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

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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
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.

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; when unavailable, variants were classified according to the criteria of the American College of Medical Genetics and Genomics. 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. Specific disorders were classified as leukodystrophies and gLEs according to the definition published by Vanderver et al.; 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 without WMAs at the time of the brain imaging were included.

Statistical analysis
Previously described methods 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. 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) during the diagnosis period (1990–2019). Proportions between two groups were compared using the standard normal deviate test. 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).

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 1667 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 19608, 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. 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 (heptocerebral type) (MIM no. 271245; n=2), and neuronal ceroid lipofuscinosis 5 (MIM no. 256731; n=1).
69 identified prospectively by attending senior physician

140 excluded:
- 59 had no genetic neurological disorder
- 38 had an undefined aetiology
- 2 were aged over 18y
- 1 lived outside the study area
- 40 had no white matter abnormalities in the radiology report or related literature

80 cases with a white matter disorder

264 selected for patient chart review

126 selected for detailed brain MRI evaluation

44 excluded:
- 25 had no available brain MRI
- 18 had no white matter abnormalities in the evaluation or related literature
- 1 had white matter abnormalities related to an acquired disorder

16 classic leukodystrophies

64 genetic leukoencephalopathies

15 mitochondrial leukoencephalopathies

49 other genetic leukoencephalopathies

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
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: Leukodystrophy due to mitochondrial complex I deficiency, 256000; MRI, 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; MTDPS5, mitochondrial DNA depletion syndrome 7; MIRAS, mitochondrial respiratory chain deficiency, 256000; MTDPS7, 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.

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

| 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)             | 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 leukencephalopathies** | |                                                                |
| MELAS, 540000 (mtDNA, e.g. MT-TL1)          | 3 (3.8)| 1.1 (0.23–3.1)                                               |
| MTDPS7 (IOSCA), 271245 (TWNK)              | 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 (CLNSb)                       | 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 (3.8–8.8)                                                 |

*a*Finnish disease heritage. *b*Recently characterised or previously undefined genetic white matter disorder. MIM, Mendelian Inheritance in Man; CI, confidence interval; LBSL, leukencephalopathy 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, leukencephalopathy, 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.
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, ICD-9-based cohorts, and registry-based cohorts 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. 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 and underreporting of cases in questionnaires and national databases. Additionally, the development of brain imaging technologies and implementation of next-generation sequencing have enabled a higher diagnosis rate. 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

| Sex       | Gene     | Zygosity | Clinical features                                                                 |
|-----------|----------|----------|-----------------------------------------------------------------------------------|
| Male      | SAMD9L   | Heterozygous | Migraine, nystagmus, ADHD, cytopenias, myelodysplastic syndrome                   |
| Haploinsufficiency, X-linked |  |  |                                                                                   |
| Female    | BRAF     | Heterozygous | Hypotonia, macrocephaly, intellectual disability, cardiomyopathy, growth failure |
|          | C12orf55 | Homozygous | Spastic paraparesis, ataxia, intellectual disability                               |
|          | SLC12A5  | Homozygous | Hypotonia, epilepsy, intellectual disability                                      |
|          |  |  | Ataxia, choreoathetosis, epilepsy, intellectual disability                         |
|          | CACNA1A  | Heterozygous | Spastic tetraparesis, ataxia, epilepsy, intellectual disability, microcephaly      |
|          | UBA5     | Heterozygous | Hypotonia, intellectual disability, microcephaly                                  |
| FINCA, 618278 |  | Compound heterozygous | Dystonic tetraparesis, epilepsy, progressive respiratory insufficiency, anaemia |
| Lissencephaly, 611603 |  | Homozygous | Spastic tetraparesis, epilepsy, intellectual disability, microcephaly             |
| Lujan-Fryns syndrome, 309520 |  | Hemizygous | Motor developmental delay, intellectual disability, optic nerve hypoplasia        |
| MDR13, 614563 |  | Heterozygous | Hypotonia, epilepsy, intellectual disability, microcephaly                        |
| MICPCH, 300749 |  | Heterozygous | Hypotonia, intellectual disability, epilepsy, microcephaly                        |
| MIRAGE, 617053 |  | Heterozygous | Spasticity, ataxia, myelodysplastic syndrome                                       |
| MRX102, 300958 |  | Heterozygous | Motor developmental delay, intellectual disability, microcephaly                 |
| Mucolipidosis II, 252500 |  | Compound heterozygous | Spasticity, intellectual disability, congestive heart failure, skeletal abnormalities |
| NBIAS0, 300894 |  | Heterozygous | Spastic tetraparesis, epilepsy, intellectual disability, microcephaly            |
| Rett syndrome, congenital variant, 613454 |  | Heterozygous | Hypotonia, ataxia, epilepsy, intellectual disability, microcephaly              |
| SPG4, 182601 |  | Heterozygous | Spastic paraparesis, mild intellectual disability                               |
| Spinocerebellar ataxia 29, 117360 |  | Heterozygous | Motor and speech development delay, ataxia, atrial septal defect                |
| TAFC-related disorder |  | Homozygous | Tetraparesis, epilepsy, intellectual disability, microcephaly, precocious puberty |
| VAIHS, 615888 |  | Homozygous | Motor developmental delay, epilepsy, intellectual disability, skin vasculitis     |

Table 4: Recently characterised or previously undefined genetic white matter disorders (n=28)

| 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 | C12orf55 | Homozygous | Spastic paraparesis, ataxia, intellectual disability |
| EIEE334, 616645      | 1 | F | SLC12A5 | Homozygous | Hypotonia, epilepsy, intellectual disability |
| EIEE442, 617108      | 1 | F | CACNA1A | Heterozygous | Ataxia, choreoathetosis, epilepsy, intellectual disability |
| EIEE444, 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 | Homozygous | 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 |
| NBIAS0, 300894       | 2 | F | WDR45 | Heterozygous | Spastic tetraparesis, epilepsy, intellectual disability, microcephaly |
| Rett syndrome, congenital variant, 613454 | 1 | F | FOXG1 | Heterozygous | Hypotonia, ataxia, 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 |
| TAFC-related disorder | 1 | F | TAFC | Homozygous | Tetraparesis, epilepsy, intellectual disability, microcephaly, precocious puberty |
| VAIHS, 615888        | 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 enteropathy; MRX, mental retardation, X-linked; NBIAS0, 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. In the study by Zhang et al., 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. 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. 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 heteroplasmny level of the point mutation).

Finland has a distinct prevalence of heritable disorders, referred to as the Finnish disease heritage. 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. 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, 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, 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. In 2019, Vidgordovich et al. 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, fibrosis, neurodegeneration, and cerebral angiomatosis disease, and TAF1C-related disorder (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 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) as well as corpus callosum abnormalities in cardiofaciocutaneous syndrome 1 (MIM no. 115150) and Lujan–Fryns syndrome. 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 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). Defects in mitochondrial transfer RNA synthetases, such as AARS2, are known to cause variable phenotypes, and improvement of MRI abnormalities may occur. 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.

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. 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.

ACKNOWLEDGEMENTS
This work was supported by the Arvo and Lea Ylppö Foundation, Stiftelsen Alma och K.A. Snellman S, Special State Grants for Health Research in the Clinic for Children and Adolescents, Oulu University Hospital, Finland. The authors thank adjunct professor Leena Vainionpää for her help with data collection and Dr Esa Kari for providing valuable comments.

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.

REFERENCES
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