UNITED STATES
SECURITIES AND EXCHANGE COMMISSION
Washington, D.C. 20549

FORM 8-K

CURRENT REPORT
Pursuant to Section 13 or 15(d)
of the Securities Exchange Act of 1934

Date of Report (Date of earliest event reported): December 6, 2022

VIGIL NEUROSCIENCE, INC.
(Exact name of registrant as specified in its charter)

Delaware	**001-41200**	**85-1880494**
(State or other jurisdiction of incorporation)	**(Commission File Number)**	**(I.R.S. Employer Identification No.)**

Vigil Neuroscience, Inc.
1 Broadway, 7th Floor, Suite 07-300
Cambridge, Massachusetts, 02142
(Address of principal executive offices, including zip code)

(857) 254-4445
(Registrant's telephone number, including area code)

Not Applicable
(Former Name or Former Address, if Changed Since Last Report)

Check the appropriate box below if the Form 8-K filing is intended to simultaneously satisfy the filing obligation of the registrant under any of the following provisions:

☐ Written communications pursuant to Rule 425 under the Securities Act (17 CFR 230.425)

☐ Soliciting material pursuant to Rule 14a-12 under the Exchange Act (17 CFR 240.14a-12)

☐ Pre-commencement communications pursuant to Rule 14d-2(b) under the Exchange Act (17 CFR 240.14d-2(b))

☐ Pre-commencement communications pursuant to Rule 13e-4(c) under the Exchange Act (17 CFR 240.13e-4(c))

Securities registered pursuant to Section 12(b) of the Act:

Title of each class	Trade Symbol(s)	Name of each exchange on which registered
Common Stock, $0.0001 par value per share	VIGL	The Nasdaq Global Select Market

Indicate by check mark whether the registrant is an emerging growth company as defined in Rule 405 of the Securities Act of 1933 (§ 230.405 of this chapter) or Rule 12b-2 of the Securities Exchange Act of 1934 (§ 240.12b-2 of this chapter).

Emerging growth company ☒

If an emerging growth company, indicate by check mark if the registrant has elected not to use the extended transition period for complying with any new or revised financial accounting standards provided pursuant to Section 13(a) of the Exchange Act. ☐

Item 7.01 Regulation FD Disclosure.

On December 6, 2022, Vigil Neuroscience, Inc. (the "Company") hosted a presentation and event focused on adult-onset leukoencephalopathy with axonal spheroids and pigmented glia ("ALSP") with Key Opinion Leaders ("KOLs"). A copy of the presentation slides that accompanied the event are furnished as Exhibit 99.1 to this Current Report on Form 8-K, respectively.

The information under this Item 7.01, including Exhibit 99.1, is being furnished herewith and shall not be deemed "filed" for the purposes of Section 18 of the Securities Exchange Act of 1934, as amended (the "Exchange Act"), or otherwise subject to the liabilities of that section, nor shall such information be deemed incorporated by reference into any filing under the Securities Act of 1933, as amended, or the Exchange Act, except as expressly set forth by specific reference in such filing.

Item 9.01 Financial Statements and Exhibits.

(d) Exhibits

Exhibit No.	Description
99.1	Slide Presentation, dated December 6, 2022 (furnished herewith)
104	Cover Page Interactive Data File (embedded within the Inline XBRL document)

SIGNATURE

Pursuant to the requirements of the Securities Exchange Act of 1934, the registrant has duly caused this report to be signed on its behalf by the undersigned hereunto duly authorized.

Vigil Neuroscience, Inc.

Date: December 6, 2022

By: /s/ Ivana Magovčević-Liebisch
Ivana Magovčević-Liebisch
President and Chief Executive Officer


Exhibit 99.
Vigil Neuroscience, Inc.
ALSP KOL Event
December 6, 2022
(vigil)™
NEURO
vigilant for you®
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FORWARD-LOOKING STATEMENTS

This presentation contains "forward-looking statements," which are made pursuant to the safe harbor provisions of the federal securities laws, including the Private Securities Litigation Reform Act of 1995. Any statements that are not statements of historical fact may be deemed to be forward-looking statements. Such statements may contain words such as "may," "might," "will," "could," "should," "would," "expect," "intend," "plan," "prepare," "look," "seek," "anticipate," "believe," "estimate," "predict," "potential," "possible," "continue," "ongoing" or the negative of these terms, or other comparable words. These forward-looking statements include, among others, statements relating to: our plans to deliver precision-based therapies to improve the lives of patients and their families and to target a broad range of neurodegenerative diseases; plans to discover and develop novel therapeutics to leverage microglial biology, such as VGL101 and small molecules active against TREM2, and to enable success in ALSP in clinical development; beliefs about TREM2 agonism's importance in Alzheimer's disease; beliefs about the profiles and potential, including the commercial potential, of our pipeline and the strength of our intellectual property position; our analyses and beliefs about data, including pathology and disease biomarkers and the signaling, engagement and potency as an agonism of TREM2 in microglia; plans and upcoming milestones, including estimated timelines, for our pipeline program development activities and pipeline expansion opportunities; expected timing and next steps regarding data announcement, clinical trial activities and regulatory filings and approvals; expectations regarding our ability to develop and advance our current and future product candidates and discovery programs; and the belief that we are well-positioned to execute on our mission.

These forward-looking statements, which are only predictions, involve risks and uncertainties, many of which are beyond our control and are based on our current beliefs, expectations and assumptions regarding our business. As such, you should not place undue reliance on any forward-looking statements because such risks and uncertainties could cause actual results, performance or achievement to differ materially and adversely from those anticipated or implied in the forward-looking statements. Factors that could cause actual results to differ from those predicted in our forward-looking statements include, among others, risks and uncertainties related to product development, including delays or challenges that may arise in the development and regulatory approval of our current and future product candidates or programs; uncertainties as to the availability and timing of results and data from preclinical and clinical studies; the timing of our ability to submit and obtain regulatory clearance for investigational new drug applications and initiate additional clinical trials; our ability to initiate and complete our current and expected clinical trials; our ability to establish and maintain collaborations, strategic relationships and supply arrangements, or that we will not realize the intended benefits from such relationships or arrangements; whether our cash resources will be sufficient to fund our foreseeable and unforeseeable operating expenses and capital expenditure requirements; our ability to raise additional funding on favorable terms, or at all; the rate and degree of market acceptance and clinical utility of our product candidates; the ability and willingness of our third-party collaborators to continue research and development activities relating to our product candidates; the accuracy of our data analyses or estimates for the potential and market for our products; our ability, and the ability of our collaborators, to protect our intellectual property and to conduct activities for the development and commercialization of our candidates in view of third party intellectual property positions; our financial performance; our ability to retain and recruit key personnel, as well as the potential contribution of our employees and board to our growth and success as a Company; developments and projections relating to our competitors or our industry; the effect of the COVID-19 pandemic, including mitigation efforts and economic impacts, on any of the foregoing or other aspects of our business operations, including our preclinical studies and clinical trials; changes in general economic conditions and global instability, in particular economic conditions in the markets on which we or our suppliers operate; changes in laws and regulations; and those risks and uncertainties identified in our filings with the Securities and Exchange Commission (SEC), including under the heading "Risk Factors" in our most-recently filed Annual Report on Form 10-K or Quarterly Report on Form 10-Q, and such other risks and uncertainties that may be described in subsequent filings we may make with the SEC.

You should not rely upon forward-looking statements as predictions of future events or performance, or as a representation or warranty (express or implied) by us or any other person that we will achieve our objectives and plans in any specified time frame, on such specified terms, or at all. Although our management believes that the expectations reflected in our statements are reasonable, we cannot guarantee that the future results, performance or events and circumstances described in the forward-looking statements will be achieved or occur. These forward-looking statements speak only as of the date such statements are made. New risks and uncertainties may emerge from time to time, and it is not possible to predict all risks and uncertainties. Except as required by applicable law, we do not plan to publicly update or revise any forward-looking statements contained herein, whether as a result of any new information, future events, changed circumstances or otherwise. Certain information contained in this presentation relates to or is based on studies, publications, surveys and other data obtained from third-party sources and the Company's own internal estimates and research. While we believe these third-party sources to be reliable as of the date of this presentation, we have not independently verified, and we make no representation as to the adequacy, fairness, accuracy or completeness of any information obtained from third-party sources


(vigil)™
NEURO
Introduction & Corporate Overview
Ivana Magovčević-Liebisch, PhD, JD
Chief Executive Officer
Vigil Neuroscience
3
vigilant for you®
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Vigil 2022 ALSP Key Opinion Leader Event – Agenda

8:30 – 10:00 AM
Opening Remarks & Corporate Overview
Ivana Magovčević-Liebisch, PhD, JD
Chief Executive Officer
Vigil Neuroscience, Inc.

What is ALSP?
David S. Lynch, MD, PhD
Consultant Neurologist
National Hospital for Neurology & Neurosurgery, Queen Square & UCL Institute of Neurology, London, U.K.
Clinical Lead, Adult Inherited White Matter Disorders Highly Specialist Service, NHS England

ALSP History & Diagnosis
Christina Sundal, MD, PhD
Chief Executive Officer
NeuroClinic Norway
Senior Consultant
University Hospital, Oslo, Norway

8:30 – 10:00 AM (continued)
ALSP Treatment & Unmet Medical Need
Troy Lund, MSMS, PhD, MD, FAAP
Associate Professor
Associate Director Metabolic Program
Leukodystrophy Center of Excellence, Division of Pediatric Blood and Marrow Transplantation & Cellular Therapy
University of Minnesota, A NORD Rare Disease Center of Excellence

10:00 – 10:15 AM
Break

10:15 – 10:45 AM
ILLUMINATE Natural History Study: Interim Findings
VGL101 Phase 2 IGNITE Trial Design & Objectives
Spyros Papapetropoulos, MD, PhD
Chief Medical Officer
Vigil Neuroscience, Inc.

10:45 – 11:30 AM
Closing and Q&A

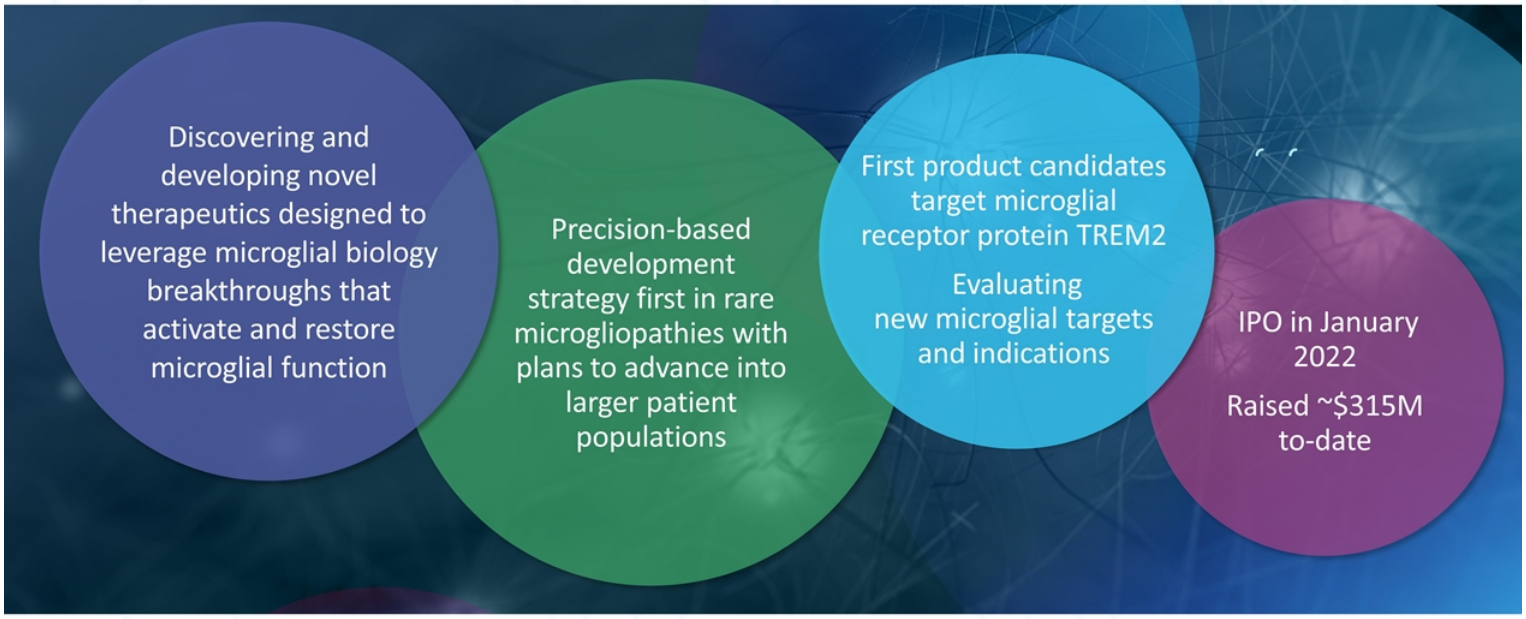
Vigil Neuroscience

Vigil Neuroscience is a clinical-stage microglia-focused therapeutics company

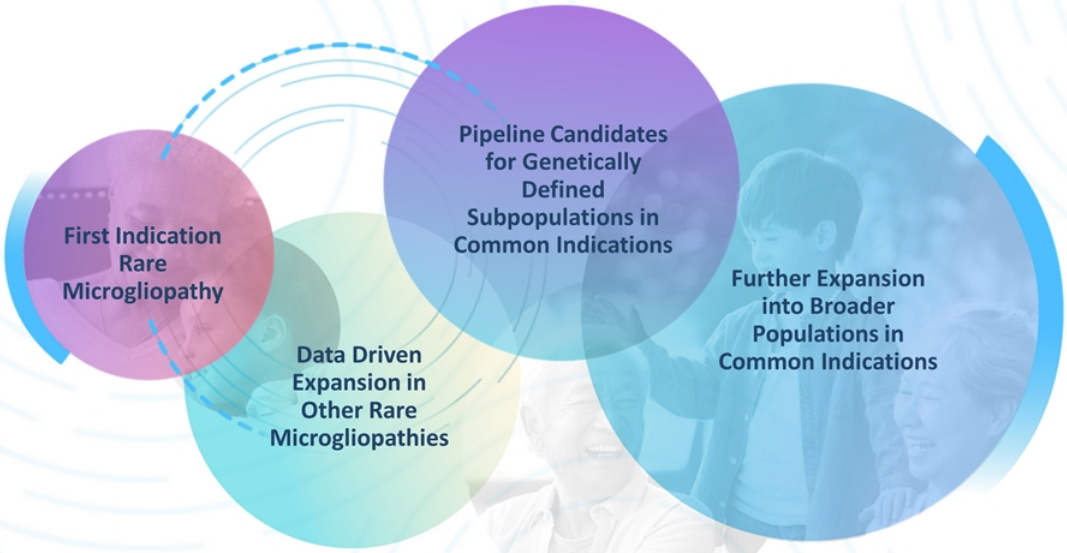
Our purpose: to treat rare and common neurodegenerative diseases by restoring the vigilance of microglia, the brain's sentinel immune cells

We are utilizing the tools of modern neuroscience drug development across multiple therapeutic modalities as we seek to deliver precision-based therapies to improve the lives of patients and their families

Vigil's Mission: Restoring Microglial Vigilance to Create Disease-Modifying Treatments for Neurodegenerative Diseases

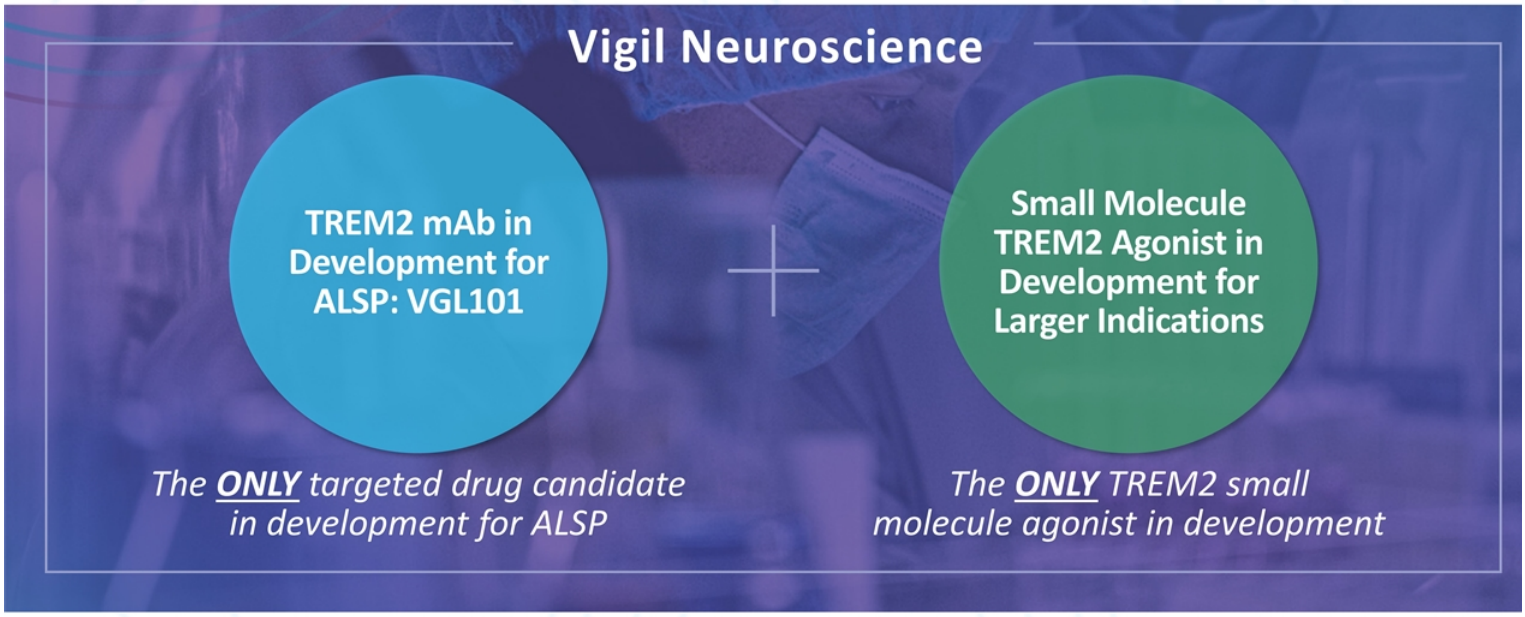


Vigil's Precision Medicine Strategy to Target Broad Range of Neurodegenerative Diseases



Apply learnings from genetically defined subpopulations to larger indications

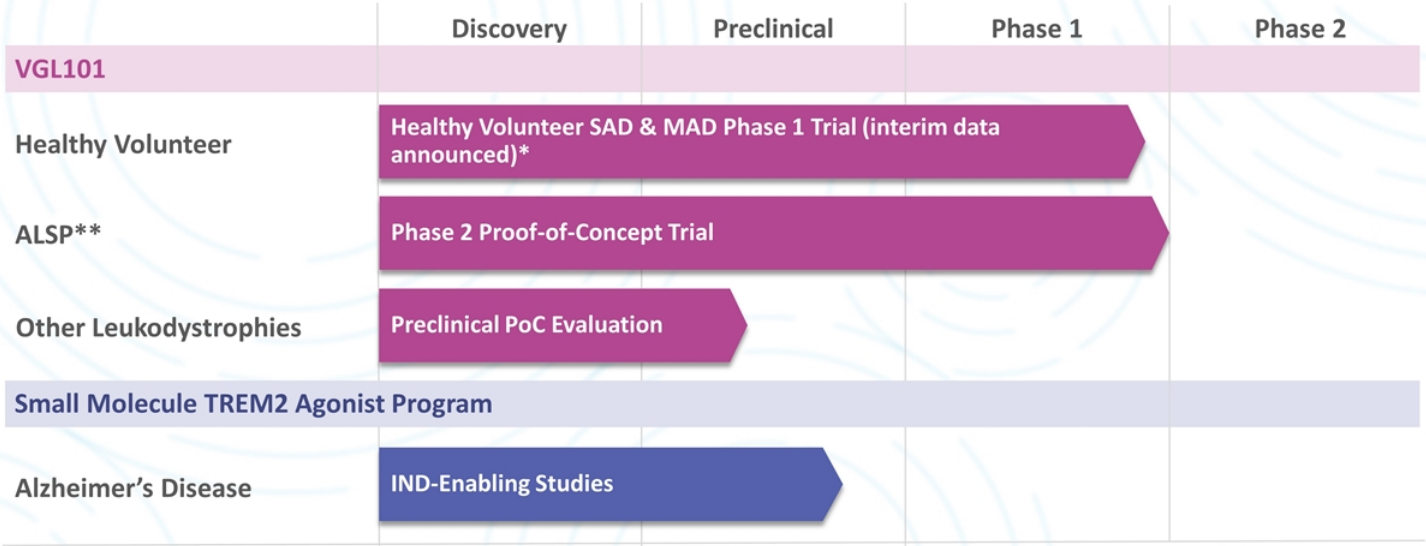
Vigil TREM2 Agonists: Differentiated Strategy & Multiple Modalities



