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Complete callosal agenesis, pontocerebellar hypoplasia, and axonal neuropathy due to *AMPD2* loss

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ABSTRACT

Objective: To determine the molecular basis of a severe neurologic disorder in a large consanguineous family with complete agenesis of the corpus callosum (ACC), pontocerebellar hypoplasia (PCH), and peripheral axonal neuropathy.

Methods: Assessment included clinical evaluation, neuroimaging, and nerve conduction studies (NCSs). Linkage analysis used genotypes from 7 family members, and the exome of 3 affected siblings was sequenced. Molecular analyses used Sanger sequencing to perform segregation studies and cohort analysis and Western blot of patient-derived cells.

Results: Affected family members presented with postnatal microcephaly and profound developmental delay, with early death in 3. Neuroimaging, including a fetal MRI at 30 weeks, showed complete ACC and PCH. Clinical evaluation showed areflexia, and NCSs revealed a severe axonal neuropathy in the 2 individuals available for electrophysiologic study. A novel homozygous stop-gain mutation in adenosine monophosphate deaminase 2 (*AMPD2*) was identified within the linkage region on chromosome 1. Molecular analyses confirmed that the mutation segregated with disease and resulted in the loss of *AMPD2*. Subsequent screening of a cohort of 42 unrelated individuals with related imaging phenotypes did not reveal additional *AMPD2* mutations.

Conclusions: We describe a family with a novel stopgain mutation in *AMPD2*. We expand the phenotype recently described as PCH type 9 to include progressive postnatal microcephaly, complete ACC, and peripheral axonal neuropathy. Screening of additional individuals with related imaging phenotypes failed to identify mutations in *AMPD2*, suggesting that *AMPD2* mutations are not a common cause of combined callosal and pontocerebellar defects. *Neurol Genet* 2015;1:e16; doi: 10.1212/NXG.0000000000000014

GLOSSARY

ACC = agenesis of the corpus callosum; **AMP** = adenosine monophosphate; **AMPD2** = adenosine monophosphate deaminase 2; **CC** = corpus callosum; **NCS** = nerve conduction study; **OMIM** = Online Mendelian Inheritance in Man; **PCH** = pontocerebellar hypoplasia; **SNP** = single nucleotide polymorphism; **WES** = whole-exome sequence.

Callosal malformations include complete or partial agenesis, hypoplasia, and dysgenesis.^{1,2} Clinical sequelae range from no or mild manifestations to severe neurodevelopmental disability.^{3,4} The latter is more common when the callosal malformation is accompanied by other brain abnormalities, is part of a multiple congenital anomaly syndrome, or is secondary to a metabolic or degenerative disorder.⁵ Agenesis of the corpus callosum (ACC) occurs in approximately 1:5,000 live births and >80 congenital syndromes,^{6,7} although the etiology remains unknown for the majority. Pontocerebellar hypoplasia (PCH) syndromes are rare, usually autosomal recessive, disorders characterized by degeneration of the cerebellum and brainstem. The term

Supplemental data
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From the Bruce Lefroy Centre for Genetic Health Research (A.P.L.M., K.P., E.M.Y., J.C.H.S., M.B.D., P.J.L.), Murdoch Childrens Research Institute, Royal Children's Hospital, Parkville, Australia; Bioinformatics Division (V.L., C.B., R.T., M.B.), The Walter and Eliza Hall Institute of Medical Research, Parkville, Australia; Department of Neurology (M.M.R., E.M.Y., R.J.L.) and Department of Paediatrics (A.P.L.M., M.M.R., E.M.Y., M.B.D., D.J.A., R.J.L., P.J.L.), The University of Melbourne, Royal Children's Hospital, Parkville, Australia; Victorian Clinical Genetics Services (D.J.A., G.M.) and Neuroscience Research (M.M.R., R.J.L.), Murdoch Childrens Research Institute, Parkville, Australia; Department of Neurology (E.H.S.), UCSF Benioff Children's Hospital, San Francisco, CA; Clinical Genetics (M.B.D.), Austin Health, Heidelberg, Australia; and Department of Mathematics and Statistics (M.B.) and Department of Medical Biology (R.T., M.B.), The University of Melbourne, Parkville, Australia. Funding information and disclosures are provided at the end of the article. Go to Neurology.org/ng for full disclosure forms. The Article Processing Charge was paid by the authors.

