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CSF1R-Related Disorder

Prevalence of *CSF1R* Variants and Their Clinical Significance in the UK Population

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Abstract

Background and Objectives

CSF1R-related disorder (*CSF1R*-RD) is a devastating neurodegenerative disorder caused by variants in the colony stimulating factor-1 receptor (*CSF1R*) gene. *CSF1R*-RD leads to a variable combination of cognitive impairment, movement disorders, upper motor neuron signs, and spasticity with associated imaging abnormalities in brain white matter. Although increasingly recognized, there is evidence that it is significantly underdiagnosed or misdiagnosed, and its true prevalence is unknown. We leveraged the large data set of the UK Biobank to determine the prevalence of *CSF1R* mutations in the UK population and identify clinical phenotypes associated with these variants.

Methods

Pathogenic and likely pathogenic *CSF1R* variants were identified in UK Biobank whole-exome sequencing data (N = 470,000). Medical history, including neurologic and psychiatric disease, were determined from self-reported and hospital collected codes, and the volume of MRI white matter hyperintensities were compared between variant carriers and controls.

Results

We identified 25 individuals carrying 18 unique pathogenic variants and 107 individuals carrying 44 unique likely pathogenic variants—combined prevalence 132 (~1 in 3,500). Pathogenic *CSF1R* variant carriers had increased risk of psychiatric disease (OR: 5.15, $p = 0.0079$), depression (OR: 10.52, $p = 0.0015$), and Parkinson disease (OR: 19.80, $p = 0.0038$). Using algorithmically defined diagnosis data, pathogenic or likely pathogenic variants (the combined group) carriers were at higher risk for both dementia (OR: 2.50, $p = 0.046$) and vascular dementia (OR: 4.72, $p = 0.032$).

Discussion

Damaging variants in *CSF1R* are more common than expected in the general population and are associated with cognitive, psychiatric, and movement disorder diagnoses, which may reflect clinical manifestation of the disease. This study suggests that *CSF1R*-RD is either underreported, not diagnosed because of lack of genetic screening or that there is reduced penetrance.

Introduction

CSF1R-related disorder (*CSF1R*-RD) is a devastating autosomal dominant inherited white matter disorder characterized by a variable combination of cognitive impairment, neuropsychiatric changes, and motor symptoms including pyramidal and extrapyramidal signs, gait ataxia

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Glossary

CSF1R = Colony stimulating factor-1 receptor; **FLAIR** = fluid-attenuated inversion recovery; **TKD** = tyrosine kinase domain.

and seizures. *CSF1R*-RD has been known previously as adult-onset leukoencephalopathy with axonal spheroids and pigmented glia; however, as the spectrum of disease associated with *CSF1R* mutations continues to evolve, *CSF1R*-RD is gaining acceptance as the preferred nomenclature.[1] The mean disease duration from onset to incapacitation is 4 years (range 0–11 years), and the mean disease duration to death is 7 years (range 1–29 years).[2] MRI demonstrates progressive accumulation of confluent white matter hyperintensities on T2W/FLAIR-weighted sequences, progressive cerebral atrophy, microcalcifications, and diffusion-weighted abnormalities.[3] There are no approved disease-modifying treatments.

Approximately 300 cases of *CSF1R*-RD have been published to date, but there are a number of factors that suggest that this could be a significant underestimate of the true prevalence.[4] This includes frequent misdiagnosis[5] which can occur because of lack of recognition, lack of access to genetic testing, and clinical presentations similar to more common neurologic disorders. Based on available literature, patients with *CSF1R*-RD are thought to constitute 10%–25% of the adult-onset leukodystrophy population.[6-9]

To further our understanding of the prevalence of pathogenic and likely pathogenic *CSF1R* variants in the UK population, we examined the whole-exome sequences of 470,000 UK Biobank participants.[10] Furthermore, we used phenotypic data and processed MRI data (where available) to determine whether these mutations were associated with evidence of disease activity.

Methods

The UK Biobank is a prospective study of 502,493 volunteers aged 40–69 years, recruited across the United Kingdom between 2006 and 2010.[10] Participants attended visits undergoing deep phenotyping, extensive questionnaires, and biological samples, including a subset of 470,000 who underwent whole-exome sequencing. A further subset (45,000 or ~10%) of participants underwent MRI. Additional links to primary care and hospital records provided data in the form of International Classification of Diseases, 10th revision (ICD-10) diagnostic codes.

