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Global Presence and Penetrance of *CSF1R*-Related Disorder

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Abstract

Objectives

To highlight the worldwide presence of *CSF1R*-related disorder (*CSF1R*-RD), discuss its penetrance, and provide the first haplotype analysis.

Methods

Data on patients worldwide were collected, including demographics, genotype, family history, and clinical status. For haplotype analysis, polymorphisms of short tandem repeats in 3 distinct families with *CSF1R* p.Ile794Thr variant were examined.

Results

Nineteen new patients were included, at a mean age of 38.7 years (ranging from 11 to 74 years), from 14 families from the Americas, Asia, Australia, and Europe, including the first from Mexico, North Macedonia, and Ukraine. Fifteen *CSF1R* variants were found, including 8 novel. Three patients were compound heterozygotes with disease onset at 1, 4, and 22 years. Patients with heterozygous *CSF1R* variants developed symptoms at a mean of 39.0 years (range 8–71 years). Four patients died at a mean of 3.3 years from onset (range 2–5 years). Negative family history was noted in 7 patients. In haplotype analysis, 2 families exhibited shared haplotype encompassing ~6-Mb region downstream of the *CSF1R* while the third family displayed a different haplotype.

Discussion

CSF1R-RD has a global prevalence. The reasons for negative family history include de novo variants (as shown by the haplotype analysis), mosaicism, and incomplete penetrance, which are possibly modulated by environmental and genetic factors.

Introduction

CSF1R-related disorder (*CSF1R*-RD) is a rare hereditary neurodegenerative disease with growing global recognition as genetic testing becomes more widely available.[1] The disorder was

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first reported in 1936 as pigmentary orthochromatic leukodystrophy (POLD).[2] Subsequently, different terminologies reflecting the contemporary state of understanding of the disease have been used, including "hereditary diffuse leukoencephalopathy with spheroids (HDLS)," "adult-onset leukoencephalopathy with axonal spheroids and pigmented glia (ALSP)," "*CSF1R*-related leukoencephalopathy," and "brain abnormalities, neurodegeneration, and dysosteosclerosis."[1,3-5] Owing to advances in research, a unified nomenclature has been proposed and the term "*CSF1R*-RD" was introduced with patients subdivided into early-onset (younger than 18 years) and late-onset (18 years and older) *CSF1R*-RD.[1]

The causative role of *CSF1R* variants was identified in 2011.[6] Over the next 7 years, 70 different *CSF1R* variants were reported in families from Asia (China, Japan, Saudi Arabia, South Korea, Taiwan), Europe (Croatia, France, Germany, Greece, Ireland, Italy, Netherlands, Norway, Sweden, United Kingdom), and North America (Canada, United States).[3] Since then, the number of reported variants has almost tripled, with 199 pathogenic or likely pathogenic *CSF1R* variants recognized as of February 2024, per Human Gene Mutation Database (HGMD) Professional 2023.4.[7] *CSF1R*-RD has been reported in Australia, Belgium, Brazil, Denmark, Hungary, India, Poland, Singapore, Spain, and Turkey (eAppendix 1).[8]

Despite the logarithmical growth in identified *CSF1R* pathogenic variants, little is known about their penetrance and other genotype-phenotype correlations. This gap may stem from the fact that most of the *CSF1R* variants are unique to specific families. Among ~200 families with *CSF1R*-RD followed by Mayo Clinic Florida (Z.K.W.), biological material was collected from 50 families. Within this subset, only a few *CSF1R* variants occur in more than 1 family, with the most common being the *CSF1R* p.Ile794Thr (c.2381T>C), which is present in 3 distinct families.

In this article, we report new patients with the disease around the world, providing the first haplotype analysis of families with *CSF1R* p.Ile794Thr variant and discussing the penetrance of the disease and related aspects important for genetic counseling and routine clinical settings.

Methods

The study originated from the senior author's (Z.K.W.) communication with international medical professionals who expressed interest in the *CSF1R*-RD. This interaction prompted the collection of epidemiologic data on new patients with *CSF1R*-RD globally. The gathered data included the country of origin, specific *CSF1R* variant(s), genotype, self-reported sex and ethnicity, family history, current age, clinical status, age at which the disease first manifested, and age at death.

In the haplotype analysis, we investigated polymorphisms of short tandem repeats (STRPs) in representative samples from our 3 distinct families, all of whom are affected by a *CSF1R*-RD due to *CSF1R* p.Ile794Thr (c.2381T>C) variant. The examined STRPs covered approximately 10-Mb region, encompassing genetic markers located upstream (D5S436, D5S434), within (D5S1469), and downstream (D5S410, D5S820) of *CSF1R*.

Standard Protocol Approvals, Registrations, and Patient Consents

The patient's data were collected under IRB 19-011016. The study data are available from the corresponding author on reasonable request.