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“hypoplasia” is used although the changes are thought to reflect prenatal onset of atrophy.⁸ Ten PCH syndromes have been described with additional features that variably include microcephaly, a movement disorder, epilepsy, optic atrophy, and axonal neuropathy.

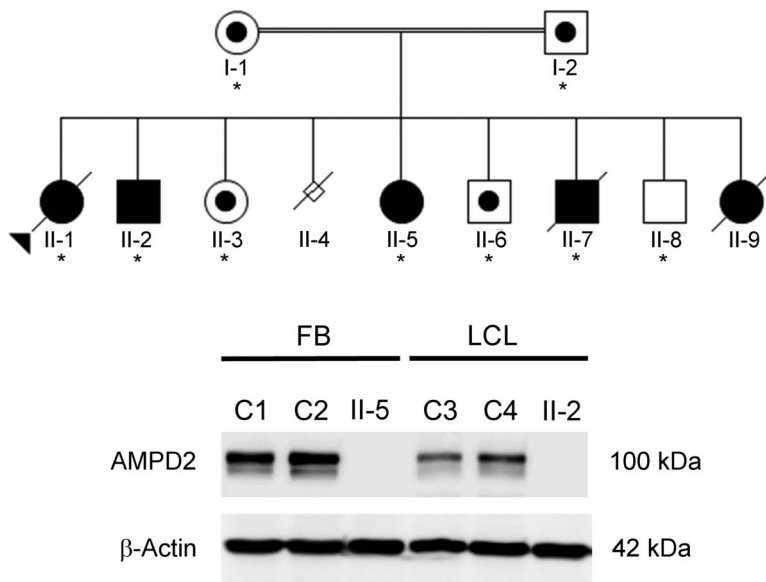
The combination of corpus callosum (CC) hypoplasia and PCH secondary to mutations in the gene encoding adenosine monophosphate deaminase 2 (*AMPD2*) was recently reported (PCH type 9, Online Mendelian Inheritance in Man [OMIM] #615809).⁹ The authors described 8 affected individuals from 5 families with severe disabilities, hypoplasia of the CC, and a characteristic midbrain “figure of 8” appearance on axial MRI. *AMPD2* encodes 1 of 3 of adenosine monophosphate (AMP) deaminase homologs, which convert AMP to inosine monophosphate. Guanine nucleotide deficiency was shown to be central to the pathogenesis of PCH9 and associated with defective protein synthesis.⁹ In this study, we characterize a large

consanguineous Middle Eastern family and expand the phenotype of PCH9, describing the novel combination of complete ACC, PCH, and an axonal neuropathy.

METHODS **Standard protocol approvals, registrations, and patient consents.** Study approval was provided by the Royal Children’s Hospital Research Ethics Committee (Human Research Ethics Committee #28097), with informed consent provided by participants or their guardians.

