Epidemiological, clinical, and genetic characteristics of paediatric genetic white matter disorders in Northern Finland

OULA A KNUUTINEN[1,2] | JAAKKO H OIKARAINEN[2,3,4] | MARIA H SUO-PALOSAARI[2,3,4] | SALLA M KANGAS[1,2,5] | ELISA J RAHIKKALA[1,2,6] | TYTTI M-L POKKA[1,7] | JUKKA S MOILANEN[1,2,6] | REETTA M L HINTTALA[1,2,5] | PÄIVI M VIEIRA[1,2,7] | JOHANNA M UUSIMAA[1,2,7]

1 PEDEGO Research Unit, University of Oulu, Oulu; **2** Medical Research Center Oulu, University of Oulu and Oulu University Hospital, Oulu; **3** Department of Diagnostic Radiology, Oulu University Hospital, Oulu; **4** Research Unit of Medical Imaging, Physics and Technology, University of Oulu, Oulu; **5** Biocenter Oulu, University of Oulu, Oulu; **6** Department of Clinical Genetics, Oulu University Hospital, Oulu; **7** Clinic for Children and Adolescents, Oulu University Hospital, Oulu, Finland.

Correspondence to Johanna M Uusimaa, Clinic for Children and Adolescents, Oulu University Hospital, Oulu, PO Box 23, 90029 OYS, Finland. E-mail johanna.uusimaa@oulu.fi

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ABBREVIATIONS

gLE	Genetic leukoencephalopathy
GWMD	Genetic white matter disorder
WMA	White matter abnormality

AIM To examine the epidemiological, clinical, and genetic characteristics of paediatric patients with genetic white matter disorders (GWMDs) in Northern Finland.
METHOD A longitudinal population-based cohort study was conducted in the tertiary catchment area of Oulu University Hospital from 1990 to 2019. Patients were identified retrospectively by International Statistical Classification of Diseases and Related Health Problems codes in hospital records and prospectively by attending physicians. Inclusion criteria were children younger than 18 years with defined GWMDs or genetic disorders associated with white matter abnormalities (WMAs) on brain magnetic resonance imaging.
RESULTS Eighty patients (mean age [SD] at the end of the study 11y [8y 6mo], range 0–35y; 45 males, 35 females) were diagnosed with a defined GWMD. The cumulative childhood incidence was 30 per 100 000 live births. Regarding those patients with 49 distinct GWMDs, 20% had classic leukodystrophies and 80% had genetic leukoencephalopathies. The most common leukodystrophies were cerebral adrenoleukodystrophy, Krabbe disease, and Salla disease. Additionally, 29 patients (36%) had genetic aetiologies not previously associated with brain WMAs or they had recently characterised GWMDs, including *SAMD9L*- and *NHLRC2*-related neurological disorders. Aetiology was mitochondrial in 21% of patients. The most common clinical findings were motor developmental delay, intellectual disability, hypotonia, and spasticity.
INTERPRETATION The cumulative childhood incidence of childhood-onset GWMDs was higher than previously described. Comprehensive epidemiological and natural history data are needed before future clinical trials are undertaken.

Genetic white matter disorders (GWMDs) are neurological diseases that affect the white matter of the central nervous system. Many genes are associated with primary defects in several white matter components, including myelin, glial cells, axons, and blood vessels.[1,2] Clinical onset often occurs in childhood and earlier presentation correlates with disease severity.[3] Disorders are generally categorised into classic leukodystrophies and genetic leukoencephalopathies (gLEs) based on the selectivity of white matter involvement.[4] Implementation of exome and genome sequencing in research and clinical practice has revolutionised diagnostics and facilitated frequent characterisation of novel disorders.[1]

Previous studies of GWMD epidemiology estimated the cumulative childhood incidence as 1.2 to 13 per 100 000 live births.[3,5–8] However, considering tertiary catchment areas, previous epidemiological analyses have likely suffered from limited study coverage.[3,6,8] The aim of the Genetics of Northern Finland Leukoencephalopathies and Leukodystrophies (GENOLED) study was to systematically evaluate the epidemiology, genetic aetiologies, and phenotypes of GWMDs in a distinct population of Northern Finland. Additional aims were to identify disorders with previously unrecognised white matter involvement and compare the global and Finnish distribution of specific disorders.

METHOD

Study setting

The study was performed at Oulu University Hospital, Finland, which serves as the only tertiary care centre for child neurology in Northern Finland and covers a geographical area representing 51% of Finland (Fig. 1a). The Child Neurology Unit of Oulu University Hospital has approximately 5500 outpatient visits and 550 inpatient admissions per year. In 2019, the total population of

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Northern Finland was 738 883 and the population under the age of 18 years was 156 347.[9]

Study design

The study population included all paediatric cases with suspected GWMDs evaluated at the Clinic for Children and Adolescents of Oulu University Hospital between 1990 and 2019. The Finnish modification of the International Statistical Classification of Diseases and Related Health Problems, Ninth Revision (ICD-9) and ICD-10 codes for known GWMDs (Table S1, online supporting information) was used. Patients under 18 years of age at the time of clinical evaluation were retrospectively identified as having GWMDs using the hospital's patient registry. Additionally, patients with a known GWMD or noted white matter abnormalities (WMAs) and a genetic diagnosis were prospectively identified by treating physicians. Identifiable patient data were removed during data collection. Clinical and laboratory data and preliminary radiological data were collected from the patient records (Appendix S1, online supporting information). Age at onset was recorded at the first observation of symptoms or findings related to the diagnosed disorder.

