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<history>
<date>February 26, 2018 - created</date>
<date>April 30, 2018 - changed encoding of entities, props and premises; misc
edits</date>
<date>May 10, 2018 - edited Arg 9</date>
<author>Nancy Green, University of N.C. Greensboro</author>

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Annotated Full-Text (CRAFT) corpus (v1.0) to which I have added annotations for
describing arguments in the Results/Discussion section of the article using
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<citation>
<author>Green, Nancy L.</author>
<title>Towards Mining Scientific Discourse Using Argumentation Schemes</title>
<journal>Argument and Computation</journal>
<date>To appear in 2018 or 2019</date>
</citation>
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<citation>
<author>van de Leemput, J., et al.</author>
<title>Deletion at ITPR1 Underlies Ataxia in Mice and Spinocerebellar Ataxia 15 in
Humans.
</title>
<journal>PLoS Genetics, June 2007, Volume 3, Issue 6, e106, 1076-1082.</journal>
</citation>

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<CRAFT-info>
CRAFT is a manually annotated corpus of full-text biomedical journal articles.
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For information on the CRAFT corpus see:
<citation>
Bada, M., Eckert, M., Evans, D., Garcia, K., Shipley, K., Sitnikov, D., Baumgartner Jr.,
W. A., Cohen, K. B., Verspoor, K., Blake, J. A., and Hunter, L. E. Concept Annotation
in the CRAFT Corpus. BMC Bioinformatics. 2012 Jul 9;13:161. doi:
10.1186/1471-2105-13-161.
[PubMed:22776079]</citation>
<citation>
Verspoor, K., Cohen, K.B., Lanfranchi, A., Warner, C., Johnson, H.L., Roeder, C.,
Choi, J.D., Funk, C., Malenkiy, Y., Eckert, M., Xue, N., Baumgartner Jr., W.A., Bada,
M.,
Palmer, M., Hunter L.E. A corpus of full-text journal articles is a robust evaluation
tool for revealing differences in performance of biomedical natural language processing
tools. BMC Bioinformatics. 2012 Aug 17;13(1):207. [PubMed:22901054]</citation>
</CRAFT-info>

<acknowledgments>
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the support of a University of North Carolina Greensboro 2016 Summer Faculty Excellence
Research Grant.
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</acknowledgments>

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<article>

<title>
<content>Deletion at ITPR1 Underlies Ataxia in Mice and Spinocerebellar Ataxia 15 in Humans.</content>
<main-claim>Deletion at ITPR1 Underlies Ataxia in Mice and Spinocerebellar Ataxia 15 in Humans.</main-claim>
</title>

<section> <section-heading>Abstract</section-heading>
<content>
We observed a severe autosomal recessive movement disorder in mice used within our laboratory.
We pursued a series of experiments to define the genetic lesion underlying this disorder and to identify a cognate disease in humans with mutation at the same locus.
Through linkage and sequence analysis we show here that this disorder is caused by a homozygous in-frame 18-bp deletion in Itpr1 (Itpr1Δ18/Δ18), encoding inositol 1,4,5-triphosphate receptor 1.
A previously reported spontaneous Itpr1 mutation in mice causes a phenotype identical to that observed here.
In both models in-frame deletion within Itpr1 leads to a decrease in the normally high level of Itpr1 expression in cerebellar Purkinje cells.
Spinocerebellar ataxia 15 (SCA15), a human autosomal dominant disorder, maps to the genomic region containing ITPR1;
however, to date no causal mutations had been identified.
Because ataxia is a prominent feature in Itpr1 mutant mice, we performed a series of experiments to test the hypothesis that mutation at ITPR1 may be the cause of SCA15.
We show here that heterozygous deletion of the 5′ part of the ITPR1 gene, encompassing exons 1–10, 1–40, and 1–44 in three studied families, underlies SCA15 in humans.</content>
<main-claim>heterozygous deletion of the 5′ part of the ITPR1 gene, encompassing exons 1–10, 1–40, and 1–44 in three studied families, underlies SCA15 in humans.</main-claim>
</section>