Clinical and molecular studies. Clinical information was obtained by review of medical records and examination of affected individuals. Neuroimaging was reviewed and included cranial ultrasound, head CT, and brain MRI. Nerve conduction studies (NCSs) were performed using a 4-channel Keypoint Electromyography machine (Natus Medical Incorporated, Pleasanton, CA), as previously described.¹⁰ Genomic DNA was isolated from peripheral blood. Single nucleotide polymorphism (SNP) genotype data were generated with the Human610-Quad BeadChip Kit (Illumina, San Diego, CA) for 7 family members (I-1, I-2, II-2, II-3, II-5, II-6, and II-8) and extracted from the whole-exome sequence (WES) data of individual II-9. Genotypes were processed using LINKDATAGEN. Parametric multipoint linkage analysis was subsequently performed using MERLIN,¹¹ specifying a rare recessive disease model. Genomic DNA derived from 3 affected siblings (II-2, II-5, and II-9) was enriched using an Illumina TruSeq capture. Sequencing was performed by Orogenetics Corporation (Norcross, GA) with 100-base paired-end reads on an Illumina HiSeq 2000 platform. Reads were aligned to the reference human genome (GRCh37/hg19) with ambiguous nucleotide codes at dbSNP132 locations using Novoalign (www.novocraft.com). Variants were called using SAMtools 0.1.17 and annotated using ANNOVAR. The candidate list was filtered to retain rare variants (minor allele frequency ≤ 0.01) within the linkage regions using public databases and our own in-house database of 132 unrelated exomes. Sanger sequencing confirmed segregation. A cohort of 42 additional individuals with imaging features of complete or partial ACC and brainstem and/or cerebellar hypoplasia was ascertained. Potentially causative copy number variation had previously been excluded by SNP array (data not shown). Sanger sequence analysis of *AMPD2* was performed by PCR amplification using M13-tagged primers (primer sequences available on request). Western blot analysis was performed as previously described¹² using monoclonal anti-*AMPD2* (1:1000 HPA036471, Sigma-Aldrich, St. Louis, MO) and anti- β -actin antibody (1:10000 A5441, Sigma-Aldrich). The reference sequences used for *AMPD2* were NG_034075.1, NM_001257360.1, and NP_001244289.1.

Figure 1 Novel stopgain mutation in adenosine monophosphate deaminase 2 segregates with disease in family ACC1 and causes complete loss of protein



(A) The ACC1 family pedigree is shown with affected individuals shaded in black and unaffected individuals in white. A dot in the pedigree symbol indicates an unaffected carrier. The proband is indicated by an arrowhead. Family members whose DNA was tested are indicated by an asterisk. Homozygosity for the adenosine monophosphate deaminase 2 (*AMPD2*) mutation segregated with disease in all family members tested. (B) Immunoblot analysis with an *AMPD2*-specific antibody identified a ~100-kDa protein in control fibroblasts (C1, C2) and control lymphoblasts (C3, C4) that was absent in extracts derived from affected individuals II-5 (fibroblasts) and II-2 (lymphoblasts). An antibody directed against β -actin confirmed equivalent protein loading.

RESULTS We describe a Middle Eastern family with 5 affected offspring from a first cousin marriage (figure 1A). Clinical and imaging details are summarized in table 1. Affected individuals had severe neurodevelopmental disability of early onset, with early death in 3 of 5. All had a normal head circumference at birth but developed microcephaly within the first year and were hyperreflexic in the first decade. Dysmorphic features in the 3 patients examined (II-2, II-5, and II-9) included bitemporal narrowing, hypotonic facies, midface hypoplasia, short or downslanting

