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ARTICLE

Evidence for a common *Spinocerebellar ataxia type 7 (SCA7)* founder mutation in Scandinavia

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Spinocerebellar ataxia type 7 (SCA7) is a neuro-degenerative disorder characterised by progressive cerebellar ataxia and macular degeneration. SCA7 is one of the least common genetically verified autosomal dominant cerebellar ataxias (ADCAs) in the world (4.5 to 11.6%), but in Sweden and Finland SCA7 is the most commonly identified form of ADCA. In an inventory of hereditary ataxias in Scandinavia (Sweden, Norway, Denmark and Finland) we identified 15 SCA7 families, eight in Sweden and seven in Finland, while no cases of SCA7 could be found in Norway or Denmark. We examined whether the relatively high frequency of SCA7 families in Sweden and Finland was the result of a common founder effect. Only two out of 15 families could be connected genealogically. However, an extensive haplotype analysis over a 10.2 cM region surrounding the *SCA7* gene locus showed that all 15 families studied shared a common haplotype over at least 1.9 cM. This strongly suggests that all Scandinavian SCA7 families originate from a common founder pre-mutation. *European Journal of Human Genetics* (2000) **8**, 918–922.

Keywords: spinocerebellar ataxia; *SCA7*; founder effect; haplotype analysis; linkage disequilibrium; Scandinavia

Introduction

Spinocerebellar ataxia type 7 (SCA7) is an autosomal dominant neuro-degenerative disease, predominantly affecting the cerebellar cortex, retina, pons and olivary nuclei. The disease-causing mutation has been shown to be the expansion of an otherwise relatively stable CAG repeat in the first coding exon of the disease gene. This results in an enlarged polyglutamine domain in the mutant protein.[1–5] A number of autosomal dominant neuro-degenerative disorders are characterised by expanded polyglutamines, including Huntington's disease (HD), dentatorubral-pallidoluysian atrophy (DRPLA), recessive X-linked spinobulbar muscular atrophy (SBMA/Kennedy's disease) and the spinocerebellar ataxias (SCA) 1,2,3,6 and 7[1,3,6–16] A common characteristic of polyglutamine disorders is genetic anticipation, resulting in an earlier age at onset and a more severe progression of disease in successive generations. This is explained by the negative correlation between longer CAG repeats and early age of onset of disease and by the frequently reported tendency for CAG repeats and to expand upon germline transmission.

Families with SCA7 have been reported in families of various ethnic background, including kindreds from Europe (Belgium, Finland, France, Germany, Sweden and the UK), the Middle East (Israel), Africa (Algeria, Morocco, Libya, Tunisia and South Africa), North America (Caucasian-Americans and African-Americans), South America (Brazil), the West Indies (Jamaica) and Asia (Korea and the Philippines).[17–24] The presence of this relatively rare disease in such a variety of populations would indicate that the SCA7 mutation may have arisen several times, rather than all families sharing a common founder mutation. Indeed, a

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recent linkage disequilibrium study by Stevanin *et al* revealed multiple origins of 41 SCA7 families of Asian, North African, European, Middle Eastern and South American origin.[24]

Preliminary data indicated that in Sweden and Finland, unlike in other populations studied, SCA7 is by far the most common of all genetically verified dominant ataxias, suggesting the existence of a founder effect for the SCA7 mutation in these countries. To investigate this possibility we have performed an extensive haplotype study including all SCA7 families available in Scandinavia (Sweden, Norway, Denmark and Finland). In this report we describe the spectrum of different hereditary ataxias in Sweden and Finland and by haplotype analysis show evidence for a founder effect of SCA7 in the Scandinavian population.

Materials and methods

Family and control material

To assess the relative frequency of different forms of hereditary ataxias genetically verified in Sweden and Finland we contacted all laboratories performing diagnostic mutation analysis of hereditary ataxias (SCA1, SCA2, SCA3, SCA6, SCA7 and FRDA), in the respective countries during 1998 and 1999. Laboratories were asked to report all cases where mutation analysis for SCA7 was positive.