<section> <section-heading>Author Summary</section-heading>
<!-- This section appeared in an inset -->
<content>
We have identified a spontaneous in-frame deletion mutation in the gene Itpr1 that causes a recessive movement disorder in mice.
In an attempt to define whether any similar disease occurs in humans we performed a literature search for diseases linked to the human chromosomal region containing ITPR1.
We identified the disease spinocerebellar ataxia 15 as linked to this region.
High-density genomic analysis of affected members from three families revealed that disease in these patients was caused by deletion of a large portion of the region containing ITPR1.
We show here that this mutation results in a dramatic reduction in ITPR1 in cells from these patients.
These data show convincingly that ITPR1 deletion underlies spinocerebellar ataxia 15 in humans.</content>
<main-claim>ITPR1 deletion underlies spinocerebellar ataxia 15 in humans.</main-claim>
</section>

<section> <section-heading>Introduction</section-heading>
<content>
The use of forward genetics to define novel loci of interest in human disease has become increasingly viable with the implementation of large-scale mutagenesis programs.
Prior to these initiatives this work was carried out in part by the investigation of spontaneous mutations that cause disorders in mouse breeding colonies.
Careful observation of these serendipitous events has led to the establishment and study of many in vivo disease models [3].
During the generation of a knockout line of mice we noted an early movement disorder that was inherited independently of targeting vector transmission.
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We embarked on a series of experiments to identify the genetic lesion underlying this movement disorder and to identify a cognate disease and corresponding mutation in humans.
Here we describe this effort and the discovery of deletion at the ITPR1 locus as a cause of this disorder in mice and of spinocerebellar ataxia 15 (SCA15) in humans.
</content>
<main-claim>deletion at the ITPR1 locus as a cause of this disorder in mice and of spinocerebellar ataxia 15 (SCA15) in humans.</main-claim>
</section>

<section> <section-heading>Results/Discussion</section-heading>
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[para-1] During the generation of a line of mice with knockout of the gene Park7 we noted an early movement disorder that was inherited independently of targeting vector transmission.
Our initial observations suggested the affected mice suffered from an apparently paroxysmal movement disorder, often induced by touch.
The abnormal movements occurred predominantly below the cervical level, and the disorder appeared progressive.
At initial examination, a human movement disorder specialist (K. G.-H.) likened the disorder to episodic intermittent ataxia or kinesiogenic paroxysmal dystonia and predicted the involvement of an ion channel mutation in the etiology.
Affected mice presented at approximately postnatal day 14, and survival time without weaning was on average 4 wk after onset.
[para-2] Breeding experiments suggested that the observed disorder was inherited in an autosomal recessive manner.
</content>

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To map the location of the disease-causing lesion, we performed genome-wide linkage analysis using strain-specific single nucleotide polymorphisms (SNPs) at 120 loci across the mouse genome.
Analysis of these data showed a single genomic region with significant linkage to disease, providing a two-point LOD score of 5.13 at marker 20.MMHAP85FLG2 Chromosome 6qE1.
The linked haplotype suggested the mutation had occurred on the 129x1/SvJ background (Figure S1).
</content>

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  may be the  cause of the ataxia-like disorder in the affected mice" />
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</DSEG>

<DSEG ID="Experiment 2" >
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<content>
[para-3]Literature searches revealed that among disease lines mapped to 6qE1, the spontaneous mutant opt mouse displays a strikingly similar presentation to that described here [1].
The underlying genetic lesion causing the opt phenotype is a homozygous in-frame deletion of exons 43 and 44 of the gene Itpr1 (Itpr1opt/opt), encoding inositol 1,4,5-triphosphate receptor 1 (Itpr1).
</content>

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<entity ID="geno2a" paraphrase="homozygous mutation of Itpr1" />
<!-- geno2a is a generalization of geno2 that was not explicitly mentioned in text -->
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  paraphrase="A homozygous mutation of Itpr1 may be the  cause of the disorder of the affected mice" />
</argument>

