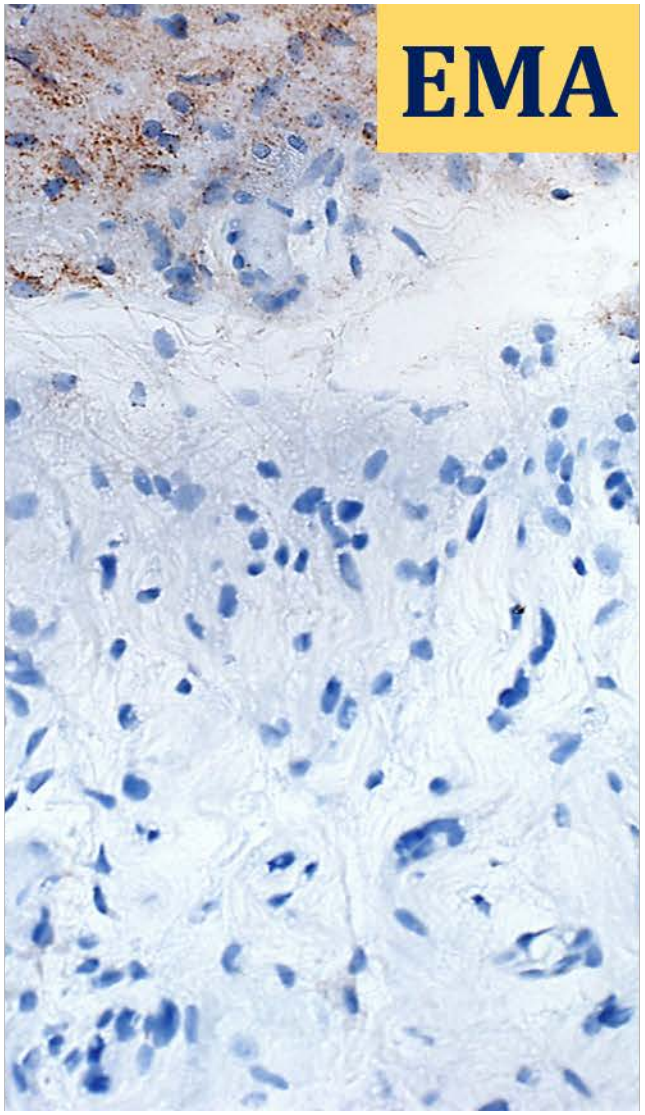
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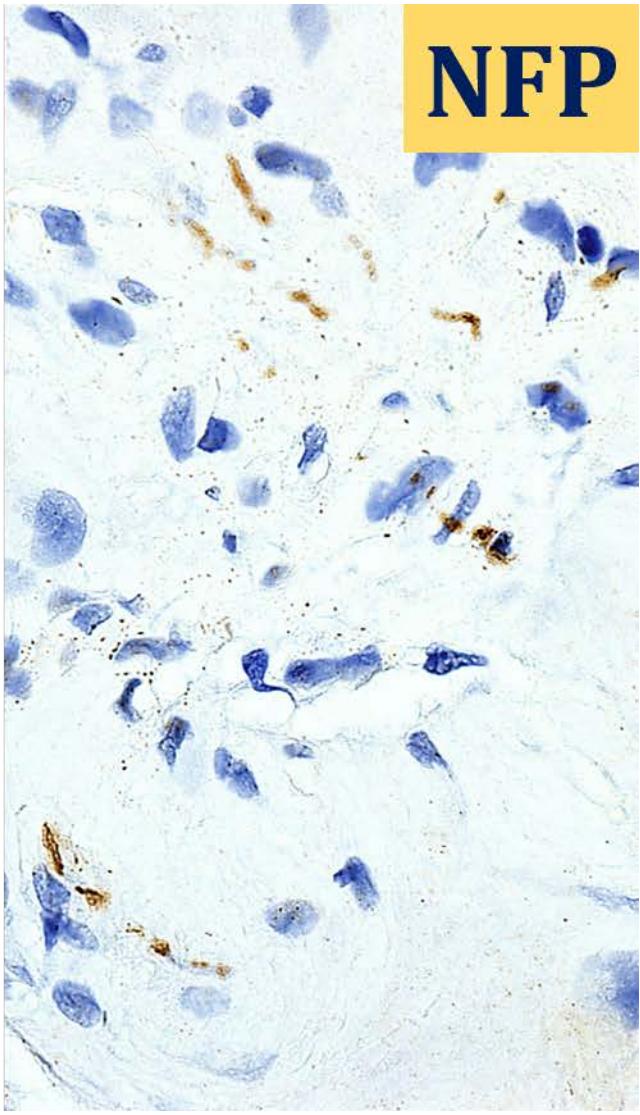