Clinical genetics/diagnostic laboratories in Sweden, Norway, Denmark and Finland were contacted and invited to participate in the haplotype study and blood samples were collected from participants by informed consent. A total of 8 Swedish and 7 Finnish SCA7 families were collected, including 37 affected SCA7 patients and 60 non-affected relatives. Control samples from healthy, non-related individuals of Swedish origin were used for allele frequency calculations for marker D3S1287, D3S1228 and the intragenic polymorphism ^{3145}G/A. DNA extractions were made from peripheral blood by standard procedures.[25]

Mutation and haplotype analysis

Mutation analysis of *SCA7* was performed as previously described.[1]

Microsatellite markers D3S3631/D3S3698/D3S1600/(*SCA7* ^{3145}G/A)/D3S1287/D3S1228/D3S3635/D3S3644/D3S3571/D3S1285 covering a 10.2 cM region harbouring the *SCA7* gene were used and ordered telomeric (D3S3631) to centromeric (D3S1285) by combining the Genome Data Base (GDB) map 'SCA7 region of chromosome 3p', the Généthon chromosome 3 map of March 1996 and the Marshfield chromosome 3 sex-averaged linkage map (all available from GDB, http://gdbwww.gdb.org/). Genetic distances in Figure 3 are given in Kosambi cM (KcM), according to the SCA7 region of chromosome 3p map.

All microsatellite markers were amplified by polymerase chain reaction using 5'-[γ^{32}P]dATP, 5'-6-FAM or 5'-HEX labelled primers. [γ^{32}P] labelled products were analysed as previously described.[26] FAM and HEX labelled products were separated on an ABI377 and analysed using the ABI Prism 377 Genescan and Genotyper software. An internal GENESCAN® 400HD [ROX] Size Standard (PE Applied Biosystems) was included to allow for precise allele numbering and comparison of allele sizes to other reports. The smallest allele for each marker was denoted number 1, the next number 2, and so forth except for the highly polymorphic marker D3S3571 where the GDB allele numbering was used. The intragenic *SCA7* polymorphism ^{3145}G/A was amplified and analysed as described.[24] One sample from a French and an Algerian family each was included and genotyped in our laboratory for comparison of allele sizes to previous studies.[24]

DNA from relatives of patients in families H, F4 and F7 was not available, therefore phase-unknown haplotypes are shown for these patients in Table 1.

Statistical analysis

Linkage disequilibrium was assessed by comparison of allele frequencies of allele 3 of marker D3S1287 and the haplotype A-3 of the intragenic polymorphism and marker D3S1287 in chromosomes from SCA7 patients using Fisher's exact test.

Table 1 Ancestral haplotypes of eight Swedish (families A-H) and seven Finnish (F1-F7) SCA7 families, covering a 10.2 cM region of chromosome 3p. The *SCA7* CAG repeat is located between D3S1600 and the ^{3145}G/A polymorphism. As DNA samples from relatives to the patient in families H, F4 and F7 were not available, phase-unknown haplotypes are shown for these families

		Swedish families								*Finnish families*						
KcM	*Marker*	*A*	*B*	*C*	*D*	*E*	*F*	*G*	*H*	*F1*	*F2*	*F3*	*F4*	*F5*	*F6*	*F7*
7.9	D3S3631	4/3	3	3	3	4	4	2	4–2	4	3	4	4–3	4	4	4–4
11.9	D3S3698	4	4	7	5	4	4	3	4–5	4	4	3	4–3	4	4	4–5
12.8	D3S1600	19	20	2	3	19	19	24	19–1	19	15	17	19–1	19	19	19–15
	^{3145}G/A	A	A	A	A	A	A	A–B	A–A	A	A	A	A–B	A–B	A	A–B
15.3	D3S1287	3	3	3	3	3	3	3	3–4	3	3	3	3–5	3	3	3–5
17.2	D3S1228	10	10	10	10	10	10	10	10–10	10	10	10	10–2	10–2	10	10–10
17.2	D3S3635	5	5	5	5	9	9	9	5–5	5	5	5	5–3	5	5	5–5
17.2	D3S3644	5	5	1	1	4	4	4	5–1	4	5	5	4–1	5	4	4–5
17.2	D3S3571	3	3	11	11	2	2	2	3–7	3	3	3	3–6	12	3	3–11
18.1	D3S1285	5	5	2	2	2	2	5–2	5–7	4	5	5	5–2	5	5	5–2

Calculations were performed using the 2BY2 linkage utilities program (available from Rockefeller University, ftp://linkage.rockefeller.edu/software/utilities/), and Bonferroni corrections of the two sides *P* values were performed using the formula $1-(1-a)^k$, where k = 7 and 14 were used for D3S1287 and the intragenic polymorphism, respectively.

Results

Spectrum of hereditary ataxias in Sweden and Finland

In order to estimate the occurrence of different forms of hereditary ataxia in Sweden and Finland a survey of all genetically verified ataxia patients in the two countries was conducted. The results showed SCA7 to be the most frequent subtype among the genetically verified dominant hereditary ataxias, both in Sweden and Finland, (25 and 12 patients from eight and seven families respectively). In Sweden, apart from SCA7, only two other forms of ADCA were found (SCA2 and SCA3, in one and four patients, respectively). In Finland three additional forms of ADCA were found; SCA1 (12 patients from five families), SCA2 (three patients from one family) and SCA6 (one patient). In contrast to Sweden, Friedreich's ataxia is quite rare in Finland (21 and 3 patients, respectively). No SCA7 families of Norwegian or Danish origin could be identified.