Table 1 Clinical phenotype and investigation of family ACC1

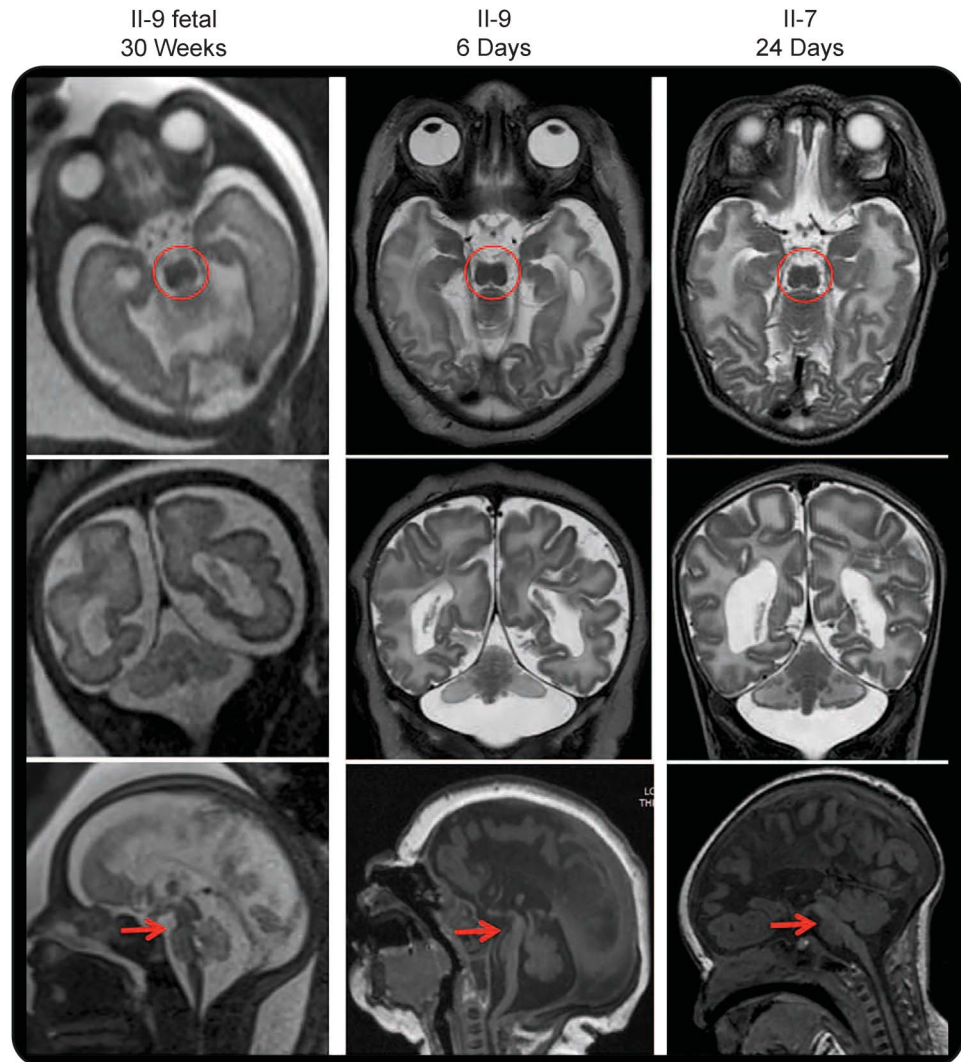
	Patients				
	II-1	II-7	II-9	II-2	II-5
Clinical features					
Sex	F	M	F	M	F
Current age	Deceased	Deceased	Deceased	20 y	17 y
Neonatal HC, percentile, %	50	25	25	25	25
HC at last examination, SD	−4/−5	−3/−4	−3/−4	−3/−4	−5/−6
Developmental delay	Profound	Profound	Profound	Profound	Profound
Dysmorphic features	Not assessed	Not assessed	Y	Y	Y
Impaired swallow	Y	Y	Y	Y	Y
Cortical visual impairment	Y	Y	Y	Y	Y
Epilepsy	Y	Y	N	Y	Y
Seizure onset	9 mo	5 wk	—	2 mo	3 y
Axial tone	Reduced	Reduced	Reduced	Reduced	Reduced
Appendicular tone	Increased	Increased	Increased	Increased	Increased
Contractures	N	N	N	Y	Y
Spasticity	Y	Y	Y	Y	Y
Reflexes	Increased	Increased	Increased	Increased UL, absent LL	Increased UL, absent LL
Plantars	Upgoing	Upgoing	Upgoing	Upgoing	Upgoing
Investigations					
EEG	Prominent fast	Multifocal epileptic activity and seizures, asynchronous and discontinuous	Not performed	Bilateral independent epileptic activity	Excess background fast, frequent bilateral independent epileptic activity
Age at NCS, y	Not performed	Not performed	Not performed	20	10
NCS	—	—	—	Axonal neuropathy	Axonal neuropathy
Neuroimaging modality	CT	MRI	Fetal and postnatal MRI	CT	US
Age at imaging	3 mo	19 d	30 wk + 3 gestation and 6 d	16 y	1 mo
Neuroimaging findings	Complete ACC, mild cerebellar and vermis hypoplasia	Complete ACC with IH cyst with septations, moderate hypoplasia of cerebellar hemispheres and vermis, mild thinning of brainstem (medulla)	Fetal: complete ACC, small IH cyst with septations, mild hypoplasia of cerebellar vermis and hemispheres; postnatal: complete ACC, small IH cyst, moderate hypoplasia of cerebellar vermis and hemispheres, brainstem hypoplasia	Complete ACC with IH cyst with septations, moderate hypoplasia of cerebellar vermis and hemispheres, mild pontine hypoplasia	Complete ACC, hypoplastic cerebellum
Age at death	22 mo	9 mo	11 mo	Alive	Alive
Cause of death	Sepsis	Pneumonia	Sepsis	—	—

