



## Incidence of Aicardi-Goutières syndrome and *KCNT1*-related epilepsy in Denmark

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### ABSTRACT

**Objective:** To estimate the incidence of Aicardi-Goutières syndrome (AGS) and potassium sodium-activated channel subfamily T member 1 (*KCNT1*)-related epilepsy in Denmark and to characterize the patients diagnosed with AGS and *KCNT1*-related epilepsy.

**Background:** AGS and *KCNT1*-related epilepsy are 2 distinct rare genetic disorders. Due to the rarity of AGS and *KCNT1*-related epilepsy, the epidemiology remains unclear. The incidences for these diseases or the carriers with disease-related genetic variants remain unknown.

**Materials and methods:** This is a retrospective, non-interventional, population-based study using aggregate data from the Danish population register and hospital-based patient-level data in Denmark to identify persons with genetically confirmed AGS between January 2010 to December 2020 and *KCNT1*-related epilepsies between January 2012 to December 2020. Cases of these disorders were identified from in-hospital databases, and pathogenic variants were identified and confirmed by Sanger and/or whole exome (panel-based) sequencing. The incidence of AGS and *KCNT1*-related epilepsy were estimated in separate statistical analyses.

**Results:** A total of 7 AGS patients were identified. The mean age at AGS diagnosis was 19.4 months (median age 14 months). *TREX1* ( $n < 5$ ) and *RNASEH2B* ( $n \geq 5$ ) genes were reported with confirmed pathogenic variants. The birth incidence of AGS was  $< 0.7600$  per 100,000 live births. The average annual incidence rate was calculated as 0.0539 (95% CI: 0.0217–0.1111) per 100,000 persons per year in the total population  $< 18$  years ( $n = 7$ ); the average annual incidence rate was  $< 0.7538$  per 100,000 persons per year ( $n < 5$ ) in the population  $< 12$  months, and the average annual incidence rate in the population  $\geq 12$  months and  $< 18$  years was  $< 0.0406$  per 100,000 persons per year ( $n < 5$ ). A total of 14 *KCNT1*-related epilepsy cases were identified during the study period ( $n = 5$  in 2016, remaining 9 cases in 2013 and 2015). The mean age at diagnosis was 20.6 years (median 19 years) for *KCNT1* cases. A total of 8 cases (57.1%) were  $\geq 18$  years, and 6 (42.9%) were  $< 18$  years at diagnosis. The phenotype autosomal dominant or sporadic sleep-related hypermotor epilepsy (ADSHE) ( $n = 10$ , 71.4%) was most reported; the remaining 4 cases had either epilepsy of infancy with migrating focal seizures (EIMFS) or an unclassifiable developmental and epileptic encephalopathy (DEE). The birth incidence of *KCNT1*-related epilepsy was  $\leq 1.1205$  per 100,000 live births. The average annual incidence rates per 100,000 persons per year during the study period were 0.0431 (95% confidence interval [CI]: 0.0236–0.0723;  $n = 14$ ) in the overall population  $\leq 50$  years, 0.0568 (95% CI: 0.0209–0.1237;  $n = 6$ ) in the population  $< 18$  years, and 0.0365 (95% CI: 0.0157–0.0718;  $n = 8$ ) in the population  $\geq 18$  and  $\leq 50$  years. There were 3 families with at least 2 cases diagnosed with *KCNT1*-related epilepsies (on average 3.3 cases per family), indicating 10 cases in total within the 3 families. All *KCNT1* cases of ADSHE phenotype came from the 3 families. The higher incidence of older ages and ADSHE cases compared with previous *KCNT1* studies is likely due to the capture of prevalent and familial

**Abbreviations:** AGS, Aicardi-Goutières syndrome; *KCNT1*, Potassium sodium-activated channel subfamily T member 1.

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previously undiagnosed cases. Excluding these family cases, the average annual incidence was 0.0123 (95% CI: 0.0034–0.0315,  $n = 4$ ) per 100,000 persons per year in the population  $\leq 50$  years during 2012–2020.

