



**Editors' Note:** In WriteClick this week, Drs. Lynch and Houlden point out an error in the Mystery Case Responses section of "Mystery Case: *CSF-1R* mutation is a cause of intracranial cerebral calcifications, cysts, and leukoencephalopathy," in which *CSF-1R*-related leukoencephalopathy is mistaken to be the same as Labrune syndrome. Drs. Lynch and Houlden and author Aygnac discuss the differences between the 2 disorders. A correction appears on page 1979.

—Megan Alcauskas, MD, and Robert C. Griggs, MD

**LETTER RE: MYSTERY CASE: *CSF-1R* MUTATION IS A CAUSE OF INTRACRANIAL CEREBRAL CALCIFICATIONS, CYSTS, AND LEUKOENCEPHALOPATHY**

**David S. Lynch, Henry Houlden, London:** Aygnac et al.<sup>1</sup> presented an interesting case that highlighted the importance of *CSF-1R* in adult-onset leukoencephalopathies. However, we are concerned that the discussion by Dr. Ganesh in the Mystery Case Responses section confused 2 different diseases as the same.<sup>1</sup> This case clearly described a typical presentation of *CSF-1R*-related disease with apparent autosomal dominant inheritance. However, Dr. Ganesh described this as a case of Labrune syndrome (leukoencephalopathy with calcifications and cysts), an autosomal recessive disorder caused by mutations in *SNORD118*.<sup>2</sup> While calcifications occur in both syndromes, they are far more widespread and severe in Labrune syndrome and the imaging appearance of both conditions is distinctive. Dr. Ganesh incorrectly attributed 11% of adult-onset leukoencephalopathy to Labrune syndrome by referencing Guerreiro et al.,<sup>3</sup> who clearly referred to *CSF-1R*-related disease.

In our experience of adult-onset leukoencephalopathy, the most common causes are classic leukodystrophies, *CSF-1R*, *CADASIL*, and *AARS2* mutations. Therefore, it is not surprising that so few residents chose Labrune syndrome or Coats-plus syndrome as likely diagnoses.

1. Aygnac X, Mouzat K, Magnin E, et al. Mystery Case: *CSF-1R* mutation is a cause of intracranial cerebral calcifications, cysts, and leukoencephalopathy. *Neurology* 2016;87:e262–e263.

2. Jenkinson EM, Rodero MP, Kasher PR, et al. Mutations in *SNORD118* cause the cerebral microangiopathy leukoencephalopathy with calcifications and cysts. *Nat Genet* 2016;48:1185–1192.
3. Guerreiro R, Kara E, Le Ber I, et al. Genetic analysis of inherited leukodystrophies: genotype-phenotype correlations in the *CSF1R* gene. *JAMA Neurol* 2013;70:875–882.

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**AUTHOR RESPONSE: MYSTERY CASE: *CSF-1R* MUTATION IS A CAUSE OF INTRACRANIAL CEREBRAL CALCIFICATIONS, CYSTS, AND LEUKOENCEPHALOPATHY**

**Xavier Aygnac, Montpellier, France:** I thank Dr. Lynch and Prof. Houlden for the important comment on our Mystery Case.<sup>1</sup> Indeed, calcifications and cysts found in patients with *SNORD118* mutations, formerly described in Labrune syndrome, are larger than those seen in patients harboring *CSF-1R* mutations. Nevertheless, the importance of calcifications in this disorder was recently emphasized.<sup>2</sup> Notably, calcifications are small and may have a particular stepping-stone appearance in the frontal pericallosal regions.<sup>2</sup>

I agree that Labrune syndrome is rare. In our series of 154 patients with adult-onset leukoencephalopathies, only one patient had a radiologic phenotype consistent with Labrune syndrome.<sup>3</sup> The one other patient identified with leukoencephalopathy with calcifications and cysts was ultimately found to have a mutation in the *CSF-1R* gene.

1. Aygnac X, Mouzat K, Magnin E, et al. Mystery Case: *CSF-1R* mutation is a cause of intracranial cerebral calcifications, cysts, and leukoencephalopathy. *Neurology* 2016;87:e262–e263.
2. Konno T, Broderick DF, Mezaki N, et al. Diagnostic value of brain calcifications in adult-onset leukoencephalopathy with axonal spheroids and pigmented glia. *AJNR Am J Neuroradiol* 2017;38:77–83.
3. Aygnac X, Carra-Dalliere C, Menjot de Champfleury N, et al. Adult-onset genetic leukoencephalopathies: a MRI pattern-based approach in a comprehensive study of 154 patients. *Brain* 2015;138:284–292.

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**SUMMARY AUTHOR RESPONSE: MYSTERY CASE: *CSF-1R* MUTATION IS A CAUSE OF INTRACRANIAL CEREBRAL CALCIFICATIONS, CYSTS, AND LEUKOENCEPHALOPATHY**

**Aravind Ganesh, Oxford, UK:** I thank Dr. Lynch and Prof. Houlden for the response to my editorial

summary accompaniment to the Mystery Case,<sup>1</sup> and for highlighting the distinction between CSF-1R-related disease and Labrune syndrome for both myself and our readers. This is a helpful learning point I hope to carry forward.

1. Ayrignac X, Mouzat K, Magnin E, et al. Mystery Case: *CSF-1R* mutation is a cause of intracranial cerebral calcifications, cysts, and leukoencephalopathy. *Neurology* 2016; 87:e262–e263.

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### CORRECTION

#### **Mystery Case: *CSF-1R* mutation is a cause of intracranial cerebral calcifications, cysts, and leukoencephalopathy**

In the Mystery Case “*CSF-1R* mutation is a cause of intracranial cerebral calcifications, cysts, and leukoencephalopathy” by X. Ayrignac et al.,<sup>1</sup> there are errors related to the description of diseases within the “Mystery Case Responses.” The case described a typical presentation of *CSF-1R*-related disease rather than a case of Labrune syndrome and should have been written as such. In addition, 11% of adult-onset leukoencephalopathy should have been attributed to *CSF-1R*-related disease rather than Labrune syndrome.<sup>2</sup> The “Mystery Case Responses” author regrets the errors.

### REFERENCES

1. Ayrignac X, Mouzat K, Magnin E, et al. Mystery Case: *CSF-1R* mutation is a cause of intracranial cerebral calcifications, cysts, and leukoencephalopathy. *Neurology* 2016;87:e262–e263.
2. Guerreiro R, Kara E, Le Ber I, et al. Genetic analysis of inherited leukodystrophies: genotype-phenotype correlations in the CSF1R gene. *JAMA Neurol* 2013;70:875–882.

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**Summary author response: Mystery Case: *CSF-1R* mutation is a cause of intracranial cerebral calcifications, cysts, and leukoencephalopathy**

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