Results

We collected data on 19 patients (9 men) from 14 families with a mean age of 38.7 years, ranging from 11 to 74 years, of White (n = 14), Latino (n = 2), Asian (n = 1), Black (n = 1), and Native American (n = 1) ethnicity (Table). They were from Asia (India), Australia, Europe (Belgium, Denmark, Hungary, North Macedonia, Ukraine), and North and South America (Brazil, Canada, Mexico, United States) (Figure). A Hungarian family, with neuropathologic confirmation of POLD, was included in the study, given the consistent observation of *CSF1R* variants in all previously documented patients with POLD. In the other patients (n = 15), 15 *CSF1R* variants were found, 8 of which were not reported previously. Three individuals were compound heterozygotes for *CSF1R* variants, with symptomatic disease onset (AOO) at age 1, 4, and 22 years, respectively. In the group with heterozygous *CSF1R* variants, the mean AOO was 39.0 years (range 8–71 years), with 1 individual remaining free of symptoms at 54 years. Four patients died at a mean of 3.3 years from onset (range 2–5 years). A negative family history for *CSF1R*-RD was noted in 5 patients with heterozygous and 2 with compound heterozygous *CSF1R* variants.

In haplotype analysis, 2 families exhibited a shared haplotype in the D5S1469, D5S410, and D5S820 markers, encompassing ~6-Mb region downstream of the *CSF1R* p.Ile794Thr variant. By contrast, the third family displayed a unique haplotype in this region.

Discussion

In this study, we present 15 patients with *CSF1R*-RD and 4 from a family with POLD, revealing 8 novel variants in *CSF1R*, and report, for the first time, patients from Mexico, North Macedonia, and Ukraine, highlighting the global distribution of this disease. Of interest, despite showing symptoms, 7 individuals had no family history of the disease. This observation suggests incomplete penetrance of some *CSF1R* variants. Our previous research has shown that glucocorticoid exposure

Table Characteristics of the Newly Reported Patients With *CSF1R*-Related Disorder

Family	Country	Ethnicity	*CSF1R* variant(s)	*CSF1R* genotype
1	Australia	White	c.1991_2005del p.Glu664_Tyr668del	Heterozygous
		White	c.1991_2005del p.Glu664_Tyr668del	Heterozygous
2	Belgium	White	c.2329 C>T (p.Arg777Trp)	Heterozygous
3	Brazil	White	c.880C>T (p.Arg294Trp	Heterozygous
4	Brazil	Native American	c.2345G>A (p. Arg782His); c.592+5G>A	Compound heterozygous
5	Brazil	White	c.1441C>T (p.Gln481*); c.592+5G>A	Compound heterozygous
6	Canada	White	c.1735C>T (p.Arg579Trp)	Heterozygous
7	Denmark	White	c.2392 G>A (p.Gly798Arg)	Heterozygous
8	Hungary	White	N/A*	N/A
		White	N/A	N/A
		White	N/A	N/A
		White	N/A	N/A
9	India	Asian	c.322_329delinsG (p.Trp108GlyfsTer2)	Heterozygous
10	Mexico	Latino	c.1047del (p.Lys350Serfs*22)	Heterozygous
		Latino	c.1047del (p.Lys350Serfs*22)	Heterozygous
11	North Macedonia	White	c.2381T>C (p.Ile794Thr)	Heterozygous
12	Ukraine	White	c. 1765 G>A (p.Gly589Arg)	Heterozygous
13	United States	White	c.2455G>T (p.Val819Leu); c.368C>A (p.Ala123Glu)	Compound heterozygous
14	United States	Black	c.1772G>A (p.Gly591Glu)	Heterozygous

