SHORT REPORT

The prevalence of cerebral autosomal dominant arteriopathy with subcortical infarcts and leucoencephalopathy (CADASIL) in the west of Scotland

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Background: Cerebral autosomal dominant arteriopathy with subcortical infarcts and leucoencephalopathy (CADASIL) is caused by mutations of the Notch3 gene on 19p13. Varying phenotypic expression leads to under recognition and misdiagnosis. Prevalence therefore remains uncertain. We sought to estimate the prevalence of CADASIL in the west of Scotland.

Methods: A register for CADASIL was established at a regional neurosciences centre in 2002. All patients with genetically (exons 3, 4, 5, and 6) or histologically confirmed CADASIL residing in two defined administrative health areas were identified. Pedigree members at varying risk of carrying the mutation were also identified and the number of probable Notch3 mutation carriers in the defined population was predicted. Prevalence was calculated for definite CADASIL cases, with and without probable carrier numbers, based upon adult population figures from the 2002 national census.

Results: Twenty two individuals from seven pedigrees with confirmed CADASIL and resident in the defined geographical area were identified, yielding a prevalence of 1.98 (95% confidence interval 1.24–3.00) per 100 000 adults. An additional 37 individuals were predicted to be carriers of the Notch3 mutation, yielding a probable mutation prevalence of 4.14 (3.04–5.53) per 100 000 adults.

Conclusions: The prevalence of genetically proven CADASIL was 1.98 per 100 000 adults in the defined population. This figure underestimates disease burden.

Cerebral autosomal dominant arteriopathy with subcortical infarcts and leucoencephalopathy (CADASIL) is caused by mutations of the Notch3 gene on chromosome 19p13.[1] The Notch3 gene contains 33 exons encoding a transmembrane receptor forming part of a highly conserved signalling pathway considered vital for maturation of certain vessels in the perinatal and early postnatal brain.[2] Characteristic clinical features include recurrent lacunar strokes, migraine with aura, psychiatric disturbances, and progressive cognitive decline.[3 4]

Most Notch3 mutations detected so far are missense mutations affecting exon 4, with the remainder distributed amongst other exons.[5] As screening all exons is time consuming, most centres test exons 4 and 3 initially and if negative proceed to screen other exons.

The prevalence and disease burden of CADASIL is yet undetermined. We sought to estimate the minimum prevalence of CADASIL in the west of Scotland.

MATERIALS AND METHODS

Formation of register

A national register of CADASIL for Scotland was established in 2002 in association with a neurovascular genetics clinic.

Patients (index cases and relatives) were referred to the service by neurologists, general practitioners, hospital physicians, and family members. Neurologists and stroke physicians in Scotland were informed of the typical features of CADASIL and the CADASIL register. In keeping with existing national guidelines on adult-onset genetic disorders, no attempt was made to directly contact pedigree members (affected or unaffected).

Clinical evaluation

Data were obtained by personal interview and review of hospital records, and verified by interview of family members.

The diagnosis of CADASIL was established by positive Notch3 mutation analysis (initially exons 3, 4, and 5, and later 6). Genomic DNA from CADASIL patients was amplified by polymerase chain reaction (PCR) using sets of oligonucleotide primers specific for Notch3 exons 3, 4, 5, and 6. The resulting amplicons were then sequenced in both directions by dye-labelled terminators on an ABI 3100 DNA sequencer (Applied Biosystems, CA, USA). Sequence was analysed using the ABI sequence editor package.

Individuals in the database were categorised as follows:

- Confirmed CADASIL—individuals with positive mutation analysis on screen of exons 3, 4, 5, or 6, or demonstration of granular osmiophilic material in the media of small arteries on electron microscopy of biopsy or postmortem material.
- 50% risk of CADASIL—first degree relatives (symptomatic and asymptomatic) of confirmed CADASIL cases in who genetic testing or biopsy had not been undertaken.
- 25% risk of CADASIL—second degree relatives (symptomatic and asymptomatic) of confirmed CADASIL cases in who genetic testing or biopsy had not been undertaken.
- 12.5% risk of CADASIL—third degree relatives (symptomatic and asymptomatic) of confirmed CADASIL cases in who genetic testing or biopsy had not been undertaken.
- Clinically possible CADASIL—patients and pedigrees personally reviewed at the neurogenetics service fulfilling all of the following criteria:

Abbreviations: CADASIL, cerebral autosomal dominant arteriopathy with subcortical infarcts and leucoencephalopathy; MRI, magnetic resonance imaging; PCR, polymerase chain reaction

- Clinical presentation with one or more syndromes consistent with CADASIL (recurrent lacunar stroke, dementia, or progressive pseudobulbar palsy).
- White matter abnormalities consistent with CADASIL on magnetic resonance imaging (MRI).
- Family history of typical syndromes in a pattern consistent with autosomal dominant inheritance.
- Negative genetic screening on exons 3 to 6 (with or without additional negative skin biopsy).

Population and geographical area

The population base was taken from two adjacent health board areas in the west of Scotland with the best coverage by neurological services: Greater Glasgow and Lanarkshire. Glasgow is Scotland's largest city, located towards the west of Scotland's central belt. Lanarkshire is a district situated south-east of Glasgow. The population is predominantly of Scottish and Irish origin with other smaller immigrant populations.

The 2002 mid-year population estimates of total residents (all ages) for Greater Glasgow and Lanarkshire health boards were 866 080 and 552 910, respectively. This gives a combined total population of 1 418 990 (676 343 male (47.66%). The adult (age 18 and above) populations were 682 006 and 427 475, respectively, giving a total of 1 109 481 (General Register Office for Scotland).[6]

Estimation of prevalence

Individuals from confirmed CADASIL pedigrees were identified and counted if alive and resident in the defined area in August 2003. The number of known mutation carriers and estimated mutation carriers (including untested individuals according to degree of risk, as above) was determined. Pedigree members probably resident in the defined area but whose exact residential details were not personally verified were also identified. Identical methods were applied to such individuals in estimating the number of mutation carriers.