<content>
Sequencing of all exons and intron-exon boundaries of Itpr1 in affected mice from the current study revealed a single mutation within Itpr1: a novel in-frame deletion of 18 bp within exon 36 (Itpr1Δ18/Δ18).
</content>

<entities-props>
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  paraphrase="The Itpr1Δ18/Δ18 mutation may be the cause of the affected mice's disorder" />
</argument>

<content>
To confirm the pathogenicity of this mutation we crossed heterozygous mice from the current study (Itpr1wt/Δ18) with mice heterozygous for the opt mutation (Itpr1wt/opt).
This resulted in two litters of mice with a total of four affected Itpr1opt/Δ18 pups (from a total of 15) with a phenotype indistinguishable from that of the Itpr1Δ18/Δ18 and Itpr1opt/opt mice [1].
Furthermore, this phenotype was similar, although less severe, to that described in a mouse line with targeted deletion of Itpr1, where ataxia was described as a prominent
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feature [4].
</content>

<argument old-id="3.3" scheme="Domain-specific: Proportional agreement">
<premise-list>
<premise paraphrase="The predicted proportion of Itpr1opt/Δ18 offspring
resulting from crossing Itpr1wt/Δ18 mice with mice Itpr1wt/opt mice is 25%" />
<premise paraphrase="Approximately 25% of the offspring resulting from crossing
Itpr1wt/Δ18 mice with Itpr1wt/opt mice had the ataxia-like phenotype (like that of the
Itpr1Δ18/Δ18 mice and Itpr1opt/opt mice)" />
</premise-list>
<conclusion paraphrase="The genotype of the offspring with the ataxia-like phenotype
was Itpr1opt/Δ18" />
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<argument old-id="3.4" scheme="Domain-specific: Pathogenic effect">
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ataxia-like phenotype was Itpr1opt/Δ18" />
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phenotype" />
<premise paraphrase="If an allele has a similar effect when
substituted for a known pathogenic allele (e.g. Itpr1opt) it may be pathogenic" />
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<conclusion paraphrase="the Itpr1Δ18 allele is pathogenic" />
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<DSEG ID="Experiment 3" >
<content>
[para-3 continued] As with the Itpr1opt/opt mice, where the deletion of exons 43 and 44
is also predicted to leave the translational reading frame unaffected, the in-frame
Itpr1Δ18/Δ18 deletion mutation results in markedly decreased levels of Itpr1 in
cerebellar Purkinje cells.
</content>

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Purkinje cells" />
<prop>have_prot(group2,prot1)</prop>
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<premise prop="have_prot(group1,prot1)" />
<premise domain-prop="similar(geno2, geno3)"
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  Itpr1)" />
<premise domain-prop="similar(pheno1, pheno2)" />
</premise-list>
<conclusion inferred-prop="cause(geno3, pheno1, group1)"
  paraphrase="The mutation Itpr1Δ18/Δ18 may cause an ataxia-like phenotype in the
  Itpr1Δ18/Δ18 mice"  />
</argument>

</DSEG>

<DSEG ID="Summary" >
<content>
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[para-3 continued]In these two spontaneous mutants [1] and in the Itpr1-deficient mouse [4] generated by gene targeting, decreased Itpr1 expression is associated with the same autosomal recessive movement disorder (Figure 1).
</content>

<entities-props>
<entity ID="group3s" paraphrase="these two spontaneous mutants and the Itpr1-deficient mouse
generated by gene targeting"/>
<entity ID="geno3s" paraphrase="homozygous deletion in Itpr1" />
<prop>have_geno(group3s,geno3s)</prop>
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</premise-list>
<conclusion inferred-prop="cause(geno3s, pheno2, group3s)"
  paraphrase="Homozygous deletions in Itpr1 may cause an ataxia-like phenotype in mice" />
</argument>