Abbreviations: ACC = agenesis of the corpus callosum; HC = head circumference; IH = interhemispheric; LL = lower limbs; NCS = nerve conduction study; UL = upper limbs; US = ultrasound.

palpebral fissures, a high or broad nasal bridge with a prominent columella, a short upper lip, macroglossia, abnormal ears with a thickened antihelix and a grooved or folded lobe, tapering fingers with dimples over the knuckles, camptodactyly of the distal interphalangeal joints, a few large pigmented nevi, and trophic skin

changes of the feet. The 2 surviving individuals (II-2 and II-5) were later noted to have absent lower limb reflexes and distal lower extremity wasting. NCSs performed on upper and lower extremities in these individuals (ages 10 and 20 years) showed low-amplitude or absent motor responses with a mild

Figure 2 Loss of adenosine monophosphate deaminase 2 results in progressive loss of brainstem and cerebellar parenchyma with prenatal onset



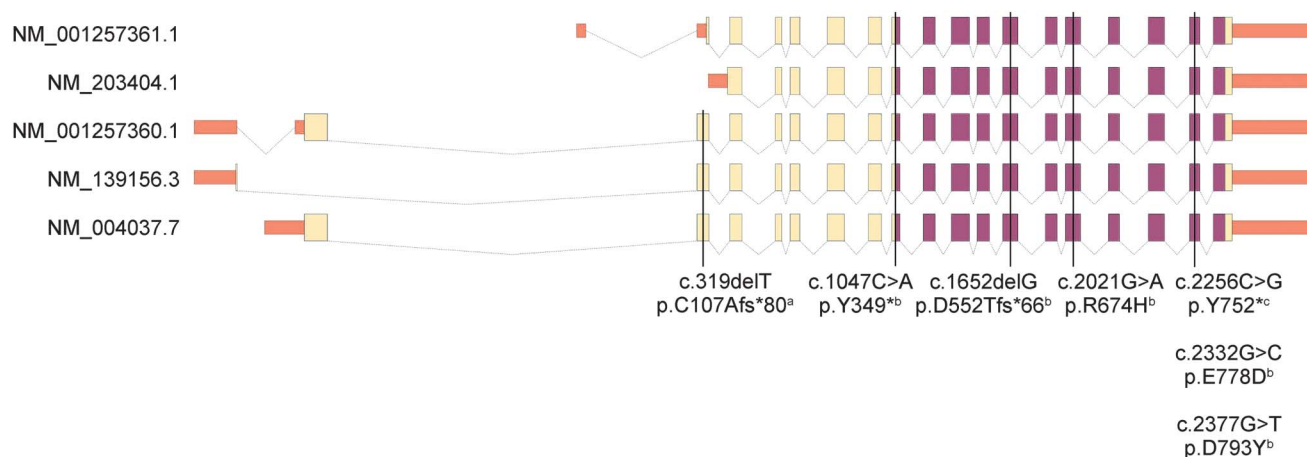
Axial (top row), coronal (middle row), and midline sagittal (bottom row) T1- and T2-weighted images. All images show a characteristic “figure of 8” appearance to the midbrain (circles), hypoplasia/atrophy of the brainstem (arrows) and cerebellar hemispheres > vermis, and complete agenesis of the corpus callosum. Comparison of the fetal and postnatal MRIs of patient II-9 suggests progressive loss of volume of the pontine belly in the last trimester.