The number of estimated mutation carriers in pedigrees with ''clinically possible'' CADASIL (according to above criteria) was calculated using the same principles.

95% confidence intervals for prevalence estimates were calculated from a Poisson distribution.

RESULTS

The number of individuals with confirmed CADASIL resident in the defined area was 22 (14 male, all adults, seven pedigrees, all confirmed by mutation analysis, all Scottish-Irish ancestry). Six pedigrees had exon 4 mutations (of three distinct genotypes) and one pedigree had an exon 5 mutation (Table 1).

The prevalence of confirmed CADASIL was therefore 1/50 430 adult residents or 1.98/100 000 (95% confidence interval 1.24–3.00) adult residents. Prevalence was non-significantly higher in Greater Glasgow (2.35 (1.34–3.81)/100 000) than in Lanarkshire (1.40 (0.52–3.06)/100 000).

Details of additional extrapolated mutation prevalences are given in Table 2.

Table 1 Notch3 mutations in study population

Mutation	Number of pedigrees	Number of confirmed affected cases
Exon 4: R141C	3	12
Exon 4: R169C	2	6
Exon 4: R133C	1	2
Exon 5: C245S	1	2

Thirty seven individuals from the seven mutation-positive pedigrees (50% of 60 at 50% risk (30), 25% of 24 at 25% risk (6), and 12.5% of 13 at 12.5% risk (1)) were also at risk of carrying a mutation. This gives an estimate of 59 Notch3 mutation carriers. The predicted prevalence of the Notch3 mutation carriers (symptomatic and asymptomatic) in the defined population was therefore 1/24 050 or 4.15 (3.04–5.53)/100 000.

If individuals probably resident in the defined area, but in whom residence details were unavailable, were included in the analysis, an additional 17 individuals were estimated to be Notch3 mutation carriers (50% of 6 at 50% risk, 25% of 43 at 25% risk, and 12.5% of 26 at 12.5% risk). This amounts to a total of 76 Notch3 mutation carriers giving a predicted prevalence of Notch3 mutation carriers (symptomatic and asymptomatic) of 1/18 670.9 or 5.35 (4.22–6.70)/100 000 residents in the defined population.

If only adults (18 years and above) were considered, the predicted prevalence of Notch3 mutation carriers was similar at 4.15 (3.04–5.53)/100 000 adults (definite residents) and 5.32 (4.05–6.86)/100 000 adults (including probable residents).

When nine additional pedigrees with clinically possible CADASIL definitely resident in the defined area were included in the analysis of definite residents, there were 16 additional affected individuals and 43 additional individuals at 50% risk of carrying the mutation. This yields a predicted prevalence estimate for inherited autosomal dominant small vessel disease (definite CADASIL and clinically possible CADASIL) of 1/14 781.1 people or 6.76 (5.48–8.26)/100 000 residents in Greater Glasgow and Lanarkshire. If probable residents from mutation-positive pedigrees were included, the predicted prevalence of inherited small vessel disease was estimated to be 1/ 12 557 or 7.96 (6.56–9.57)/100 000 residents.

DISCUSSION

The minimum prevalence of CADASIL in Greater Glasgow and Lanarkshire is 1.98/100 000 adult residents. The predicted prevalence of Notch3 mutation carriers (exons 3 to 6) in Greater Glasgow and Lanarkshire is 4.15/100 000 adult residents.

These prevalence figures are an underestimate for several reasons. CADASIL has been characterised only quite recently, is frequently misdiagnosed, and there is a bias towards recognition in larger pedigrees with typical features. The high local prevalence of conventional cerebrovascular disease and of multiple sclerosis in the west of Scotland also confounds individual diagnosis and family history. This suggests that a substantial number of symptomatic individuals and pedigrees will not have been referred to our service.

Molecular genetic screening at our centre is presently confined to exons 3, 4, 5, and 6. Although this screening strategy is in keeping with a study of the distribution of mutations in the United Kingdom, which suggested that screening of exons 3 to 6 would detect 90% of affected individuals,[7] there may be geographical variation in the frequency of individual mutations[8] and further molecular genetic characterisation of exon 3–6 negative pedigrees with clinically possible CADASIL is necessary.

Extrapolated mutation prevalence based upon pedigree data is prone to error—for example, affected individuals may die of unrelated illness without manifesting typical features. Estimates may include those too young to manifest symptoms, or older asymptomatic individuals in whom CADASIL is less likely than the 50% figure assumed. Locale specific factors, average family size, and immigration/emigration patterns may influence prevalence. As apparent by the presence of differing mutations in our pedigrees, there is

Table 2 Genetically confirmed Notch3 mutation-positive pedigrees

	Genetically confirmed and alive (n)	At 50% pedigree risk (n)	At 25% pedigree risk (n)	At 12.5% pedigree risk (n)
Definite residents	22	60	24	13
Probable residents		6	43	26

likely to be limited impact of a possible founder effect in the studied population.

Our prevalence estimate for the number of Notch3 mutation carriers (with CADASIL or at risk for developing CADASIL in the future) compares with the prevalence of motor neuron disease in the United Kingdom (7/100 000). In typical symptomatic disease duration of 20–25 years, patients may require considerable levels of care for perhaps 10–15 years.

It is anticipated that wider awareness of CADASIL will increase the number of patients being diagnosed with CADASIL and that this prevalence estimate will steadily increase with improved recognition and diagnosis.

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