The results of genetic studies conducted on a clinical basis were collected. The clinical significance of genetic variants was retrieved from the ClinVar database;[10] when unavailable, variants were classified according to the criteria of the American College of Medical Genetics and Genomics.[11] Digital or film brain magnetic resonance imaging (MRI) scans were evaluated by a radiologist in training (JO, 5y of experience in radiology) and a paediatric radiologist (MS-P, 17y of experience in radiology and 10y of experience in paediatric neuroradiology). Neuroradiological data were analysed systematically according to pattern recognition criteria.[12] Specific disorders were classified as leukodystrophies and gLEs according to the definition published by Vanderver et al.;[4] gLEs were further divided into mitochondrial and other gLEs.

The patient selection process is shown in Fig. 1b. The inclusion criteria were patients younger than 18 years at the time of clinical evaluation, who were living in the tertiary catchment area of Oulu University Hospital and who had a GWMD associated with WMAs either previously or as identified in the current study. Exclusion criteria are shown in Fig. 1b. Leukodystrophy cases without available brain MRI data were included only if an original written radiology report by a specialist in radiology confirmed the presence of WMAs. Additionally, patients with known gLEs[4] without WMAs at the time of the brain imaging were included.

Statistical analysis

Previously described methods[13] for calculating the cumulative childhood incidence were the 'Dx', life table, and 'DOB' methods. The Dx is calculated by taking the number of observed cases divided by the number of total births during the diagnosis period.[13] In this study, the cumulative childhood incidence was calculated using the Dx method by dividing the number of observed cases under 18 years of age by the number of live births (obtained from Statistics Finland)[14] during the diagnosis period (1990–2019). Proportions between two groups were compared using the standard normal deviate test.[15] Continuous, non-normally distributed variables were compared using the two-tailed Mann–Whitney *U* test. A *p*-value equal to or less than 0.05 was considered statistically significant. Statistical analyses were performed using SPSS for Windows v 25.0 (IBM Corp., Armonk, NY, USA) and StatsDirect v3 (StatsDirect Ltd, Birkenhead, UK).

What this paper adds

- Forty-nine distinct genetic white matter disorders (GWMDs) were identified, with 20% of cases being classic leukodystrophies.
- The cumulative childhood incidence of GWMDs was higher than described previously.
- A considerable proportion (36%) of GWMDs were previously undefined or recently characterised GWMDs.
- Mitochondrial aetiology was more common (21%) than previously reported.

Ethical approval

The study was approved by the ethics committee of the Northern Ostrobothnia Hospital District and carried out in accordance with the Declaration of Helsinki.

RESULTS

In total, 80 cases with 49 distinct GWMDs were identified (Tables 1 and 2), including 16 with leukodystrophy (20%) and 64 with gLE (80%). The cumulative childhood incidence was 30 per 100 000 live births (1 in 3333 live births) for all GWMDs, six (1 in 16 667 live births) for classic leukodystrophies, and 24 (1 in 4167 live births) for gLEs. When the decades 1990 to 1999, 2000 to 2009, and 2010 to 2019 were examined separately, the cumulative childhood incidence of all GWMDs was 5.1, 17.9, and 71.8 (1 in 19 608, 1 in 5587, and 1 in 1393) respectively (Table S2, online supporting information). Fig. 1c shows the diseases divided into GWMD categories according to van der Knaap et al.[1] Of the 64 cases with gLE, 15 (23%) were mitochondrial and 49 (77%) were other gLEs. In total, 16 cases (21%) with mitochondrial aetiologies were identified, including 15 with mitochondrial gLEs and one with leukodystrophy (leukoencephalopathy with brain stem and spinal cord involvement and lactate elevation; MIM no. 611105). The most common mitochondrial disorder was mitochondrial myopathy, encephalopathy, lactic acidosis, and stroke-like episodes (MIM no. 540000; *n*=3). Eight patients (10%) with disorders belonging to the Finnish disease heritage were identified. These included Salla disease (MIM no. 604369; *n*=3), muscular dystrophy-dystroglycanopathy (congenital with brain and eye anomalies) type A3 (previously known as muscle-eye-brain disease; MIM no. 253280; *n*=2), mitochondrial DNA depletion syndrome 7 (hepatocerebral type) (MIM no. 271245; *n*=2), and neuronal ceroid lipofuscinosis 5 (MIM no. 256731; *n*=1).