reduction in motor nerve conduction velocity. Sensory responses were normal in both. EMG showed positive sharp waves and markedly reduced recruitment of high-amplitude polyphasic motor unit potentials, consistent with either a motor axonal neuropathy or neuronopathy. Neuroimaging comprised brain MRI in 2, head CT in 2, and cranial ultrasound in 1. Complete ACC and hypoplasia of the cerebellum and/or brainstem were confirmed in all. Fetal MRI in one showed that all of the brain abnormalities were present at 30 weeks’ gestation (figure 2), suggesting prenatal onset of PCH.

The clinical features suggested a potentially novel genetic cause; therefore, a linkage-gene discovery strategy was used. Two regions on chromosome 1 achieved the maximal autosomal logarithm of the

odds score of 2.73 (figure e-1 at Neurology.org/ng). WES and in silico filtering identified 1 variant within the linkage regions, homozygous in all 3 affected siblings, that was predicted to be damaging to the protein sequence. The novel stopgain mutation (NM_001257360.1:c.2256C>G, p.Tyr752*) in *AMPD2* (figure e-1) was subsequently shown to segregate with disease in the extended family. Western blot analysis of control cells using a monoclonal antibody directed against AMPD2 identified a single band of the expected size. However, this protein was absent in fibroblast and lymphoblast cell extracts derived from affected individuals (figure 1B). Sequence analysis of *AMPD2* was performed in a cohort of 42 unrelated individuals with a neuroimaging phenotype of combined abnormalities of the CC

Figure 3 Schematic representation of the structure of the 5 predicted adenosine monophosphate deaminase 2 transcripts and exonic distribution of all mutations reported to date



The protein-coding sequence is colored yellow, the conserved adenosine monophosphate (AMP) deaminase domain (also protein coding) purple, and untranslated regions red. All pontocerebellar hypoplasia type 9 mutations reside within the catalytic AMP deaminase domain and therefore affect all 5 protein isoforms, while the one spastic paraplegia type 63 mutation falls outside this region and disrupts the coding region of only 3 of 5 adenosine monophosphate deaminase 2 transcripts. ^aNovarino et al.¹³ ^bAkizu et al.⁹ ^cACC1.

and cerebellum. A number of known polymorphisms were observed (table e-1), but no causative mutations were identified.

DISCUSSION We used linkage mapping and WES to identify loss of function of *AMPD2* as the molecular basis of a severe neurologic disorder in a consanguineous family presenting with progressive postnatal microcephaly, complete ACC, PCH, and a motor axonal neuropathy/neuronopathy. *AMPD2* mutations have recently been shown to cause PCH9, a disorder with clinical features that overlap with those of our family (table 1).⁹ Fetal and postnatal MRI support a prenatal onset to the neurodegenerative process in PCH9, as is postulated for other PCH forms.⁸ Like all reported individuals with PCH9, the mutation in our family is within the conserved AMP deaminase domain (figure 3). It is currently unclear why our patients display a severe phenotype with both central and peripheral neurologic manifestations. The 8 previously reported patients are described as having hypoplasia of the CC, whereas our patients have complete ACC. Although there is no specific mention of neurophysiologic testing of the previously reported patients, all were noted to have brisk or hyperactive reflexes. The areflexia seen in our family was only noted after the second decade, suggesting age-dependent onset. In the absence of autopsy findings, it is not possible to determine whether the lower motor neuron involvement identified in our family reflects a pure motor axonal neuropathy or an anterior horn cell disorder similar to that described in PCH1 (OMIM #607596).