ALSP: Adult-onset leukoencephalopathy with axonal spheroids and pigmented glia

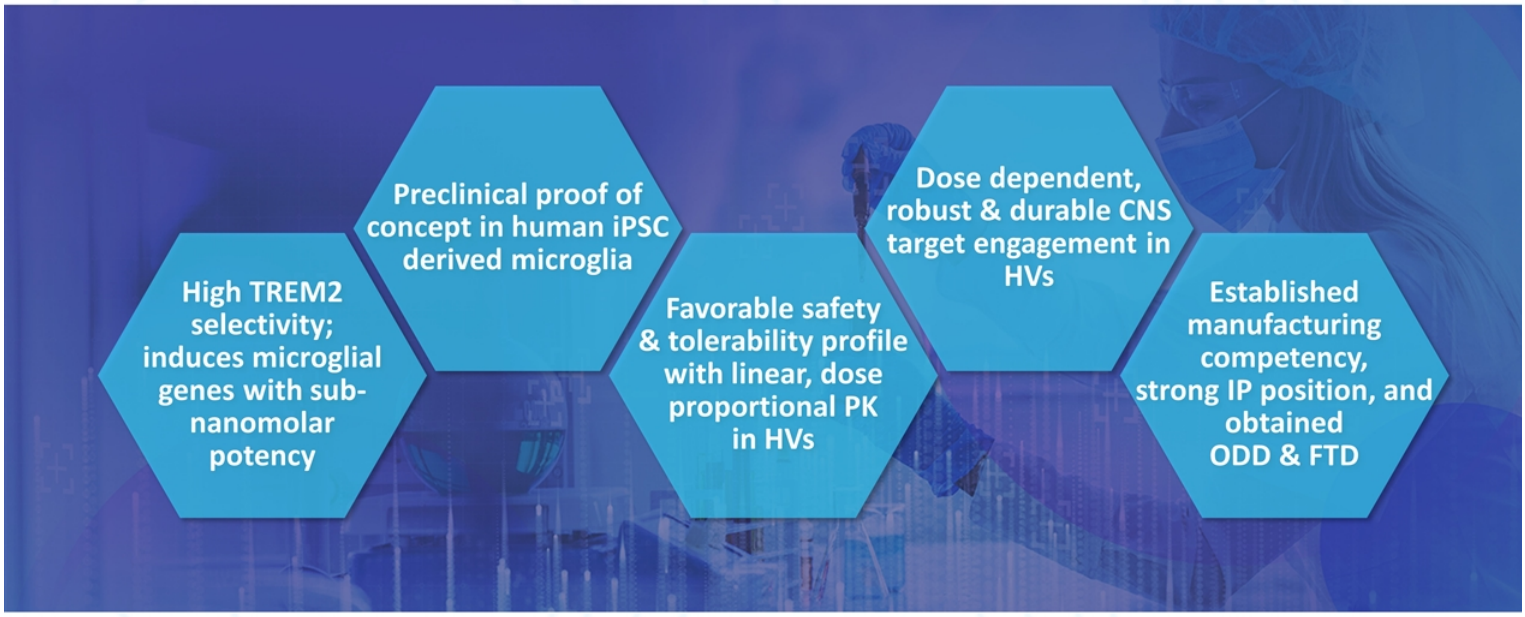
Our Pipeline

Vigil Has Exclusive Rights to All Programs



*SAD: single ascending dose; MAD: multiple ascending dose; Phase 1 completed dosing and interim analysis for certain cohorts
** Additional observational Natural History Study in ALSP is ongoing

VGL101 – Human mAb Agonist of TREM2 with a Compelling Profile



mAb: monoclonal antibody; HVs: healthy volunteers; ODD: Orphan Drug Designation; FTD: Fast Track Designation

Summary of Interim Topline VGL101 Phase 1 Data in Healthy Volunteers*

Demonstrated a favorable safety and tolerability profile

Pharmacokinetics showed linear, predictable characteristics across doses
- Half-life supports monthly dosing

Demonstrated proof of target engagement and pharmacological activity
- Dose-dependent, robust and durable reductions in sTREM2, and durable increases in sCSF1R with repeat dosing
- 1st antibody to report durability of TREM2 engagement in a clinical setting

Phase 1 data support VGL101 20 mg/kg as a pharmacologically active dose for Phase 2 proof-of-concept trial in ALSP patients

Phase 2 IGNITE trial in ALSP initiated

**As of October 7, 2022, and includes doses up to 40 mg/kg SAD and 20 mg/kg MAD*

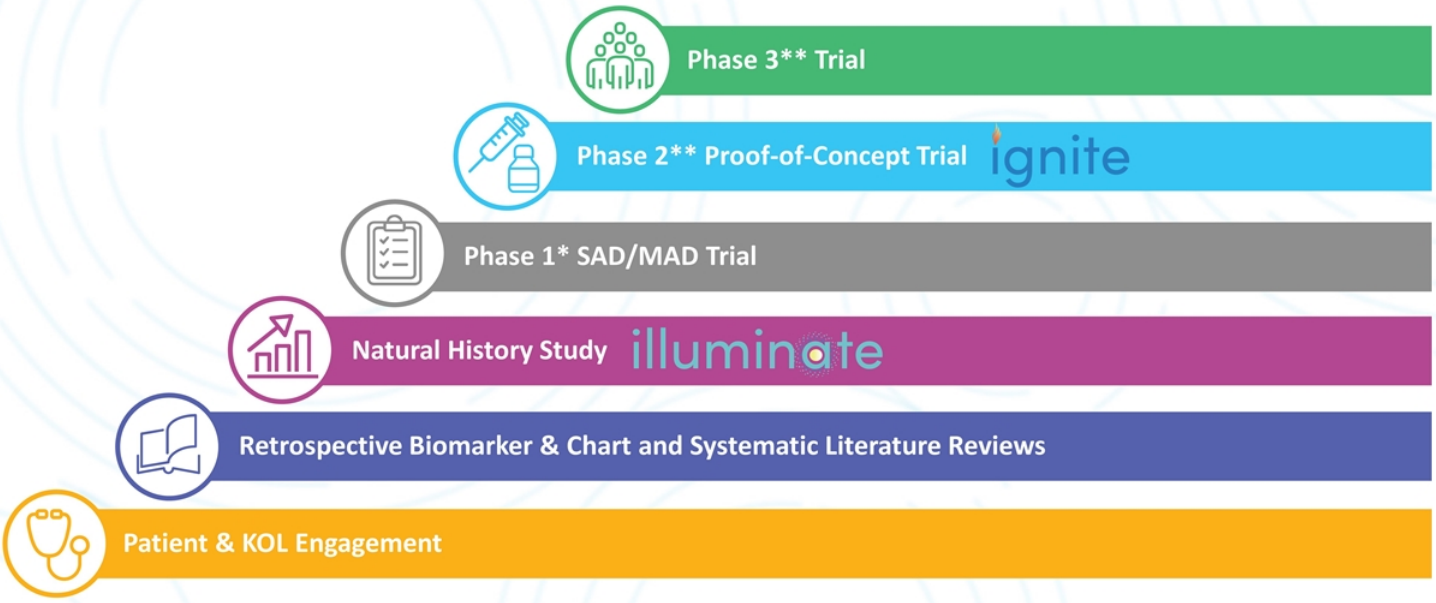
VGL101 is an investigational therapy and has not been reviewed or approved by any regulatory authority

Driving ALSP Awareness via Comprehensive Stakeholder Engagement

Focused on increasing accurate & timely diagnosis

Building Strong Foundation with Patient Advocacy Groups (PAGs)	Incorporating Patient & Caregiver Insight/Perspectives	Promoting Disease Awareness on Multiple Fronts	Increasing Clinical Trial Awareness Cross-Functionally
▪ Established relationships with regional & global PAGs across relevant neurodegenerative diseases (including ALSP, leukodystrophies, MS, FTD)	▪ Established Patient & Caregiver Advisory Council ▪ Executing Natural History Study in ALSP ▪ Enhancing resources on patient journey, & genetic testing & counseling	▪ Launched patient-facing ALSPinfo.com & social media accounts ▪ Developed disease education materials ▪ Engaging KOLs in diseases ALSP is frequently misdiagnosed (e.g. MS, FTD)	▪ Launched clinical trial websites ▪ Provided PAGS with trial awareness materials ▪ Collaborating with ALSP KOLs ▪ Engaging MS and FTD specialists

Building Toward Success in ALSP Clinical Development



**Involving healthy volunteers; **Planning for seamless Phase 2/3 design*

Featured Key Opinion Leaders

David S. Lynch, MD, PhD
Consultant Neurologist, National Hospital for Neurology & Neurosurgery, Queen Square & UCL Institute of Neurology, London, U.K.
Clinical Lead, Adult Inherited White Matter Disorders Highly Specialist Service, NHS England

Christina Sundal, MD, PhD
CEO, NeuroClinic Norway
Senior Consultant, University Hospital of Oslo, Norway

Troy Lund, MSMS, PhD, MD, FAAP
Associate Professor, Associate Director Metabolic Program, Pediatric Blood and Marrow Transplant Fellowship Director, Leukodystrophy Center of Excellence, Division of Pediatric Blood and Marrow Transplantation & Cellular Therapy, University of Minnesota, A NORD Rare Disease Center of Excellence, Stem Cell Institute, Global Pediatrics

What is ALSP?

David S. Lynch, MD, PhD

Consultant Neurologist
National Hospital for Neurology & Neurosurgery, Queen Square & UCL Institute of Neurology, London

Clinical Lead
Inherited White Matter Disorders Highly Specialist Service, NHS England

Adult-onset Leukoencephalopathy with Axonal Spheroids and Pigmented Glia (ALSP)

- An inherited neurodegenerative disorder
- Rare and under-recognized
- Primarily causing degeneration of brain white matter (i.e., an ‘Inherited White Matter Disorder’ or ‘leukoencephalopathy/leukodystrophy’)
- The hallmark axonal ‘spheroids’ (swellings) and pigmented glia give the disorder its name

ALSP

- Has been known by a number of alternative names, largely hangovers from the era before MRI and genetics were widely available
- First described as pigmentary orthochromatic leukodystrophy (POLD) in 1936
- Later, the name hereditary diffuse leukoencephalopathy with spheroids (HDLS) became more widely used because of an influential and important report on the disease in 1984
- In recent years, ALSP has become the preferred term as it recognizes the importance of both the axonal spheroids and abnormal microglia

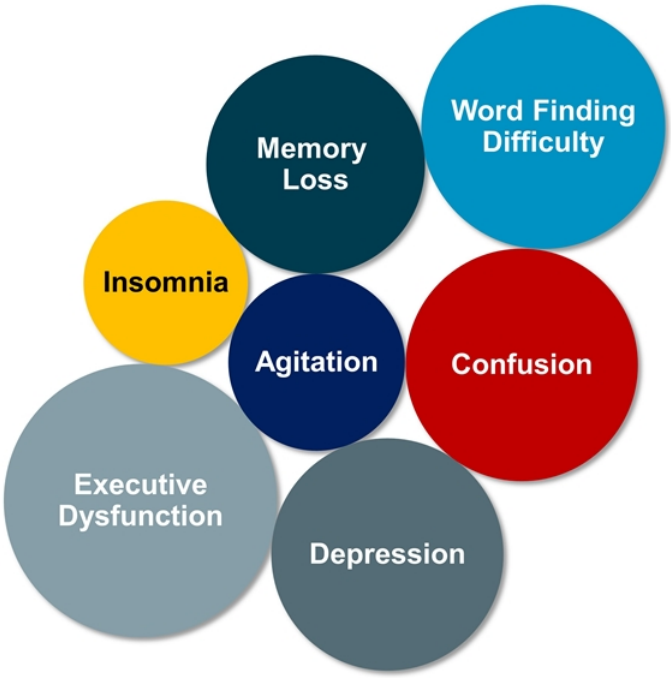
Wider et al. Neurol 2009

ALSP Symptoms

- A progressive, neurodegenerative disorder
- Demyelination (destruction) of white matter in the brain has widespread and devastating effects
- Symptoms can be similar to more widely recognized diseases
  - Cognitive symptoms: similar to Frontotemporal Dementia (FTD)
  - Motor symptoms: similar to Progressive MS, Parkinson Disease

ALSP Symptoms

- Symptoms most often develop in the 40s but the range is wide (18–86 years)
- Cognitive and ‘neuropsychiatric’ symptoms are often first to emerge



ALSP Symptoms

Cognitive

- Personality change
- New anxiety, depression
- Difficulty in work, decision making
- Inappropriate behavior
- Memory problems
- Word finding and speech problems

As the Disease Progresses, Symptoms Multiply

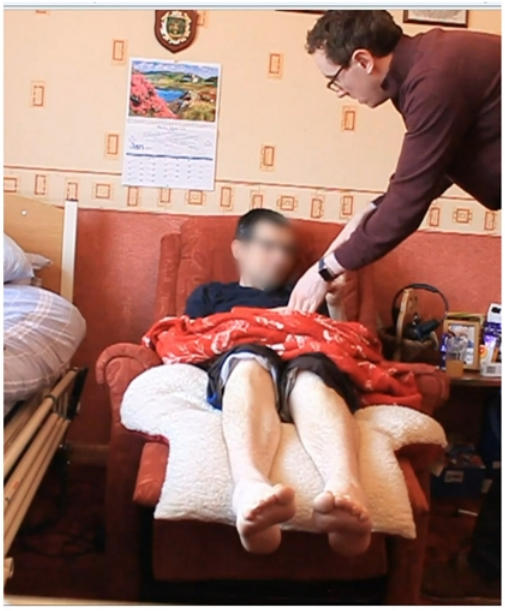
ALSP Symptoms

Motor

- Gait and balance problems
- Stiffness, slowness of movement
- Incoordination, tremor
- Swallowing and speech difficulty

As Symptoms Progress, Patients Become More Immobile to the Point of Being Bedbound and Totally Dependent for Care

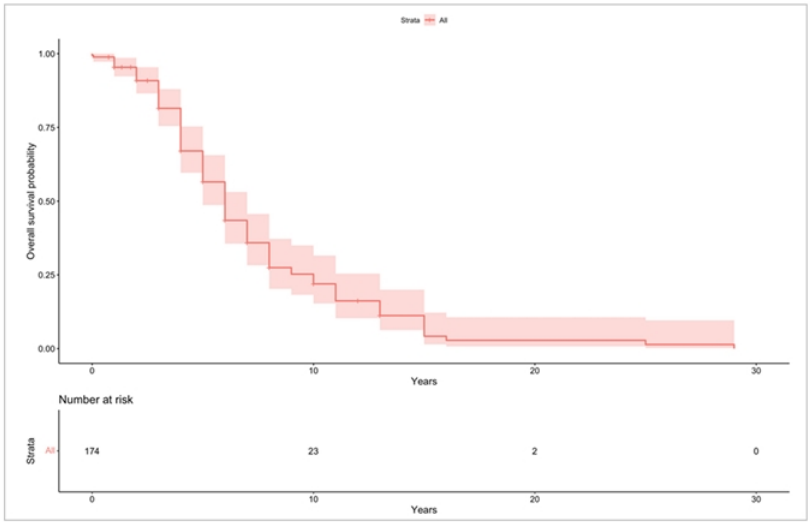
ALSP Patient Video



ALSP Progression

Relentlessly Progressive

- 75% survival for approximately 3 years, 50% for 5 years, 25% for 10 years and < 5% for 30 years

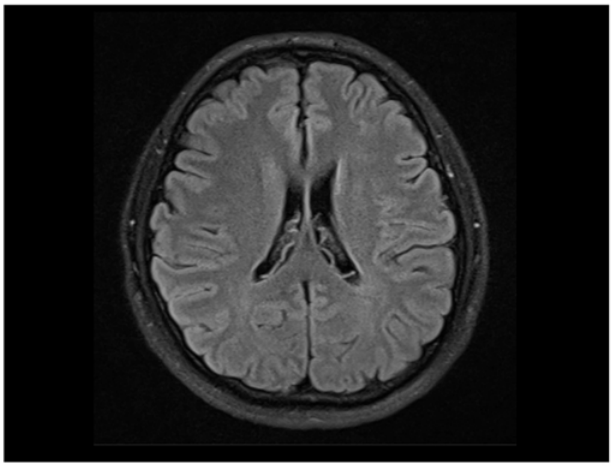
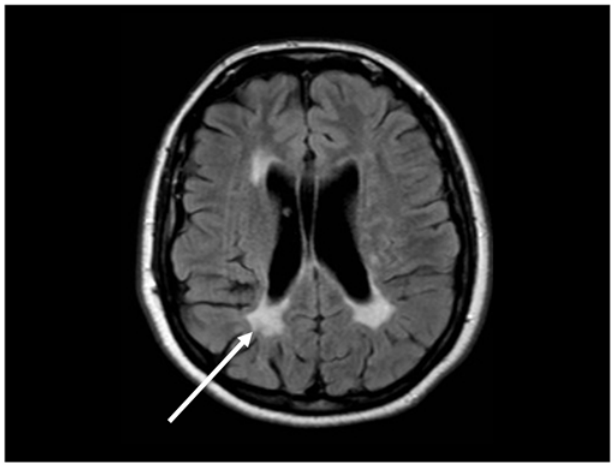


Papapetropoulos et al. American Academy of Neurology Conference 2022

Symptom Overlap with Other Diseases (Misdiagnosis)

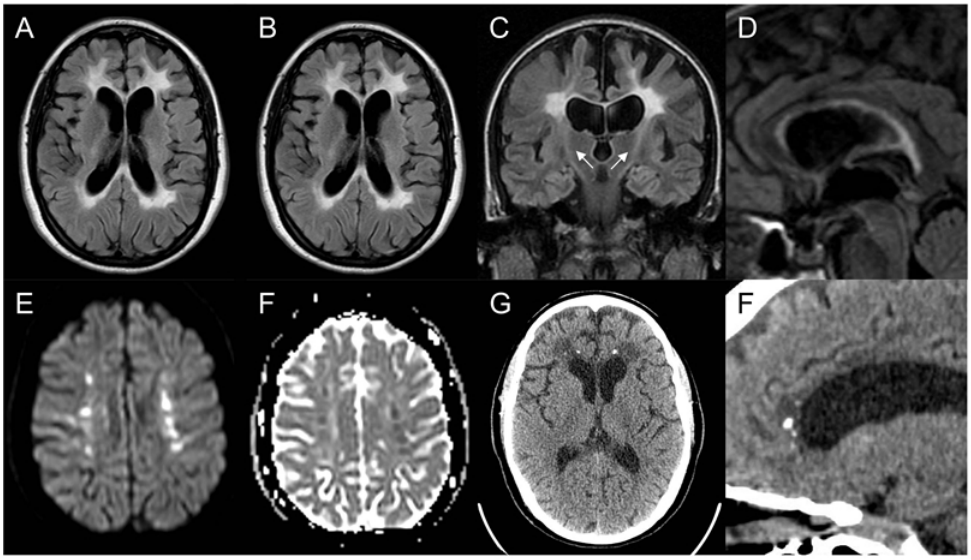
- Frontotemporal Dementia (FTD)
- Alzheimer Disease (AD)
- Primary Progressive Multiple Sclerosis (PPMS)
- Parkinson Disease (PD)
- Other inherited white matter disorders
  - Mostly Cerebral Autosomal Dominant Arteriopathy with Sub-cortical Infarcts and Leukoencephalopathy (CADASIL)
- Corticobasal Syndrome

ALSP Magnetic Resonance Imaging

Normal MRI	ALSP
	

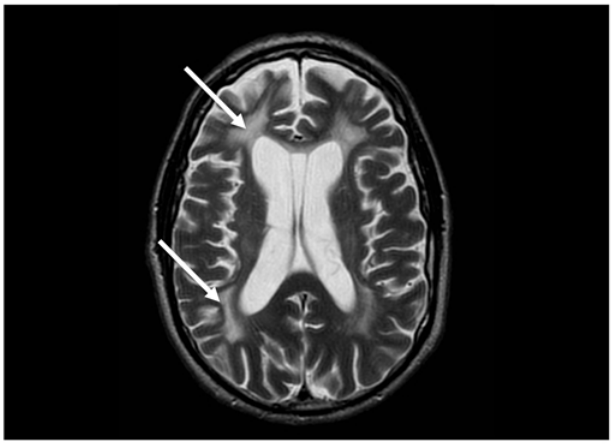
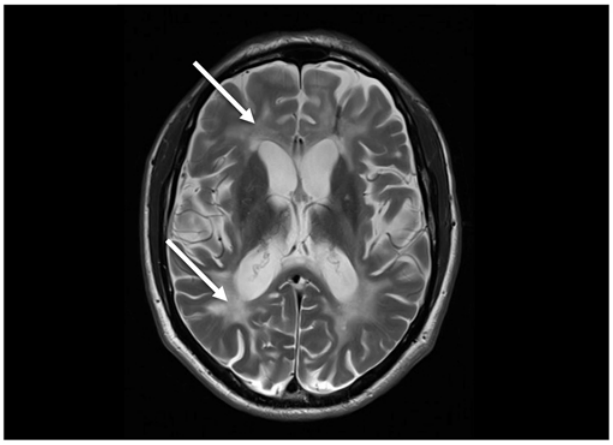
D. Lynch unpublished data

ALSP Typical Imaging



Wade & Lynch: Handbook of Clinical Neurology, Inherited White Matter Disorders

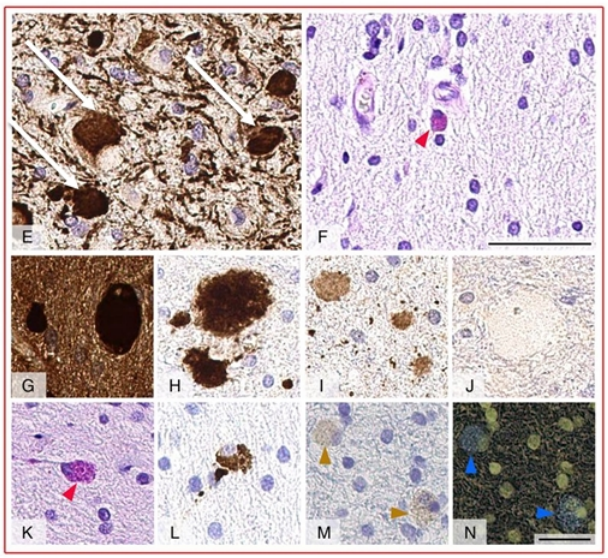
Misdiagnosis

ALSP	Progressive MS
	

The Direction of Misdiagnosis is the Failure to Recognize ALSP

D. Lynch unpublished data

Neuropathology – Axonal Swellings (Spheroids) and Pigmented Glia



Lynch DS et al, Journal of Neurology, Neurosurgery & Psychiatry 2016.