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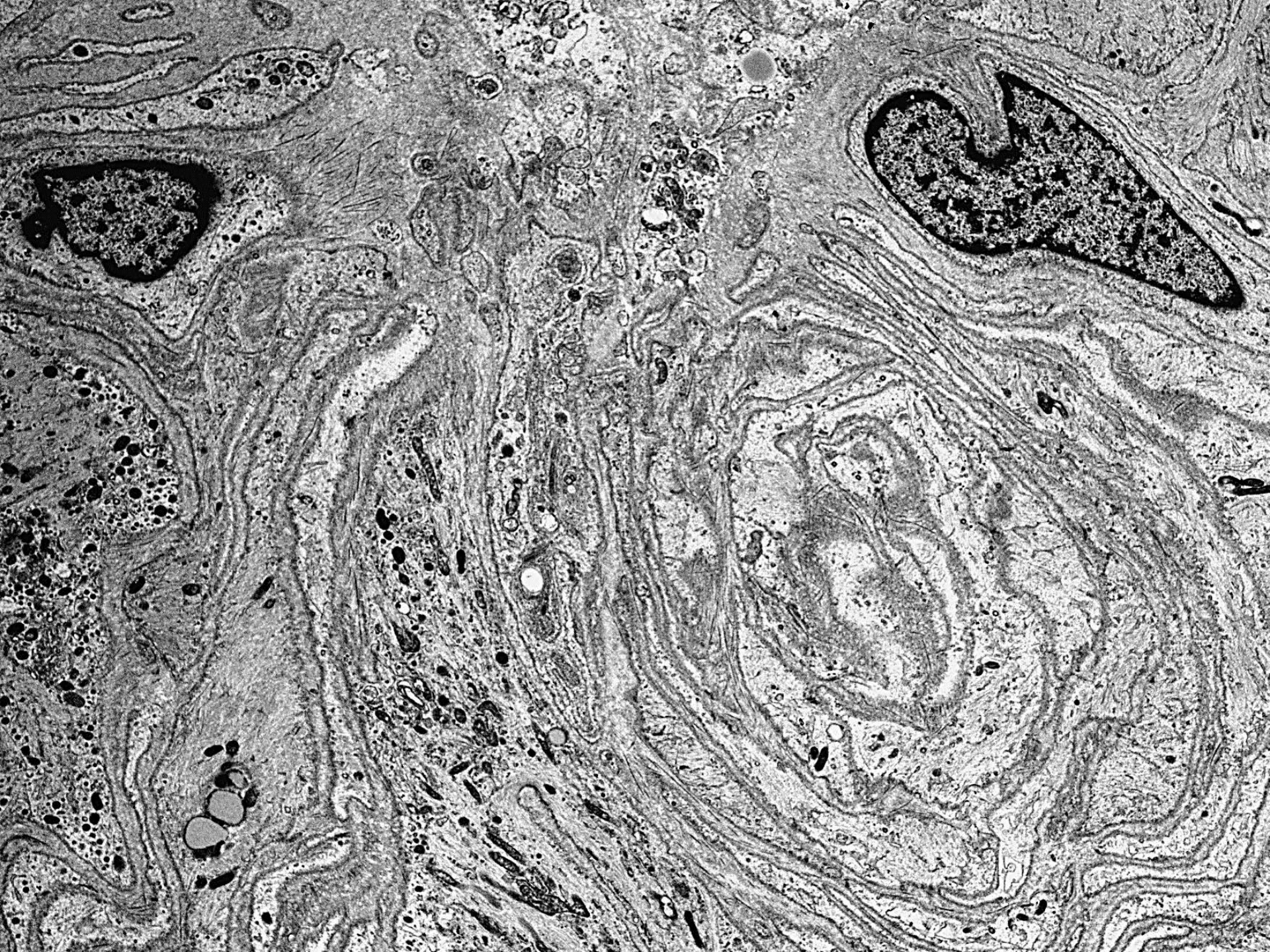