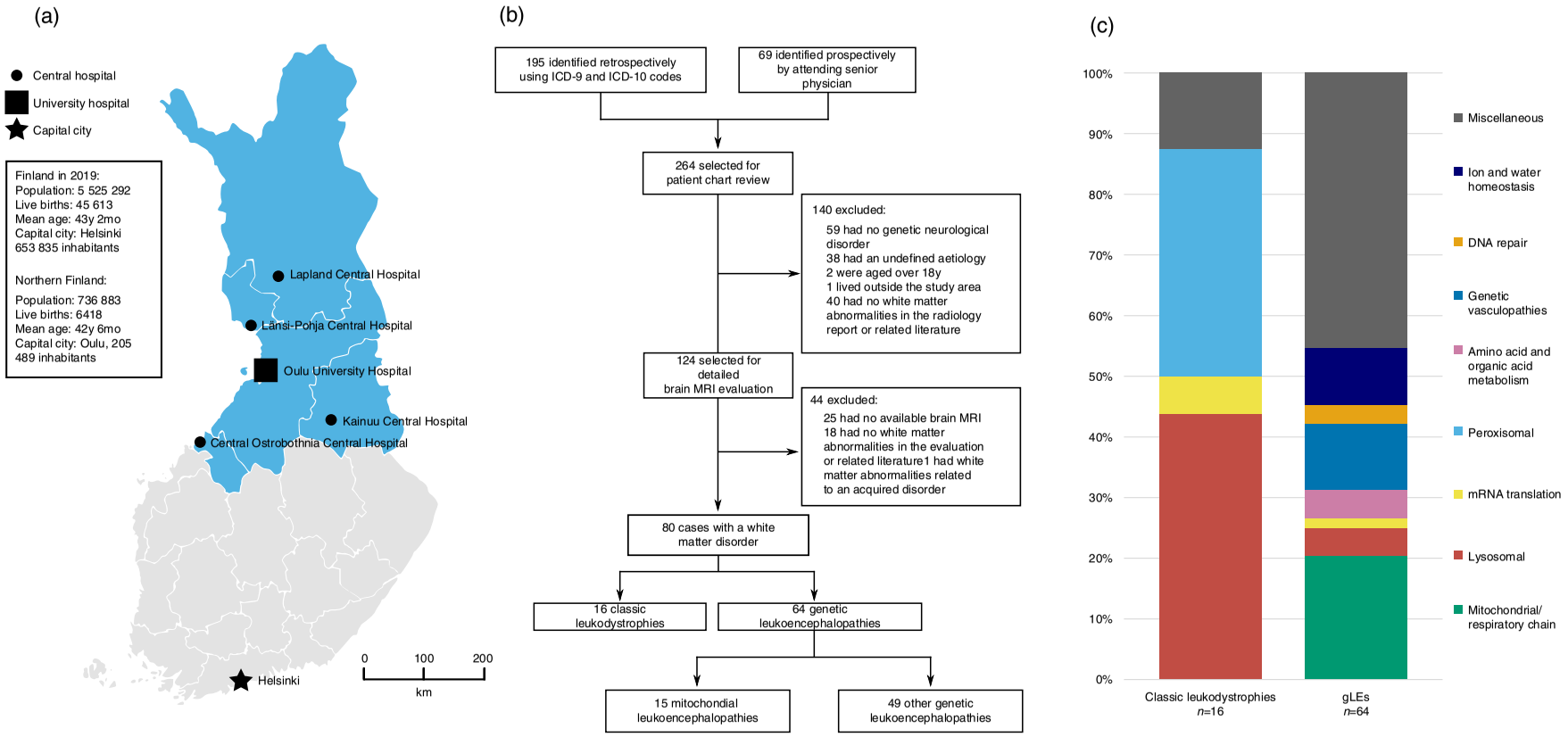

Figure 1: (a) Oulu University Hospital in Northern Finland (blue) provides specialised tertiary level care for the population living in a geographical area covering 51% of Finland. Four central hospitals refer paediatric tertiary level care to Oulu University Hospital. (b) Flow diagram of patient selection, which identified 80 patients fulfilling the inclusion criteria for confirmed genetic white matter disorders. (c) Proportions of leukodystrophies and genetic leukoencephalopathies (gLEs) in Northern Finland categorised according to van der Knaap et al.[1]

Table 1: Genetic white matter disorders in Northern Finland: classic leukodystrophies and mitochondrial genetic leukoencephalopathies