Epidemiology

- Inherited white matter disorders (IWMD) are rare but recognition is growing due to:
  - Better access to genetics
  - Widespread availability of imaging
  - Increased understanding of phenotypes, particularly in adults
- UK has just established first national specialist service for IWMD

>300 Reported Cases globally; Significant Underestimate

Papapetropoulos et al. Front Neurol 2022

Epidemiology – at Least 10–15% of IWMDs

doi:10.1093/brain/awx045 BRAIN 2017: 140; 1204–1211 | 1204

BRAIN
A JOURNAL OF NEUROLOGY

REPORT

Clinical and genetic characterization of leukoencephalopathies in adults

David S. Lynch,[1,2] Anderson Rodrigues Brandão de Paiva,[3] Wei Jia Zhang,[1] Enrico Bugiardini,[4] Fernando Freua,[3] Leandro Tavares Lucato,[5] Lucia Inês Macedo-Souza,[6]

Published in final edited form as:
JAMA Neurol. 2013 July ; 70(7): 875–882. doi:10.1001/jamaneurol.2013.698.

Genetic Analysis of Inherited Leukodystrophies:

Genotype-Phenotype Correlations in the *CSF1R* Gene

Rita Guerreiro, PhD[#1], Eleanna Kara, MD, MSc[#1], Isabelle Le Ber, MD, PhD[#5,6], Jose Bras, PhD[1], Jonathan D. Rohrer, MD[2], Ricardo Taipa, MD[3,12], Tammaryn Lashley, PhD[3], Céline Dupuits, BS[7], Nicole Gurunlian, MS[1], Fanny Mochel, MD, PhD[5,7], Jason D. Warren, MD,

RESEARCH PAPER

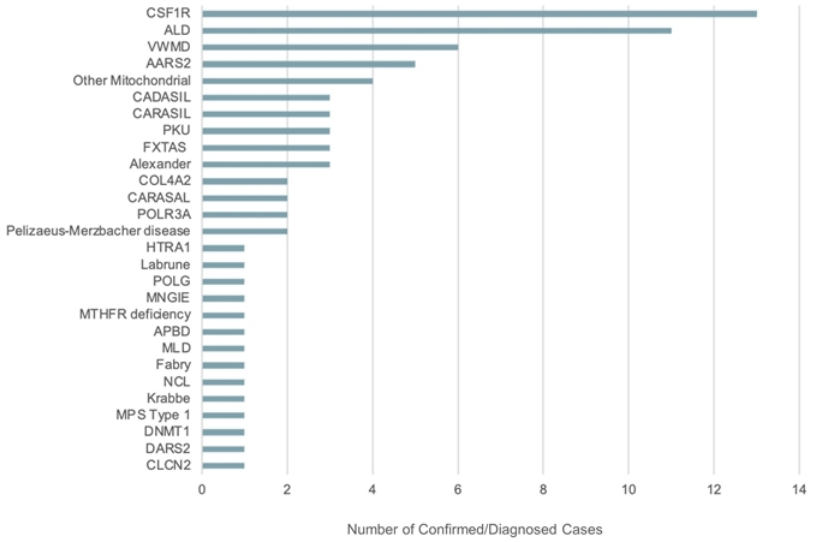
Hereditary leukoencephalopathy with axonal spheroids: a spectrum of phenotypes from CNS vasculitis to parkinsonism in an adult onset leukodystrophy series

David S Lynch,[1,2] Zane Jaunmuktane,[3] Una-Marie Sheerin,[1] Rahul Phadke,[3] Sebastian Brandner,[3] Ionnis Milonas,[4] Andrew Dean,[5] Nin Bajaj,[6] Nuala McNicholas,[7] Daniel Costello,[7] Simon Cronin,[7] Chris McGuigan,[8] Martin Rossor,[9] Nick Fox,[9]

Latest Unpublished Data

Queen Square & UCL Institute of Neurology

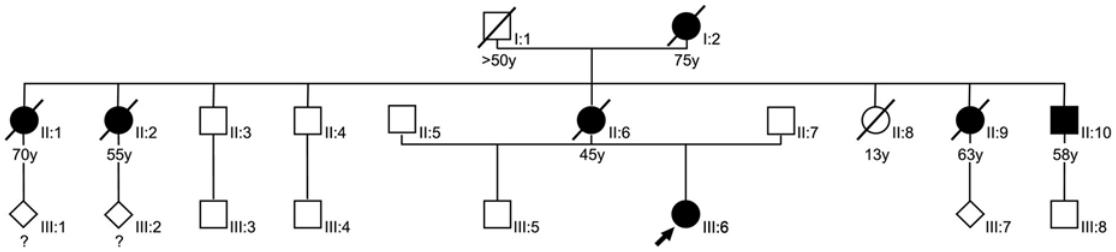
ALSP 13/76 Most Recent IWMD Diagnoses (17%)



Charlie Wade, UCL, 2022, unpublished

Genetics

- Autosomal dominant inheritance
- Multiple generations can be affected
- Children and siblings of a patient are at 50% risk of being affected
- *De novo* cases also occur (children remain at 50% risk)
- Penetrance is incomplete but very high



Kraya et al, Mol Genet Genomic Med 2019

Genetics

In 2011, the Causative Gene Was Identified

Mutations in the colony stimulating factor 1 receptor (*CSF1R*) cause hereditary diffuse leukoencephalopathy with spheroids

Rosa Rademakers[1,*], Matt Baker[1], Alexandra M. Nicholson[1], Nicola J. Rutherford[1], NiCole Finch[1], Alexandra Soto-Ortolaza[1], Jennifer Lash[2], Christian Wider[1,3], Aleksandra Wojtas[1], Mariely DeJesus-Hernandez[1], Jennifer Adamson[1], Naomi Kouri[1], Christina Sundal[1],

Original Investigation

Genetic Analysis of Inherited Leukodystrophies
Genotype-Phenotype Correlations in the *CSF1R* Gene

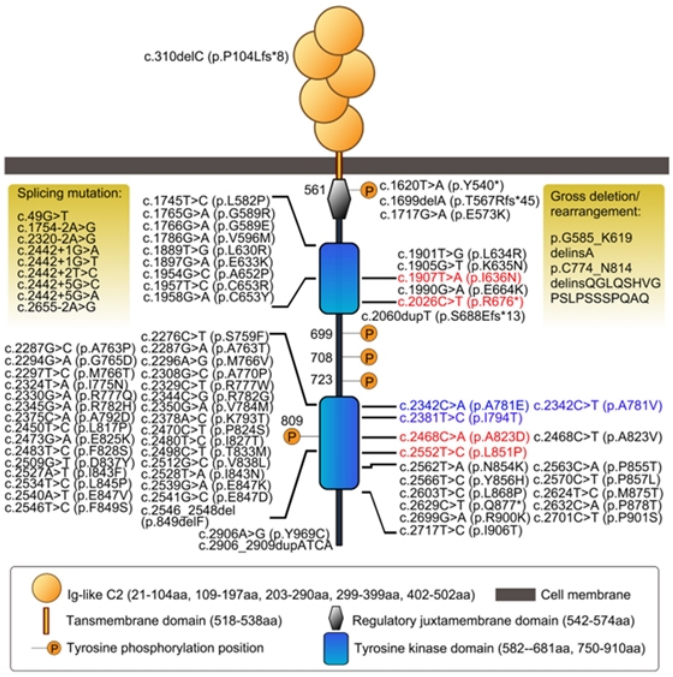
Rita Guerreiro, PhD; Eleanna Kara, MD, MSc; Isabelle Le Ber, MD, PhD; Jose Bras, PhD; Jonathan D. Rohrer, MD; Ricardo Taipa, MD; Tammaryn Lashley, PhD; Céline Dupuits, BS; Nicole Gurunlian, MS; Fanny Mochel, MD, PhD; Jason D. Warren, MD, PhD; Didier Hannequin, MD; Frédéric Sedel, MD, PhD; Christel Depienne, PhD;

CSF1R

- Colony stimulating factor-1 receptor gene
- Encodes a cell surface receptor highly expressed on myeloid cells including brain microglia
- Microglia are critically important immune cells with diverse functions
- ALSP is a *microgliopathy*

CSF1R

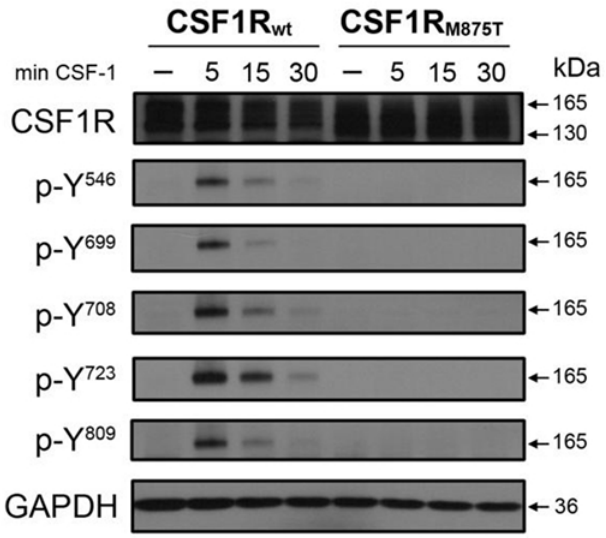
- Majority of mutations affect tyrosine kinase activity → loss of function
- No genotype/phenotype correlation



Tian et al. Transl Neurodegener 2019

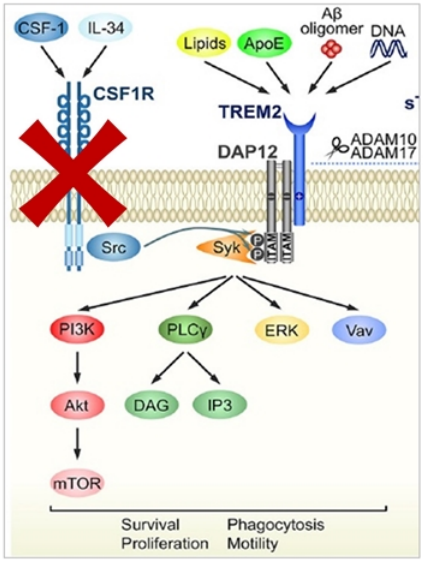
CSF1R Activation

- Ligand binding leads to
  - Receptor homodimerization
  - Tyrosine kinase domain (TKD) autophosphorylation
  - Downstream signaling for microglial proliferation, survival and differentiation
- Inhibition of CSF1R rapidly depletes the brain of microglia

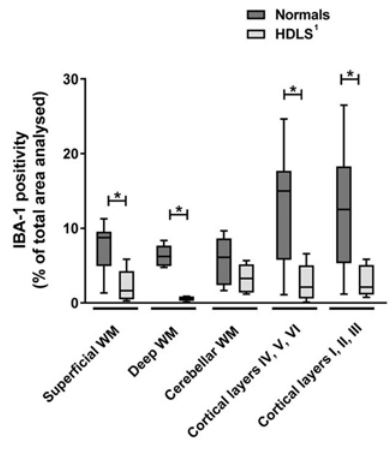


Elmore et al Neuron 2014; Rademakers et al, Nature Genetics 2011

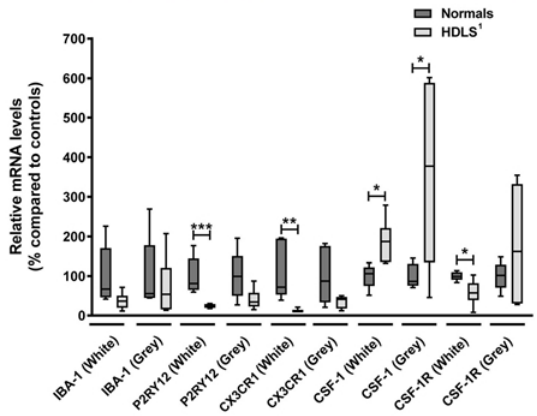
CSF1R LoF Leads to Microglial Loss and Dysfunction in ALSP



Microglia Numbers Based on IBA-1 Staining



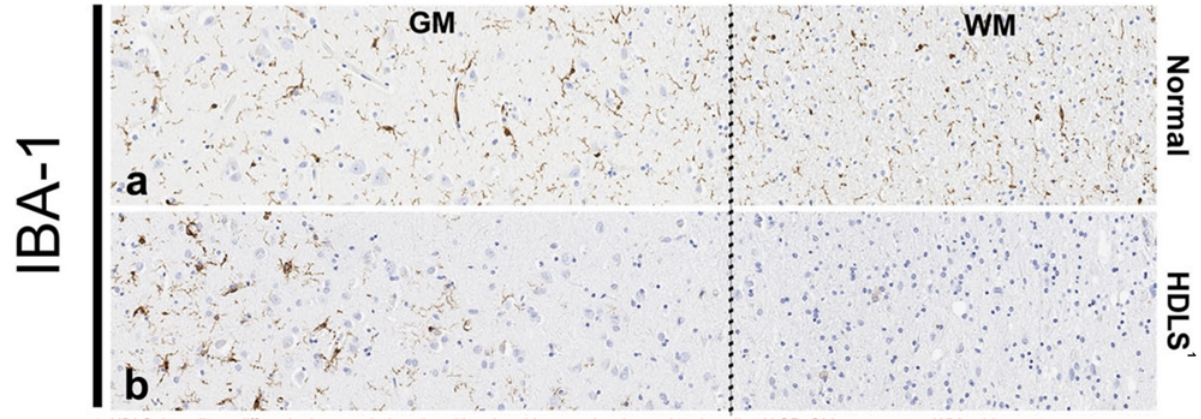
Microglial Phenotype Based on Gene Expression



*1. HDLS: hereditary diffuse leukoencephalopathy with spheroids – previously used to describe ALSP; WM: white matter; * p < 0.05*

Konishi & Kiyama Front. Cell. Neurosci. 2018; Kempthorne et al. Acta Neuropathologica. 2020

Microglial Loss and Dysfunction in ALSP



1. HDLS: hereditary diffuse leukoencephalopathy with spheroids – previously used to describe ALSP; GM: grey matter; WM: white matter

Kempthorne et al. Acta Neuropathologica. 2020

Genetic Diagnosis

- The cost of sequencing has plummeted in recent years
- Diagnostic rates for genetic disorders are improving
- Most clinicians are using panels of many genes
- Diagnosis can be made even without a high suspicion of ALSP

ALSP Diagnosis

- Referrals come from a variety of sources
  - Cognitive clinics
  - MS clinics
  - Movement Disorders
  - Clinical/Neurogenetics
  - Neuroradiology

Summary

- ALSP is rare but under-recognized
- It is a devastating neurodegenerative disorder
- ALSP is a microgliopathy
- Diagnostic rates are rapidly improving due to advances in genetic technology

UNIVERSITY OF GOTHENBURG

ALSP History and Diagnosis

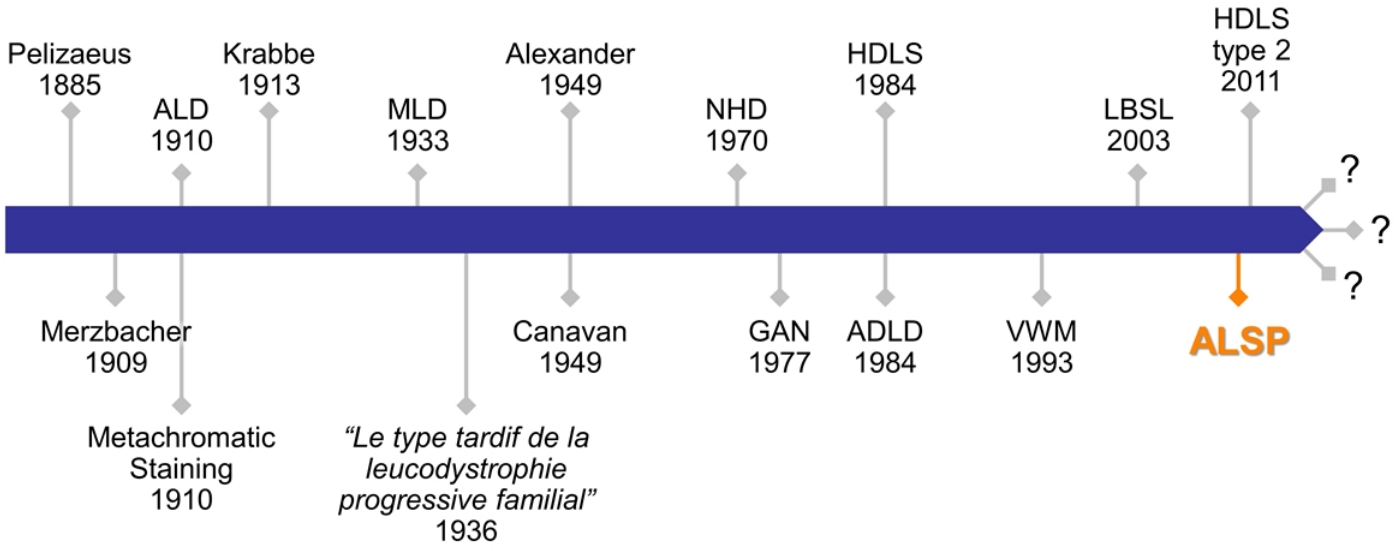
Christina Sundal, MD, PhD
CEO NeuroClinic Norway
Senior Consultant University Hospital, Oslo, Norway
Department of Neuroscience and Physiology, Sahlgrenska Academy,
Gothenburg University, Gothenburg, Sweden

The Sahlgrenska Academy

Background

Leukoencephalopathy	Encompasses a heterogenous group of disorders that predominantly affect the brain's white matter (WM), regardless if myelin damage is primary or secondary, and irrespective of a molecular cause *(Van der Knaap)*
Leukodystrophy	*(Leuko-white, Dystrophy-defective Nutrition):* Progressive, inherited demyelinating disorders *(Van der Knaap)*
Neuroaxonal Degeneration	WM damage is secondary to axonal pathology *(Van der Knaap)*

Hereditary Leukoencephalopathies



ALD: adrenoleukodystrophy, MLD: metachromatic leukodystrophy; NHD: Nasu Hakola Disease; ADLD: Adult onset autosomal dominant leukodystrophy; VWM: Vanishing White Matter; LBSL: Leukoencephalopathy with brainstem and spinal cord involvement

Adult Hereditary Leukoencephalopathies

Leukodystrophies:

- Pelizaeus-Merzbacher disease (PMD)
- Adrenoleukodystrophy (ALD)
- Metachromatic Leukodystrophy (MLD)
- Krabbe disease

Other 2. Leukodystrophies:

- Alexander disease
- Vanishing White Matter (VWM)
- Adult-onset Autosomal Dominant Leukodystrophy (ADLD)
- Leukoencephalopathy with Brainstem and Spinal Cord Involvement (LBSL)

