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LETTER

The prevalence of genetically diagnosable epilepsies in young adulthood: How many should we be looking for?

To the Editors:

We were encouraged to read about the successes of genetic testing in adults at the Danish Epilepsy Center.¹ Together with a previous adult study,² the yield of opportunistic testing in selected adults is about 22% and molecular diagnoses sometimes improved treatment.

However, the number of adults with epilepsies attributable to known genetic causes that could currently be diagnosed remains unknown. To measure the true prevalence directly would require comprehensive ascertainment in a population-based study, such as that conducted in children by Symonds et al.³ This would be challenging in adults. Clinicians trying to gauge their diagnostic gap to justify resources for testing and to identify adults who might benefit from genetically stratified interventions need an estimate of the prevalence. Additionally, many genetic causes have only recently been elucidated, predominantly in children. Identifying adults with these disorders is necessary for studies of their clinical trajectory to improve prognostic counseling and of genetically stratified treatment responses.

The data of Johannesen et al¹ can be used to estimate the prevalence of molecularly diagnosable genetic epilepsies among young adults because it is reasonable to use the population of Denmark as a denominator. By 2019, a molecular diagnosis was obtained in 24 from a cohort of 910 000 adults aged 18-30 years in 2015,⁴ of whom eight were for *SCN1A*-related Dravet syndrome (precise years of diagnoses were provided by K. Johannesen). This equates to 2.6 positive genetic epilepsy diagnoses per 100 000 young adults, of whom one-third, 0.9, were *SCN1A*-associated Dravet syndrome. Assuming the lifetime risk of *SCN1A*-associated Dravet syndrome in Denmark to be 6.49/100 000 as in Scotland³ and its childhood mortality to be 15%,⁵ one would expect to find 50 young adults with *SCN1A*-associated Dravet syndrome in Denmark. Thus, 16% of young adults expected to have *SCN1A*-related Dravet syndrome were diagnosed in this study (the remainder will have been diagnosed in childhood or elsewhere, or are as yet unrecognized). Using this diagnosis rate as a benchmark, we estimate a Danish prevalence of epilepsies diagnosable by these gene panels of 16/100 000 in young adults. This probably underestimates the true prevalence of potentially diagnosable cases, because testing did not include

copy number or chromosomal abnormalities and older gene panels may miss recently established causes. Additionally, although the yield of testing is suspected to be greatest in people with intellectual disability, testing of adults with epilepsy and normal intellect may yield further diagnoses (for example, nonencephalopathic genetic epilepsy with febrile seizures plus and *DEPDC5*-related epilepsies were conspicuously absent in this study).

We have previously estimated that 10-50/100 000 people will develop a genetically diagnosable epilepsy that requires neurological care in early adulthood⁶ based on literature-informed extrapolation of population-based pediatric data.³ This new estimate, from adult data, concurs with our previous estimate looking forward from a pediatric perspective. Both emphasize that neurologists should expect to find molecular diagnoses among young adults with epilepsy, who may benefit increasingly from genetically stratified care.

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CONFLICT OF INTEREST

R.H.T. has received honoraria and meeting support from Arvelle, Bial, Eisai, GW Pharma, LivaNova, Novartis, Sanofi, UCB Pharma, and Zogenix. D.L.-S. has no conflicts of interest. We confirm that we have read the Journal's position on issues involved in ethical publication and affirm that this report is consistent with those guidelines.

David Lewis-Smith¹ 
Rhys H. Thomas² 

¹*Translational and Clinical Research Institute, Newcastle University, Newcastle Upon Tyne, UK*
Email: david.lewis-smith@newcastle.ac.uk

²*Department of Clinical Neurosciences, Newcastle Upon Tyne Hospitals National Health Service Foundation Trust, Newcastle Upon Tyne, UK*

Correspondence

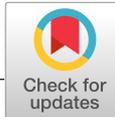
David Lewis-Smith, Translational and Clinical Research
Institute, Medical School, Newcastle University, Newcastle
Upon Tyne, NE2 4HH, UK.
Email: david.lewis-smith@newcastle.ac.uk