	Disorder, MIM number (disease-causing gene)	*n* (%)	Cumulative childhood incidence per 100 000 live births (95% CI)
Classic leukodystrophies	Adrenoleukodystrophy, 300100 (*ABCD1*)	6 (7.5)	2.2 (0.8–4.6)
	Krabbe disease, 245200 (*GALC*)	3 (3.8)	1.1 (0.23–3.1)
	Salla disease, 604369 (*SLC17A5*)[a]	3 (3.8)	1.1 (0.23–3.1)
	Alexander disease, 203450 (*GFAP*)	1 (1.3)	0.37 (0.009–2.0)
	Chromosome 18q deletion syndrome, 601808	1 (1.3)	0.37 (0.009–2.0)
	LBSL, 611105 (*DARS2*)	1 (1.3)	0.37 (0.009–2.0)
	Metachromatic leukodystrophy, 250100 (*ARSA*)	1 (1.3)	0.37 (0.009–2.0)
	Total	16 (20)	6.0 (3.5–9.1)
Mitochondrial genetic leukoencephalopathies	MELAS, 540000 (mtDNA, e.g. *MT-TL1*)	3 (3.8)	1.1 (0.23–3.1)
	MTDPS7 (IOSCA), 271245 (*TWNK*)[a]	2 (2.5)	0.7 (0.09–2.6)
	Kearns–Sayre and Pearson marrow-pancreas syndromes, 530000 and 557000 (mtDNA deletions)	2 (2.5)	0.7 (0.09–2.6)
	LKENP, 615889 (*AARS2*)	2 (2.5)	0.7 (0.09–2.6)
	CLN5, 256731 (*CLN5*)[b]	1 (1.3)	0.37 (0.009–2.0)
	COXPD7, 613559 (*MTRFR*)[b]	1 (1.3)	0.37 (0.009–2.0)
	Glutaric acidemia IIc, 231680 (*ETFDH*)	1 (1.3)	0.37 (0.009–2.0)
	Leigh syndrome due to mitochondrial complex I deficiency, 256000 (*SURF1*)	1 (1.3)	0.37 (0.009–2.0)
	MIRAS, 607459 (*POLG*)	1 (1.3)	0.37 (0.009–2.0)
	MTDPS5, 612073 (*SUCLA2*)	1 (1.3)	0.37 (0.009–2.0)
	Total	15 (19)	5.6 (3.8–8.6)

[a]Finnish disease heritage. [b]Recently characterised or previously undefined genetic white matter disorder. MIM, Mendelian Inheritance in Man; CI, confidence interval; LBSL, leukoencephalopathy with brainstem and spinal cord involvement and lactate elevation; MELAS, mitochondrial myopathy, encephalopathy, lactic acidosis, and stroke-like episodes; mtDNA, mitochondrial deoxyribonucleic acid; MTDPS7, mitochondrial DNA depletion syndrome 7; IOSCA, infantile-onset spinocerebellar ataxia; LKENP, leukoencephalopathy, progressive, with ovarian failure; CLN5, neuronal ceroid lipofuscinosis 5; COXPD7, combined oxidative phosphorylation deficiency 7; MIRAS, mitochondrial recessive ataxia syndrome; MTDPS5, mitochondrial DNA depletion syndrome 5.

Diagnosis was made with genetic testing (93.7%) or, in deceased patients without genetic testing, through enzymatic studies (6.3%). Chromosomal analysis results were available in 64% of cases. In total, 72 cases (90.0%) had single nuclear gene defects, five cases (6.3%) had mitochondrial DNA defects, and three cases (3.8%) had chromosomal abnormalities (6p25 deletion, 18q deletion, and ring chromosome 18). Of the causal nuclear variants, 60% were inherited recessively (37% homozygous and 24% compound heterozygous variants), 28% were heterozygous variants consistent with dominant inheritance, and 12% were hemizygous consistent with X-linked recessive inheritance (see Table S3, online supporting information, for all causal variants).

Patient demographics and clinical characteristics are summarised in Table 3. At the end of the study period, the mean age was 11 years (SD 8y 6mo, range 0–35y). Out of 80 cases, 45 were male. Male sex was more frequent in leukodystrophies than in gLEs (81% vs 50% respectively; p=0.016). Most patients were ethnic Finns (n=69, 86%). Patients' parents were consanguineous in six cases (7.5%); a family history of GWMD was reported in 26 cases (33%). The most common clinical findings were motor developmental delay (79%), intellectual disability (56%), hypotonia (60%), and spasticity (49%). Epilepsy was diagnosed in 29 cases (36%) and the median age at seizure onset was 12 months (range: 4d–15y). The median age at disease onset was 5 months (range: 0–15y) while the median age at diagnosis was 46 months (range: 0–23y). Age at diagnosis was significantly earlier (p=0.013) in the leukodystrophy group (median: 20mo) than in the gLE group (median: 57mo). At the end of the study, 21 cases (26%) were deceased and the median age at death was 31 months (range: 0–22y). The death rate was 44% and 22% for leukodystrophies and gLEs respectively (p=0.068). A feeding tube was placed in 31 cases (39%) and the median age at placement was 18 months. There were no additional statistically significant differences between leukodystrophies and gLEs (p>0.05).

Eight cases with a defined disorder previously defined as a GWMD had no WMAs on detailed brain MRI assessments (Table S4, online supporting information). The median age at the latest MRI in this patient group was 8 months (range: 0–21y); the available brain MRIs of four patients had been taken before the age of 12 months. Three patients with carbamoyl phosphate synthetase I deficiency (MIM no. 237300) and one with 3-hydroxy-3-methylglutaryl-CoA lyase deficiency (MIM no. 246450) were placed on dietary restrictions.