Diagnosis:

Localized hypertrophic neuropathy

Molecular testing

- *KRAS*: c38_40dupGCG found at low level (MAF~16%) by NGS in fresh tissue, cultured Schwann cells, and café-au-lait spots
- No genetic alterations in blood by Sanger Sequencing
- Consistent with a RASopathy with mosaic genetic alteration

Localized hypertrophic neuropathy (LHN)

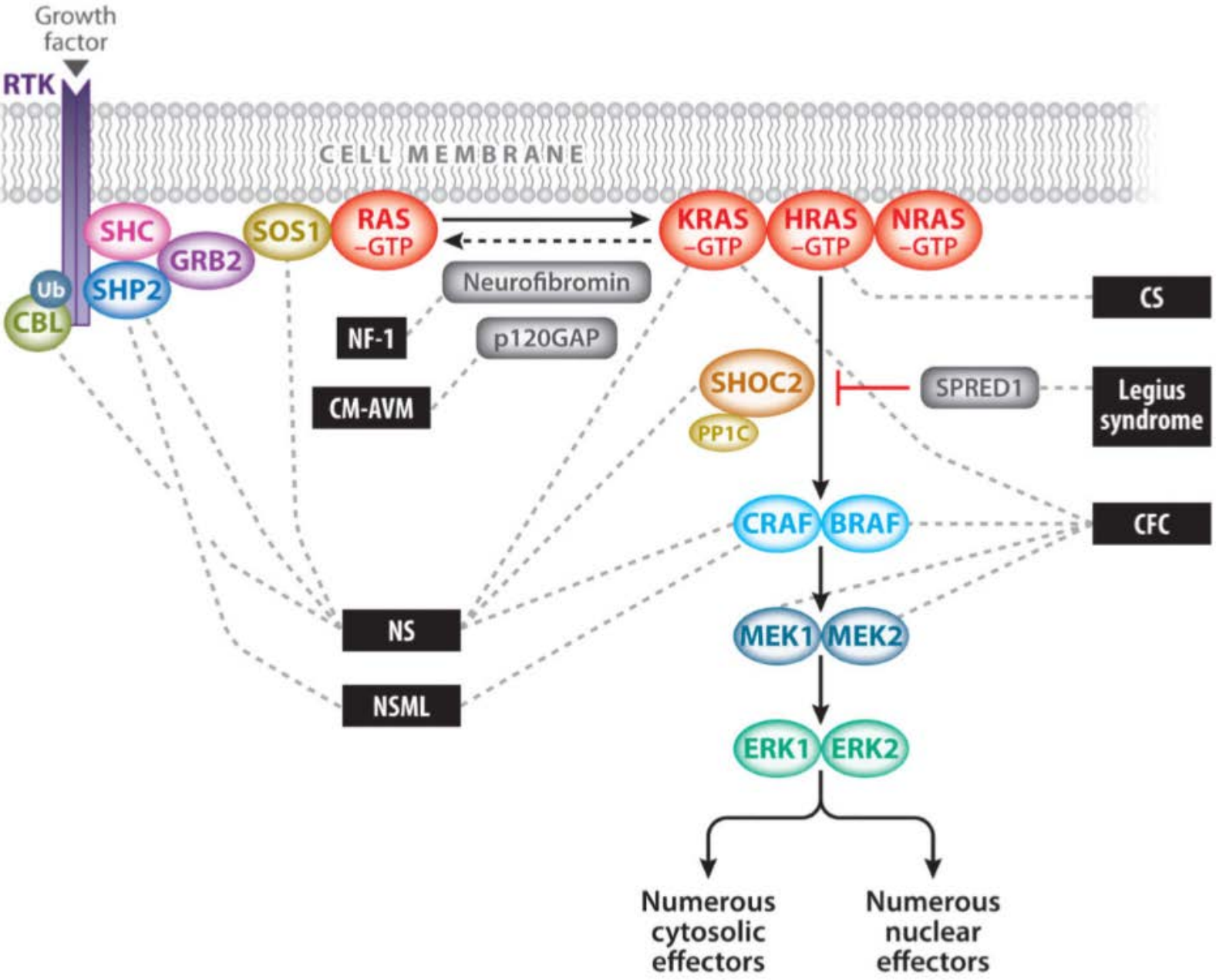
- Rare Schwann cell proliferation with onion bulb formation
- Most cases are now thought to represent intraneural perineuriomas