**Conclusions:** AGS and *KCNT1*-related epilepsy are particularly rare diseases. The annual average incidence rate of AGS was 0.0539 per 100,000 persons per year in the population  $< 18$  years and birth incidence was  $< 0.7600$  per 100,000 live births during 2010–2020. The average annual incidence rate of *KCNT1*-related epilepsy was 0.0431 per 100,000 persons per year in the population  $\leq 50$  years and the birth incidence was  $\leq 1.1205$  per 100,000 live births during 2012–2020. Given similar healthcare systems and genetic pools, these findings may provide insight on the incidence of these rare diseases in the Nordics.

## 1. Introduction

Epilepsy is a common neurological disorder in childhood [1]. The incidence rates of epilepsy are higher in early childhood, low in the middle age and higher in old age [2,3]. Epilepsy is notably associated with cognitive comorbidities, and children with early-onset developmental and epileptic encephalopathies (DEEs) are especially more likely to have subnormal global cognitive function [4]. More specifically, there are DEEs with genetic causes being studied in recent years, including e. g., Ohtahara syndrome, West syndrome, Dravet syndrome, and Lennox-Gastaut syndrome. The most common DEE of infancy is West syndrome with a reported incidence of 25–42 per 100,000 per year [5].

Aicardi-Goutières syndrome (AGS) is a familial encephalopathy, and nearly 69% of AGS patients demonstrate obvious neurological dysfunctions before the age of 1 year [6]. The symptoms associated with AGS are heterogenous and may include developmental delays, fever, irritability, chilblains, hypotonia, dystonia, feeding difficulties, decline in head growth, and seizures [7]. The AGS disease exhibits high genetic heterogeneity with pathogenic variants in any of the following 7 genes: *TREX1* (AGS1), *RNASEH2A* (AGS2), *RNASEH2B* (AGS3), *RNASEH2C* (AGS4), *SAMHD1* (AGS5), *ADAR1* (AGS6), and *IFIH1* (AGS7) [8]. Most AGS genes are associated with an autosomal recessive inheritance pattern, whereas de novo or inherited single pathogenic alleles of *TREX1*, *IFIH1*, *ADAR1* result in symptoms [9]. AGS is diagnosed through typical clinical presentations, blood test, cerebrospinal fluid investigation, neuroimaging, and genetic testing [10].

Pathogenic variants in potassium sodium-activated channel subfamily T member 1 (*KCNT1*) have been associated with a wide spectrum of epilepsies. The most common phenotypes are epilepsy of infancy with migrating focal seizure (EIMFS) with onset before 6 months of age [11], other DEEs (non-EIMFS) with onset before 12 months of age, and familial autosomal dominant or sporadic sleep-related hypermotor epilepsy (ADSHE) with onset after 12 months of age [12–14]. The diagnosis of *KCNT1*-related epilepsy is established based on the clinical symptoms and the identification of a heterozygous pathogenic variant.

Due to the rarity of these diseases, the epidemiology of AGS and *KCNT1*-related epilepsy remains unclear. Previous epidemiological studies of AGS were largely case reports and descriptive in nature [6,10,15,16], and similarly only a limited number of *KCNT1*-related epilepsy cases have been reported in the literature [11,17,18]. Accordingly, the incidence for these diseases remains unknown. AGS and *KCNT1*-related epilepsy are 2 distinct conditions, however both are rare genetic conditions with limited existing epidemiological understanding, thus were studied together in this paper due to a similar data collection method. The present study aims to estimate the incidence of AGS and *KCNT1*-related epilepsy in the Danish population and to characterize the patients diagnosed with AGS and *KCNT1*-related epilepsy.

## 2. Material and methods

### 2.1. Study design

This is a retrospective, non-interventional, population-based study using aggregate data extracted from the Danish population register and hospital-based patient-level data in Denmark to estimate the incidence

of AGS and *KCNT1*-related epilepsies. The cases were identified via in-house genetic databases stored at 3 participating study sites in Denmark: the Department of Clinical Genetics at the University Hospital Copenhagen and the Centre for Rare Diseases at the Aarhus University Hospital for the cases of AGS, and the Danish Epilepsy Centre (Filadelfia) for *KCNT1*. In total, there are five clinical genetics departments and two rare disease clinics located in Denmark, including the AGS sites participating in this study. All clinics were consulted to identify any additional cases of *KCNT1*-related epilepsies that had not been referred to Filadelfia.