Twenty-nine patients (36%) with 20 disorders had a defined genetic aetiology not previously associated with brain WMAs or a recently characterised GWMD, including ataxia-pancytopenia syndrome (MIM no. 159550; *SAMD9L*; n=3),[16] fibrosis, neurodegeneration, and cerebral angiomatosis disease (MIM no. 618278; *NHLRC2*; n=3),[17] Lujan–Fryns syndrome (MIM no. 309520; *MED12*; n=2), spastic paraplegia 4, autosomal dominant (MIM no. 182601; *SPAST*; n=2), and *TAF1C*-related neurological

Table 2: Genetic white matter disorders in Northern Finland: other genetic leukoencephalopathies

	Disorder, MIM number (disease-causing gene)	*n* (%)	Cumulative childhood incidence per 100 000 live births (95% CI)
Other genetic leukoencephalopathies	CRMCC1 (Coats plus syndrome), 612199 (*CTC1*)	5 (6.0)	1.8 (0.6–4.2)
	ATXPC, 159550 (*SAMD9L*)[a]	3 (3.8)	1.1 (0.23–3.1)
	FINCA disease, 618278 (*NHLRC2*)[a]	3 (3.8)	1.1 (0.23–3.1)
	MDDGA3 (muscle-eye-brain disease), 253280 (*POMGNT1*)[b]	2 (2.5)	0.7 (0.09–2.6)
	AHDS, 300523 (*SLC16A2*)	2 (2.5)	0.7 (0.09–2.6)
	Cockayne syndrome, type B, 133540 (*ERCC6*)	2 (2.5)	0.7 (0.09–2.6)
	Hereditary homocystinurias, 236250 and 250940 (*MTHFR* and *MTR*)	2 (2.5)	0.7 (0.09–2.6)
	Lujan–Fryns syndrome, 309520 (*MED12*)[a]	2 (2.5)	0.7 (0.09–2.6)
	MICPCH, 300749 (*CASK*)[a]	2 (2.5)	0.7 (0.09–2.6)
	Mucolipidosis II, 252500 (*GNPTAB*)[a]	2 (2.5)	0.7 (0.09–2.6)
	NBIA5, 300894 (*WDR45*)[a]	2 (2.5)	0.7 (0.09–2.6)
	SPG4, 182601 (*SPAST*)[a]	2 (2.5)	0.7 (0.09–2.6)
	Cardiofaciocutaneous syndrome 1, 115150 (*BRAF*)[a]	1 (1.3)	0.37 (0.009–2.0)
	Chromosome 6pter-p24 deletion syndrome, 612582	1 (1.3)	0.37 (0.009–2.0)
	CPS I deficiency, 237300 (*CPS1*)	1 (1.3)	0.37 (0.009–2.0)
	EIEE34, 616645 (*SLC12A5*)[a]	1 (1.3)	0.37 (0.009–2.0)
	EIEE42, 617106 (*CACNA1A*)[a]	1 (1.3)	0.37 (0.009–2.0)
	EIEE44, 617132 (*UBA5*)[a]	1 (1.3)	0.37 (0.009–2.0)
	Fabry disease, 301500 (*GLA*)	1 (1.3)	0.37 (0.009–2.0)
	HMGCLD, 246450 (*HMGCL*)	1 (1.3)	0.37 (0.009–2.0)
	Lissencephaly 3, 611603, (*TUBA1A*)[a]	1 (1.3)	0.37 (0.009–2.0)
	MDR13, 614563 (*DYNC1H1*)[a]	1 (1.3)	0.37 (0.009–2.0)
	MIRAGE syndrome, 617053 (*SAMD9*)[a]	1 (1.3)	0.37 (0.009–2.0)
	MRX1, 309530 (*IQSEC2*)	1 (1.3)	0.37 (0.009–2.0)
	MRX102, 300958 (*DDX3X*)[a]	1 (1.3)	0.37 (0.009–2.0)
	NECFM, 617393 (*NACC1*)	1 (1.3)	0.37 (0.009–2.0)
	Rett syndrome, congenital variant, 613454 (*FOXG1*)[a]	1 (1.3)	0.37 (0.009–2.0)
	Ring chromosome 18 syndrome	1 (1.3)	0.37 (0.009–2.0)
	Spinocerebellar ataxia 29, 117360 (*ITPR1*)[a]	1 (1.3)	0.37 (0.009–2.0)
	TAF1C-related disorder (*TAF1C*)[a]	1 (1.3)	0.37 (0.009–2.0)
	VAIHS, 615688 (*ADA2*)[a]	1 (1.3)	0.37 (0.009–2.0)
	Wilson disease, 277900 (*ATP7B*)	1 (1.3)	0.37 (0.009–2.0)
	Total	49 (61)	18 (15–21)

[a]Recently characterised or previously undefined genetic white matter disorder. [b]Finnish disease heritage. MIM, Mendelian Inheritance in Man; CI, confidence interval; CRMCC1, cerebroretinal microangiopathy with calcifications and cysts 1; ATXPC, ataxia-pancytopenia syndrome; FINCA, fibrosis, neurodegeneration, and cerebral angiomatosis; MDDGA3, muscular dystrophy-dystroglycanopathy (congenital with brain and eye anomalies) A3; AHDS, Allan–Herndon–Dudley syndrome; MICPCH, mental retardation and microcephaly with pontine and cerebellar hypoplasia; NBIA5, neurodegeneration with brain iron accumulation 5; SPG4, spastic paraplegia 4, autosomal dominant; CPS I, carbamoyl phosphate synthetase I deficiency; EIEE, epileptic encephalopathy, early infantile; HMGCLD, 3-hydroxy-3-methylglutaryl-CoA lyase deficiency; MDR13, mental retardation, autosomal dominant 13; MIRAGE, myelodysplasia, infection, restriction of growth, adrenal hypoplasia, genital phenotypes, and enteropathy; MRX, mental retardation, X-linked; NECFM, neurodevelopmental disorder with epilepsy, cataracts, feeding difficulties, and delayed brain myelination; VAIHS, vasculitis, autoinflammation, immunodeficiency, and hematologic defects syndrome; GWMD, genetic white matter disorder.