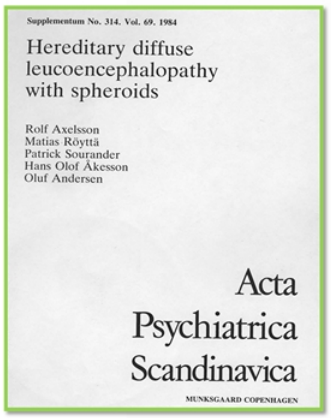
Neuroaxonal Degeneration:

- ALSP
- Nasu-Hakola disease

STROKE-LIKE Symptoms/Small Vessel Disease

- Fabrys
- Cerebral Autosomal Dominant Arteriopathy with Sub-cortical Infarcts and Leukoencephalopathy (CADASIL)
- Multi-Infarct Dementia (MIDS)
- Mitochondrial disorders

Swedish ALSP Family



- ✓ 166 Individuals
- ✓ 6 Generations: born 1855–1990
- ✓ 15 Affected: 2 New Cases
- ✓ 4 Cases healthy

ALSP

14 Families Studied

United States
Norway
Germany
Scotland

Inclusion criteria

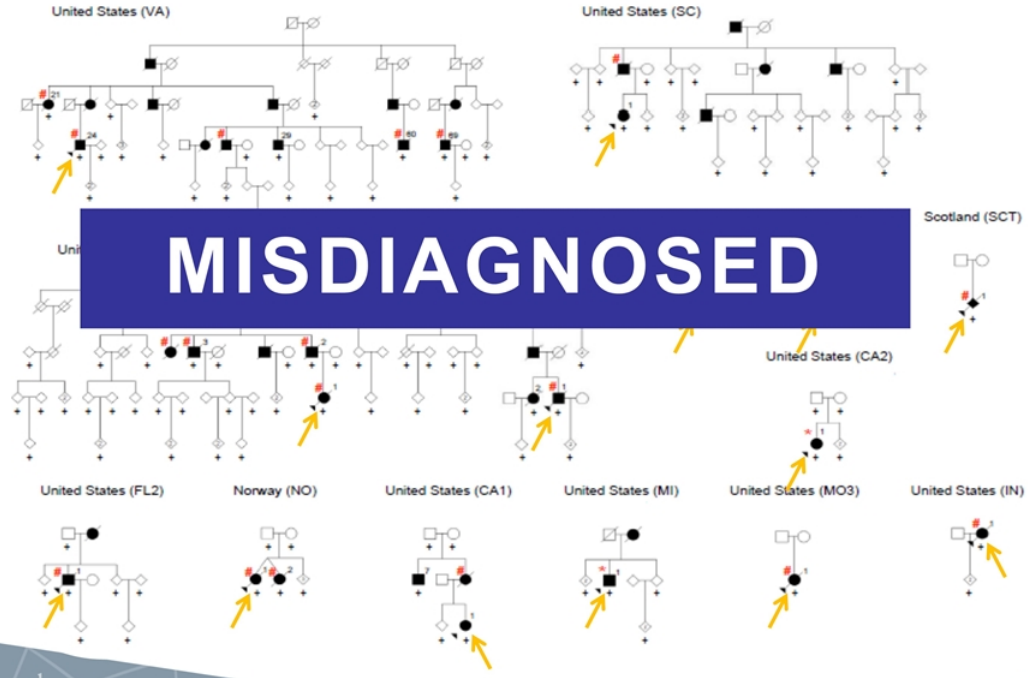
Clinical
MRI
Neuropathology
Blood

Neuropathological Examination

Dr. Dennis Dickson, neuropathologist at the Mayo Clinic confirmed the presence of axonal spheroids embedded in the abnormal white matter, consistent with the original Swedish HDLS/ALSP cases

Rademakers et al . Nat Genet. 2012

ALSP



Rademakers et al . Nat Genet. 2012

ALSP

- ✓ **Misdiagnosed:**

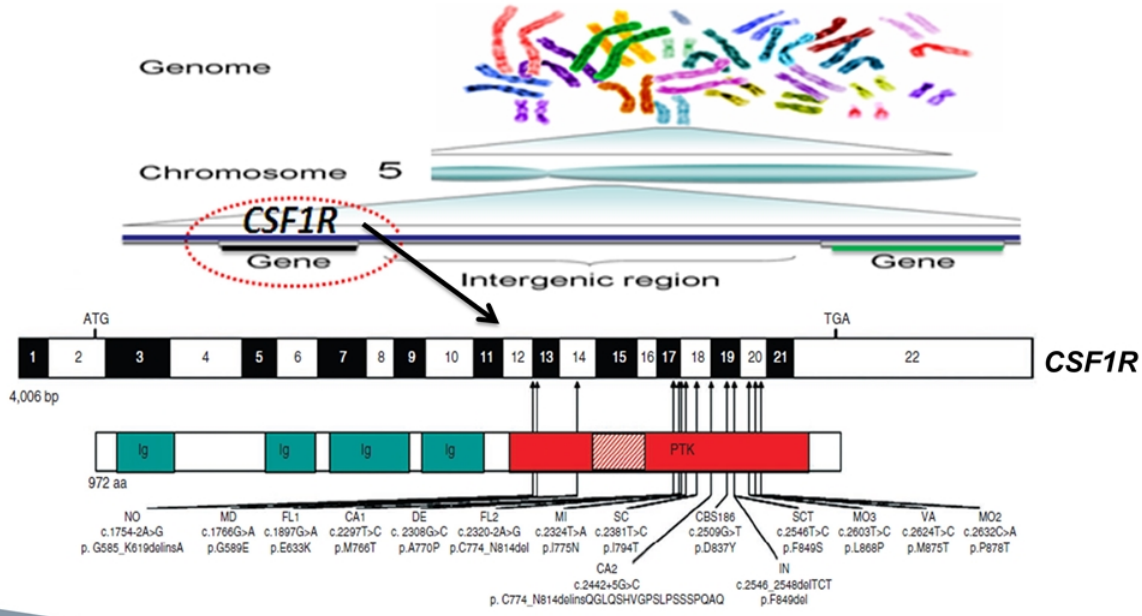
  Multiple Sclerosis, Alzheimer's Disease, CADASIL, Atypical Parkinson's Disease, Neuromyelitis Optica, other neurodegenerative disorders

- ✓ Average age of symptom onset: 44 years (range: 36-52)
- ✓ Average disease duration: 6 Years (range: 3-11)
- ✓ Average age of death: 48 years (range: 40-63)

- ✓ Initial symptoms: Frontal lobe syndrome, gait problems
- ✓ Advanced stage: Multifocal neurological deficits

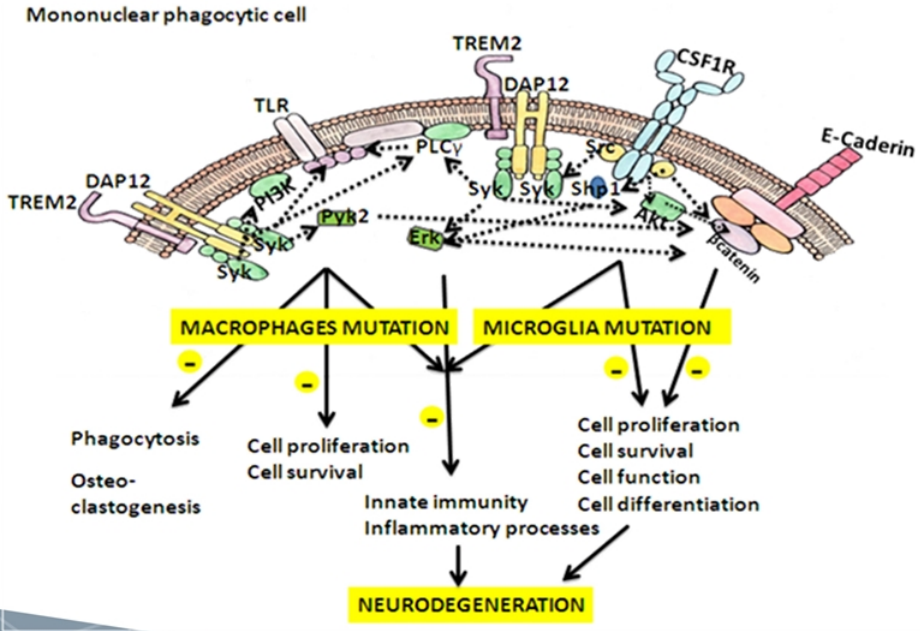
Rademakers et al . Nat Genet. 2012

CSF1R Mutation



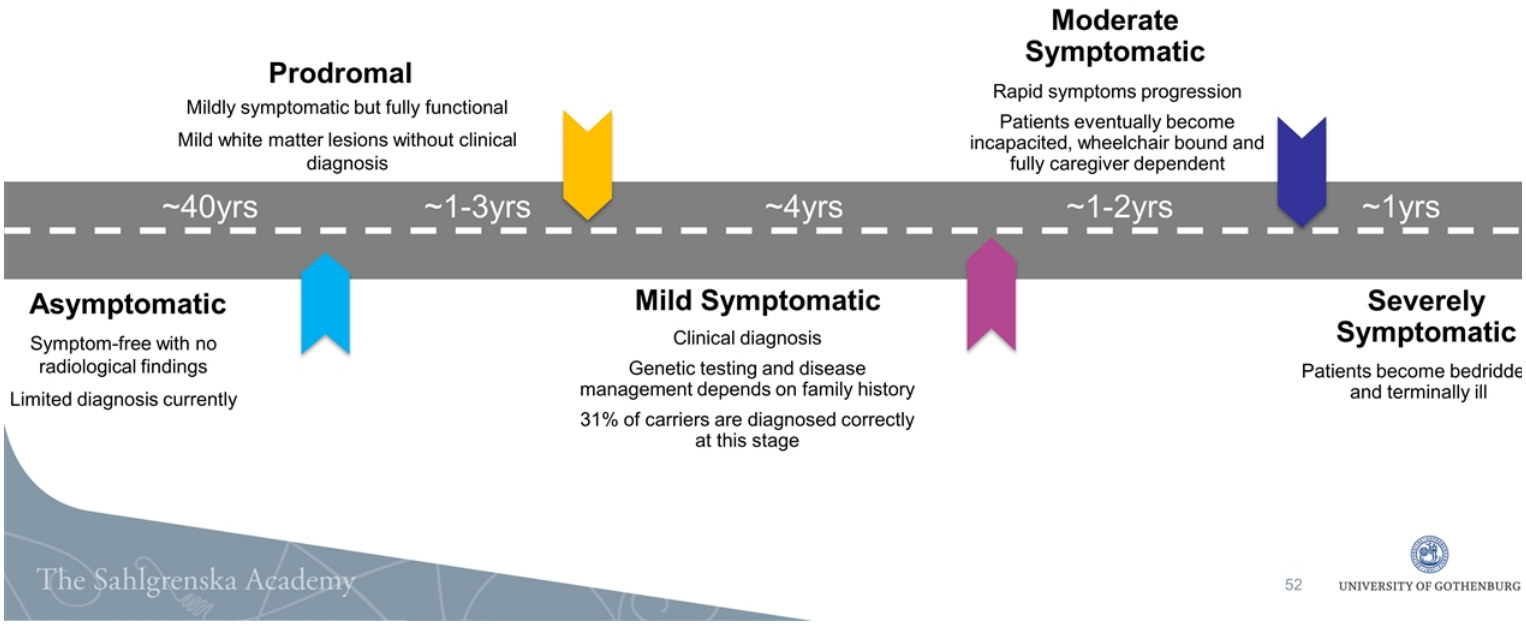
Rademakers et al . Nat Genet. 2012

Cross Talk: CSF1R-TREM2/DAP12

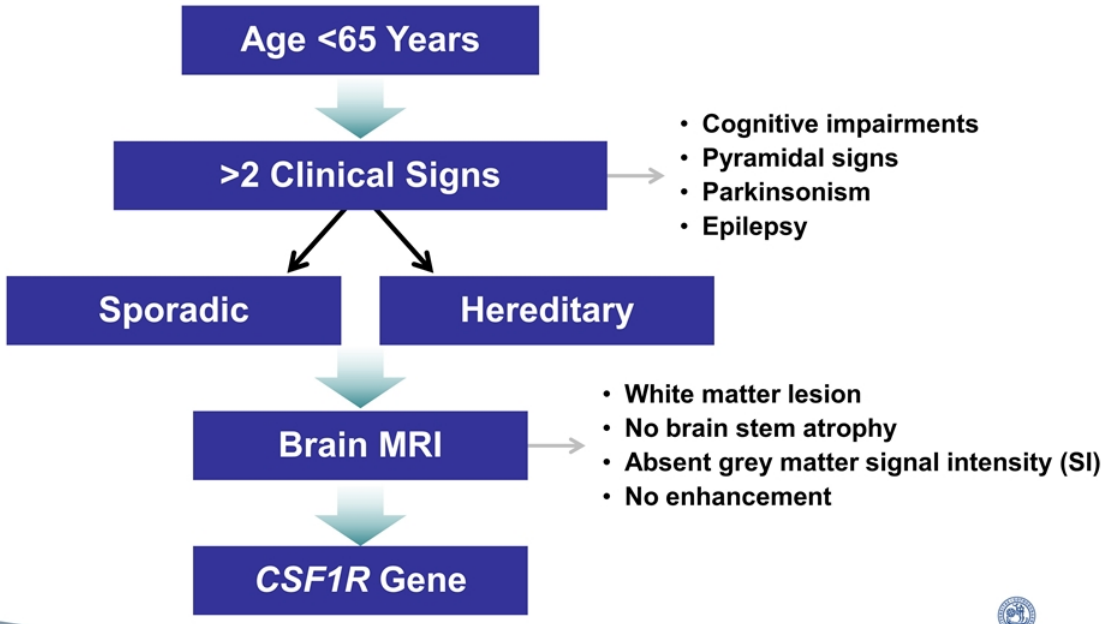


Sundal C. Hereditary Diffuse Leukoencephalopathy with Spheroids ; Insights into an adult onset neurodegenerative disease , PhD dissertation 2013

ALSP Carrier/Patient Journey



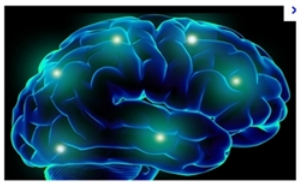
Diagnostic Criteria for ALSP



ALSP Clinical Course

- ✓ Psychiatric disorders
- ✓ Cognitive impairments
- ✓ Behavioral/Personality changes
- ✓ Dementia
- ✓ Paresis
- ✓ Parkinsonian signs/Movement disorders
- ✓ Seizure
- ✓ End stage: urinary incontinence, dysphagia/aphasia, weight loss
- ✓ Death: Aspiration pneumonia

Multisystem Encephalopathy

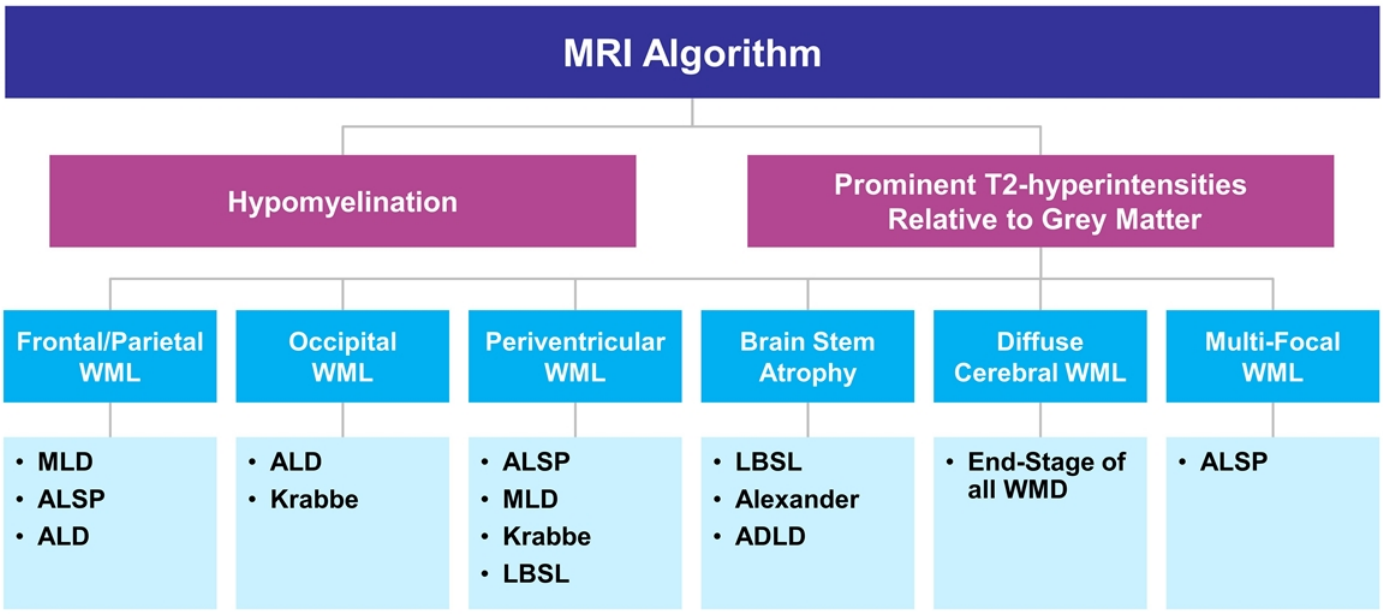


What Do You See on the Brain MRI?

- Adult-onset Leukoencephalopathy with Axonal spheroids and Pigmented Glia (ALSP)
- X-linked Adrenoleukodystrophy (X-ALD)
- Metachromatic Leukodystrophy (MLD)
- Krabbe disease
- Alexander disease
- Adult-onset Autosomal Dominant Leukodystrophy (ADLD)
- Vanishing white matter (VWM)
- Leukoencephalopathy with Brainstem and Spinal Cord Involvement (LBSL)
- Nasu-Hakola Disease (NHD)
- Mitochondrial diseases (Leigh, MELAS, MNGIE)
- Inborn error of metabolism
- Small vessel diseases (CADASIL, MIDS)
- Multiple sclerosis
- Susac's syndrome
- Others

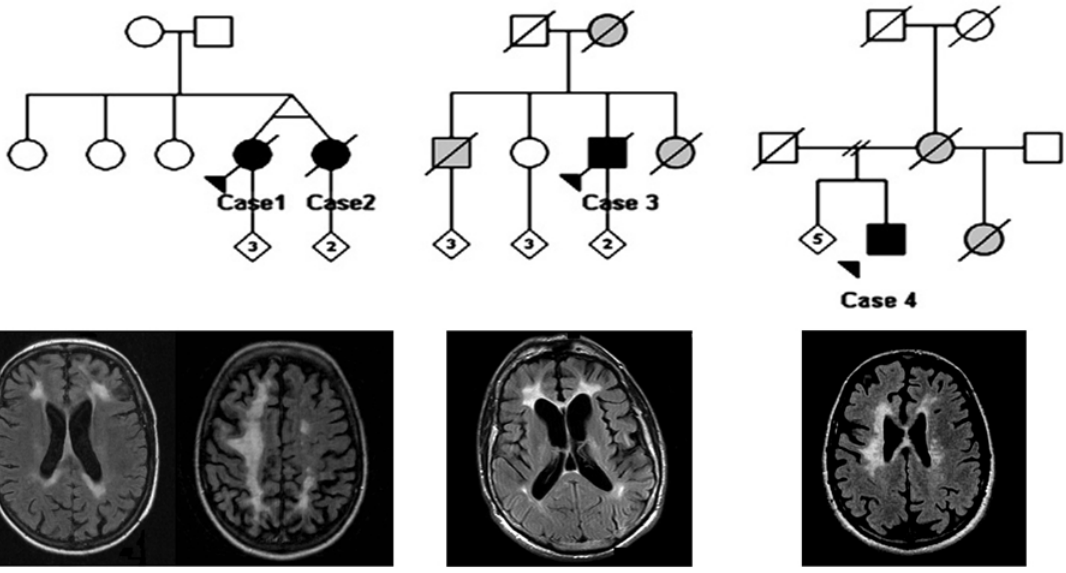
Inheritable

Sporadic



WML: white matter lesion; WMD: white matter diseases

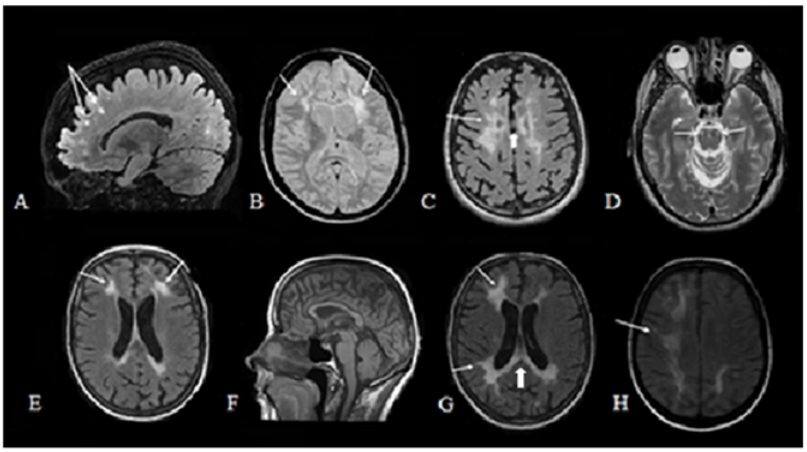
MRI of ALSP



Sundal C et al. J Neurol Sci. 2012

MRI's Role in Diagnosis and ALSP Research

- ✓ All WML bilateral, asymmetric; predominantly frontal
- ✓ Grey matter signal intensity changes absent
- ✓ No brain stem atrophy
- ✓ Corticospinal tracts involved later
- ✓ No enhancement
- ✓ Minimal cerebellar pathology



