# Two Cases of Slowly Progressive Distal Weakness

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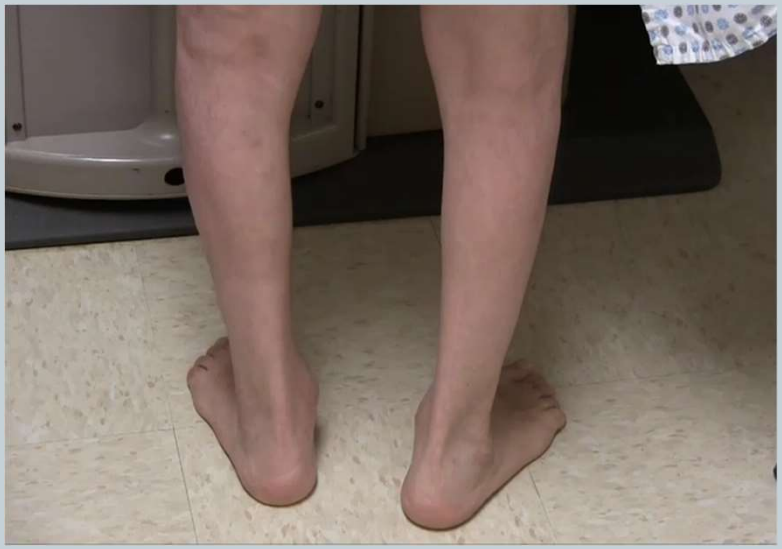
# Case 1

- History of Present Illness
  - 51 yo Hispanic man presents with slowly progressive weakness over 20 years
  - Unable to stand on heels and toes
  - Difficulty with climbing stairs and rising from a deep chair
  - No weakness in the upper extremities
  - No myalgias, dysarthria, dysphagia, double vision, or sensory symptoms
  - No significant family history of similar symptoms or neurologic disorders

# Case 1

- Physical Exam
  - Normal mental status
  - Cranial nerves intact. Speech fluent without dysarthria. No tongue atrophy or fasciculations
  - Atrophy of the calves and intrinsic hand muscles
  - Strength 4+/5 bilateral hip flexion, 3/5 ankle dorsiflexion and plantar flexion. Otherwise full strength in the upper and lower extremities
  - Reflexes brisk at the knees and absent at the ankles
  - Normal sensation to all modalities



# Case 1

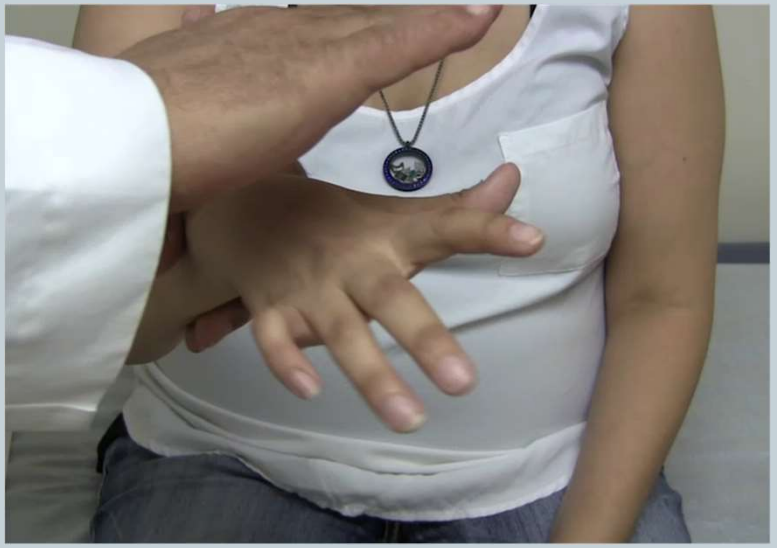
- Workup
  - CK 3400
  - EMG/NCS
    - Normal sensory nerve conductions in upper and lower extremities
    - Motor nerve conductions showed severely decreased amplitudes in the lower extremity and were normal in the upper extremities
    - Decreased recruitment and high amplitude (8-9 mV) motor units in the lower extremities. No spontaneous activity
    - Normal thoracic paraspinal muscles
  - MRI brain normal
  - Genetic testing for *SMN1* mutations and Kennedy disease were negative

# Case 2

- History of Present Illness
  - 55 yo Hispanic woman presents with slowly progressive lower extremity weakness
  - Symptoms began as a teenager when she had difficulty marching in band
  - 2-3 years later, began walking with a limp due to bilateral foot drop
  - Over years, weakness in the lower extremities progressed and also developed weakness in the hands and twitching in the thighs
  - No sensory symptoms, dysphagia, dysarthria, double vision, muscle cramps
  - No significant family history of similar symptoms or neurologic disorders