</DSEG>

<DSEG ID="Experiment 4">
<content>
[para 4] Given our interest in human neurological disease we sought to identify any cognate human disorders where linkage had been established to the syntenic region of the human genome, but where no causal mutation had been identified.
SCA15, an adult-onset autosomal dominant progressive ataxia is linked to this locus [5].
Although missense mutation of ITPR1 had previously been ruled out [2] and the mode of inheritance was inconsistent with that seen in the Itpr1Δ18 and Itpr1opt mice, the phenotypic presence of ataxia in the mice led us to reexamine this candidate gene as a possible cause of SCA15.
</content>
<entities-props>
<entity ID="geno4" paraphrase="autosomal dominant mutation in ITPR1" />
<entity ID="group4" paraphrase="human" />
<entity ID="pheno3" paraphrase="SCA15" />
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<!-- The conclusion of ARG4s is an inferred prop -->
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<conclusion prop="cause(geno4,pheno3,group4)" />
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<content>
[para 5] We obtained genomic DNA from three affected family members and one family member with unknown disease status from the kindred originally used to define and map SCA15 (family AUS1, of Australian Anglo-Celtic origin) [2].
We performed two experiments concurrently in three affected members of this family: sequence analysis of the coding exons of ITPR1 and high-density genome-wide SNP

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genotyping.
Sequence analysis failed to show any coding alterations segregating with disease or any alterations that were inconsistent with Mendelian patterns of inheritance within the family.
However, visualization of log R ratio and B allele frequency metrics from the genome-wide SNP genotyping experiments clearly showed data consistent with a heterozygous genomic deletion across the first one-third of ITPR1 and across the first half of a neighboring gene, SUMF1 (Figure 2).
This deletion was apparent in all three affected family members studied and absent from the family member with unknown affection status (Figure 3).
The SNP data showed a deletion of between 188 kb and 210 kb in size;
examination of SNPs at the flanking unknown regions of this deletion allowed us to delimit the borders of the deletion to 7.5 kb on the telomeric side of the deletion (between rs12634249 and rs793396) and ~14.4 kb on the centromeric side of the deletion (between rs4073665 and rs17709863).
</content>

<entities-props>
<entity ID="group5" paraphrase="three affected family members ... from the kindred originally used to define and map SCA15 (family AUS1, of Australian Anglo-Celtic origin)" />
<entity ID="geno5" paraphrase="heterozygous genomic deletion across the first one-third of ITPR1 and across the first half of a neighboring gene, SUMF1" />
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  paraphrase="The ITPR1-SUMF1 deletion may be the cause of the family members SCA15"  />
</argument>

</DSEG>

<DSEG ID="Experiment 5">
<content>
In an attempt to define whether this variation was a benign polymorphism we analyzed genome-wide SNP data at this locus, produced using the same genotyping chip, from 577 individuals of European descent who were either controls or individuals with an unrelated neurological disorder.
We failed to find any deletions affecting the coding sequence of either gene, ITPR1 or SUMF1;
we did, however, identify a single individual with a possible heterozygous deletion approximately 6 kb in size within intron 40–41 of ITPR1, at least 5 kb away from exon 40.
Given the location of this alteration it is unlikely to effect the expression or splicing of ITPR1.
</content>

<entities-props>
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</premise-list>
<conclusion inferred-prop="cause(geno5, pheno3, group5)"
  paraphrase="The ITPR1-SUMF1 deletion may be the cause of the family members SCA15"  />
<!-- Could be analyzed as two arguments, one for control group and another for
individuals with unrelated neurological disorder.
Domain expert says that evidence from individuals with an unrelated neurological
disorder is stronger than evidence from control group. -->
</argument>

