

Adult-Onset Spinal Muscular Atrophy due to Mutations in the *VRK1* Gene

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Abstract

Objective

To expand our knowledge of the range of clinical phenotypes associated with vaccinia-related kinase 1 (*VRK1*) gene mutations.

Methods

We present clinical and molecular data of 2 individuals with slowly progressive weakness and a clinical syndrome consistent with adult-onset spinal muscular atrophy without pontocerebellar atrophy.

Results

Genetic testing revealed likely pathogenic variants in the *VRK1* gene in both subjects. One individual carried homozygous p.R321C (c.961 C>T), likely pathogenic variants. The other carried compound heterozygous p.V236M (c.706 G>A) and p.R321C (c.961 C>T), likely pathogenic variants. Notably, both patients were of Hispanic descent.

Conclusions

We report 2 cases with *VRK1* mutations presenting as adult-onset spinal muscular atrophy without pontocerebellar hypoplasia and review the current literature of similar cases. Our report expands the clinical spectrum of neurologic disorders associated with *VRK1* mutations.

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Glossary

gnomAD = Genome Aggregation Database; **NCS** = nerve conduction study; **SMA** = spinal muscular atrophy; **SMN1** = survival motor neuron 1; **VRK1** = vaccinia-related kinase 1; **WES** = whole-exome sequencing.

The spinal muscular atrophies (SMAs) are a heterogeneous group of disorders characterized by degeneration of the anterior horn cells, resulting in progressive muscle weakness and atrophy. Although the classic form of SMA is caused by mutations in the survival motor neuron 1 (*SMN1*) gene on chromosome 5q, there are a host of rare non-5q spinal muscular atrophies with varying clinical phenotypes. The vaccinia-related kinase 1 (*VRK1*) gene is a gene located on chromosome 14q32 that was fairly recently identified as associated with SMA, particularly a phenotype of SMA with pontocerebellar hypoplasia. The initial case report described infantile onset with clinical features of microcephaly, upper

limb ataxia, hyperreflexia, intellectual disability, and motor and sensory neuropathy with cerebellar hypoplasia on imaging.¹

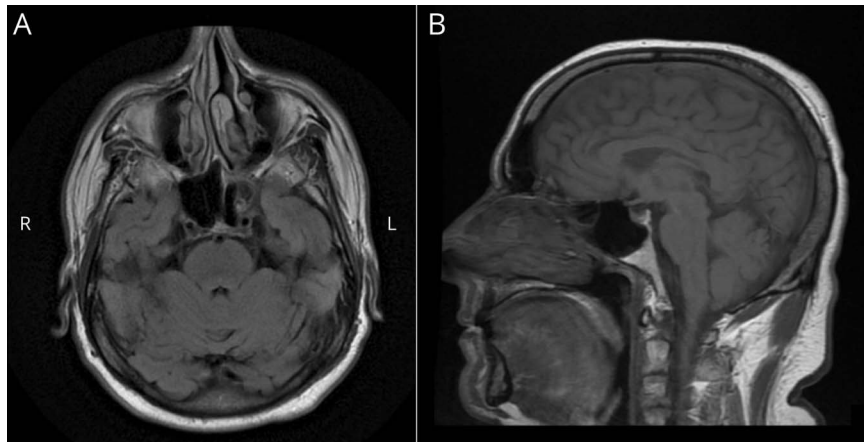
Since identification, several other cases of *VRK1* mutation have been identified with clinical features including congenital/infantile-onset progressive sensorimotor neuropathy with microcephaly,² as well as reports of adult-onset progressive weakness with features consistent with amyotrophic lateral sclerosis³ or adult-onset distal hereditary motor neuropathy⁴ without brain abnormalities. The previously reported *VRK1* mutations and associated clinical phenotypes are summarized in the table. Despite these reports of new