# Case 2

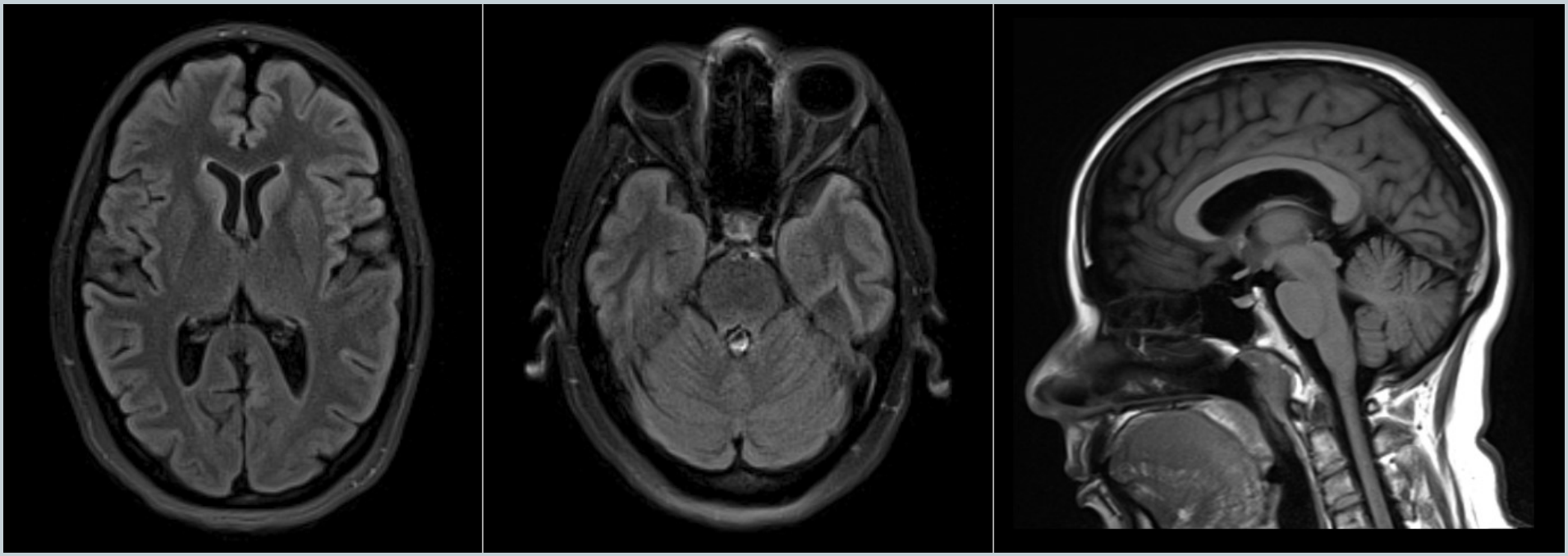
- Physical Exam
  - Normal mental status
  - Cranial nerves intact. Speech fluent without dysarthria. No tongue atrophy or fasciculations
  - Atrophy in the distal arms and legs. No fasciculations
  - Strength 2/5 ankle dorsiflexion and plantar flexion, 3/5 hip flexion, 3/5 intrinsic hand muscles, 4/5 deltoid and triceps
  - Reflexes were brisk in the arms and knees, absent at the ankles
  - Normal sensation to all modalities



# Case 2

- Workup
  - EMG/NCS
    - Normal sensory nerve conductions in upper and lower extremities
    - Motor nerve conductions showed severely decreased amplitudes in the lower extremities > upper extremities
    - Decreased recruitment and high amplitude motor units in upper and lower extremities, distal worse than proximal
    - Fibrillation potentials and positive sharp waves in the distal lower extremities
  - Genetic testing for *SMN1* mutations was negative

# Case 2



# Differential Diagnosis?

**ADDITIONAL WORKUP?**

# Whole Exome Sequencing

- Case 1: Homozygous, pathogenic variant in *VRK1* gene
  - c.C961T, p.R321C
- Case 2: Compound heterozygous pathogenic variants in *VRK1* gene
  - c.C961T, p.R321C
  - c.G706A, p.V236M

# Non-5q Spinal Muscular Atrophy

- Genetically and clinically heterogenous group
- Over 30 genes identified
- Classified according to the distribution of the weakness and the mode of inheritance
- *VRK1* is categorized as an SMA+ syndrome
  - Phenotype of anterior horn cell disease combined with pontocerebellar hypoplasia (SMA-PCH)
  - First genetically confirmed case described in 2009

Darras BT. *Neurology* 2011.

