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THE MINIMUM PREVALENCE OF CADASIL IN NORTHEAST ENGLAND

Cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy (CADASIL) is the most common form of hereditary small vessel brain disease, and is caused by mutations in *NOTCH3*. The disorder is often overlooked and misdiagnosed, and the population prevalences are generally not known. Over 100 families exist in France, with similar numbers in the United Kingdom,¹ and >200 in Germany.² In Finland, the reported prevalence is 2–4 per 100,000,³ and in west Scotland, 1.98 per 100,000 have a definite diagnosis, and 4.14 per 100,000 are predicted mutation carriers.⁴ However, both of these study populations include relative genetic isolates. We carried out a study to determine the prevalence of CADASIL in an outbred Western European population in the northeast of England.

Methods. Probands were identified within the north-east government office region of England (figure e-1 on the *Neurology*[®] Web site at www.neurology.org) between 1999 and 2009 using modified published criteria through clinical referral to the National Health Service neurology and genetics departments, and a systematic search of clinical databases (see table e-1 for details), followed by targeted sequence analysis of *NOTCH3* known to capture >95% of UK cases (exons 3, 4, 5, 6, 8, 11, 18, and 22).⁵ Affected relatives were assessed using the same criteria. Minimum prevalence rates were estimated for the midyear period of 2009 when the total population was 2,584,300. Possible affected subjects were not included if >64 years for men and >60 years for women due to the high prevalence of confounding comorbidity in this age group, allowing the calculation of prevalence rates for 1,601,600 subjects defined in census data as “of working age.”

Results. Prevalence. Eighteen families contained 34 definite cases, 12 probable cases, and 60 possible cases (figure 1, which does not include the singleton cases). This gave a minimum prevalence of 1.32 (95% confidence interval [CI] 0.87–1.76) for definite cases, 0.46 (95% CI 0.20–0.73) for probable cases, and 2.32 (95% CI 1.73–2.91) per 100,000 for

possible cases across the whole of population. The combined group had a prevalence of 4.10/100,000 (95% CI 3.32–4.88). For subjects of working age, the prevalence rates were 1.91/100,000 (95% CI 1.25–2.62) for the definite cases, 0.75/100,000 (95% CI 0.33–1.17) for the probable cases, and 3.75/100,000 (95% CI 2.80–4.69) for the possible cases, and 6.43/100,000 (95% CI 5.19–7.65) for the combined group. The total number of at-risk first-degree relatives without symptoms was 6.11/100,000 (95% CI 5.16–7.07). The prevalence of CADASIL in different adult age groups is shown in table e-2 and clinical features summarized in table e-3. There was no significant difference in the frequency or age at onset, or the major clinical features of CADASIL between probands and other family members.

NOTCH3 mutations. Most *NOTCH3* mutations were in exon 4 (table e-4), and have been reported before. Two were novel (p.Tyr189Cys and p.Cys245Ser). There were no clear genotype–phenotype relationships, as noted in previous studies (table e-5).⁶

Discussion. The clinical phenotype and mutational spectrum of CADASIL in our cohort was typical of those described in other studies. The minimum prevalence of definite CADASIL cases and at-risk individuals in the northeast of England is similar to the prevalence in the west of Scotland ($p = 0.68$).⁴ Both the Scottish study and ours were based on the ascertainment of an affected individual through the National Health Service and used similar diagnostic criteria. Although the prevalence estimate could increase with more comprehensive mutation analysis and clinical follow-up, this is unlikely to have a major impact, since >90% of affected individuals have *NOTCH3* mutations in the exons sequenced.⁵ We conclude that 1 in 25–50,000 is a reliable estimate of the minimum prevalence of this disorder in the general population.

It is intriguing that there was a higher prevalence of definite CADASIL in the 45- to 50-year age group when compared to the whole adult age range (table e-2). This was mirrored by fewer probable and possible cases of the disease, and thus is likely to reflect the conversion from one group to another as the patients acquire additional features throughout life. In keep-

Supplemental data at
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Supplemental Data

Figure 1 Pedigree charts of affected families

ing with this, there was no significant difference between the total number of definite, probable, and possible cases in each age group.

By studying the extended family, our study has shown that >1 in 13,500 individuals either have or are at risk of developing CADASIL in the general population. Identifying and treating modifiable risk factors in this group may delay the age at presentation with the first stroke.⁷ This adds emphasis to the importance of early genetic counseling for patients and at-risk family members, in order to reduce the impact of the disorder on future generations.

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Author contributions: S.K.N. and G.G. carried out the clinical assessments. P.F.C. devised and supervised the study, and wrote the first draft manuscript with S.K.N., R.N.K. and G.F. critically revised the manuscript.

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Editor's Note to Authors and Readers: Levels of Evidence coming to *Neurology*®

Effective January 15, 2009, authors submitting Articles or Clinical/Scientific Notes to *Neurology*® that report on clinical therapeutic studies must state the study type, the primary research question(s), and the classification of level of evidence assigned to each question based on the classification scheme requirements shown below (left). While the authors will initially assign a level of evidence, the final level will be adjudicated by an independent team prior to publication. Ultimately, these levels can be translated into classes of recommendations for clinical care, as shown below (right). For more information, please access the articles and the editorial on the use of classification of levels of evidence published in *Neurology*.^{1–3}

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Classification scheme requirements for therapeutic questions

Class I. A randomized, controlled clinical trial of the intervention of interest with masked or objective outcome assessment, in a representative population. Relevant baseline characteristics are presented and substantially equivalent among treatment groups or there is appropriate statistical adjustment for differences.

Class II. A randomized, controlled clinical trial of the intervention of interest in a representative population with masked or objective outcome assessment that lacks one criterion a-e in Class I or a prospective matched cohort study with masked or objective outcome assessment in a representative population that meets b-e in Class I. Relevant baseline characteristics are presented and substantially equivalent among treatment groups or there is appropriate statistical adjustment for differences.

Class III. All other controlled trials (including well-defined natural history controls or patients serving as their own controls) in a representative population where outcome is independently assessed or independently derived by objective outcome measurements.

Class IV. Studies not meeting Class I, II, or III criteria including consensus or expert opinion.

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A = Established as effective, ineffective, or harmful (or established as useful/predictive or not useful/predictive) for the given condition in the specific population. (Level A rating requires at least two consistent Class I studies.)

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C = Possibly effective, ineffective, or harmful (or possibly useful/predictive or not useful/predictive) for the given condition in the specific population. (Level C rating requires at least one Class II study or two consistent Class III studies.)

U = Data inadequate or conflicting; given current knowledge, treatment (test, predictor) is unproven.