Norris B et al. J Clin Neurosci. 2011

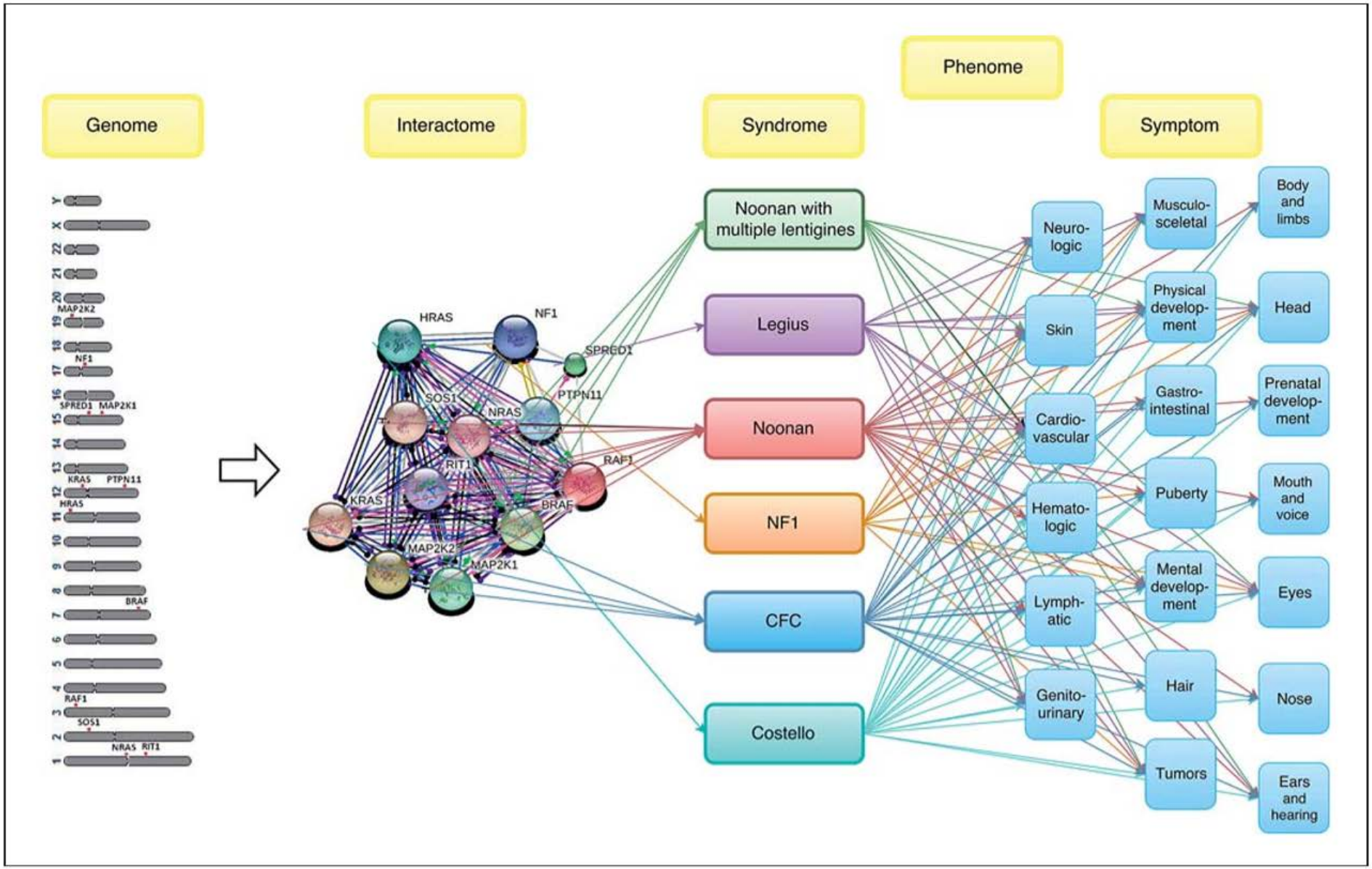
RASopathies

- Clinically defined group of overlapping genetic syndromes
- Usually germline mutations in genes encoding components or regulators of the RAS/MAPK pathway
- ~ 1 : 1000 births

Tidyman W, Rauen KA. Curr Genet Med Rep. 2016
Rauen KA. Annu Rev Genomics Hum Genet. 2014
Lissewski et al. Am J Med Genet. 2015