We extracted all variants in *CSF1R* with a minor allele frequency of <0.001 in the UK Biobank data set of 470,000 whole-exome sequences, which were released in July 2022. Variants were then annotated with ANNOVAR to determine functional outcome, frequency in other population databases, and in silico prediction tools of pathogenicity.[11] We used the American College of Medical Genetics (ACMG) criteria to classify variants as pathogenic or likely pathogenic.[12]

Most pathogenic mutations causing *CSF1R*-RD are missense mutations within the tyrosine kinase domain (TKD). These mutations are generally predicted pathogenic by computational tools. In addition to the pathogenic and likely pathogenic mutations described above, we identified a group of variants within the TKD with a high score calculated by MetaRNN,[13] a deep learning model with high accuracy in classifying potentially pathogenic variants.[13] We used a MetaRNN cutoff of >0.93 to classify these variants as high likelihood of pathogenicity.[13] Although ACMG would classify these as variants of uncertain significance, we predict that at least some of this group are potentially pathogenic and therefore present these data separately.

Numerous demographic and phenotypic data were extracted and analyzed for both the variant participants and a 20,000-person cohort of random controls. Medical history, including history of neurologic and psychiatric disease, were determined from self-reported (noncancer codes) and hospital-collected (ICD-10) codes. Patients with one or more codes for each medical condition were considered positive for that condition. Frequency of cognitive disease was also collected using the UK Biobank's algorithmically defined outcomes, which are obtained through combinations of coded information from UK Biobank's baseline assessment data collection (which included data from participants on their self-reported medical conditions, operations, and medications), along with linked data from hospital admissions (diagnoses and procedures) and death registries. The use of UK Biobank algorithmically defined outcomes in dementia has been validated previously.[14,15] Family history (including age of death of parents and history of illness in parents and siblings) was also extracted. Logistic regression was then used to calculate odds ratios, which represent the probability of each condition occurring in pathogenic, likely pathogenic, and combined patient groups relative to the control group.

Performance on cognitive tests (including vocabulary levels, reaction time, numeric memory, symbol digit substitution test, pairs matching time, word interpolation, and prospective memory) were collected where available.

Processed, quantitative MRI metrics including brain atrophy and white matter hyperintensity (WMH) volume were compared between a subset of variant cases and controls, as MRI was only performed in a limited subgroup of participants. For this, the processed UK Biobank neuroimaging working group-derived MRI measures for brain volume and WMH volume were used, generated by an image-processing pipeline developed and run on behalf of UK Biobank.[16] Brain volume was estimated by SIENAX while WMHs were quantified on

Table 1 Frequency of Pathogenic and Likely Pathogenic *CSF1R* Variants in UK Biobank and Extrapolated Numbers of Variant Carriers in the United Kingdom and Worldwide

			Est. UK prevalence[a]		Est. global prevalence[b]	
	Frequency in UK Biobank	Frequency per 100,000	Penetrance	Cases	Penetrance	Cases
Pathogenic	25	5.32	25%	904	25%	103,740
			50%	1,809	50%	207,480
			75%	2,713	75%	311,220
			100%	3,618	100%	414,960
Likely pathogenic	107	22.77	25%	3,870	25%	443,936
			50%	7,740	50%	887,872
			75%	11,611	75%	1,331,809
			100%	15,481	100%	1,775,745
Total	132	28.09	25%	4,774	25%	547,660
			50%	9,549	50%	1,095,319
			75%	14,323	75%	1,642,979
			100%	19,098	100%	2,190,638

[a] Assumes UK population 68,000,000.
[b] Assumes Global population 78,000,000,000.

fluid-attenuated inversion recovery (FLAIR) images.[17,18] Qualitative review of images was not undertaken.

Results

CSF1R Variant Frequency in UK Biobank

Using ACMG criteria, we identified 18 unique CSF1R pathogenic variants present across 25 participants (range 1–4), and 44 unique likely pathogenic mutations across 107 participants (range 1–45). These mutations are listed in eTables 1 and 2 respectively. The frequency of these mutations within the UK Biobank was used to determine the frequency per 100,000 and therefore the predicted prevalence in the United Kingdom and worldwide (Table 1). We found that approximately 1 in 3,500 individuals carry a pathogenic or likely pathogenic mutation in *CSF1R*. As the penetrance of *CSF1R*-RD is unknown, we have shown the estimated prevalence at a range of penetrance levels.