</DSEG>

<DSEG ID="Experiment 6">
<content>
[para 6] In an attempt to fine-map the breakpoints of the disease-causing deletion we
performed a series of experiments designed to refine the unknown intervals at the edges
between definite deleted and definite diploid sequences.
These data narrowed the unknown borders to ~4 kb on the telomeric side and ~7 kb on the
centromeric side.
We used all possible combinations of forward orientation primers designed within the
newly defined telomeric boundary and of reverse orientation primers designed within the
newly defined centromeric boundary in PCR assays in an attempt to amplify across the
deletion in affected family members.
Using PCR primers T3F and C11R, which should be more than 200 kb apart, we were able to
amplify a fragment 953 bp in size using DNA from each of the three affected family
members as template.
Sequencing of this fragment revealed a deletion of 201,509 bp (Figure S3), removing the
first three of the nine exons of SUMF1 and the first ten of the 58 exons of ITPR1.
We were unable to amplify the deletion-specific fragment in the family member of
unknown affection status, or in 275 neurologically normal controls.
</content>

<argument ID="8" old-id="6.1" scheme="Difference">
<!-- Domain expert says this argument uses different evidence than previous
arguments, so provides additional evidence for conclusion -->
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</premise-list>
<conclusion inferred-prop="cause(geno5, pheno3, group5)"
  paraphrase="A deletion in SUMF1-ITPR1 may be the cause of SCA15 in the affected
  group."  />
</argument>

</DSEG>

<DSEG ID="Experiment 7">
<content>
[para 7] To further establish genetic deletion at ITPR1 as the cause of SCA15 we
analyzed two additional families with an inherited cerebellar ataxia similar to that
described in the AUS1 family, ascertained through neurology clinics in London, United
Kingdom.
DNA extracted from probands from these two families (family H33 and family H27) were
also analyzed using Illumina Infinium HumanHap550 genotyping chips.
These experiments showed deletion at the SCA15 locus in all affected members assayed,
from SUMF1 through ITPR1.
These mutations segregated with disease in these two families (Figure S3).
A strategy similar to the one outlined above enabled us to sequence over the breakpoint
in family H27 but not family H33.
In the former, the deletion spans 344,408 bp, removing exons 1–3 of SUMF1 and 1–44 of
ITPR1;
in the latter, we estimate that the deletion is 310 kb in length and that it removes
exons 1–3 of SUMF1 and exons 1–40 of ITPR1.
The site of mutation is of interest, particularly the fact that in each of the three
families the telomeric end of the deletion is anchored between exons 3 and 4 of SUMF1;
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sequence searches failed to identify any repeat sequences that might explain this phenomenon.
</content>

<entities-props>
<entity ID="group7" paraphrase="family H33 and family H27 affected members" />
<entity ID="group8" paraphrase="family H33 and family H27 unaffected members" />
<entity ID="pheno4" paraphrase="inherited cerebellar ataxia" />
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<conclusion inferred-prop="cause(geno5, pheno4, group7)"
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  family members' cerebellar ataxia similar to AUS1's ataxia (SCA15)" />
</argument>

</DSEG>

<DSEG ID="Summary" >
<content>
With three cerebellar ataxia families segregating a SUMF1–ITPR1 deletion, and this deletion not observed in a control population, we may reasonably conclude that the association is causal, and that the deletion is indeed the genetic basis of the disease, with SCA15 the diagnosis in the two British families as well as the original Australian family.
</content>

<entities-props>
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<entity ID="group10" paraphrase="unaffected members of AUS1, H33, and H27 and controls"
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  />
<!-- Strictly speaking the conclusion should be cause(geno5, pheno4, group9) but the
text specifies SCA15 (pheno3). -->
</argument>
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<DSEG ID="Discussion" >
<content>
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[para 8] It is improbable that heterozygosity for the deletion of SUMF1, encoding
sulfatase modifying factor 1, of itself causes or contributes to SCA15.
Homozygous mutation of SUMF1 results in autosomal recessive multiple sulfatase
deficiency, a metabolic disorder characterized by hepatosplenomegaly, deafness, and
developmental delay [6,7].
No co-occurrence of ataxia has been described in (heterozygous) parents of patients
with multiple sulfatase deficiency.
</content>