Data extracted from the Danish population register were age and population size (FOLK1A; StatBank Denmark), and the number of live births (FODDAG; StatBank Denmark) during the study period. Individual-level data collected from the participating study sites for AGS and *KCNT1*-related epilepsy patients were diagnosis, year and month of diagnosis, sex, *KCNT1* phenotype, family ID of *KCNT1* cases, and AGS genetic variants (Supplementary Tables 1–3).

### 2.2. Study period

The study period for incidence of AGS was January 1, 2010 to December 31, 2020, which included the period 2010–2015 when 2 of the genes (*TREX1* and *RNASEH2B*) were screened by Sanger sequencing and the period 2016–2020 when whole exome sequencing (WES) was used for all known AGS genes. The study period for the analysis of incidence of *KCNT1*-related epilepsy began in 2012, when the *KCNT1* gene was first reported, and lasted until 31 December 2020, and *KCNT1* was tested by gene panel or WES during this period.

### 2.3. Population at risk

The population at risk, or source population, in this study was defined as the number of persons registered and living in Denmark during the selected study periods. Population at risk was defined as the population  $< 18$  for AGS and  $\leq 50$  years for *KCNT1*. The age limits for population at risk for *KCNT1*-related epilepsy were empirical and based on the age at genetic confirmation of the *KCNT1*-related epilepsy cases. In addition, all live births were used to define population at risk for calculating birth incidence.

### 2.4. Patient population

Inclusion criteria for the AGS or *KCNT1*-related epilepsy patient population were the availability of information on the year and month of birth, confirmed diagnosis of AGS or *KCNT1*-related epilepsy during the respective study periods, available information on year and month of diagnosis, and residency in Denmark at the time of diagnosis. Patients not meeting all the inclusion criteria were ineligible for study inclusion.

### 2.5. Statistical methods

Patient characteristics of included AGS and *KCNT1*-related epilepsy cases were described separately.

Incidence was calculated in 2 ways in the study. Average annual incidence rates were calculated for AGS and *KCNT1*-related epilepsy.

The respective number of identified cases of the patient population was used as the numerator. The denominator was the sum of individuals in the population at risk at the beginning of each year during the study period. Average annual incidence rates were also stratified by age at diagnosis, i.e., <12 months and  $\geq 12$  months and < 18 years for AGS; <18 years and  $\geq 18$  and  $\leq 50$  years for *KCNT1*-related epilepsy. Additionally, birth incidence was derived by the number of cases divided by the total number of live births during the study period. The 95% confidence interval was derived based on exact Poisson confidence limits.

Due to Danish rules of reporting small numbers, the exact patient counts <5 could not be reported. Other values were 'masked' if they may disclose the low patient counts <5.

### 3. Results

#### 3.1. Patient characteristics of Aicardi-Goutières syndrome

A total of 7 AGS patients were identified during 2010–2020 in the study, and the mean age at diagnosis was 19.4 months (median 14 months). Table 1 describes the patient characteristics for AGS. The number of AGS cases were < 5 either in age group of <12 months at diagnosis or  $\geq 12$  months and < 18 years at diagnosis, with the 5th and 95th percentiles being 1 month and 80 months, respectively. Both male and female counts were fewer than 5 cases each. There were only 2 genes reported with confirmed pathogenic variants: *TREX1* and *RNA-SEH2B*. Most pathogenic variants ( $n \geq 5$ ) were in *RNA-SEH2B* with the remaining in *TREX1*.