Rauen KA. Annu Rev Genomics Hum Genet. 2014

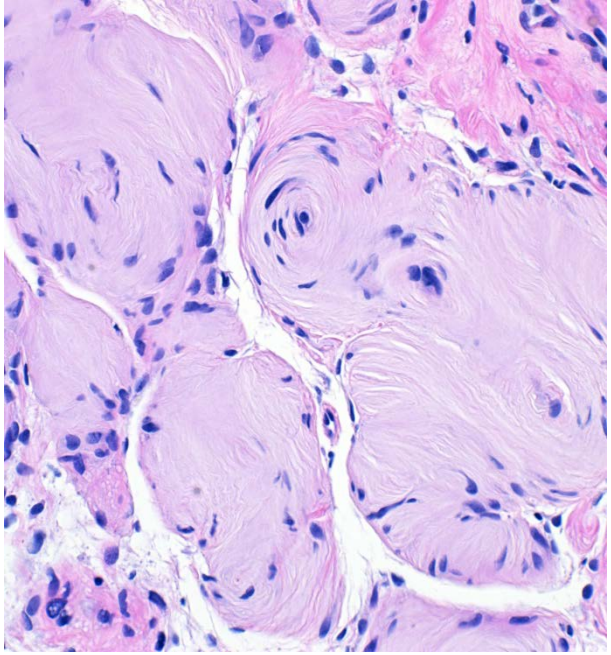


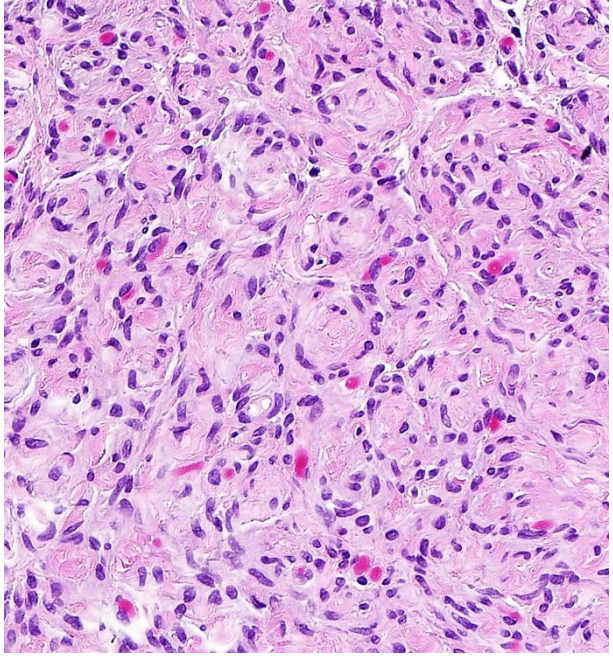
Pevec U et al. Mol Syndromol. 2016

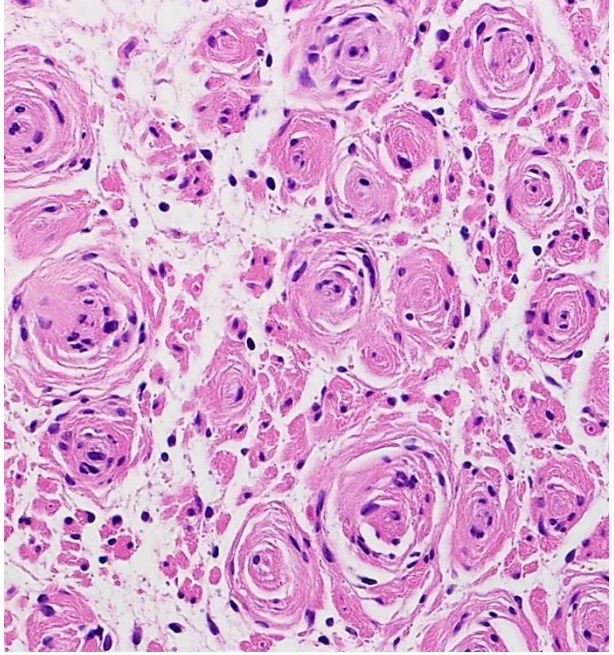
LHN
Differential diagnosis

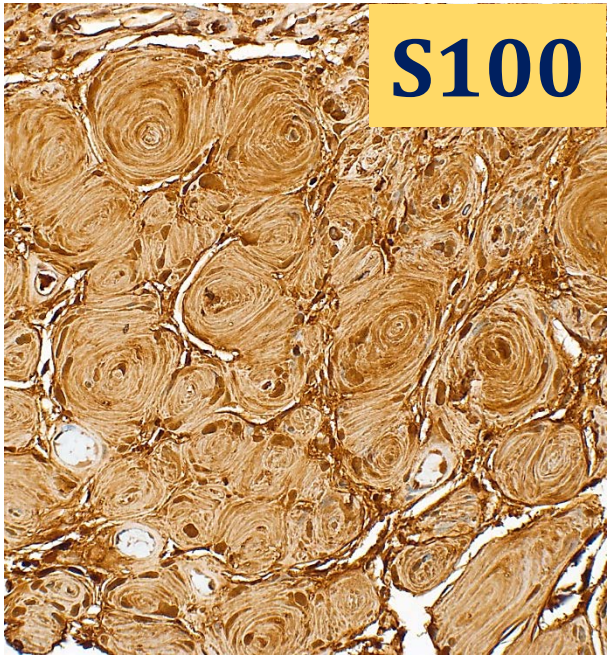
- Intraneural perineurioma
- Neurofibroma with onion bulb-like formation
- Hereditary neuropathies associated with onion-bulb formation (e.g. Charcot-Marie-Tooth)

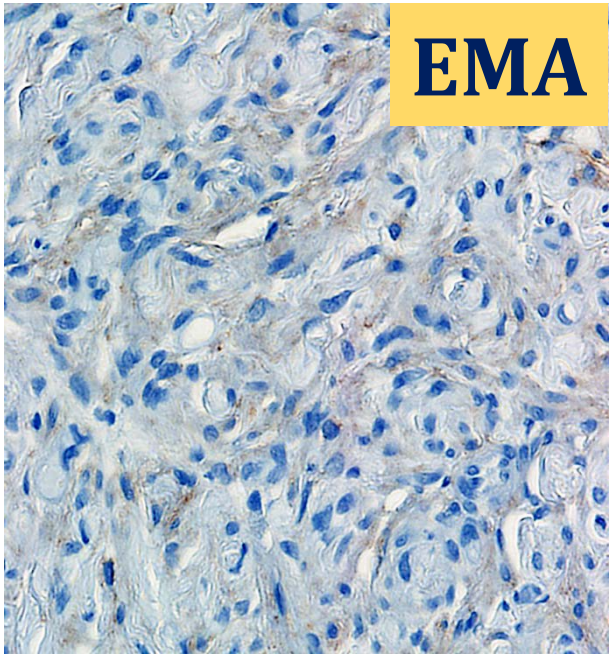