Sundal C et al. Neurology. 2012

Qualitative MRI Measures

Qualitative MRI Severity Score

White Matter Signal	Max Score
Frontal	7
Parietal	7
Temporal	7
Occipital	7
Corpus Collosum	6
Projection fibers	6
Brainstem	1
Cerebellum	1
WML Score	**42**
Basal Ganglia	1
Thalamus	1
Deep Gray Matter	**2**

Atrophy	Max Score
Frontal	2
Parietal	2
Temporal	2
Occipital	2
Central	2
Corpus Collosum	1
Brainstem	1
Cerebellum	1
Atrophy Score	**13**

MRI Severity Score (0-57)

Sundal et al Neurology (2012)

MRI Severity Score

Based on 15 patients with CSF1R mutations in 2012

Mild Disease (Score 1-6; n = 1)

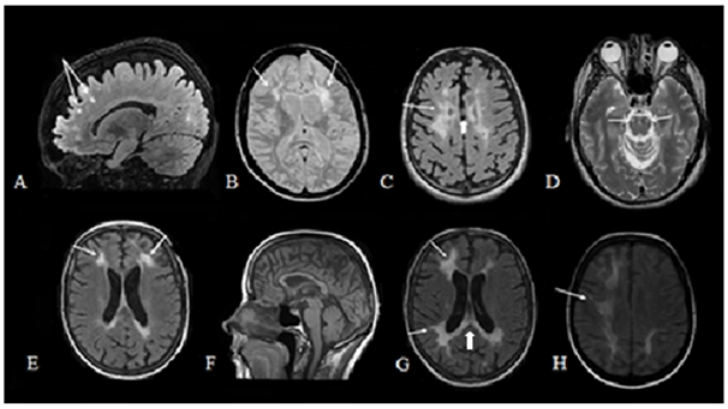
Score: 4
(Figure A)
Stable disease course

Moderate Disease (Score 7-15; n = 4)

Mean Score: 12.7 [range 10-15]
(Figures B, E & F
Mean disease duration of 6.7 years
(range, 5.0 -9.8)

Severe Disease (Score 16-57; n = 10)

Mean Score: 20.5 [range 16.5-33.5]
(Figures C, D, G & H)
Mean disease duration of 5.2 years
(range, 3.0-11.0)

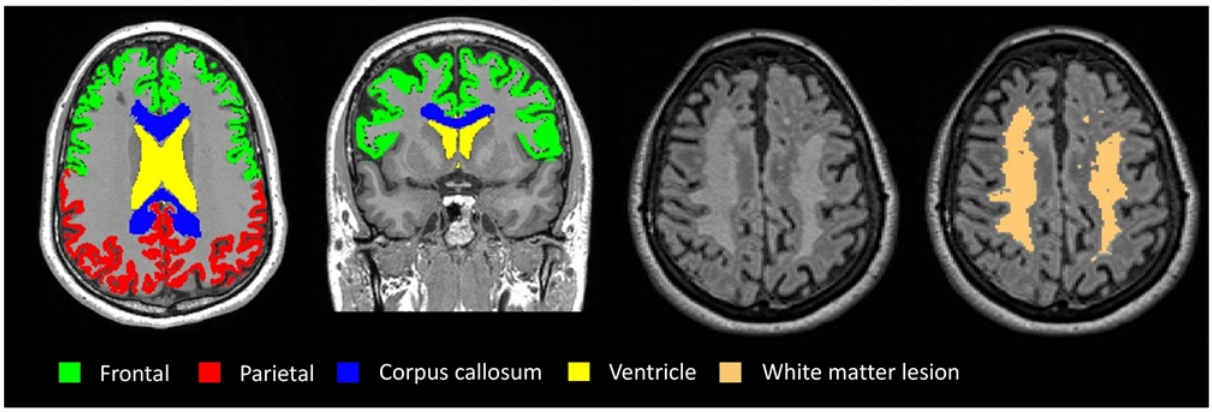


Sundal C et al. Neurology. 2012

Quantitative MRI Measures

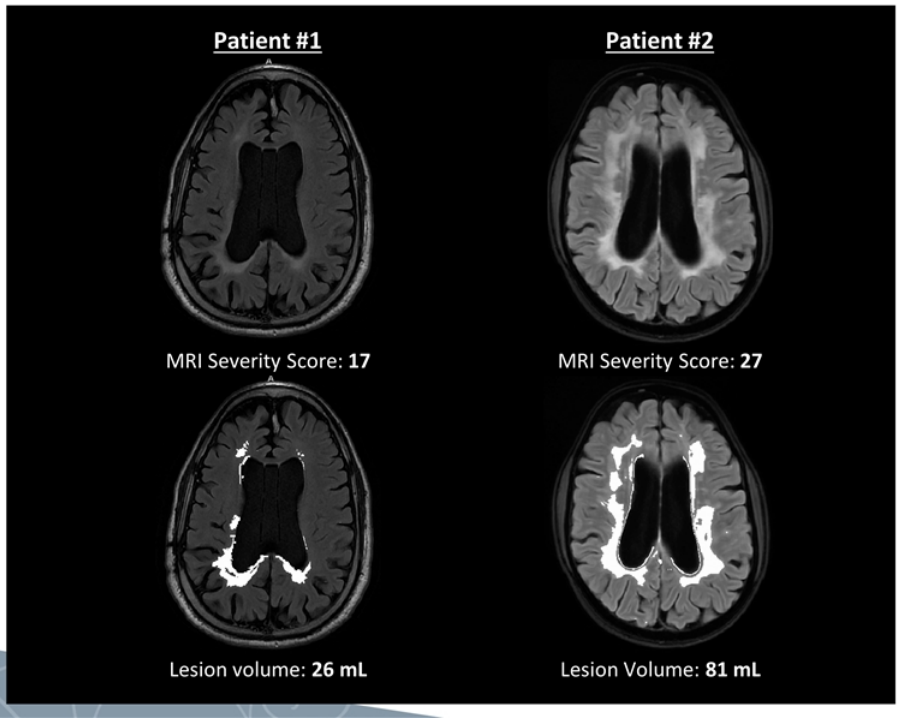
Disease burden on MRI can be quantified by measures of brain region volume e.g.

- Frontal, parietal, corpus callosum, ventricle and lesion volumes



Smith et al Neuroimage (2002); Griffanti et al Neuroimage (2016)

Quantitative and Qualitative MRI Measures

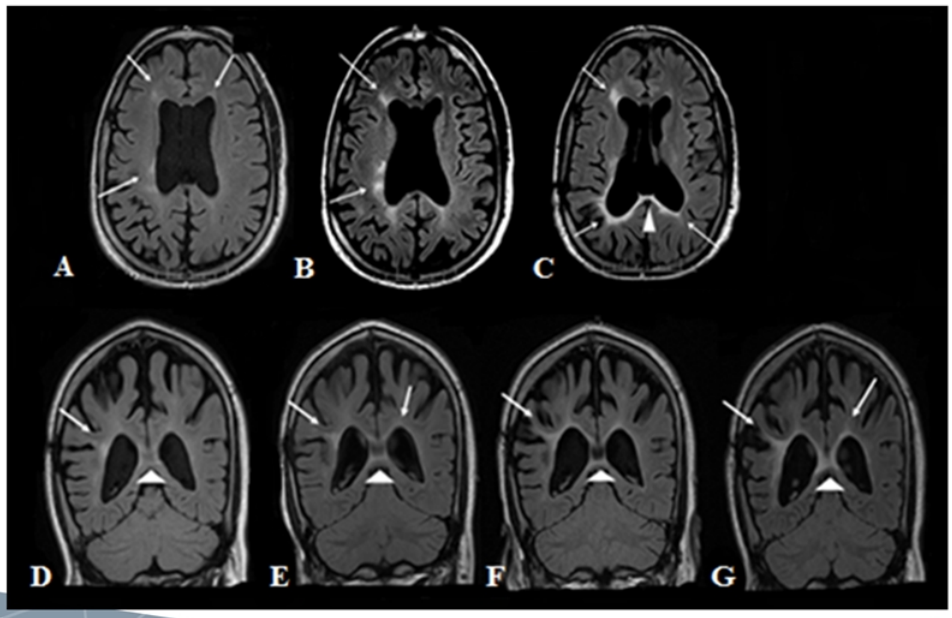


The Sahlgrenska Academy
Vigil retrospective chart review data

UNIVERSITY OF GOTHENBURG

Longitudinal MRI Follow-up on *CSF1R* Mutation Patient

Every 6 months



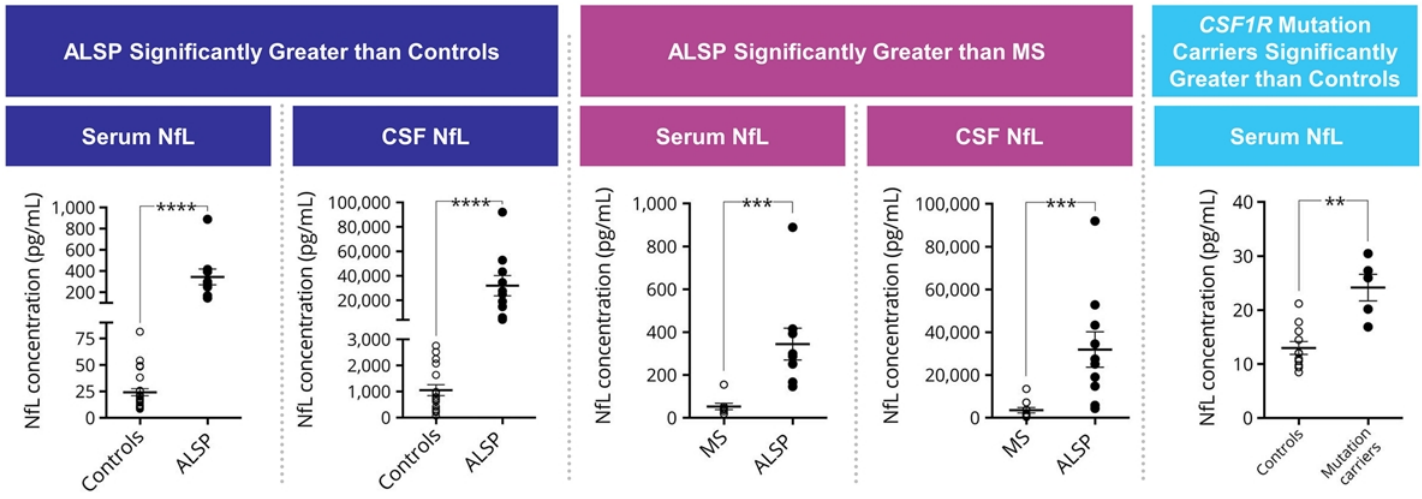
Sundal C et al. Neurology. 2012

MRI Summary

Indicators of Progressive Disease	MRI Characteristic Pattern
✓ Disease onset before 45 years	
✓ Female	
✓ WMLs extending beyond the frontal regions (MRI Scoring System & volumetric analysis)	✓ Most recognizable in the **middle** stages of the disease
✓ MRI severity score greater than 15 points	

MRI volumetric measures and Severity Score are valuable for monitoring disease progression and evaluating efficacy of potential treatments

NfL as Disease Biomarker for ALSP



Controls: healthy individuals; ALSP : symptomatic ALSP patients; MS: multiple sclerosis patients; Mutation Carriers: pre-symptomatic individuals with *CSF1R* mutations; **p < 0.005, ***p < 0.0005, ****p <0.0001

Hayer et al, Neurology 2018.

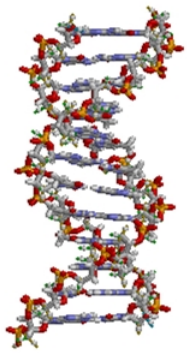
Combining the Results

Disorder	ALSP	Neurodegenerative disorders
MRI	Distinct distribution	Depending on disorder
CSF	NfL ↑↑↑	Depending on disorder
Neuropathology	Many Spheroids Thin layer of Myelin surrounding some Spheroids	Depending on disorder
CSF1R gene mutation	Yes	No

Primary Neuroaxonal Degeneration

Summary on ALSP Diagnosis

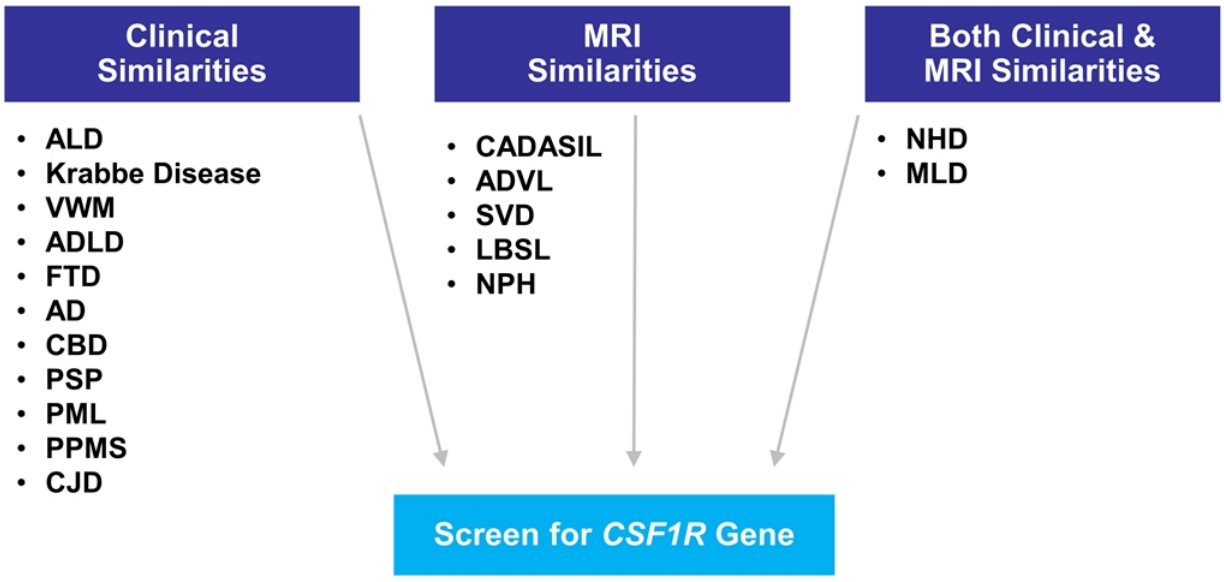
- Clinical symptoms to provide clues
- MRI to guide diagnosis
- *CSF1R* genetic testing to confirm diagnosis



Current Challenges of Correctly Diagnosing ALSP

- Awareness of adult onset hereditary leukoencephalopathies
- Leukodystrophies/Neuroaxonal dystrophies (degeneration)
- MRI: Pattern recognition
- Gene testing: *CSF1R*

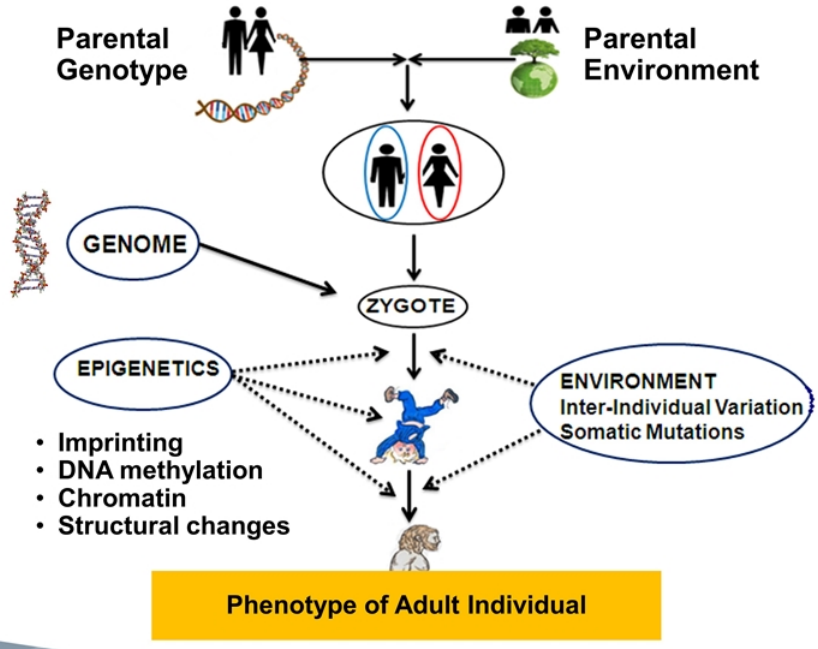
Differential Diagnosis to ALSP



Screen for *CSF1R* Gene

AD: Alzheimer's Disease; CBD: Corticobasal Degeneration; PSP: Progressive Supranuclear Palsy; PML: Progressive Multifocal Leukoencephalopathy; PPMS: Primary Progressive Multiple Sclerosis; CJD: Creutzfeldt Jakob Disease; SVD: Small Vascular Disease; NPH: Normal Pressure Hydrocephalus

Phenotypic Variation



Misdiagnosis of ALSP

Journal of the Neurological Sciences 314 (2012) 130–137

Contents lists available at SciVerse ScienceDirect

Journal of the Neurological Sciences

journal homepage: www.elsevier.com/locate/jns

Hereditary diffuse leukoencephalopathy with axonal spheroids (HDLS): A misdiagnosed disease entity

Christina Sundal [a,j], Jennifer Lash [a], Jan Aasly [b], Sarka Øygarden [c], Sigrun Roeber [d,e], Hans Kretzschman [d], James Y. Garbern [f], Alex Tselis [g], Rosa Rademakers [h], Dennis W. Dickson [h], Daniel Broderick [i], Zbigniew K. Wszolek [a,*]

Awareness of ALSP

Misdiagnosis of ALSP

ORIGINAL ARTICLE

Treatable Neurological Disorders Misdiagnosed as Creutzfeldt-Jakob Disease*

Numthip Chitravas, MD,[1] Richard S. Jung, MD,[1] Diane M. Kofskey, BS, MBA,[2] Janis E. Blevins, BS,[2] Pierluigi Gambetti, MD,[2] R. John Leigh, MD,[1] and Mark L. Cohen, MD[3]

TABLE 2: Pathology of Incurable Neurological Disorders Misdiagnosed as CJD

Disease	No.
Total	233
Alzheimer disease	154
Vascular dementia	36
Unspecified degenerative brain disease	10
Frontotemporal lobar degeneration	9
Mesial temporal lobe sclerosis	5
Diffuse Lewy body disease	4
Tauopathy, NOS	4
Hereditary diffuse leukoencephalopathy with spheroids	3
Progressive supranuclear palsy	3
Corticobasal ganglionic degeneration	1
Adult polyglucosan body disease	1
Huntington disease	1
Marchiafava-Bignami disease	1
Superficial siderosis	1

CJD = Creutzfeldt-Jakob disease; NOS = not otherwise specified.

3 ALSP Cases 1.3%

ORIGINAL CONTRIBUTION

Multiple Sclerosis With Predominant, Severe Cognitive Impairment**

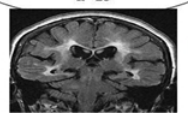
Nathan P. Staff, MD, PhD; Claudia F. Lucchinetti, MD; B. Mark Keegan, MD, FRCPC

MS & cognitive impairment n= 549

MS & *severe* cognitive impairment n=172

149

Strict criteria i.e. MS & severe cognitive impairment without other significant neurological impairment n=23



ALSP?