#### 3.2. Incidence rates of Aicardi-Goutières syndrome

Based on the number of cases and the average population in all regions of Denmark during 2010–2020, the average annual incidence rate was calculated as 0.0539 (95% CI: 0.0217–0.1111) per 100,000 persons per year in the population < 18 years ( $n = 7$ ). For the population < 12 months, the average annual incidence rate was <0.7538 per 100,000 persons per year ( $n < 5$ ), and the average annual incidence rate in the

**Table 1**  
Patient characteristics for AGS from 2010 to 2020 in Denmark.

Variable	Characteristics Statistics	N = 7
Age at diagnosis (months)*	N	7
	Mean	19.4
	SD	27.4
	5th percentile	1
	Median	14
	95th percentile	80
Age at diagnosis - n(%)	<12 months	<5
	$\geq 12$ months and < 18 years	<5
Year of diagnosis - n(%)	2010–2015	$\geq 5$
	2016–2020	<5
Sex - n(%)	Male	<5
	Female	<5
Genes with pathogenic variants- n (%)**	<i>TREX1</i>	<5
	<i>RNA-SEH2A</i>	0 (0.0%)
	<i>RNA-SEH2B</i>	$\geq 5$
	<i>RNA-SEH2C</i>	0 (0.0%)
	<i>SAMHD1</i>	0 (0.0%)
	<i>ADAR1</i>	0 (0.0%)
	<i>IFIH1</i>	0 (0.0%)
	Missing	0 (0.0%)

AGS: Aicardi-Goutières syndrome; SD: Standard Deviation.

Data sources: In-house databases at the Department of Clinical Genetics in Copenhagen and Centre for Rare Diseases at Aarhus University Hospital.

\* Age at diagnosis was calculated by month and year of diagnosis and month and year of birth.

\*\* Only patients with bi-allelic (or monoallelic in case of dominant inheritance) class 4 and 5 variants in the *ADAR1*, *RNA-SEH2A*, *RNA-SEH2B*, *RNA-SEH2C*, *SAMHD1*, *TREX1* and *IFIH1* genes associated with AGS were included.

population  $\geq 12$  months and < 18 years was <0.0406 per 100,000 persons per year ( $n < 5$ ) (Supplementary Table 4).

Regarding birth incidence, when only considering the AGS cases diagnosed before the age of 12 months using the number of live births in Denmark as the denominator, the incidence proportion was <0.7600 per 100,000 live births (based on  $n < 5$  cases). Assuming all cases ( $n = 7$ ) were born during the study period and regardless of age at diagnosis, the incidence of AGS would be 1.064 per 100,000 live births (Supplementary Table 5).

#### 3.3. Patient characteristics of *KCNT1*-related epilepsy

A total of 14 *KCNT1*-related epilepsy cases were identified during the study period. The mean age of diagnosis was 20.6 years (median 19 years). A total of 5 patients were genetically confirmed in 2016; the exact number of diagnosed patient counts were masked for 2 years, 2013 and 2015. The number of female and male cases of *KCNT1*-related epilepsy were 9 (64.3%) and 5 (35.7%) respectively. There were 8 (57.1%) *KCNT1*-related epilepsy cases, who were  $\geq 18$  years at diagnosis, and only 6 (42.9%) were < 18 years at diagnosis. ADSHE was the most common of the 3 phenotypes that were reported ( $n = 10$ , 71.4%). The remaining 4 cases were either EIMFS or DEE phenotypes. There were 3 families with at least 2 cases diagnosed with *KCNT1*-related epilepsies. There were 3.3 cases of *KCNT1* per family on an average, indicating a total of 10 cases in the 3 families. The patient characteristics are presented in Table 2.

**Table 2**  
Patient characteristics for *KCNT1*-related epilepsy from 2012 to 2020 in Denmark.

Variable	Characteristics Statistics	N = 14
Age at diagnosis (years)*	N	14
	Mean	20.6
	SD	12.2
	5th percentile	2
	Median	19
	95th percentile	47
Age group at diagnosis - n(%)	<18 years	6 (42.9%)
	$\geq 18$ years	8 (57.1%)
Year of diagnosis - n(%)	2012	0 (0.0%)
	2013	Masked <sup>‡</sup>
	2014	0 (0.0%)
	2015	Masked <sup>‡</sup>
	2016	5 (35.7%)
	2017–2020	0 (0.0%)
Sex - n(%)	Male	5 (35.7%)
	Female	9 (64.3%)
Phenotype - n(%)	EIMFS	<5
	ADSHE	10 (71.4%)
	DEE	<5
	Missing	0 (0.0%)
Families recorded**	N	3
Number of cases per family	Mean	3.3
	SD	1.5