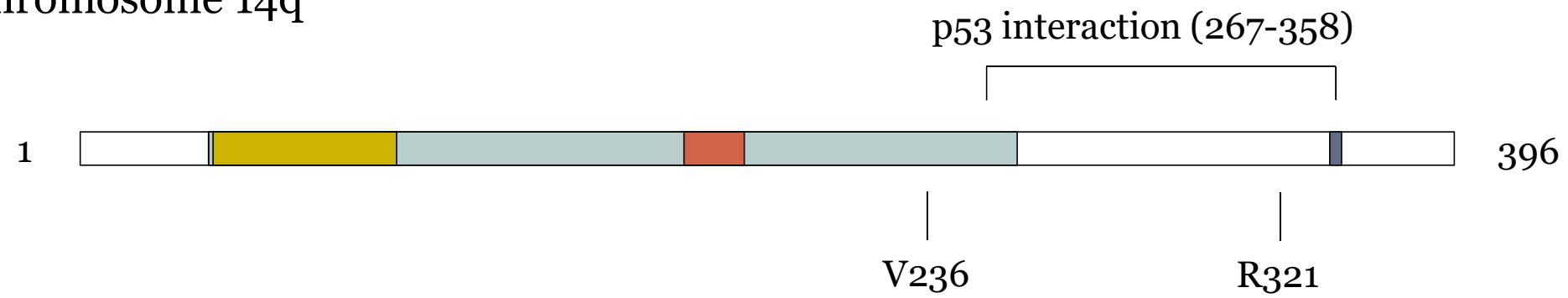
# *VRK1* gene

- 9 confirmed cases are reported in the literature
  - Most commonly infant onset weakness
  - Some reports of hyperreflexia, ataxia, dysarthria, respiratory weakness, or cognitive impairment
  - MRI brain: microcephaly and pontocerebellar hypoplasia
- Only 1 reported adult onset case
  - Progressive, distal symmetric weakness and atrophy
  - MRI brain: Normal, no cerebellar atrophy
  - EMG/NCS: Motor neuronopathy
  - WES: Compound heterozygous variants in *VRK1* (c.A356G, p.H119R; c.C961T, p.R321C)

Nguyen TP et al. *J Clin Neuromuscul Dis* 2015.

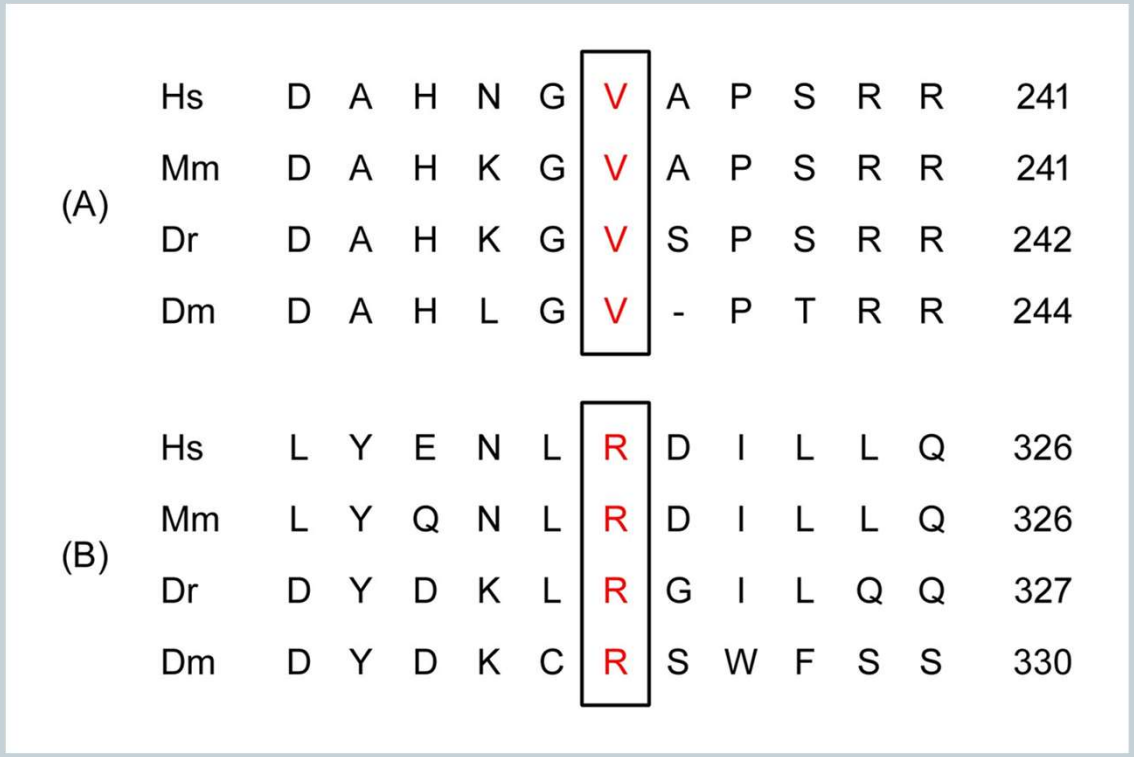
# *VRK1* gene

Chromosome 14q




- Protein kinase domain (35-275)
- ATP binding site (36-87)
- Kinase active site (173-185)
- Nuclear localization signal (356-360)

# Sequence Variants



# Sequence Variants

- c.G706A, p.V236M
  - Has been identified in 6 individuals in gnomAD, none in homozygous state
  - Allele frequency: 0.014% in Latino population, 0.002% in general population

- c.C961T, p.R321C
  - Has been identified in 49 individuals in gnomAD, none in homozygous state
  - Allele frequency: 0.089% in Latino population, 0.019% in general population

# Conclusion

- *VRK1* associated spinal muscular atrophy is a diagnostic consideration in adult patients presenting with progressive distal weakness and atrophy
- Although pontocerebellar hypoplasia has been demonstrated in infant onset cases, adult onset cases have not shown evidence of cerebellar abnormalities
- The R321C variant may be associated with adult-onset disease
- Disease caused by these variants may be more common in the Latino population

# References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