As mentioned above, as ACMG criteria are strict in the classification of missense variants in autosomal dominant disorders and the majority of disease causing *CSF1R* mutations are missense mutations in the tyrosine kinase domain, we also describe the frequency of mutations within the tyrosine kinase domain with a high score on the computational tool MetaRNN, identifying 20 such variants across 50 participants (range 1–10), as some of these variants may be pathogenic (eTable 3).

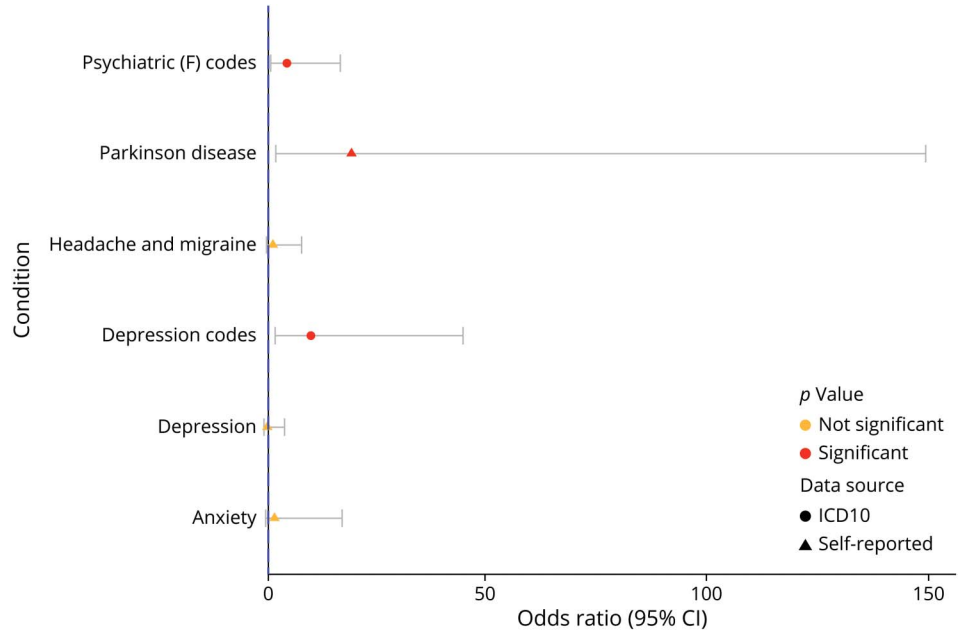
We also identified a very high frequency p.L868R variant (rs281860278), present in 173 participants (eTable 4). A mutation at the same residue (p.L868P) has been reported as pathogenic in *CSF1R*-RD, and this variant can therefore be classified as 'likely pathogenic' by ACMG criteria (PM1, PM5, PP3, PM2).[19] A functional study of the p.L868P variant also demonstrated a lack of CSF1R autophosphorylation.[20] However, 2 reports of individuals carrying the p.L868R variant who had neurodegenerative diseases and came to postmortem neuropathology have been published, and neither demonstrated pathologic findings of *CSF1R-RD*.[21,22] We therefore have low confidence that the p.L868R variant is pathogenic and present these data separately.

Clinical Implications of *CSF1R* Variants

The demographic profile of cases with pathogenic and likely pathogenic CSF1R variants and a random control group (n = 20,000) are show in eTable 4 (ethnicity and location) eTable 5 (age, sex). The amalgamated cohort comprising pathogenic and likely pathogenic groups mirrors the demographic profile of the UK Biobank, and there were no significant differences between groups with regard to age, sex, ethnicity, or cardiovascular risk factors including hypertension, hypercholesterolemia, HbA1C, or presence of APOE ε4 genotype (eTables 6 and 7).