phenotype (n=1).[18] Clinical features and neuroimaging findings are shown in Table 4. Causal variants were consistent with a recessive mode of inheritance in 34.5% (13.8% homozygous, 20.7% compound heterozygous), dominant in 58.6%, and X-linked in 6.9% of cases. Heterozygous variants were more frequent in this patient group compared to all GWMDs (68% vs 27%; p=0.001).

DISCUSSION

The current study was a longitudinal, population-based cohort study of all GWMD cases in Northern Finland between 1990 and 2019. Eighty patients were diagnosed with 49 distinct defined GWMDs. The cumulative childhood incidence was 30 per 100 000 live births (1 in 3333 live births), which was higher than previous estimates. Surveys,[7] ICD-9-based cohorts,[3,8] and registry-based cohorts[5–7] reported figures between 1.2 and 13.0 (Table S5, online supporting information). Based on allele frequencies of GWMD-causing variants, a recent study by Soderholm et al.[19] predicted an incidence of 21 per 100 000 live births. This closely matches the current study findings, demonstrating concordance between genomic database and population-based estimates. The lower incidence in previous observational studies may be explained by limited coverage of observed population areas[3,6,8] and underreporting of cases in questionnaires and national databases.[5,7] Additionally, the development of brain imaging technologies and implementation of next-generation sequencing have enabled a higher diagnosis rate.[20] When we examined the decades separately, the cumulative childhood incidence increased towards the later decades in the current study. This is likely due to improved clinician awareness and GWMD diagnostics in addition to selection bias favouring more recently diagnosed cases.

Table 3: Patient demographics and clinical characteristics of white matter disorders in Northern Finland from 1990 to 2019

	All GWMDs (*n*=80)	Classic leukodystrophies (*n*=16)	gLEs (*n*=64)	*p*[a]
Cumulative childhood incidence per 100 000 live births[b]	30	6	24	NA
Male	45 (56)	13 (81)	32 (50)	0.016
Finnish ethnicity	69/78 (88)	14 (88)	55/62 (89)	0.999
Parental consanguinity	6/69 (9)	0/14 (0)	6/55 (11)	0.174
Family history of GWMD	26/78 (33)	7 (44)	19/63 (30)	0.256
Intellectual disability	45/71 (63)	5/11 (45)	40/60 (66)	0.123
Motor developmental delay	63 (79)	13 (81)	50/61 (82)	0.999
Hypotonia	48/79 (61)	9 (56)	39/63 (62)	0.585
Spasticity	39 (49)	8 (50)	31 (48)	0.999
Extrapyramidal signs	18 (23)	2 (13)	16 (25)	0.340
Ataxia	23 (29)	6 (38)	17 (27)	0.376
Epilepsy	29 (36)	5 (31)	24 (38)	0.582
Age at onset, mo, median (range)	12 (0–180)	110 (0–130)	12 (0–180)	0.524
Age at disease onset, mo, median (range)	5 (0–180)	6 (0–100)	5 (0–180)	0.312
Age at diagnosis, mo, median (range)	46 (0–270)	20 (1–120)	57 (0–270)	0.013
Deceased	21 (26)	7 (44)	14 (22)	0.068
Age at death, mo, median (range)	31 (1–260)	41 (1–120)	31 (5–260)	0.659
Required feeding tube	31/79 (39)	7 (44)	24/63 (38)	0.585
Age at placement, mo, median (range)	18 (5–190)	18 (6–120)	18 (5–190)	0.773

Data are *n* (%) unless otherwise stated. [a]Compared between classic leukodystrophies and genetic leukoencephalopathies. [b]Calculated using 268 636 live births between January 1990 and December 2019.[14] GWMD, genetic white matter disorder; gLE, genetic leukoencephalopathy; NA, not applicable.