*Ann Neurol. 2011;70:437–444. **Arch Neurol. 2009; 66(9):1139–1143

Misdiagnosis of ALSP

Misdiagnosis highlights importance of early genetic testing and increased disease awareness

- Rate of initial misdiagnosis significant in ALSP
- Accurate initial diagnosis is observed in only 31.5% of ALSP patients
- Misdiagnosis involved broad spectrum of neurodegenerative, neuroimmune and vascular disorders
- Clinics of initial consultation include dementia, psychiatry, leukodystrophy, multiple sclerosis and movement disorders clinics

Initial Misdiagnosis in ALSP

Initial Diagnosis	Number of Patients (Percent)
***CSF1R*-ALSP**	92 (31.5%)
Alzheimer's Disease/ Frontotemporal Dementia	47 (16.1%)
Multiple Sclerosis	23 (7.9%)
Adult-Onset Leukodystrophy	20 (6.8%)
Familial Leukoencephalopathy	20 (6.8%)
Vascular Disease	10 (3.4%)
Other	8 (2.7%)
Missing	72 (24.7%)

Papapetropoulos et al. European Academy of Neurology Congress 2022

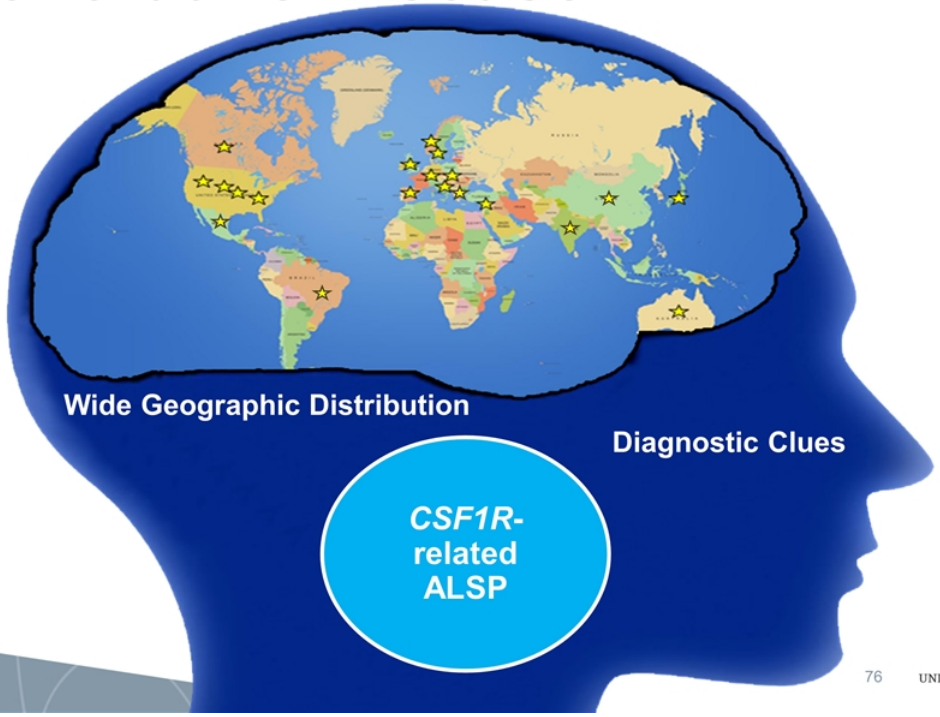
How Can We Improve ALSP Diagnosis

- Definitive diagnosis through genetic testing for *CSF1R* mutations
- Need to increase awareness of ALSP to drive earlier referrals of potential patients for definitive genetic testing

Overall Conclusion on ALSP

- ✓ Distinct disease entity
- ✓ Divergent clinical courses
- ✓ Initial symptoms
- ✓ Later symptoms
- ✓ *CSF1R gene* mutation
- ✓ MRI – pattern recognition
- ✓ Advanced neuroimaging
- ✓ Primary neuroaxonal degeneration
- ✓ Misdiagnosed disease

ALSP: Devastating Adult-onset Neurodegenerative Disease



The Swedish ALSP Research Team:

THANK YOU

ALSP Treatment and Unmet Medical Need

Troy Lund, MSMS, PhD, MD, FAAP

Leukodystrophy Center of Excellence
Division of Pediatric Blood and Marrow Transplantation & Cellular Therapy
University of Minnesota, A NORD Rare Disease Center of Excellence

Current ALSP Treatment Options

- No approved therapies for ALSP
- Most off-label treatments focus on symptom alleviation
  - Minimal to modest QoL improvements
  - No effect on underlying disease process or progression
- Hematopoietic stem cell transplant (HSCT) has been provided as a treatment option by very few institutions
  - HSCT is a treatment for certain leukodystrophies including ALD, MLD and Krabbe disease
  - HSCT serves to attenuate (or halt) progression through an unclear mechanism
- Limited information is available on treatment outcome of HSCT in ALSP
  - Clinical benefit and patient suitability unclear
  - Significant morbidity and mortality risks

HSCT Case Report in ALSP – Patient 1

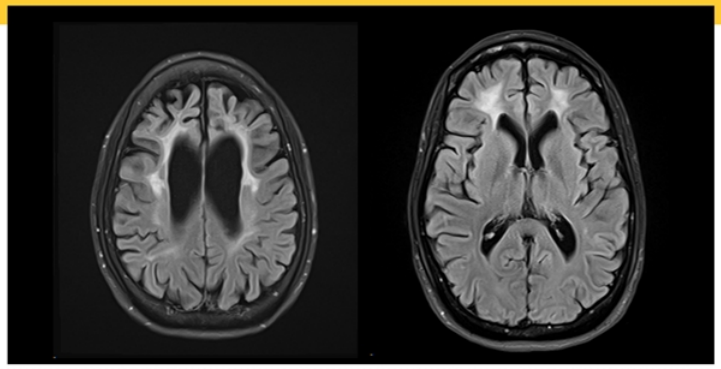
- 44 year-old female
- *CSF1R* mutation: Q642X
- Memory problems, disinhibition, “early onset dementia”
- Noted on exam: patient showed intermittent tongue and lip movements, resembling tics
- MRI showed confluent, frontal-predominant white matter T2 hyperintensities
- Other past medical information:
  - History of deep vein thrombosis (DVTs)
  - Heterozygous for factor V Leiden, and mutations in prothrombin (PT) gene and methylenetetrahydrofolate reductase (MTHFR) genes
    - Genes involved in blood clotting

Patient 1: Post-HSCT Complications with Cognitive Worsening

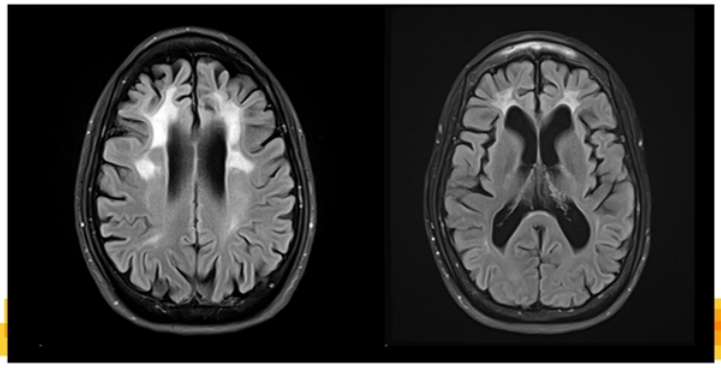
- Unrelated donor (URD) marrow (HLA match = 12/12)
- Transplant related morbidity (TRM): mild gastrointestinal graft-vs-host disease (GvHD) and cystitis
  - Potential GCSF neurologic exacerbations?
- Through 27 months post HSCT:
  - Went to transition care unit for aggressive rehab and nutrition
  - Worsening of cognitive deficits without motor or sensory abnormalities
    - Score of 11/38 on the Short Test of Mental Status (STMS)
- Subsequent radiological assessments showed stabilization of MRI Sundal Severity Scale (SSS) on MRI with stable white matter subscores, but incremental worsening of atrophy subscores
- Some substantial improvements in behavior and recovery with physical/ occupational therapy (PT/OT)
- Said to have “good” QoL

Patient 1 MRI: Post-HSCT White Matter Lesion and Ventricular Increase

PRE HSCT



3 Years Post HSCT



HSCT Case Report in ALSP – Patient 2

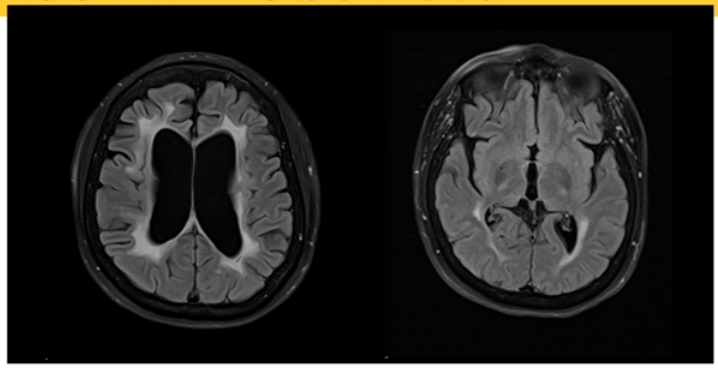
- 46 year-old female
- *CSF1R* mutation: W893R
- With rapidly progressively gait deterioration over a 4-month period, resulting in loss of employment
- Neurological examination showed global hyperreflexia, parkinsonism, and gait impairment requiring a wheelchair
- Neuropsychological evaluation showed impairment of visually mediated processing, executive functioning, cognitive speed, nonverbal learning, and psychomotor speed

Patient 2: Post-HSCT Stabilization; Still Dependent on Care

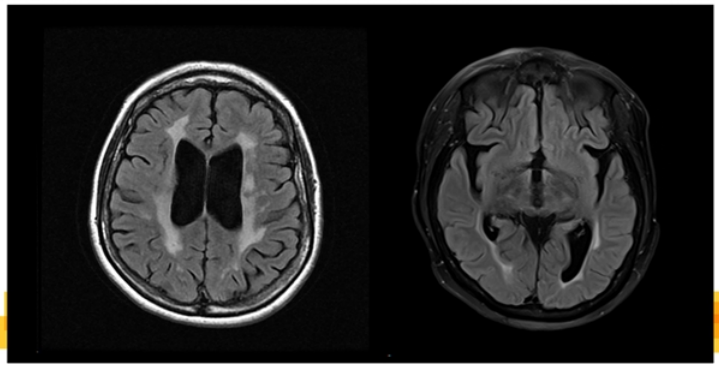
- Received matched sibling bone marrow
- Neuropsychological evaluation 4 months post-HSCT showed declines in some aspects of attention, executive function, and processing speed but with improvements in verbally mediated tasks, including naming and fluency
- Neurological examination at 9 months post-HSCT was unchanged from pre-HSCT exam
- Patient successfully resumed her role in managing family's finances
- At 2 years post-HSCT, patient walking 1-2 miles per day, dressing herself, makes breakfast

Patient 2: Post-HSCT MRI Stabilization

PRE HSCT



2 Years Post HSCT



HSCT Case Report in ALSP – Patient 3

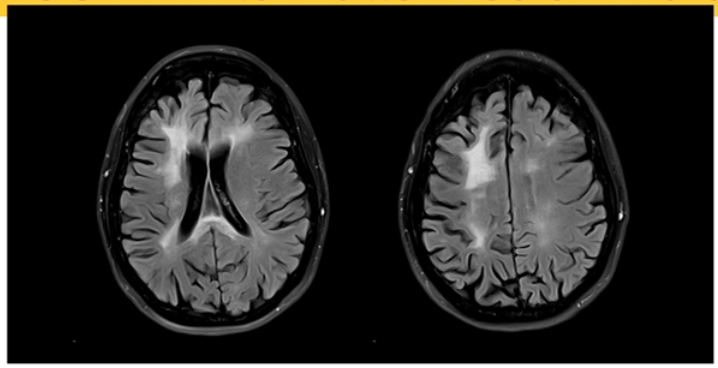
- 44 year-old female
- *CSF1R* mutation: p.R782H
- 2 years of progressive personality changes resulting in employment termination
- Associated with memory decline, perseveration, spelling difficulties, and falls
- Also, patient was losing objects and having difficulty clothing herself
- An acute episode of language disturbance resulted in a hospital evaluation including a brain MRI
- Anxiety and irritability were also increasing
- Scored 27/38 on the STMS

Patient 3: Post-HSCT Neurological Decline

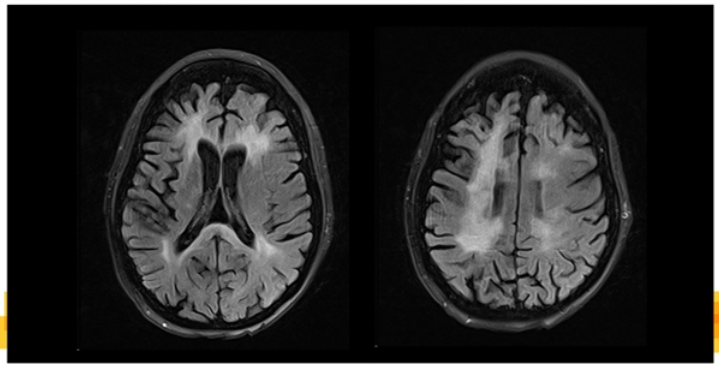
- Received matched sibling bone marrow
- Post-HSCT complications: GvHD of the gut, acute kidney injury, *strep mitis* of the blood, pulseless electrical activity (cardiac arrest)
  - Patient was resuscitated and extubated but quickly deteriorated from a neurological standpoint
- Day 81 post-HSCT – brain MRI showed an SSS of 25 without evidence of stroke or severe hypoxic injury
- Given the patient's substantial neurological deterioration, her family transitioned her to comfort care, and she died on Day 88 post-HSCT

Patient 3: Post-HSCT White Matter Lesion Increase

PRE HSCT



2 Months Post HSCT



HSCT Case Report in ALSP – Patient 4

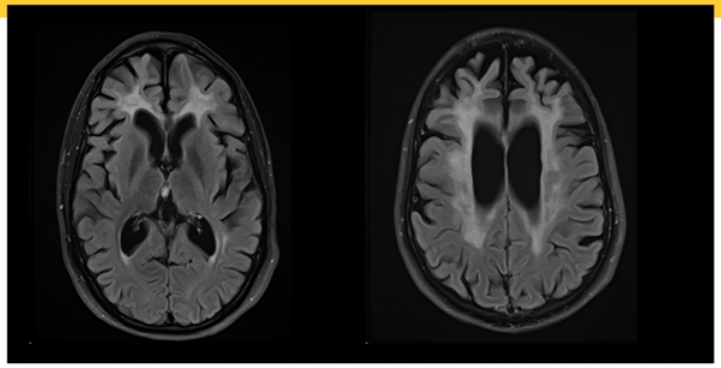
- 41 year-old male
- *CSF1R* mutation: NM_005211.3; c.2381T>C (p.Ile794Thr)
- 1-2 years with some lower leg weakness, some memory problems, and losing track of conversation
  - His wife filled in many of the gaps and answered many of the questions
- 1-2 years of depression and anxiety
  - He was losing his temper easily
- T2 signal changes in the frontotemporal lobe

Patient 4: Post-HSCT Mobility Gain but Has Cognitive Decline

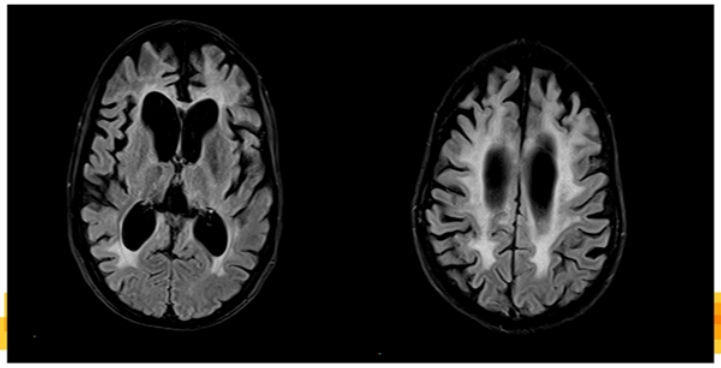
- 8/8 URD, 100% engrafted
- Complications include pseudomonas pneumonia, *Burkholderia* infection, sinusitis, weight loss requiring G-tube, possible idiopathic pneumonia syndrome (IPS)
- Progressive dementia
- Became very weak and lost a lot of physical conditioning
- After 1-year post-HSCT, patient regained weight with continued gains in mobility
- Had to move to a care facility for part-time to full care

Patient 4: Post-HSCT White Matter Lesion Increase and Atrophy

PRE HSCT



10 M Post HSCT



Case Reports from Limited HSCT in ALSP

- These case reports represent a broad spectrum of post-HSCT outcomes on clinical measures and MRI, and show that:
  - HSCT appears to have variable impact on ALSP which is yet to be fully characterized
  - Risks of HSCT come from being an adult and possibly poor mobility
  - Post-HSCT disease progression can be terrible and require full-time (permanent) care of the adult patient
- HSCT timing can be critical
  - HSCT performed “too late” is very problematic – earlier would be better and allow for improved outcomes

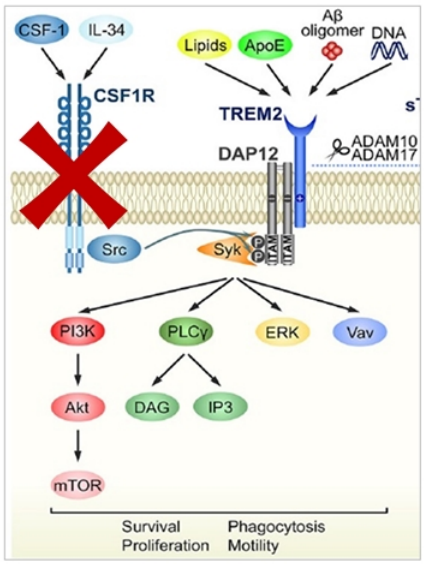
High Unmet Need for ALSP Disease Modifying Treatments

No Approved Treatments for ALSP

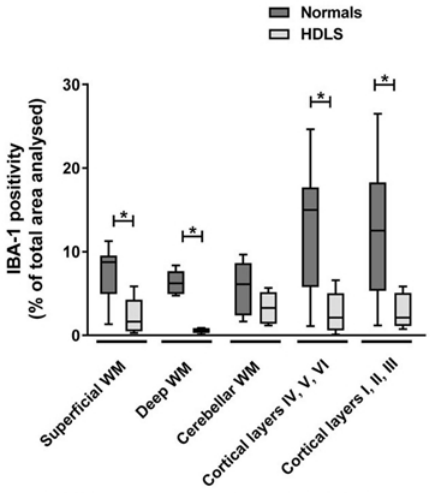
- Symptomatic treatments provide transient and limited benefit to ALSP patients
- Allogeneic HSCT:
  - Limited experience with HSCT
  - Case reports show mixed outcomes
  - HSCT in ALSP is associated with significant morbidity and mortality
  - Main risks of HSCT come from being an adult and possibility poor mobility status
  - Progression after HSCT can be unfavorable and require full-time (permanent) care of the adult patient

Safe and efficacious treatments with patient-friendly administrations which modify underlying disease biology needed

CSF1R Mutations Lead to Microglia Loss & Dysfunction in ALSP



Quantification of Microglia in Brain Regions



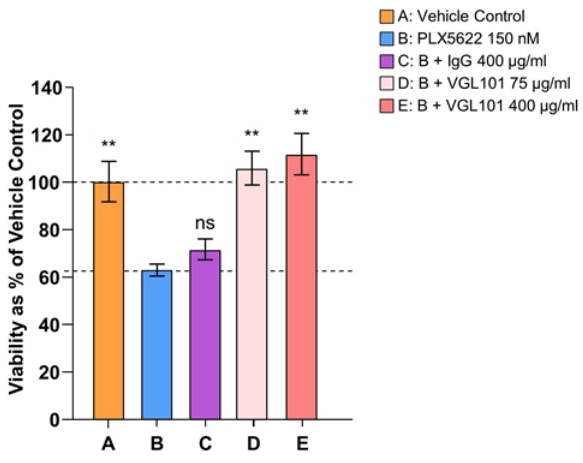
*1. HDLS: hereditary diffuse leukoencephalopathy with spheroids – previously used to describe ALSP; WM: white matter; * p < 0.05*

Konishi & Kiyama Front. Cell. Neurosci. 2018; Kempthorne et al. Acta Neuropathologica. 2020

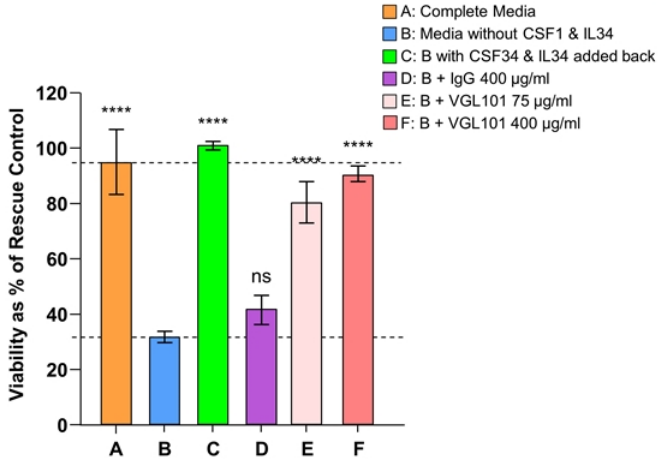
VGL101 Rescued Microglial Viability under CSF1R Deficiency