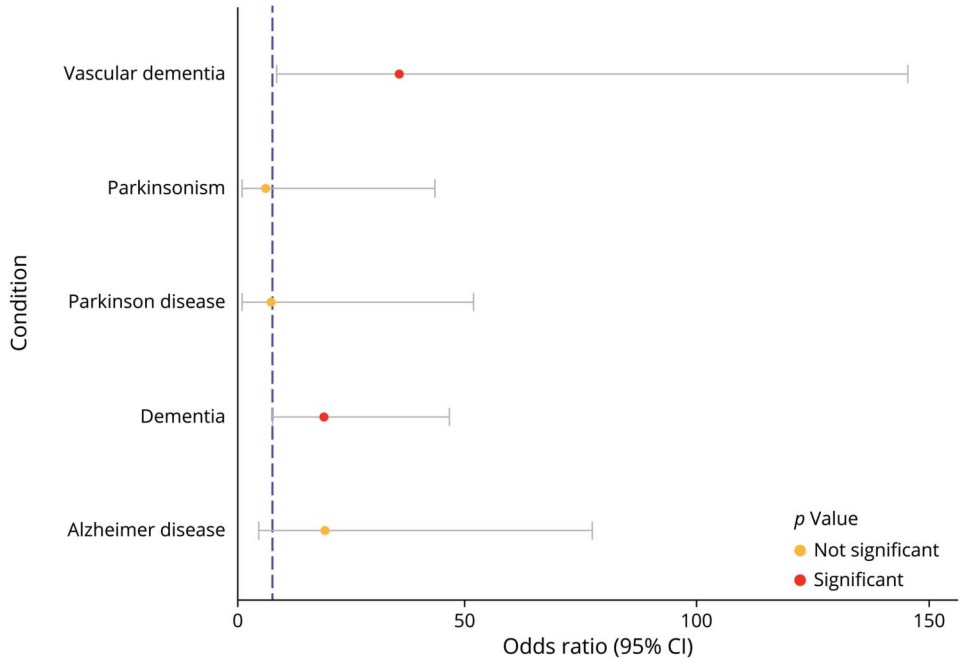
Logistic regression analysis revealed statistically significant associations for psychiatric codes with an odds ratio (OR) of 5.15 (95% CI 1.54–17.26, $p = 0.0079$), depression with an OR of 10.52 (95% CI 2.46–44.97, $p = 0.0015$), and self-reported Parkinson disease with an OR of 19.80 (95% CI 2.62–149.73, $p = 0.0038$) within the pathogenic variant carrier subgroup (Figure 1, eTable 8). These results suggest a significantly

Figure 1 Forest Plot of Odds Ratios of Different Conditions Occurring in Participants With Pathogenic *CSF1R* Variants vs Healthy Controls—Either Sourced From Self-Reported or ICD-10 Coded Data



increased likelihood of these conditions among individuals carrying pathogenic *CSF1R* mutations. In addition, our analysis indicated that individuals with likely pathogenic variants had higher odds of algorithmically defined vascular dementia (OR [95% CI] = 5.84 [1.41–24.17]; $p = 0.015$), and those with either pathogenic or likely pathogenic variants (the

Figure 2 Forest Plot of Odds Ratios of Different Cognitive Conditions Occurring in Participants With Either Pathogenic or Likely Pathogenic *CSF1R* Variants (the Combined Group) vs Healthy Controls—Sourced From Algorithmically Defined Outcomes



combined group) were at higher odds for both algorithmically defined dementia (OR (95% CI) = 2.50 (1.02–6.15); p = 0.046) and vascular dementia (OR (95% CI) = 4.72 (1.15–19.48); p = 0.032) (Figure 2, eTable 9). There were no significant differences found when analyzing the family history data between groups (eTable 10).

On enrollment to the UK Biobank, pathogenic and likely pathogenic *CSF1R* variant carriers were not found to have lower scores on cognitive tests when compared with controls (eTable 11). There were no significant differences found on MRI measures of white or gray matter volume or white matter hyperintensities between groups; however, the number of participants with available MRI data was limited, and longitudinal MRI data were not available (eTable 12).