Norris B et al. J Clin Neurosci. 2011

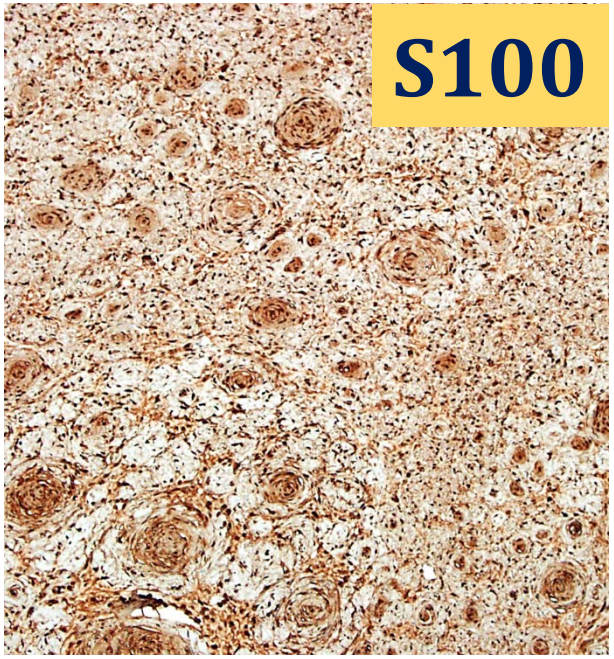












LHN

Perineurioma

Neurofibroma w/onion bulb-like

Conclusions

1. True LHN is a rare disorder that may be associated with activating RAS mutations
2. RASopathies comprise one of the largest groups of familial genetic syndromes
3. Targeted therapies are being developed and may become of practical use to treat a subset of clinical manifestations

Acknowledgments:

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