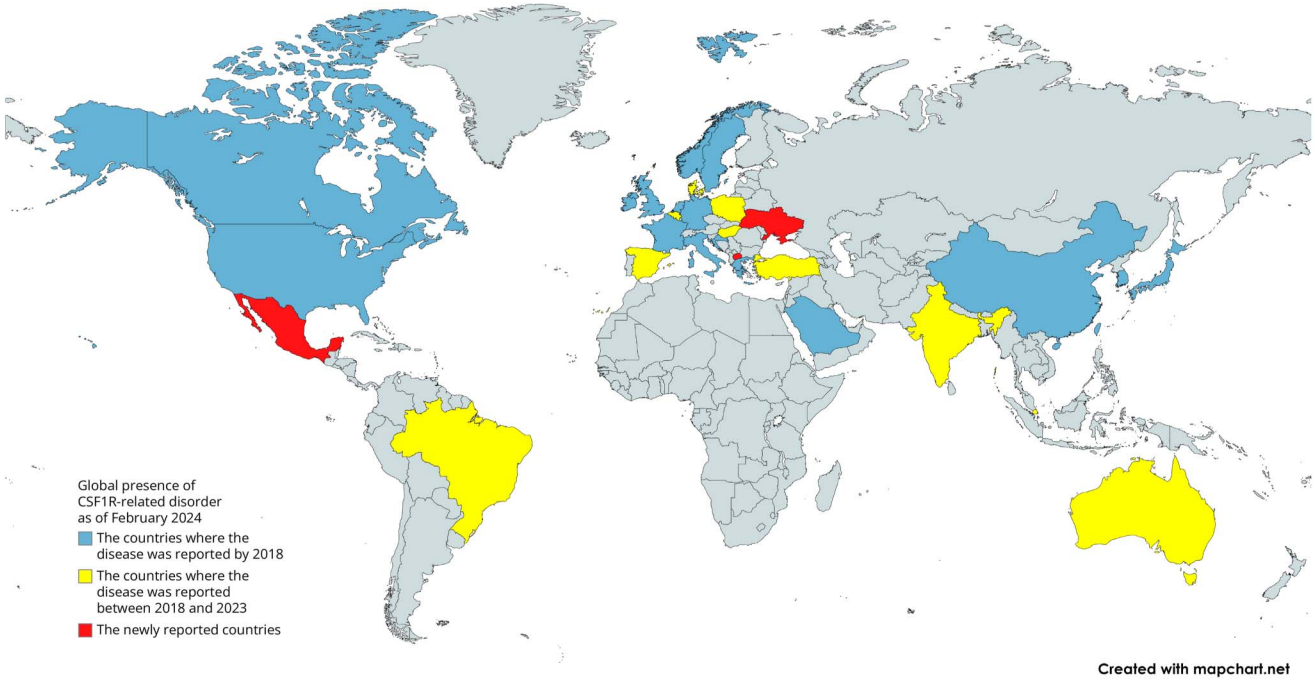
N/A = not applied; *neuropathologic confirmation of pigmentary orthochromatic leukodystrophy.

can protect against the development of symptomatic disease in individuals carrying *CSF1R* variants, as demonstrated in a retrospective cohort study and a mouse model study.[9-11] This finding opened the possibility that other environmental factors may also play a role in the penetrance of *CSF1R* variants. Moreover, similar to other disorders, individual genetic architecture may also affect the penetrance of *CSF1R* variants. Therefore, the AOO and penetrance are most likely modulated by a combination of environmental factors, including but not limited to glucocorticoid exposure and genetic factors.

The haplotype analysis in our families with *CSF1R* p.Ile794Thr variant indicated a possible common ancestral origin for the variant in the 2 families, whereas the variant in the third family seems to be of independent origin. The 2 families with shared haplotype could not be genealogically linked in recent generations, indicating that the *CSF1R* p.Ile794Thr variant likely originated at least several generations before. The independent haplotype in the third family evidences the recurrence of de novo mutations in the *CSF1R*. This observation was first made in our original article on *CSF1R* variant discovery, in which both parents of the 2 affected Norwegian twins with *CSF1R* p.G585_K619delinsA variant tested negative for the variants.[6] Thus, a negative family history in some individuals affected by *CSF1R*-RD may be explained by the de novo variants. Another possible explanation is mosaicism, i.e., the presence of 2 or more populations of cells with different genotypes in 1 individual, which can arise from variants occurring during development. Mosaic parents may not show symptoms of a *CSF1R*-RD due to a limited distribution of mutant cells but can still pass on the *CSF1R* variant to offspring.[12]

To date, most of the pathogenic *CSF1R* variants are missense/nonsense (75%, n = 149/199), followed by structural (small and gross deletions, insertion, indels, complex rearrangements) (16%, n = 32/199) and splicing variants (9%, n = 18/199), per HGMD Professional 2023.4[7]. The advent of next-generation sequencing technologies (multigene panels, exome

Figure Global Presence of *CSF1R*-Related Disorder as of February 2024



The countries where the disease was reported by 2018 are shown in blue. The countries where the disease was reported between 2018 and 2023 are shown in yellow. The newly reported countries are shown in red.

and genome sequencing) has made genetic testing more accessible, leading to a significant increase in the detection of *CSF1R* variants.[13,14] Many of the newly identified *CSF1R* variants are labeled as variants of unknown significance (VUSs), posing a challenge to interpret them in a clinical context, particularly in patients with negative family history. To better understand the clinical relevance of VUS, we suggest a review of the up-to-date literature, segregation studies, and in silico predictions. However, the functional studies in cellular and animal models remain the gold standard for elucidating the pathogenicity of these variants.

In conclusion, as genetic testing for *CSF1R* variants becomes more widespread, the identification of VUS is expected to increase, emphasizing the need for more research to elucidate these variants. Further research is required, including the investigation of asymptomatic and symptomatic carriers of *CSF1R* variants, to better understand the penetrance of variants and the influence of environmental and genetic modifiers on the disease phenotype. This information is important for enhancing genetic counseling, guiding the development of prophylactic interventions, and improving risk prediction for disease onset.

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