Discussion

Colony stimulating factor-1 receptor (CSF1R), primarily expressed on microglia, is a tyrosine kinase receptor for cytokines CSF-1 and interleukin-34. Ligand-binding triggers multiple signal transduction pathways that regulate not just microglial proliferation and survival but also that of neural progenitor cells. Abrogation of CSF1R kinase activity is thought to be key to the pathology of *CSF1R-RD*.[23,24] As stated, the majority of pathogenic mutations are located in the TKD of *CSF1R*, most frequently identified in exons 18 and 19, but frameshift or nonsense mutations that induce premature stop codons have been found outside the TKD.[2]

This is the first study providing insights into the frequency of pathogenic and likely pathogenic *CSF1R* mutations in a large population-scale data set and provides a significant contribution to our understand of *CSF1R*-RD. In total, 62 such variants were identified in 132 individuals. Variants were predominantly located within the tyrosine kinase domain but were spread across 20 different exons between exons 2 and 22 of the *CSF1R* gene. Given the frequency of these mutations in the Biobank data set, we predict a frequency of 28.09 pathogenic or likely pathogenic variants per 100,000 or 2,190,638 carriers worldwide. This is likely to be an underestimate given that short-read exome sequencing will miss a proportion of structural variants, repeats, and variants in highly homologous genetic regions. UK Biobank is also unlikely to have enrolled patients already clinically affected by *CSF1R*-RD at baseline, given the severity of the disease and burden of study participation, which would also contribute to an underestimate of disease prevalence. Nevertheless, the frequency of damaging *CSF1R* variants found in the UK Biobank population is substantially higher than would be expected given that only 300 *CSF1R*-RD patients have been published in the literature to date.[4]

Of interest we found that individuals carrying pathogenic *CSF1R* variants were significantly more likely to have a an ICD10 psychiatric diagnosis or a self-reported diagnosis of Parkinson disease. We also found that those with either pathogenic or likely pathogenic variants (the combined group) were significantly more likely to have algorithmically defined diagnoses of dementia (unspecified) and vascular dementia. As neuropsychiatric presentations, cognitive dysfunction, and movement disorders are very common in *CSF1R*-RD and given the high rates of misdiagnosis especially in early phases of the disease, this may suggest that some individuals in this group were in an early symptomatic or prodromal phase of *CSF1R*-RD.

Limitations of our study include the scope of phenotypic data available in the UK Biobank and the small size of the variant population. Self-reported diagnostic data may not be reliable or complete. For this reason, we also used both ICD-10 coded diagnoses and algorithmically defined diagnoses to provide more complete phenotypic data. Imaging data were limited to MRI in a small subset of participants and was not longitudinal. No autopsy data are available to provide description of pathologic tissue. In addition, the majority of included participants are of White British background, which limits generalizability to other population groups.

The *CSF1R*-RD pedigrees reported so far suggest that mutations in *CSF1R* have a high penetrance, but our data set, and reported sporadic cases, implies penetrance may be lower than first thought.[25] It is likely that a "second hit"—which could be environmental, such as head injury, or viral illness, as increasingly recognized in MS, missed additional genetic variants *in cis* or *trans* around the *CSF1R* locus or a permissive genetic background—is necessary for a mutation carrier to develop clinical *CSF1R*-RD. Indeed, patients with identical *CSF1R* variants differ in the age at onset, severity of clinical presentation, and progression rate, meaning it is possible that multiple factors converge to result in an individual *CSF1R*-RD disease phenotype.[1] A large multicenter study of *CSF1R*-RD patients and families is needed to determine penetrance by age definitively.

The accurate diagnosis of *CSF1R*-RD is essential for prognosis and treatment decisions. Although currently there are no approved disease-modifying pharmacotherapies, the early identification of early disease allows for tertiary symptom management in an appropriate specialist center and appropriate genetic counseling for affected families.[26] A phase 2 trial of a fully humanized agonist TREM2 monoclonal antibody is currently underway in *CSF1R*-RD (ClinicalTrials.gov ID NCT05677659) and microglial replacement—either by infiltration of microglia-like cells, proliferation of resident microglia, or hematopoietic stem cell therapy—has also shown promise.[27-29]

In conclusion, this study provides the first insight into *CSF1R* variant frequency in the general population and suggests that *CSF1R*-RD may be more common than previously recognized.

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Henry Houlden, PhD	Department of Neuromuscular Disease, UCL Queen Square Institute of Neurology, London, United Kingdom	Drafting/revision of the manuscript for content, including medical writing for content; study concept or design
David S. Lynch, MBBS, PhD, MRCPI	National Institute for Health Research, University College London Hospitals, Biomedical Research Centre; National Hospital for Neurology and Neurosurgery, Queen Square, London, United Kingdom	Drafting/revision of the manuscript for content, including medical writing for content; major role in the acquisition of data; study concept or design

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