<entities-props>
<entity ID="group11" paraphrase="individuals heterozygous for deletion of SUMF1" />
<entity ID="geno6" paraphrase="heterozygous deletion of SUMF1" />
<prop>have_geno(group11, geno6)</prop>
<prop>not(have_pheno(group11,pheno4))</prop>
<prop>not(cause(geno6, pheno4, group4))</prop>
</entities-props>

<argument ID="11" old-id="8.1" scheme="Failed Method of Agreement (no effect)">
<premise-list>
<premise prop="have_geno(group11, geno6)"
  paraphrase="Parents of children affected by multiple sulfatase deficiency
who do not themselves have the deficiency are heterozygous for SUMF1 mutation
(according to Mendelian inheritance principles and since homozygous mutation
of SUMF1 results in that deficiency)"  />
<premise prop="not(have_pheno(group11,pheno4))" />
</premise-list>
<conclusion prop="not(cause(geno6, pheno4, group4))" />
<!-- The conclusion generalizes scope from group11 to group4 (humans). -->
</argument>

<content>
Conversely, mutation of ITPR1 is biologically plausible as a cause of ataxia: the
protein is highly expressed in Purkinje cells;
as we have shown here, mice with mutation at this locus present with ataxia;
and perturbed Ca2+ signaling has previously been implicated in the etiology of ataxia,
notably in episodic ataxia type 2 and SCA6 [8].
</content>

<entities-props>
<entity ID="prot2" paraphrase="perturbed Ca2+ signaling" />
<entity ID="geno7" paraphrase="mutation of ITPR1" />
<prop>cause(geno3s, prot1, group3s)</prop>
<prop>cause(prot1, prot2, geno3s)</prop>
<prop>have_geno(group3s, geno3s)</prop>
<prop>have_pheno(group3s, pheno2)</prop>
<prop>cause(geno7, prot1, group4)</prop>
<prop>cause(prot1,prot2, group4)</prop>
<prop>cause(prot2, pheno4, group4)</prop>
<prop>cause(geno7, pheno4, group4)</prop>
</entities-props>

<argument ID="12" old-id="8.2" scheme="Eliminate Difference">
<premise-list>
<premise prop="not(cause(geno6, pheno4, group4))" conclusion-of="Arg 11" />
<premise prop="cause(geno5, pheno3, group9)" conclusion-of="Arg 10"
    paraphrase="The ITPR1-SUMF1 deletion may be the cause of cerebellar ataxia in AUS1,
    H33 and H27" />
</premise-list>
<conclusion prop="cause(geno7, pheno4, group4)"
  paraphrase="ITPR1 mutation may be the cause of cerebellar ataxia in humans" />
</argument>

<argument ID="13" old-id="8.3" scheme="Consistent Explanation" >
<!-- This argument is based on in-vivo mouse and in-vivo human data. -->
<premise-list>
<premise prop="cause(geno3s, prot1, group3s)" />
```

```
<premise prop="cause(prot1, prot2, geno3s)"
  paraphrase="Decreased levels of Itpr1 protein in cerebellar Purkinje cells in mice
  results in perturbed Ca2+ signaling" />
<premise prop="have_geno(group3s, geno3s)" />
<premise prop="have_pheno(group3s, pheno2)" />
<premise prop="cause(geno7, prot1, group4)"
  paraphrase="Mutation of ITPR1 in humans results in decreased levels of ITPR1 protein
  in cerebellar Purkinje cells in humans" />
<premise prop="cause(prot1, prot2, group4)"
  paraphrase="Decreased levels of ITPR1 protein in cerebellar Purkinje cells in humans
  results in perturbed Ca2+ signaling" />
<premise prop="cause(prot2, pheno4, group4)" />
</premise-list>
<conclusion prop="cause(geno7, pheno4, group4)"
  paraphrase="Mutation of ITPR1 causes ataxia in humans" />
</argument>