CSF1R Deficiency in iMGL Caused by PLX5622 Inhibition or CSF1/IL34 Withdrawal

Inhibition by PLX5622 & Rescue by VGL101



CSF1/IL34 Withdrawal & Rescue by VGL101

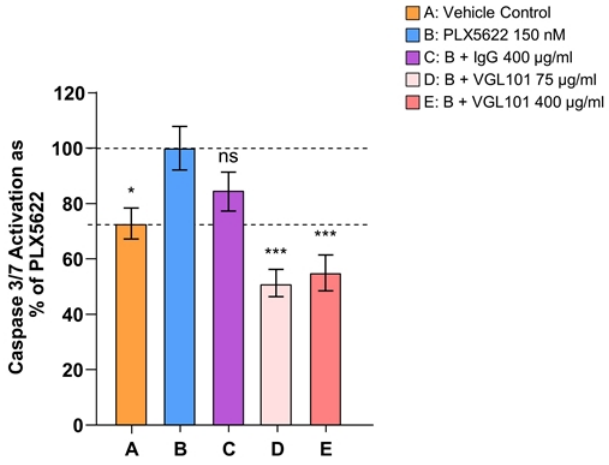


*iMGL: human Induced pluripotent stem cells (iPSC) derived microglia; PLX5622 – known small molecule inhibitor of CSF1R; P-values are as determined by Ordinary One-Way ANOVA with Multiple Comparisons: ns: not statistically significant; **p < 0.005; ****p < 0.00005*

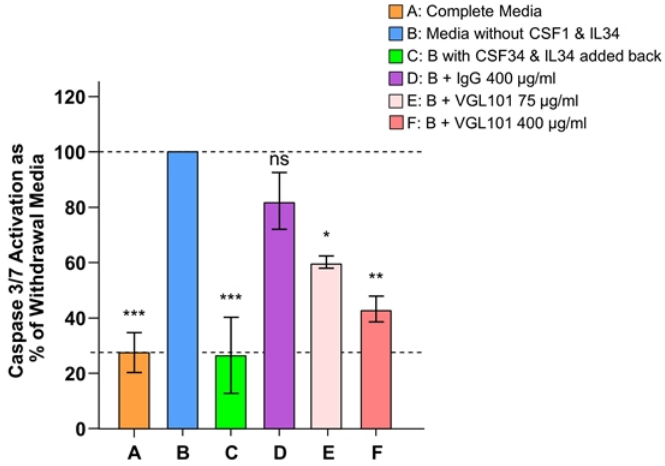
VGL101 Reduced Microglial Apoptosis under CSF1R Deficiency

CSF1R Deficiency in iMGL Caused by PLX5622 Inhibition or CSF1/IL34 Withdrawal

Inhibition by PLX5622 & Rescue by VGL101



CSF1/IL34 Withdrawal & Rescue by VGL101

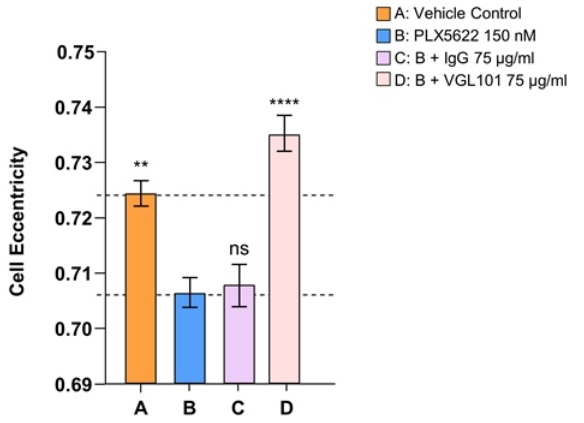


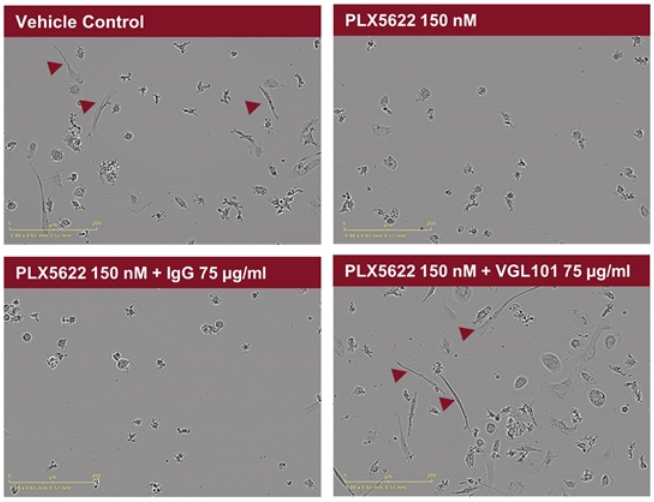
*iMGL: human Induced pluripotent stem cells (iPSC) derived microglia; PLX5622 – known small molecule inhibitor of CSF1R; P-values are as determined by Ordinary One-Way ANOVA with Multiple Comparisons: ns: not statistically significant, *p < 0.05, ** p < 0.005, ***p < 0.0005*

VGL101 Restored Microglial Morphology under CSF1R Deficiency

CSF1R Deficiency in iMGL Caused by PLX5622 Inhibition

Inhibition by PLX5622 & Rescue by VGL101





iMGL – human Induced pluripotent stem cells derived microglia; PLX5622 – known small molecule inhibitor of CSF1R

Cell Eccentricity – degree of cellular processes emanating from longitudinally imaged human microglia, quantified by optical loss of eccentricity using a commercially available analytical software (Incucyte Live-Cell®)

*P-values are as determined either using Ordinary One-Way ANOVA with multiple comparisons, or using two-tailed, paired T-tests: ns: not statistically significant; ** $p < 0.005$, **** $p < 0.00005$*

VGL101 as Potential Disease Modifying Therapy for ALSP via TREM2 Agonism

- VGL101 demonstrated ability to restore microglia numbers and function in human microglia cultures (Larson *et al.* Keystone Symposium 2022)
- Represents a potential disease modifying therapeutic for ALSP with monthly IV administration
- Clinical trials are needed to show proof-of-concept, safety/tolerability and efficacy in ALSP patients
- If VGL101 shows a compelling clinical profile and is approved, it may be considered as a first-line treatment for ALSP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ILLUMINATE Natural History Study in ALSP
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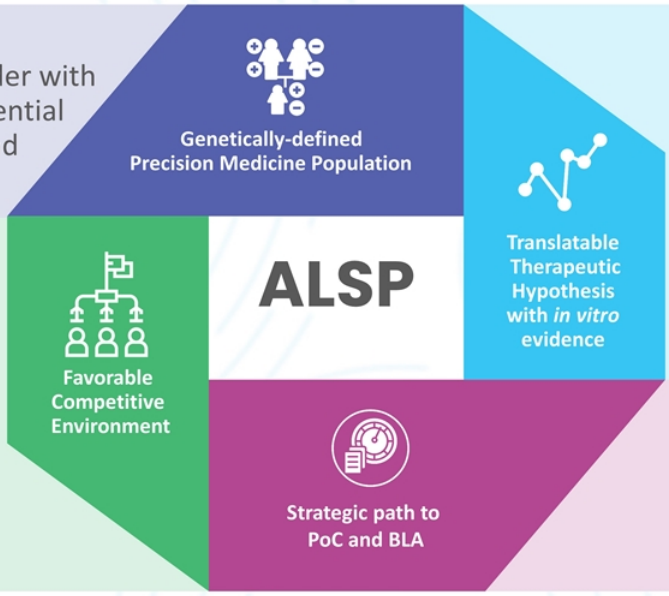
Compelling Rationale for ALSP as Initial Indication for VGL101

Orphan, under-recognized autosomal dominant disorder with prevalence feasible for potential full clinical development and commercialization

Vigil's VGL101 program is the first and only drug candidate in development in this indication seeking full engagement of patient and scientific community

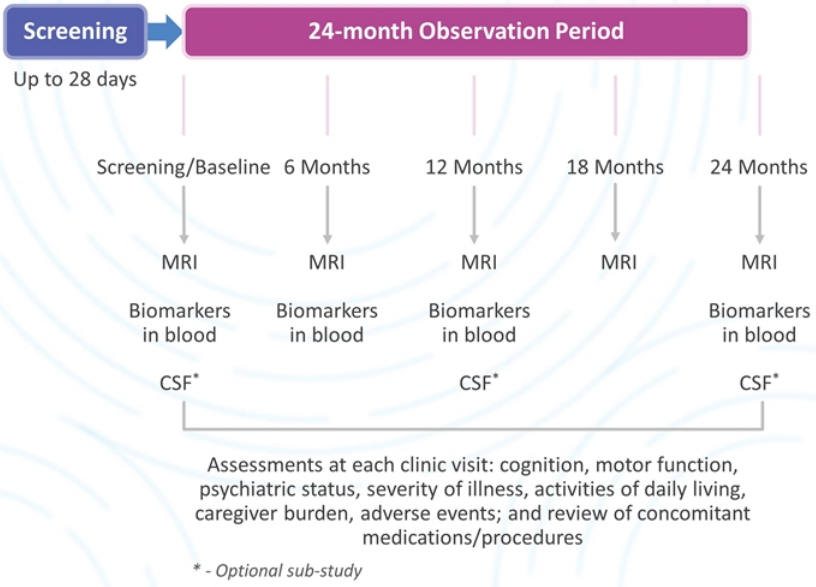


TREM2 agonism rescues CSF1R deficit *in vitro* due to the convergence of these 2 microglial receptors on a common signaling pathway

Opportunity to be first to achieve human PoC with a TREM2 agonist

ALSP Natural History Study Design

illuminate
A NATURAL HISTORY STUDY OF | Patients with Adult-Onset Leukoencephalopathy with Axonal Spheroids and Pigmented Glia (ALSP)



Assessments at each clinic visit: cognition, motor function, psychiatric status, severity of illness, activities of daily living, caregiver burden, adverse events; and review of concomitant medications/procedures

** - Optional sub-study*

The Illuminate Study

- Natural history study of ALSP patients with *CSF1R* gene mutation
- Sample size up to 36 subjects (global)
- Objectives:
  - Characterize biomarkers & clinical measures of disease progression in ALSP
  - Possibility for contemporaneous external comparator arm
- Observation period: 24 months
- Key assessments:
  - MRI at baseline & every 6 months
  - CSF biomarkers at baseline, 12- & 24-months
  - Clinical assessments at baseline & every 6 months

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ALSP Natural History Study – Current Status

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A NATURAL HISTORY STUDY OF Patients with Adult-Onset Leukoencephalopathy with Axonal Spheroids and Pigmented Glia (ALSP)

- **Study Timeline:** first patient enrolled in Q3 2021
  - Enrollment ongoing in US and ex-US
- **Current Locations:**
  - US: Jacksonville, FL; Boca Raton, FL; San Francisco, CA; Englewood, CO
  - Canada: London, Ontario
  - Germany: Leipzig; Tübingen
  - Netherlands: Amsterdam
  - UK: London

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Natural History Study – Interim Dataset

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- Interim data includes participants enrolled as of October 1, 2022
- 29 participants enrolled at 6 sites comprising
  - 18 symptomatic and 11 prodromal* participants

Baseline Demography				
Clinical stage	**N**	**Age (years; mean ± sd)**	**Gender (% Female / % Male)**	**MoCA (mean ± sd)**
Prodromal	11	46.3 ± 17.8	54.5% / 45.5%	27.6 ± 1.7
Symptomatic	18	46.5 ± 9.7	44.4% / 56.6%	20.3 ± 6.4

- 18 participants completed 6-month MRI visit
  - 9 symptomatic and 9 prodromal participants

*Prodromal – participants with confirmed *CSF1R* mutation and MRI findings; MoCa: Montreal Cognitive Assessment

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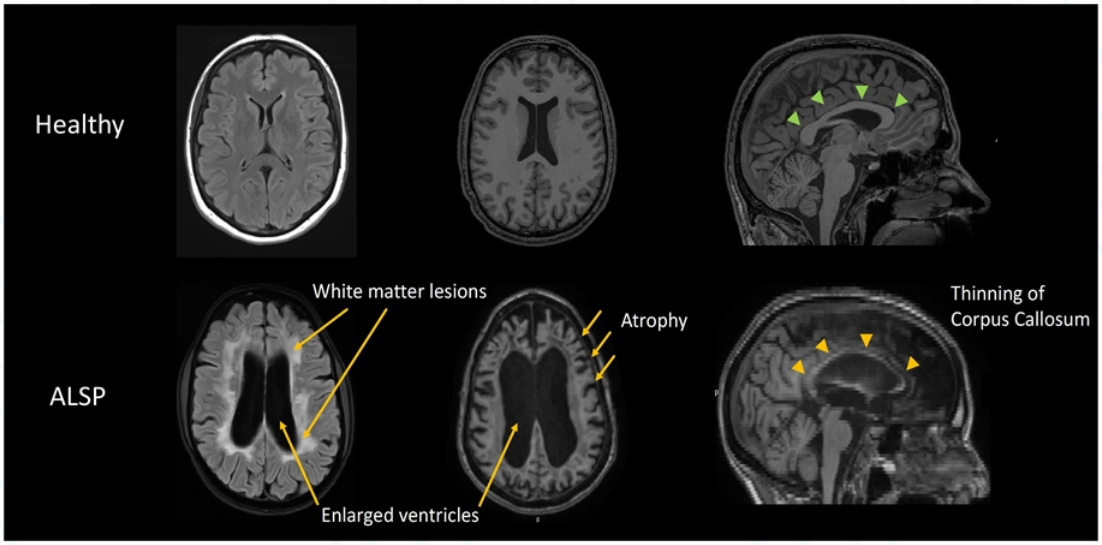
Quantifying MRI Features of ALSP

Brain Atrophy and White Matter Lesions Are Key Radiological Features of ALSP



Disease Burden on MRI Was Assessed by Quantitative MRI Measures of Brain Region Volume

Greater Baseline Disease Burden for Symptomatic vs Prodromal Participants

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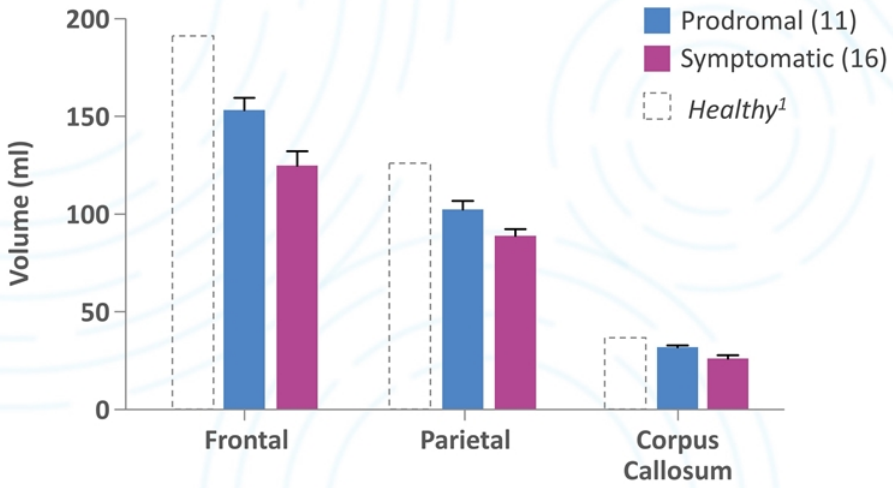
Baseline volumetric MRI findings

Greater Disease Burden Associated with Lower Brain Tissue Volume



1. Volume estimated from the MNI-ICBM152 template which was derived from 152 normative young adult population (Mazziotta et al Phil Trans R Soc Lond. 2001)

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Greater Baseline Disease Burden for Symptomatic vs Prodromal Participants

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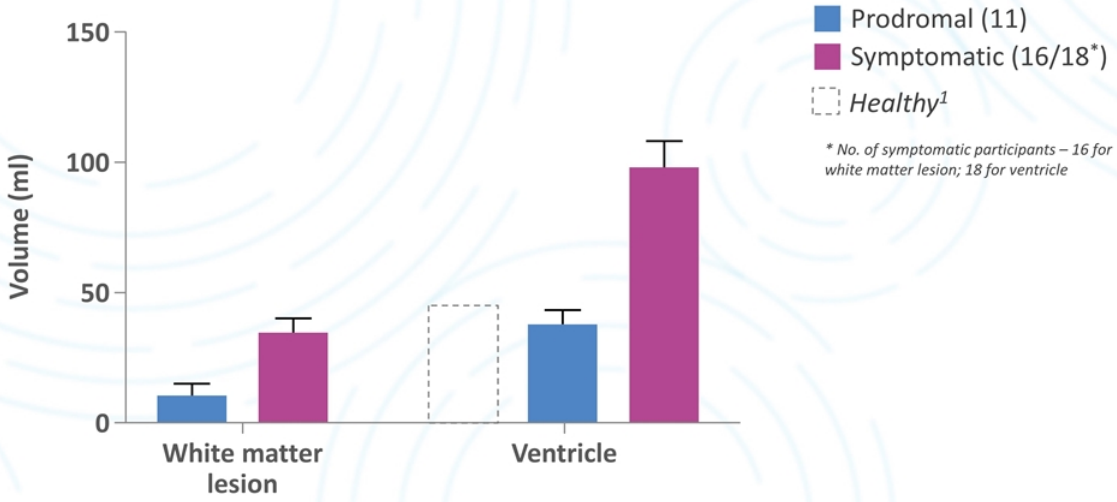
Baseline volumetric MRI findings

Greater Disease Burden Associated with Higher Lesion and Ventricle Volume



1. Volume estimated from the MNI-ICBM152 template which was derived from 152 normative young adult population (Mazziotta et al Phil Trans R Soc Lond. 2001)

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Greater Disease Progression for Symptomatic vs Prodromal Participants at 6 Months

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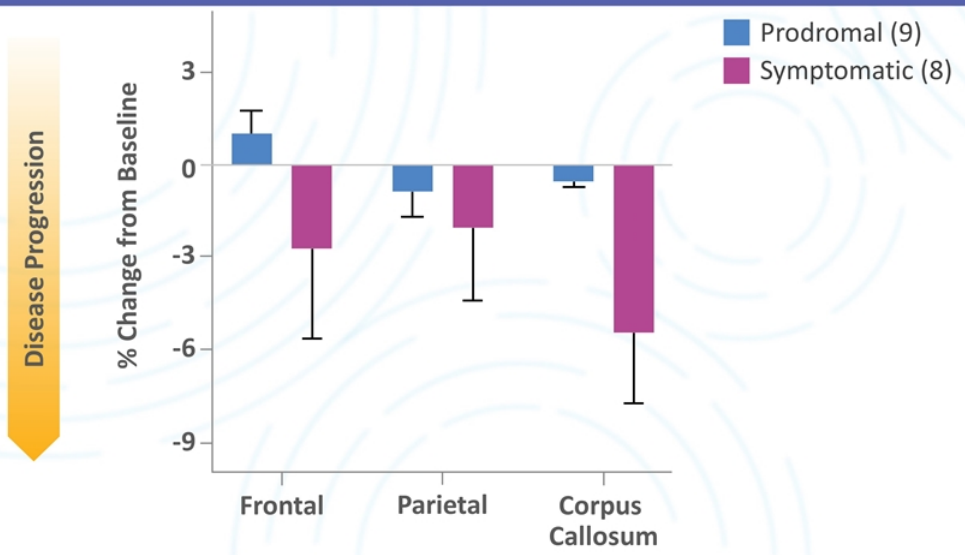
6-month volumetric MRI findings

Greater Disease Progression Based on Greater Reductions in Brain Tissue Volume



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Greater Disease Progression for Symptomatic vs Prodromal Participants at 6 Months

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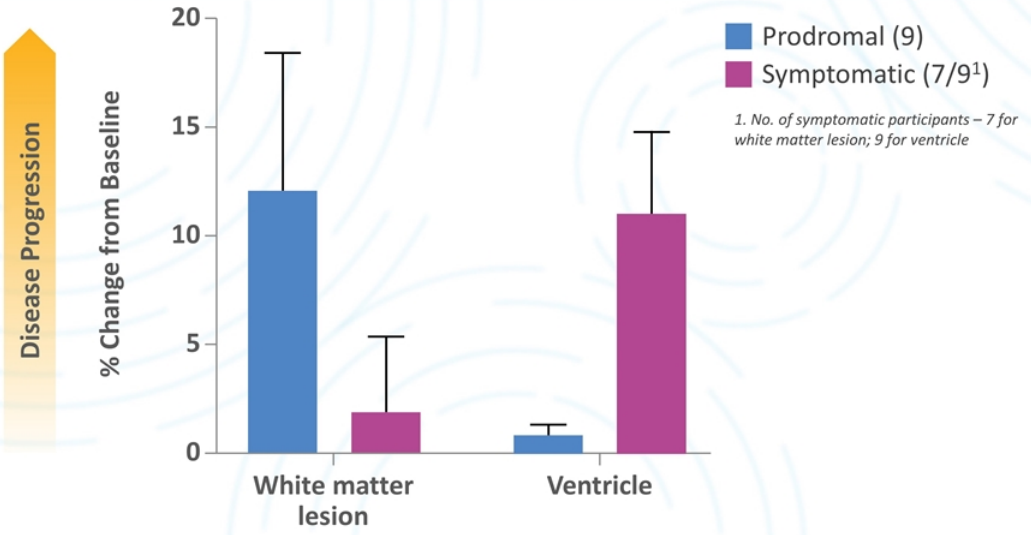
6-month volumetric MRI findings