Abbreviations: ADSHE: Familial Autosomal Dominant or Sporadic Sleep-related Hypermotor Epilepsy; DEE: Developmental and Epileptic Encephalopathy; EIMFS: Epilepsy of Infancy with Migrating Focal Seizure; *KCNT1*: Potassium Sodium-Activated Channel Subfamily T Member 1; SD: Standard Deviation. Only patients with a clear-cut pathogenic variant were included. Unaffected carriers were excluded from the analyses.

Data sources: In-house database at the Danish Epilepsy Centre (Filadelfia).

\* Age at diagnosis was calculated by month and year of diagnosis and month and year of birth.

\*\* The number of families recorded included families with 2 or more *KCNT1* cases.

<sup>‡</sup> Presenting the range of the low patient count may disclose the exact number and violate the small number rule, and therefore is not specified.

### 3.4. Incidence rate of *KCNT1*-related epilepsy

The average annual incidence rates per 100,000 persons per year during the study period were 0.0431 (95% CI: 0.0236–0.0723;  $n = 14$ ) in the overall population  $\leq 50$  years, 0.0568 (95% CI: 0.0209–0.1237;  $n = 6$ ) in the population  $< 18$  years, and 0.0365 (95% CI: 0.0157–0.0718;  $n = 8$ ) in the population  $\geq 18$  and  $\leq 50$  years.

Since all 10 ADSHE cases were reported in 3 families, it was likely that the cases were prevalent before the study period with delayed genetic confirmation after the *KCNT1* gene was discovered. Thus, when the 10 ADSHE cases (assumed prevalent) were excluded from the incidence calculation, the average annual incidence rate of the EIMFS and other DEEs was 0.0123 (95% CI: 0.0034–0.0315,  $n = 4$ ) per 100,000 persons per year in the population  $\leq 50$  years during 2012–2020 (Supplementary Table 6).

Regarding birth incidence, only considering the cases born during the study period 2012–2020 ( $n \leq 6$ ), the birth incidence was  $\leq 1.1205$  per 100,000 live births (Supplementary Table 5).

## 4. Discussion

The present study ascertained the incidence of AGS and *KCNT1*-related epilepsy in the Danish population and characterized patients with clinically and genetically confirmed cases. Knowledge on the incidence of the diseases is necessary and valuable for understanding the relevance of the diseases in a real-world setting.

### 4.1. Identification of cases in the Danish healthcare system

The Danish healthcare system provides free healthcare to all residents in Denmark through a tax-funded model. The universal coverage of the residents provides the opportunity to make credible incidence estimates of the disease since no Danish residents are excluded from the system. General practitioners and other specialists are able to refer patients to specialized neurology and rare disease departments for diagnosis and treatment [19,20], and subsequently to genetic screening [21]. In this study, the patients were identified through the contacts of epilepsy centers and key neurology departments for *KCNT1*-related epilepsy, and through clinical genetic departments and rare disease clinics for AGS. Through comprehensive liaisons by the investigators, all patients who were sequenced and diagnosed with AGS and *KCNT1*-related epilepsy by the healthcare system during the study periods were likely included in the study. It is possible that the most severe cases were not captured if not diagnosed in the case of early mortality. In addition, very mild cases might be underdiagnosed due to lack of referral for genetic testing, although this may be more likely for *KCNT1*-related epilepsy given its clinical presentation may be less obvious. However, genetic screening for patients with epilepsy and neurodevelopmental disorders has been available throughout the study period in Denmark. The patients who are treated by adult or pediatric neurologists are likely included in the study as it is common practice to have centralized follow-up of the patients in Denmark. With comprehensive coverage of the healthcare system in Denmark, the cases identified in this study are likely representative of the cases that need specialist's healthcare and of clinical relevance.