<content>
In further support of this conclusion, analysis of protein levels of ITPR1 in
Epstein-Barr virus (EBV) immortalized lymphocytes from affected and unaffected AUS1
family members revealed that all affected members showed a dramatic decrease in ITPR1
levels when compared with the family member without the deletion (Figure 4). </content>

<entities-props>
<entity ID="group12" paraphrase="AUS1 family members without deletion in ITPR1" />
<prop>have_prot(group5, prot1)</prop>
<prop>not(have_prot(group12, prot1))</prop>
<prop>cause(prot2,pheno4,group4)</prop>
</entities-props>

<!-- This argument is stronger than 12 because it is based on human data.
Domain expert says human data is stronger than mouse data, but in-vivo data is stronger
than
in-vitro data for the same species. -->

<argument ID="14" old-id="8.4" scheme="Difference Consistent Explanation">
<premise-list>
<premise prop="have_prot(group5, prot1)" />
<premise prop="not(have_prot(group12, prot1))" />
<premise prop="cause(prot1, prot2, group4)"
  paraphrase="Decreased levels of ITPR1 protein in cerebellar Purkinje
  cells in humans results in perturbed Ca2+ signaling" />
<premise prop="cause(prot2, pheno4, group4)" />
</premise-list>
<conclusion prop="cause(geno7, pheno4, group4)" />
<!-- conclusion generalizes to group4 (humans). -->
</argument>

<content>
[para 9] Itpr1 contains three domains, an N-terminal inositol triphosphate binding
domain, a coupling domain, and a C-terminal transmembrane domain;
it also contains two protein kinase A phosphorylation sites and an ATP-binding site.
Itpr1 is coupled to Ca2+ channels and facilitates Ca2+ release from the endoplasmic
reticulum after binding by the intracellular second messenger inositol
1,4,5-triphosphate [9].
Itpr1 is enriched in the Purkinje cells of the cerebellum [4].
ITPR1 mutations have more than one potential pathogenic mechanism.
First, the disease may be a result of haploinsufficiency at ITPR1;
this concept is consistent with the observation that heterozygous deletion leads to a
later onset disorder in humans, whereas homozygous deletion in mice leads to an early
onset disorder, able to be expressed within the much shorter life span of the mouse.
Second, we cannot rule out the existence of an alternate start site for ITPR1 that may
result in a product that confers a pathogenic gain of function to the protein;
however, Western blot analysis of cells derived from affected AUS1 family members,
which was performed using an antibody raised against the C-terminal portion of ITPR1,
failed to identify any disease-specific truncated protein products.
```

Clearly, the identification of distinct ITPR1 mutations underlying SCA15 will help elucidate the pathogenic mechanism of this disorder.
</content>

<content>
[para 10]
We show here the utility of investigating spontaneous mouse mutations in understanding human disease.
Currently, the small number of aged Itpr1wt/Δ18 animals precludes us from examining these mice for subtle signs and symptoms similar to those seen in SCA15 patients; however, these mice are clearly of interest to us as a potential model of SCA15.
These data also demonstrate that genome-wide SNP assay can facilitate rapid detection of structural genomic mutations that may underlie disease.
The data provided by these approaches provide compelling evidence that heterozygous deletion of ITPR1 causes SCA15.
Clearly, sequence analysis of ITPR1 in potential SCA15 cases may provide additional insight into the disease, particularly if a stop mutation were to be identified; however, the mutational mechanism noted here means that standard sequencing approaches alone are insufficient to confidently rule out ITPR1 mutation as a cause of disease: a comprehensive gene dosage approach is also required.
Given that SCA16 and autosomal dominant congenital nonprogressive ataxia have both recently been mapped to regions overlapping with the SCA15 locus [10,11], ITPR1 is a gene of importance for screening in these families.
These data add weight to a role for aberrant intracellular Ca2+ signaling in Purkinje cells in the pathogenesis of spinocerebellar ataxia.
</content>

<main-claim>heterozygous deletion of ITPR1 causes SCA15</main-claim>
</DSEG>
</section>

</article>
</document>