ORCID

David Lewis-Smith  <https://orcid.org/0000-0002-1735-8178>
Rhys H. Thomas  <https://orcid.org/0000-0003-2062-8623>

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**LETTER****Genetic testing in adult epilepsy patients: A call to action for clinicians**

To the Editors:

We thank Lewis-Smith and Thomas for their interest in our paper and for their interesting comments on the prevalence of molecularly diagnosable genetic epilepsies in the Danish population of young adults with *SCN1A*-associated Dravet syndrome (*SCN1A*-DS).

In their letter, they calculate the actual prevalence in adulthood of *SCN1A*-DS in Denmark based on the lifetime risk ascertained in the prospective Scottish study by Symonds et al,¹ concluding that there currently should be 50 young adult patients (18-30 years old) affected by *SCN1A*-DS. In our study, we diagnosed eight adult patients with *SCN1A*-DS, corresponding to 16% of their estimate of 50 patients, and thus Lewis-Smith and Thomas speculate that the remaining patients might have been diagnosed in childhood or elsewhere, or have not been recognized. Following their reasoning, we investigated our *SCN1A* database to find out how many *SCN1A*-DS patients we have collected at present and found five additional young patients (same age range, 18-30 years old), who were diagnosed with *SCN1A*-DS in childhood, increasing the number from eight to 13 adult patients in our cohort or 26% of the estimated 50 patients.

In our previous publication,² we reported 17 patients born with *SCN1A*-DS in the years 2004-2009, resulting in a prevalence of 1:22 000 births with *SCN1A*-DS per year. We have reviewed the *SCN1A*-DS birth rate between 2004 and 2009 and found three additional patients who were diagnosed after the initial study was completed. Therefore, the updated birth rate between 2004 and 2009 was 20 patients with *SCN1A*-DS, equaling an incidence of 1:19 400 *SCN1A*-DS patients born per year. This number is still lower than that reported in the Scottish study, which is 1:15 400.¹ This discrepancy might partially depend on Symonds et al's paper investigating only 3 consecutive years (in our studies both analyzed 6-year intervals). This short time span might present the risk of 1 (or 2) year(s) with a birth rate well above or below the average birth rate, which might significantly affect the calculation of the cumulative incidence rate in the 3-year interval. This hypothesis is supported by the observation in Denmark of a relatively

high variability of the *SCN1A*-DS birth rate per year, ranging from zero (in 2011) to six (in 2012) and averaging three per year (unpublished data).

These observations show once again how the ascertainment of the prevalence of genetic epilepsies in adulthood can be challenging, and they indicate the need of well-designed, possibly population-based studies.

Nevertheless, we believe that our findings, even though limited to the population of patients with epilepsy and intellectual disability, should alert the physicians treating these patients of the opportunity to offer them genetic testing not only for diagnostic but possibly also for treatment purposes.

CONFLICT OF INTEREST

None of the authors has any conflict of interest to disclose. We confirm that we have read the Journal's position on issues involved in ethical publication and affirm that this report is consistent with those guidelines.

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Guido Rubboli^{1,2}

Rikke S. Møller^{1,3}

Katrine M. Johannesen^{1,3}

¹Department of Epilepsy Genetics and Personalized Treatment, Danish Epilepsy Center, Dianalund, Denmark

²Faculty of Health, University of Copenhagen, Copenhagen, Denmark

³Institute for Regional Health Research, University of Southern Denmark, Odense, Denmark

Correspondence

Katrine M. Johannesen, Department of Epilepsy Genetics
and Personalized Treatment, Danish Epilepsy Center,
Kolonivej 1, 4293 Dianalund, Denmark.
Email: kamaa@filadelfia.dk

ORCID

Guido Rubboli  <https://orcid.org/0000-0002-5309-2514>
Rikke S. Møller  <https://orcid.org/0000-0002-9664-1448>
Katrine M. Johannesen  <https://orcid.org/0000-0002-7356-3109>