### 4.2. Availability of genetic tests over time

There were more genes discovered and linked with AGS over the study period, which may bias the incidence estimate. Sanger sequencing for *RNASEH2B* and *TREX1* was used in 2010–2015, while WES was used for diagnosing AGS starting in 2015 and since 2016 has been used exclusively. The fact that only the 2 genes were reported for AGS may be partially a result of the different availability of tests for the 7 AGS disease-causing genes. Since no other genes than *RNASEH2B* and *TREX1* were reported for the cases during 2016–2020 when WES was used, it

could also be a result of the low frequencies of pathogenic variants of the other 5 AGS genes in the Danish population. Further, it was expected that an increase in the number of cases would be observed over time given the increasing availability of genetic testing for AGS and that knowledge of the genetic etiology of the diseases has been fast evolving in general; however, more cases were diagnosed for both diseases in the earlier part of the study period (before 2016). For *KCNT1*, this could be explained by the diagnosis of familial cases in the earlier years of the study period that were likely prevalent, not incident, cases. Both diseases had some years without any cases, which confirmed the rarity of the diseases from our study.

### 4.3. Information bias of age at diagnosis

There is a limitation that the genetic confirmation of the diseases may lead to the information bias for age at diagnosis. However, time to diagnosis is generally not expected to be long in Denmark, as the results of AGS study showed: age at diagnosis was low and around half of the patients were diagnosed in the first year of life. However, delayed diagnosis is possible, which would bias the overall incidence estimates downwards since incident cases later in the study period may be diagnosed after the end of study period due to such delay or misclassify the cases as late onset during the study period. However, the delay due to referrals and genetic sequencing on average in Denmark is expected to be minimal. Since pathogenic variants in *TREX1* have been reported to result in higher fatality rates than in *RNASEH2B* [22], it is possible that *RNASEH2B* cases may be delayed more in the process of referral and diagnosis; however, this was not observed in this study and the mean and median age at diagnosis were both lower among the patients with *RNASEH2B* than patient(s) with *TREX1* (low patient count not presented in tables). Misclassification of age at diagnosis is possible, especially for the cases with age at diagnosis around 12 months. The birth incidence of AGS was  $< 0.7600$  per 100,000 live births based on fewer than 5 cases diagnosed in the first 12 months of life. Assuming there were delays in the diagnosis, or misclassification of the age group at diagnosis, the birth incidence would be 1.064 per 100,000 live births ( $n = 7$ ).

The limitation of delayed genetic confirmation appears to be more prominent for *KCNT1*-related epilepsies. A recent publication by Bonardi et al. [14], summarizing 248 cases of *KCNT1*-related epilepsy, reported lower ages of seizure onset than the ages at diagnosis of *KCNT1* patients reported in our study. The calculated incidence is therefore likely an overestimate that includes prevalent cases which were incident before the discovery of the *KCNT1* gene but only genetically confirmed during the study period, as well as familial ADSHE cases that were diagnosed after one member (i.e., the proband) was diagnosed (Section 4.4). Notably, the phenotypes included in the Bonardi et al. study [14] largely consisted of EIMFS, which tend to be sporadic and not familial, while in our study ADSHE was the most common phenotype. Compared with EIMFS, ADSHE cases tend to be less severe in the prognosis and are associated with longer survival. Since there may be a stronger tradition to perform genetic testing for pediatric epileptic patients, this also explains the age discrepancy between the very predominantly young pediatric cases in Bonardi et al. [14] in contrast to the adult and older pediatric cases in our study. The average annual incidence estimated in the population aged 18–50 years is likely biased as it included prevalent cases; in addition, the upper age limit of the population at risk was set at 50 years of age empirically based on the data since they fulfilled the common definition of incident cases as newly diagnosed cases despite that the diagnoses were delayed due to unavailability of genetic testing before 2012. However, individuals would likely be diagnosed earlier in life if genetic screening of *KCNT1* was available, thus the population at risk of being diagnosed with *KCNT1*-related epilepsy should be confined to a lower age limit for future studies given the longer availability of genetic testing for *KCNT1*.