Table 4: Recently characterised or previously undefined genetic white matter disorders (*n*=29)

Disorder, MIM number	*n*	Sex	Gene	Zygosity	Clinical features
ATXPC, 159550	3	M (2) and F (1)	*SAMD9L*	Heterozygous	Migraine, nystagmus, ADHD, cytopenias, myelodysplastic syndrome
Cardiofaciocutaneous syndrome 1, 115150	1	F	*BRAF*	Heterozygous	Hypotonia, macrocephaly, intellectual disability, cardiomyopathy, growth failure
COXPD7, 613559	1	M	*C12orf65*	Homozygous	Spastic paraparesis, ataxia, intellectual disability
EIEE34, 616645	1	F	*SLC12A5*	Homozygous	Hypotonia, epilepsy, intellectual disability
EIEE42, 617106	1	F	*CACNA1A*	Heterozygous	Ataxia, choreoathetosis, epilepsy, intellectual disability
EIEE44, 617132	1	M	*UBA5*	Compound heterozygous	Spastic tetraparesis, ataxia, epilepsy, intellectual disability, microcephaly
FINCA disease, 618278	3	M	*NHLRC2*	Compound heterozygous	Dystonic tetraparesis, epilepsy, progressive respiratory insufficiency, anaemia
Lissencephaly 3, 611603	1	F	*TUBA1A*	Heterozygous	Spastic tetraparesis, epilepsy, intellectual disability, microcephaly
Lujan–Fryns syndrome, 309520	2	M	*MED12*	Hemizygous	Motor developmental delay, intellectual disability, optic nerve hypoplasia
MDR13, 614563	1	M	*DYNC1H1*	Heterozygous	Hypotonia, epilepsy, intellectual disability, microcephaly
MICPCH, 300749	2	F	*CASK*	Heterozygous	Hypotonia, intellectual disability, epilepsy, microcephaly
MIRAGE, 617053	1	M	*SAMD9*	Heterozygous	Spasticity, ataxia, myelodysplastic syndrome
MRX102, 300958	1	F	*DDX3X*	Heterozygous	Motor developmental delay, intellectual disability, microcephaly
Mucolipidosis II, 252500	2	F	*GNPTAB*	Compound heterozygous	Spasticity, intellectual disability, congestive heart failure, skeletal abnormalities
NBIA5, 300894	2	F	*WDR45*	Heterozygous	Spastic tetraparesis, epilepsy, intellectual disability
Rett syndrome, congenital variant, 613454	1	F	*FOXG1*	Heterozygous	Hypotonia, athetosis, epilepsy, intellectual disability, microcephaly
SPG4, 182601	2	M and F	*SPAST*	Heterozygous	Spastic paraparesis, mild intellectual disability
Spinocerebellar ataxia 29, 117360	1	M	*ITPR1*	Heterozygous	Motor and speech development delay, ataxia, atrial septal defect
TAF1C-related disorder	1	F	*TAF1C*	Homozygous	Tetraparesis, epilepsy, intellectual disability, microcephaly, precocious puberty
VAIHS, 615688	1	F	*ADA2*	Homozygous	Motor developmental delay, epilepsy, intellectual disability, skin vasculitis

MIM, Mendelian Inheritance in Man; ATXPC, ataxia-pancytopenia syndrome; M, male; F, female; ADHD, attention-deficit/hyperactivity disorder; COXPD7, combined oxidative phosphorylation deficiency 7; EIEE, epileptic encephalopathy, early infantile; FINCA, fibrosis, neurodegeneration, and cerebral angiomatosis; MDR13, mental retardation, autosomal dominant 13; MICPCH, mental retardation and microcephaly with pontine and cerebellar hypoplasia; MIRAGE, myelodysplasia, infection, restriction of growth, adrenal hypoplasia, genital phenotypes, and enteropathy; MRX, mental retardation, X-linked; NBIA5, neurodegeneration with brain iron accumulation 5; SPG4, spastic paraplegia 4, autosomal dominant; VAIHS, vasculitis, autoinflammation, immunodeficiency, and hematologic defects syndrome.

The hallmarks of leukodystrophies, that is, motor developmental delay, intellectual disability, and spasticity were common (79%, 56%, and 49% respectively). The median age at disease onset was relatively early (5mo), which is consistent with an Iranian study by Ashrafi et al.[6] In the study by Zhang et al.,[21] the median age at seizure onset was 20 months. In the current study, the median age at seizure onset was 9 years in patients with leukodystrophy. Onset differed between leukodystrophies and gLEs, with the median age at epilepsy onset being 12 months in gLEs (p=0.524). Several disorders with early-onset epilepsy were identified but the overall incidence of epilepsy was only 31%. This is at the lower end of the incidence noted in previous studies, which reported the incidence of epilepsy as between 31% and 49% in children with leukodystrophy.[6,21] The relatively low incidence of epilepsy could have contributed to the later median onset of seizures in this study.

The genetic phenotypes included a substantial proportion of mitochondrial disorders (21%). In a study from the UK, 6.4% of observed GWMDs were mitochondrial.[5] Nuclear genome sequencing can identify the majority of mitochondrial disorders observed. However, two disorders in the cohort (6.3%), mitochondrial myopathy, encephalopathy, lactic acidosis, and stroke-like episodes (n=3) and Kearns-Sayre/Pearson marrow-pancreas syndrome (MIM no. 530000 and no. 557000; n=2) require mitochondrial DNA analyses (sequencing, quantitative, and qualitative analyses for mitochondrial DNA deletions and heteroplasmy level of the point mutation).