Greater Disease Progression Based on Greater Increases Lesion and Ventricular Volume



1. No. of symptomatic participants – 7 for white matter lesion; 9 for ventricle

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Radiographic Progression Measurable at Month 6

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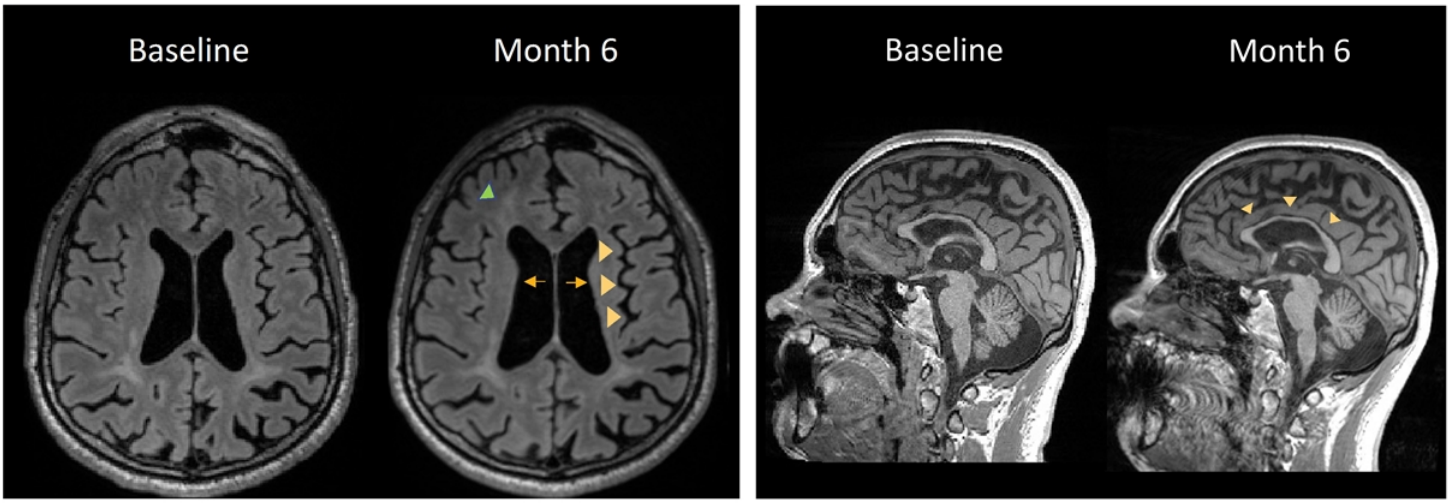
Case Example #1: 31 year | Male | *CSF1R* mutation | Symptomatic ALSP | MoCA at Baseline / 6 month: 15 / 12



- Increased white matter lesion
- Increased atrophy
- Increased ventricular volume

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Radiographic Progression Measurable at Month 6

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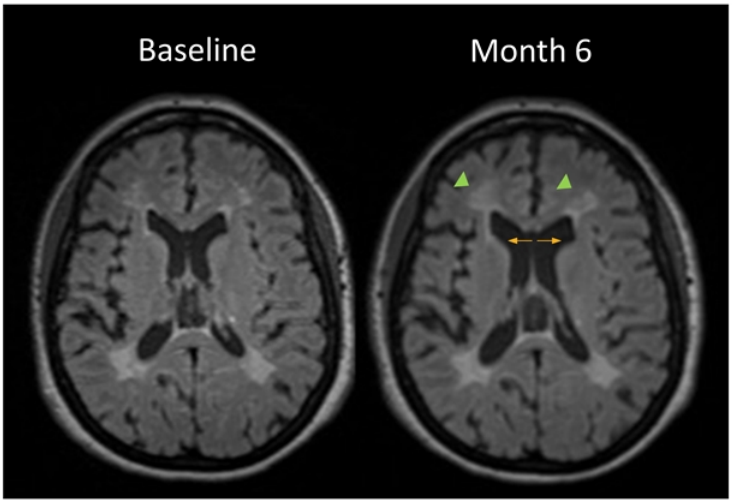
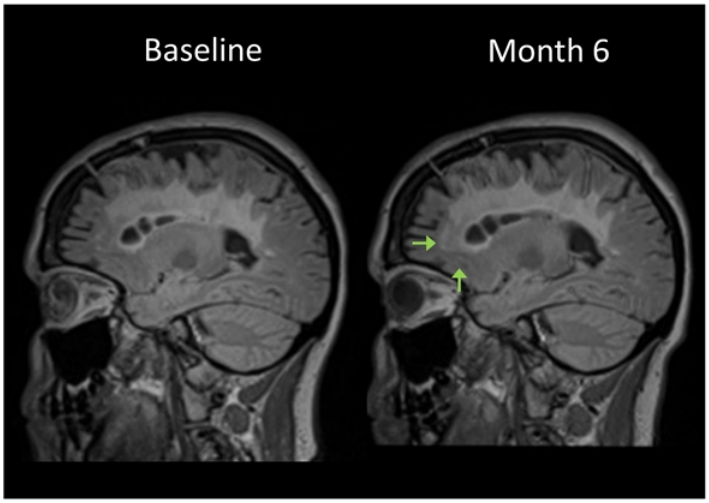
A NATURAL HISTORY STUDY OF Patients with Adult-Onset Leukoencephalopathy with Axonal Spheroids and Pigmented Glia (ALSP)

Case Example #2: 37 year | Female | *CSF1R* mutation | Symptomatic ALSP | MoCA at baseline / 6 month: 15 / 9



▶ Increased white matter lesion
→ Increased ventricular volume



→ Increased white matter lesion

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Fluid Biomarker Baseline Levels Altered in ALSP Individuals

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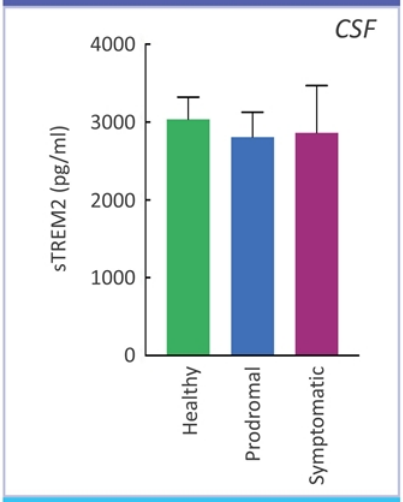
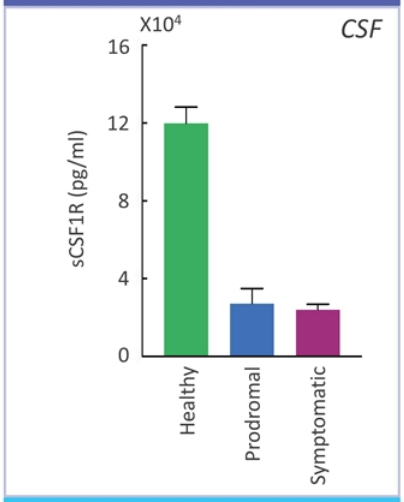
A NATURAL HISTORY STUDY OF | Patients with Adult-Onset Leukoencephalopathy with Axonal Spheroids and Pigmented Glia (ALSP)

sTREM2



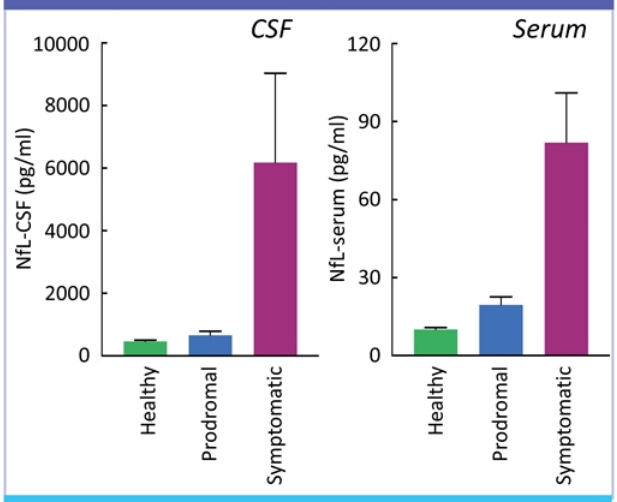
sTREM2 Levels Comparable between Prodromal/Symptomatic and Healthy

sCSF1R



sCSF1R Levels Reduced in Prodromal/Symptomatic vs Healthy

NfL



NfL Levels Increased in Symptomatic Reflecting Active Neurodegeneration

Healthy: healthy volunteers from Vigil's VGL101 Phase 1 trial; Prodromal: participants with confirmed CSF1R mutation and MRI findings in Vigil's Natural History Study; Symptomatic: subjects with CSF1R mutations and ALSP symptoms in Vigil's Natural History Study; no. of samples for all CSF analyses: 25 (Healthy); 3 (Prodromal); 6 (Symptomatic); No. of samples for serum analysis: 67 (Healthy); 10 (Prodromal); 11 (Symptomatic); all biomarker values are in mean ± standard error of mean (SEM)

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Emerging ILLUMINATE Data Support IGNITE Design

- Symptomatic ALSP patients exhibit greater baseline disease burden based on MRI vs healthy and prodromal individuals
  - Lower brain volume
  - Greater white matter lesion and ventricular volumes
- Measurable MRI changes observed at 6 months indicating disease progression in symptomatic ALSP patients
  - Reduction in brain volume
  - Increase in white matter lesion and ventricular volumes
- Symptomatic ALSP patients also exhibit significantly higher NfL levels at baseline vs healthy and prodromal individuals
- Emerging 6-month data from ongoing ILLUMINATE NHS support the rationale of IGNITE Phase 2 secondary measures of MRI and NfL as imaging & fluid biomarkers for efficacy


VGL101 IGNITE Phase 2 Design & Objectives
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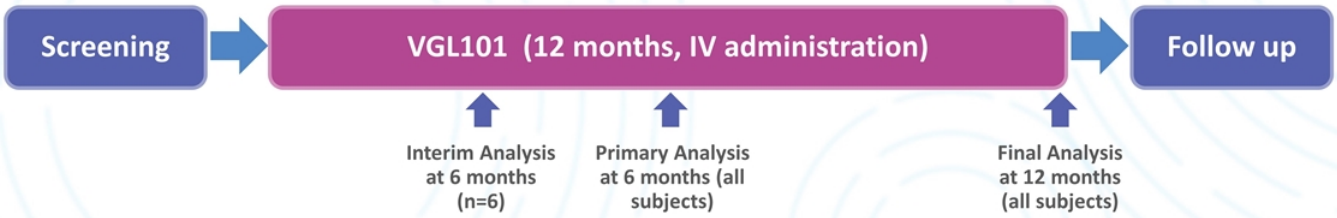
VGL101 ALSP Phase 2 Open-label Proof-of-Concept Trial Design



Study Population	▪ Patients with symptomatic ALSP related to *CSF1R* gene mutation
Study Design	▪ Open-label, up to 15 patients
Treatment Duration	▪ 12 months (with opportunity for further extension), monthly IV administration
Outcome Assessments	▪ Safety and tolerability of VGL101 ▪ MRI-based assessment of white matter lesions ▪ CSF biomarkers for target engagement and neurodegeneration ▪ Clinical outcome measures and PK

VGL101 ALSP Phase 2 Patient Population

Key Clinical Inclusion Criteria

- Documentation of a *CSF1R* gene mutation
- Clinical symptoms consistent with ALSP
- MRI findings consistent with ALSP
- Mild and early-moderate stages defined by cognitive and ambulation status

Key Clinical Exclusion Criteria

- Any neurological disease that poses a risk to the participant or produces symptoms like ALSP
- Patients unable to complete study procedures
- Comorbidities not permitting safe study participation

VGL101 ALSP Phase 2 Objectives & Outcomes

Primary Outcome	**To evaluate safety & tolerability of VGL101 in ALSP** ▪ Nature and frequency of AEs, discontinuations due to AEs ▪ Safety lab tests, vital sign measurements, ECG
Secondary Outcomes	**To evaluate effects of VGL101 on imaging & biomarkers of neurodegeneration & target engagement in ALSP** ▪ Changes from baseline in volumetric MRI measures, MRI ALSP severity score, NfL level in CSF and blood, and sCSF1R level in CSF

Exploratory Outcomes	**To evaluate clinical efficacy & PK of VGL101 in ALSP**
	▪ Change from baseline in clinical outcome measures:
	  ▪ Cognitive Assessments including MoCA, CDR®+NACC-FTLD
	  ▪ Motor Assessments including 2 Minute Walk Test, Timed Up & Go Test
	  ▪ Functional, psychiatric, and patient- and caregiver-reported assessments
	▪ Serum and CSF concentrations of VGL101

Primary analysis conducted after 6 months treatment period; additional analysis of outcome measures after 12 months

AE: adverse event; ECG: electrocardiogram; MRI: magnetic resonance imaging; NfL: Neurofilament Light Chain Protein; sCSF1R: soluble colony-stimulating factor 1 receptor; CSF: cerebrospinal fluid; MoCa: Montreal Cognitive Assessment; CDR®+NACC-FTLD: Clinical Dementia Rating (CDR®) for evaluation of patients with frontotemporal lobar degeneration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Closing Remarks
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Chief Executive Officer
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Unmet Need & Clinical Trial Readiness Support Development of VGL101 in ALSP

- ALSP is a rare devastating, progressive and fatal microgliopathy that is significantly under-recognized
  - Significant portion of patients initially misdiagnosed with other neurodegenerative diseases
- Advances in MRI and genetic testing can enable correct diagnosis
- Increasing disease awareness amongst physicians and patients is key in driving correct diagnosis early
- ALSP has high unmet medical need
  - Current off-label symptomatic treatments have no impact on underlying disease biology
  - HSCT remains experimental with unclear effects on ALSP patients and significant morbidity/mortality

Unmet Need & Clinical Trial Readiness Support Development of VGL101 in ALSP

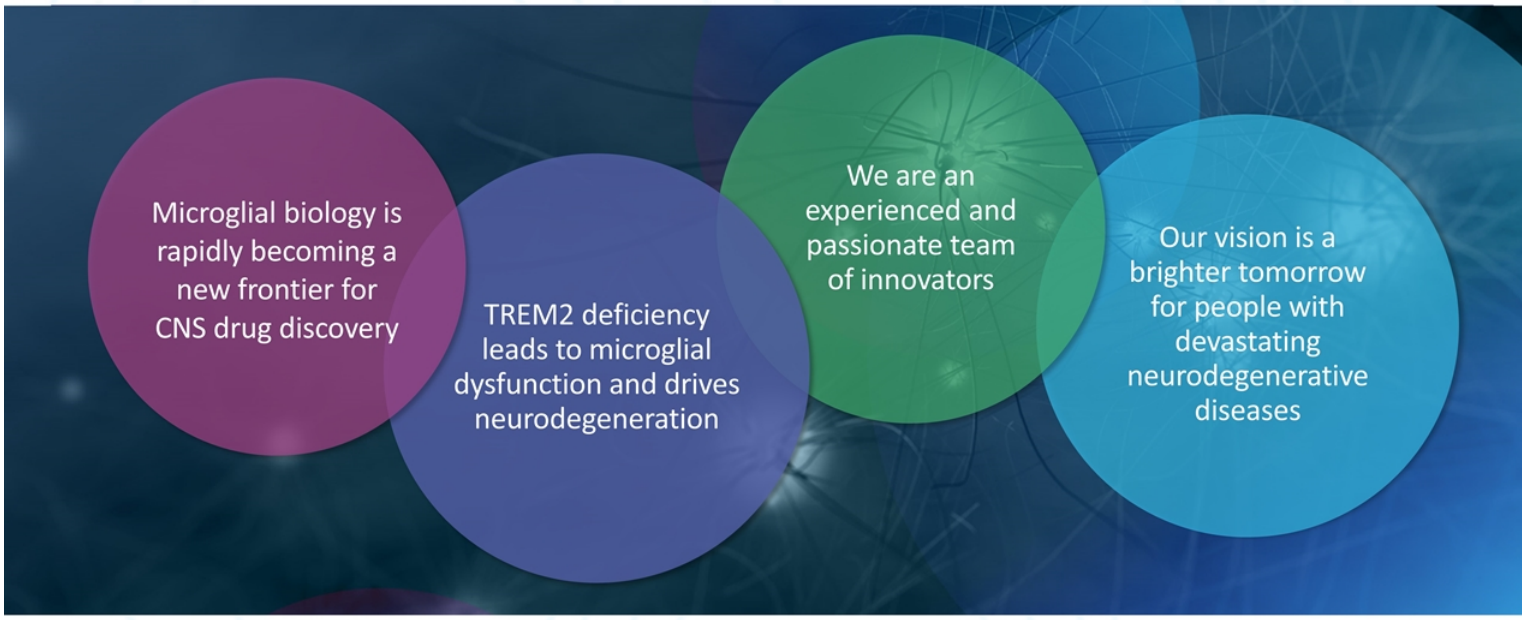
- VGL101 represents a potential disease modifying therapeutic for ALSP
  - Phase 1 data in healthy volunteers support entry into Phase 2 proof-of-concept trial in ALSP patients
- Emerging ILLUMINATE NHS data support exploring imaging and fluid biomarkers on efficacy in Phase 2 IGNITE trial for VGL101
- Vigil continues to actively partner and engage with the ALSP community to drive disease awareness among physicians, patients and caregivers

2022–2023 Anticipated Milestones

☑ Announce topline data for Phase 1 clinical trial with VGL101 in healthy volunteers*	**Q4 2022**
☑ Initiate Phase 2 clinical trial with VGL101 in ALSP	**Q4 2022**
☐ Establish Phase 2 proof of concept in ALSP	**2023**
☐ Submit IND and initiate clinical development for small molecule TREM2 agonist	**2023**

**The healthy volunteer single and multiple ascending dose trial is a first-in-human Phase 1 clinical trial, principally to evaluate VGL101's safety and tolerability. The trial, depending on the safety and tolerability results, is expected to provide a basis for conducting subsequent clinical trials in ALSP, AD and other rare CNS indications.*

Vigil is Well-positioned to Execute on Our Mission

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David S Lynch, MD, PhD

Dr. David Lynch is a consultant neurologist at the National Hospital for Neurology & Neurosurgery at Queen Square, in London. His subspecialty interest is neurogenetics, with a particular focus on adult presentations of inherited white matter disorders (IWMD), also called leukodystrophies. Dr. Lynch has been a core member of the UK's only specialist multidisciplinary team and clinic for this group of patients since 2013, and he has recently been appointed a clinical lead in the newly created NHS England IWMD Highly Specialist Service. Dr Lynch has particular expertise in some of the more common forms of adult onset IWMD, including adult-onset leukoencephalopathy with spheroids and pigmented glia (ALSP) and on clinical and imaging phenotypes of hereditary neurodegenerative disorders.

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Christina Sundal, MD, PhD

Dr. Sundal is the CEO of the Neuroclinic, Norway and an active lecturer in several neurological fields with emphasis on brain white matter disorders and unusual neurological diseases. She completed a research fellowship in the Parkinson's Disease, Clinical Genomics and Movement Disorders Laboratory under the direction and mentorship of Zbigniew K. Wszolek, M.D., at Mayo Clinic in Jacksonville, Florida where her research focused on hereditary diffuse leukoencephalopathy with spheroids (HDLS). She has collaborated on many scientific papers on HDLS, including CSF1R-Related ALSP and the CSF1R-MRI scoring system.

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Troy Lund, MSMS, PhD, MD, FAAP

Dr. Troy Lund is an Associate Professor in the Department of Pediatrics, Division of Blood and Marrow Transplantation & Cellular Therapy and the Associate Director of the Metabolic Program at the University of Minnesota.

He is an international expert on the use of cell and gene therapy for patients with inherited metabolic disorders and lysosomal storage disorders including adrenoleukodystrophy (ALD), adult-onset leukoencephalopathy with axonal spheroids and pigmented glia (ALSP), metachromatic leukodystrophy (MLD), globoid leukodystrophy (GLD), mucopolysaccharidosis type I (MPS I), and osteopetrosis (OP).

Dr. Lund has published extensively on various aspects of these rare diseases and has made substantial contributions to the field with his work both in the clinic and the laboratory. He has more than 100 publications in peer-reviewed journals, including Blood, Biology of Blood and Marrow Transplantation, Stem Cells, Nature Reviews Clinical Oncology, and PLoS One. He has presented more than 100 abstracts and lectures at national and international meetings on a variety of topics.

Dr. Lund is a key opinion leader in all these areas. He has been consulting on rare diseases, cell and gene therapy, and clinical research for more than 15 years. He has strategically partnered with other investigators, institutions, and industry to further his goal of developing safer, more effective therapies that will improve outcomes and save lives.

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