Table Summary of Previously Reported *VRK1* Mutations

| Ref | Sequence variants | Onset | Family history | Phenotype | MRI |
|-----|--|-------|--|---|---|
| 1 | Homozygous p.R358X | I | Ashkenazi Jewish | Delayed motor milestones, ataxia, hyperreflexia, and intellectual disability | Microcephaly and cerebellar hypoplasia |
| 8 | Homozygous p.R133C | I | Consanguineous family | Intellectual disability | Cerebellar hypoplasia |
| 2 | Heterozygous p.R89Q, p.V236M | I | 2 sisters | Delayed motor milestones, hypotonia, hyporeflexia, scoliosis, respiratory compromise, and normal cognition | Microcephaly and simple gyral pattern |
| | Homozygous p.R358X | I | Ashkenazi Jewish | Delayed motor milestones, hypotonia, tremor, hypophonia, dysarthria, and scoliosis | Microcephaly, abnormal gyri, and vermis |
| 3 | Heterozygous p.H119R, p.R321C | A | Hispanic | Progressive, distal symmetric weakness/atrophy, pes cavus, hammer toes, hyperreflexia, and normal cognition | Normal |
| 9 | Heterozygous p.H119R, p.R358X | C | Ashkenazi Jewish | Progressive lower limb weakness/atrophy and normal cognition | Spinal cord and brain atrophy |
| | Heterozygous p.G135R, p.L195V | C | | Short stature, microcephaly, distal weakness/atrophy, hyperreflexia, scoliosis, and respiratory dysfunction | Normal |
| 10 | Homozygous p.R358X | F | Ashkenazi Jewish | Microcephaly, cortical dysplasia, and clubfoot | Microcephaly |
| 11 | Homozygous p.R358X | C | | Distal weakness in the legs progressing to the arms and pes cavus | Normal |
| 12 | Homozygous c.1159 + 1G>A splice variant | C | Family with 5 affected individuals | Childhood-onset SMA, brisk tendon reflexes, and normal intellectual ability | Normal |
| 13 | Heterozygous p.T256I, p.D267G | C | | Childhood-onset ALS and intellectual disability | Pineal cyst, otherwise normal |
| 14 | Homozygous p.W375X | C | 2 siblings, Han Chinese | Symmetric, distal weakness/atrophy | Normal |
| 4 | Homozygous p.R387H | A | 2 cases from unrelated consanguineous Moroccan Jewish families | Weakness, calf atrophy, absent Achilles reflexes, and normal sensation | Normal |
| 15 | Heterozygous p.R89X, p.G257S Heterozygous c.T71014C (intron 8), p.R241C | C | 2 unrelated cases | Weakness and pyramidal signs | Normal |

Abbreviations: A = adult; C = childhood; F = fetal; I = infancy; Ref = reference (see References section for corresponding reference).

Figure 1 Brain MRI of Patient 1



(A) Axial T2 fluid-attenuated inversion recovery through the pons and cerebellum and (B) sagittal T1 through the brainstem and cerebellar vermis without any evidence of pontocerebellar atrophy.

phenotypes, the Online Mendelian Inheritance in Man database still lists pontocerebellar hypoplasia type 1A as the single phenotype associated with *VRK1* pathogenic variants. Here, we report 2 cases of *VRK1* mutations resulting in an adult-onset SMA-like phenotype without pontocerebellar hypoplasia.

Methods

Clinical evaluation of patients was performed at the Nerve and Muscle Center of Texas. Verbal consent for publication was obtained from the patients. Diagnostic workup included brain MRI, EMG, and nerve conduction studies (NCSs), and whole-exome sequencing (WES). NextGen whole-exome sequencing was performed on an Illumina system with 100 base pairs or greater paired-end reads. Depth of coverage ranged between 121× maximum and 10× minimum and 98.7% of the exome was surveyed. Hundred percent of the *VRK1* coding region was covered at a minimum of 10×.

Standard Protocol Approvals, Registrations, and Patient Consents

Verbal consent for publication was obtained from the patients.