A frameshift mutation in *AMPD2* was recently reported to cause hereditary spastic paraplegia type 63 (OMIM #615686) in a single family.¹³ The clinical presentation was relatively mild, with normal cognition, normal NCSs, and no cerebellar signs. MRI of 1 affected individual identified thinning of the CC and periventricular deep white matter changes but no brainstem or cerebellar abnormalities. The identified truncation [p.(Cys107Alafs*80)] disrupts only 3 of 5 predicted *AMPD2* isoforms (figure 3), whereas disruption of the deaminase domain affects all, suggesting functional redundancy of isoforms as a molecular explanation for variability in disease severity. Functional redundancy has been observed in mutant mice. Targeted knockout of *Ampd2* resulted in proteinuria but no overt brain phenotype,¹³ whereas a severely shortened lifespan and a neurodegenerative phenotype were observed in mice when 2 AMP deaminase homologs (*Ampd2* and *Ampd3*) were knocked out.⁹

This is the second report of mutations in *AMPD2* as a cause of a callosal abnormality associated with PCH and is the largest multiplex pedigree reported with this disorder. The clinical phenotype associated with loss of *AMPD2* function extends from spastic paraplegia to PCH with hypoplasia of the CC, PCH with complete ACC, and motor neuropathy/neuronopathy. Our patients expand the spectrum of emerging PCH disorders with combined callosal, brainstem, and peripheral nervous system manifestations.

AUTHOR CONTRIBUTIONS

A.P.L.M. formulated the study, performed molecular analysis, and cowrote the manuscript. V.L. performed linkage analysis, analyzed exome sequence data, and read/ contributed to the manuscript. K.P. performed

patient recruitment and read/contributed to the manuscript. C.B. and R.T. performed linkage analysis, analyzed exome sequence data, and read/contributed to the manuscript. M.M.R. and E.M.Y. provided and interpreted the clinical data and read/contributed to the manuscript. J.C.H.S. analyzed the molecular data and read/contributed to the manuscript. M.B.D., D.J.A., and G.M. provided and interpreted the clinical data and read/contributed to the manuscript. E.H.S. performed patient recruitment, provided and interpreted the clinical data, and read/contributed to the manuscript. M.B. advised on linkage and exome sequencing study design, analyzed data, and revised the manuscript. R.J.L. performed patient recruitment, provided and interpreted the clinical data, formulated the study, and cowrote the manuscript. P.J.L. formulated the study, interpreted the data, and wrote the manuscript.

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DISCLOSURE

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Method of determining response to treatment with immunomodulatory composition Details genetic markers that predict response to Hepatitis C treatment; has consulted for MacTel, Human Genetics Society of Australia, Australian Statistical Society-Institute of Mathematical Statistics, International Conference on Systems Biology, Sixth Barossa Meeting, and the 8th International Conference on Genomics & Bio-IT APAC; has received research support from NHMRC, National Heart Foundation, Australian Research Council (ARC), Victorian Life Sciences Computing Initiative (VLSI), Royal Melbourne Hospital Home Lottery Research Awards, Leukemia Foundation, ARC, Cancer Australia, DEST International Science Linkages, Human Genetics Society of Australia, Royal Statistical Society—Institute of Mathematical Statistics, Biometrics Society of Australasia, Australian Statistics Society, American Society of Human Genetics, and International Genetic Epidemiology Society. R.J.L. has received honoraria related to the 2015 Asia Oceania Congress of Child Neurology and has received research support from National Health and Medical Research Council and Campbell Edwards Trust Research Support. P.J.L. has served on the editorial boards of *Genetics Research International* and *Open Access (OA) Genetics* and has received research support from National Health and Medical Research Council (Australia). Go to Neurology.org/ng for full disclosure forms.

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