Finland has a distinct prevalence of heritable disorders, referred to as the Finnish disease heritage.[22] Several bottlenecks in the history of the Finnish population and the colonisation of remote areas by small groups of settlers caused enrichment of some disease-causing genes and the loss of others. This unique feature has been beneficial for researchers to identify novel disease-causing genes from individual patients, especially in Northern Finland.[23] Causal variants of the GWMDs Salla disease and neuronal ceroid lipofuscinosis 5 were first identified in Finland. The Finnish disease heritage accounted for 10% of all GWMD cases in this study. In a UK study,[5] 4.2% of participants had disorders belonging to the Finnish disease heritage. In contrast, some GWMDs common in the UK, including Pelizaeus–Merzbacher disease, vanishing white matter disease, and Aicardi–Goutières syndrome,[5] were absent in the Finnish cohort.

Cytogenetic studies were performed on a clinical basis. All three observed chromosomal abnormalities have previously been associated with WMAs.[24,25] In 2019, Vigdorovich et al.[24] described copy number variants in a selected cohort of 13 patients with WMAs. However, no systematic evaluation of WMAs in patients with chromosomal abnormalities has been conducted. Characterisation of this patient entity and the underlying complex molecular aetiologies is a potential future research field of GWMDs.

The current study identified 29 patients with a defined genetic aetiology not previously associated with brain WMAs or recently characterised GWMDs, including ataxia-pancytopenia syndrome,[16] fibrosis, neurodegeneration, and cerebral angiomatosis disease,[17] and *TAF1C*-related disorder[18] (Table 4). Next-generation sequencing techniques have led to a surge in the discovery of novel GWMDs. Heterozygous variants and dominant inheritance patterns are increasingly reported in GWMDs[20] and were significantly more common in this sub-cohort of 29 patients. Still, rare WMAs have been described with many such disorders, for example, white matter atrophy in lissencephaly 3 (MIM no. 611603)[26] as well as corpus callosum abnormalities in cardiofaciocutaneous syndrome 1 (MIM no. 115150) and Lujan–Fryns syndrome.[27,28] Future studies should further define the white matter involvement and neuroradiological features of these disorders.

Eight patients with a diagnosis compatible with previously defined gLEs[4] had no WMAs on brain MRI scans (Table S4). Several explanations exist for this finding. First, in carbamoyl phosphate synthetase I deficiency and 3-hydroxy-3-methylglutaryl-CoA lyase deficiency, early diagnosis and dietary restrictions may have prevented the development of detectable WMAs on brain MRI scans. Second, a variable disease course with variants in the disease-causing genes may have contributed to absent white matter findings. Not all GWMDs are linearly progressive, as demonstrated by episodic deterioration in mitochondrial disorders (e.g. mitochondrial DNA depletion syndrome 5).[1] Defects in mitochondrial transfer RNA synthetases, such as *AARS2*, are known to cause variable phenotypes, and improvement of MRI abnormalities may occur.[1] Third, four patients were younger than 12 months at the time of the latest brain MRI. During the early myelination period, white matter is developing rapidly and abnormalities can be undetectable or may not appear until a later age. In the future, novel imaging technologies as well as computational and artificial intelligence-based methods may improve the early MRI diagnostics of neonatal and infantile GWMDs.[29]

The strengths of this study include high coverage of the tertiary catchment area of Oulu University Hospital and good availability of clinical data. The Finnish health care system provides good opportunities to perform epidemiological studies because its registers represent, to a large extent, the total morbidity in the population. In Finland, municipal child health clinics follow child welfare, including neurological development. This service is included free of charge as part of centralised health care and has a coverage of over 90% of children.[30] This enables early recognition of GWMD-related symptoms (e.g. developmental delay or hypotonia) and referral to a child neurologist and neuroimaging. Limitations of the current study include the inability of ICD-10-based searches to identify all patients with GWMDs and WMAs. To counteract this, a prospective cohort of patients recognised by the attending senior physician was included. Additionally, cases were excluded if brain MRI data were unavailable. Introduction of digital MRI archives has increased data availability, favouring

younger patients. Changes in these circumstances explain the increased prevalence during the study period. When generalising the study findings to other populations, the effect of the Finnish disease heritage should be noted.[22]

In conclusion, the current population-based study evaluated the epidemiology and clinical characteristics of childhood-onset GWMDs in a population within a defined geographical area. The cumulative childhood incidence was higher than previously described in the literature. Most disorders were categorised as gLEs and mitochondrial aetiology was common. Additionally, the study identified several recently characterised disorders or disorders where white matter involvement was not previously recognised properly. The study provides comprehensive epidemiological and natural history data to facilitate future clinical trials of novel therapies and screening strategies.

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DATA AVAILABILITY STATEMENT

The genetic data that support the findings of this study are available in the supplementary material of this article. Clinical patient data are not publicly available due to privacy and ethical restrictions.

SUPPORTING INFORMATION

The following additional material may be found online:

Table S1: International Classification of Diseases codes used to identify leukodystrophy and gLE cases

Table S2: The cumulative childhood incidence of genetic white matter disorders and the number of live births by decade

Table S4: Previously defined GWMD cases without white matter abnormalities on brain MRI scans

Table S5: Summary of studies on the cumulative childhood incidence of GWMDs in children

Table S3: Identified genetic variants

Appendix S1: Epidemiological, clinical, and genetic characteristics of paediatric genetic white matter disorders in Northern Finland.

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