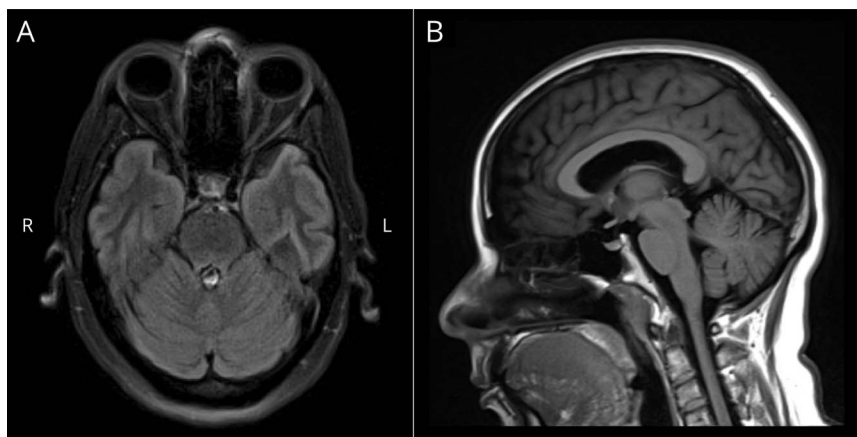
Data Availability

Anonymized data will be shared by request from any qualified investigator.

Case 1

A 51-year-old Hispanic man presented for evaluation of worsening weakness over 20 years. He reported weakness mainly in the lower extremities, resulting in difficulty with climbing stairs and rising from a deep chair. In addition, he experienced muscle cramps and low back pain but no myalgias, dysarthria, dysphagia, or double vision. On examination, he had bilateral calf atrophy and 4+/5 strength in hip flexion and plantar flexion and 3+/5 strength in dorsiflexion as rated

Figure 2 Brain MRI of Patient 2



(A) Axial T2 fluid-attenuated inversion recovery through the pons and cerebellum and (B) sagittal T1 through the brainstem and cerebellar vermis without any evidence of pontocerebellar atrophy.

Figure 3 Serine/Threonine-Protein Kinase *VRK1* Conservation Across Evolution

| A | |
|----|----------------------------------|
| Hs | D A H N G V A P S R R 241 |
| Mm | D A H K G V A P S R R 241 |
| Dr | D A H K G V S P S R R 242 |
| Dm | D A H L G V - P T R R 244 |
| B | |
| Hs | L Y E N L R D I L L Q 326 |
| Mm | L Y Q N L R D I L L Q 326 |
| Dr | D Y D K L R G I L Q Q 327 |
| Dm | D Y D K C R S W F S S 330 |

Multiple protein alignments highlight the high degree of evolutionary conservation of valine at position 236 (A) and arginine at position 321 (B) of the human amino acid sequence. The numbers on the right side of each sequence correspond to the last amino acid depicted. Dm = *Drosophila melanogaster*; Dr = *Danio rerio*; Hs = *Homo sapiens*; Mm = *Mus musculus*.

on the Modified Research Council grading scale. He had normal strength in the arms. Reflexes were normal except for absent ankle reflexes. The rest of the neurologic examination, including mental status, speech, sensation, and coordination, was unremarkable.

EMG/NCSs showed normal sensory nerve conductions, low-amplitude motor responses, and neurogenic motor units predominantly in the lower extremities. This was consistent with a picture of motor neuron disease. Creatine kinase was elevated at 3,400 IU/L. Brain MRI was normal (figure 1). Genetic testing for *SMN1* gene deletion was not detected. WES identified a homozygous, likely pathogenic variant in the *VRK1* gene (c.C961T, p.R321C).

Case 2

A 55-year-old Hispanic woman presented for evaluation of progressive lower extremity weakness. She had noticed symptoms since age 16 years when she had difficulty marching in the band, and 2–3 years later, she began walking with a limp. Gradually, she developed bilateral foot drop and weakness of hand grips. She reported twitching in the thigh muscles and poor balance. She denied sensory symptoms, dysphagia, dysarthria, visual symptoms, and muscle cramps. On examination, she was noted to have distal atrophy in the arms and legs without fasciculations. Strength was 1/5 in dorsiflexion/plantar flexion, 2/5 in hip flexion, and 4/5 in the deltoids and biceps. She had absent ankle reflexes, but otherwise normal reflexes. The rest of the neurologic examination was unremarkable.