#### 4.4. Family cases of *KCNT1*-related epilepsy

There were 10 cases of *KCNT1*-related epilepsy from 3 families that had 2 or more cases confirmed, all of whom were diagnosed with ADSHE. ADSHE is sometimes referred to as a late onset syndrome [14] and is more likely to be inherited than EIMFS and other DEEs. While these 10 cases represented the majority of *KCNT1*-related epilepsy cases identified during the study time period, they were likely prevalent cases experiencing symptoms prior to 2012 but only able to receive a diagnosis after genetic screening for *KCNT1* became available in 2012. Additionally, it is possible that the diagnosis of a single family member led to the subsequent screening and diagnosis of additional family members. Therefore, we also estimated the average annual incidence rate and excluding the 3 families with ADSHE, which lowered the incidence estimates.

#### 4.5. Other studies of AGS and *KCNT1*-related epilepsy

While there are few published estimates of AGS, existing literature suggests that the incidence is approximately 1 per 100,000 live births. The incidence in the UK was estimated over a 3-year period and briefly summarized as 1 case per 110,000 live births [16]. A study using data from publications in the Human Genetic Mutation Database and from predictions in Genome Aggregation Database was used to determine the birth incidence of several leukodystrophies. Using autosomal recessive variants in the healthy population, this study projected the birth incidence of AGS to be 1 per 73,494 live births [23]. A study in Scotland reported 1 case of *KCNT1*-related epilepsy over a 3-year period with a corresponding birth incidence of 1 per 169,470 live births [24]. Our study also estimated the incidence approximately <1 in 100,000 live births for the 2 diseases. The publication by Bonardi et al. [14] reported 248 *KCNT1*-related epilepsy cases in 10 countries, the largest number of cases of the disease to date; however, the incidence could not be estimated by the study as the source population was not defined. The results of these studies confirm the rarity of AGS and *KCNT1*-related epilepsy.

These studies also suggest the importance of global cooperation on studies of rare diseases. Transparency in reporting and thorough discussion, including the healthcare settings, data collection methods, and limitations, are important in interpreting the data and synthesizing evidence to better understand the global epidemiology of AGS and *KCNT1*-related epilepsy.

## 5. Conclusions

AGS and *KCNT1*-related epilepsy are particularly rare diseases. A total of 7 AGS cases and 14 *KCNT1*-related epilepsy cases were identified that were genetically and clinically diagnosed during the study period. For AGS, the average annual incidence rate was estimated to be 0.0539 per 100,000 persons per year in the population < 18 years and birth incidence was <0.7600 per 100,000 live births during 2010–2020. The average annual incidence rate of *KCNT1*-related epilepsy was 0.0431 per 100,000 persons per year in the population ≤ 50 years, and birth incidence was ≤1.1205 per 100,000 live births during 2012–2020. As the complexity in the study suggested, the availability of sequencing methods and isolated populations may limit extrapolating the incidence estimates to other settings; however, given comparable healthcare systems and similar genetic pools, results from this study may provide some insight on the incidence of these rare diseases in the Nordics.

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## Ethical approval statement

This study was approved by the Danish Health Authorities Region Hovedstaden (Center for Regional Udvikling). No formal ethics approval was required for this study. According to Danish law (§ 46 stk. 2 i LBK nr 903–26/08/2019) patient consent was not required for this type of study and data collection.

## Declaration of Competing Interest

JS, VN, TCF, and VK are employees of Biogen, the sponsor of this study. IQVIA performs commissioned pharmacoepidemiological studies, including this one, for multiple pharmaceutical companies. RT and LZ are employees of IQVIA. Other authors do not have conflicts of interest to declare.

## Data availability

Data are reported in the main text or supplementary material of the manuscript. More data may be requested upon queries if patient protection rules allow.

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## Appendix A. Supplementary data

Supplementary data to this article can be found online at <https://doi.org/10.1016/j.ymgmr.2022.100924>.

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