EMG/NCSs showed normal sensory nerve conductions, low-amplitude motor responses, and widespread active and

chronic denervation in the upper and lower extremities proximally and distally. Brain MRI was normal (figure 2). WES identified compound heterozygous (c.G706A, p.V236M and c.C961T, p.R321C) pathogenic variants in the *VRK1* gene.

Discussion

The *VRK1* gene encodes a serine kinase that is ubiquitously expressed, including in the fetal and adult brain and cerebellum. The serine/threonine-protein kinase *VRK1* has been shown to phosphorylate a number of substrates, including p53, in an autoregulatory loop that is important for the development and maintenance of the nervous system.^{5,6} Although the survival motor neuron protein is also known to interact with p53, whether disease mechanisms are shared between *SMN1*- and *VRK1*-related disorders is currently not known.

We identified 2 individuals with clinical features of lower motor neuron disease consistent with adult-onset spinal muscular atrophy. Compared with previous SMA cases reported in the literature, these 2 cases demonstrate later onset of disease with milder clinical symptoms. Unlike most of the previously reported cases, there was no evidence of pontocerebellar hypoplasia or cognitive symptoms.

Of all current *VRK1* variants identified in individuals with neurologic disease, only p.R358X is currently reported in ClinVar as pathogenic. Increasing our understanding of *VRK1* variants in neurologic disease in different populations is an important goal. Both of our subjects were found to carry the R321C sequence variant. In the first case, the variant was found in the homozygous state, and in the second subject, it was in a compound heterozygous state with V236M. *VRK1* R321C was previously reported as a compound heterozygous variant with H119R in an individual with adult-onset amyotrophic lateral sclerosis.³ *VRK1* V236M was previously reported as a compound heterozygous variant with R89Q in 2 siblings with rapidly progressive sensorimotor polyneuropathy and microcephaly.²

VRK1 residues 321 and 236 are evolutionarily conserved from fruit flies to humans, and the variants identified are predicted to be deleterious (figure 3). Of interest, both variants are present at very low frequency in control individuals of European, African, and Asian descent in the Genome Aggregation Database (gnomAD).⁷ In contrast, allele frequency of R321C and V236M is higher in the Latino population (0.095% and 0.015%, respectively). It is important that no homozygous individuals for either of these 2 variants are found in gnomAD, suggesting that despite the heterozygote frequency in the Latino population, these variants are likely pathogenic. As a comparison, R358X, an established *VRK1* pathogenic variant,

is found at higher frequency in individuals of Ashkenazi Jewish descent in gnomAD (0.14%) compared with other populations and is also not observed in the homozygous state in this database.

Our 2 cases, combined with the previous reports by Nguyen and Greenbaum, suggest that *VRK1* variants may present with adult-onset motor neuron disease without pontocerebellar atrophy. In addition, our data suggest a role in pathogenicity for both *VRK1* R321C and V236M. Identification of R321C in the homozygous state in an affected individual (case 1) and its absence in homozygosity in control populations, despite the presence of this variant in heterozygosity in a large percentage of normal individuals, argues for a pathogenic role of R321C. Moreover, our data show that disease caused by R321C and V236 may be more common in Latinos compared with other populations.

Spinal muscular atrophy related to mutations in the *VRK1* gene is a relatively recently identified association. We reported 2 cases with *VRK1* mutations presenting as adult-onset spinal muscular atrophy without pontocerebellar hypoplasia. Genetic testing in patients like ours is important to expand understanding of the clinical spectrum of this disorder.

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Disclosure

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Appendix Authors

| Name | Location | Contribution |
|-------------------|--|--|
| Angela Sung, MD | University of California, San Diego | Reviewed the literature, drafted the initial manuscript, and made multiple revisions |
| Paolo Moretti, MD | University of Utah Health Science Center, Salt Lake City | Interpreted data, investigated sequence variants in genetic databases, and made multiple revisions |
| Aziz Shaibani, MD | Nerve and Muscle Center of Texas, Houston | Collected clinical data, directed clinical testing for the patients, and made multiple revisions |

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