SCA7 founder effect in Scandinavia

In order to find out whether the relatively large number of SCA7 cases in Sweden and Finland is the result of a common founder mutation/premutation, we performed mutation and haplotype analysis in all known Swedish (*n* = 8) and Finnish (*n* = 7) SCA7 families. Swedish families A, B, C, D and Finnish families F4 and F5 have been described elsewhere,[5,17,23] whereas Swedish SCA7 families E, F, G, H and Finnish families F1–F3 and F6–F7 represent novel families identified in this inventory. The geographical distribution of Scandinavian SCA7 families is concentrated in six different areas in Sweden and Finland, as shown in Figure 1. On mutation analysis all affected patients (*n* = 37) displayed expanded CAG repeats. In addition, nine clinically non-affected relatives also showed CAG expansions ranging from 38 to 53 CAG repeats. Two carriers with 39 and 40 CAG repeats, as typed by PCR, was still healthy at 68 and 85 years of age, respectively. In contrast, one individual with 39 CAG repeats presented with SCA7 symptoms as late as age 74 (data not shown).

For haplotype analysis, nine microsatellite markers and one intragenic polymorphism, covering a 10.2 cM region of chromosome 3p containing the *SCA7* gene were used. The results show that all 15 Scandinavian families share a common haplotype A-3-10 for the intragenic polymorphism ^{3145}G/A and the centromeric markers D3S1287 and D3S1228. The markers cover more than 1.9 cM of the SCA7 disease gene region (Table 1), but many families share chromosomal segments larger than the > 1.9 cM. Nine families (A, E, F, H, F1, F4, F5, F6 and F7) share a haplotype over as much as

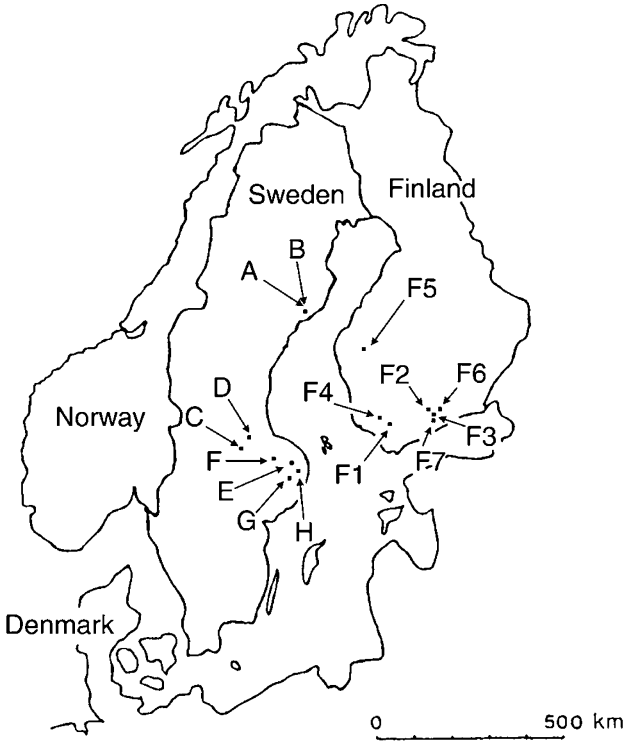

Figure 1 Geographic origin of eight Swedish and seven Finnish SCA7 families included in the haplotype study. Swedish families A and B originate in the county of Västerbotten, families C and D the county of Dalarna, and families E, F, G and H the county of Uppland. Finnish family F5 originates in the county of Österbotten. Finnish families F1–F4 and F6–F7 all originate in the counties of South Häme and Varsinais-Suomi in south west Finland.

9.3 cM between markers D3S3631 and D3S1228, and six families (A, B, H, F2, F3 and F7) share more than 2.8 cM between the intragenic polymorphism ^{3145}G/A and marker D3S1285. The same > 2.8 cM region, but with a different haplotype, is also shared by families C and D. In general, larger haplotypes were shared by families within a geographical region than by families from different geographical regions. We have previously demonstrated genealogically that Swedish families A and B share a common ancestor, born in the mid-seventeenth century.[5] It is therefore possible that the discrepancies in haplotype consistency between families A and B (note markers D3S3631 and D3S1600, Table 1) are due to satellite permutation rather than historic recombinations.

To investigate the strength of these data, a control material of healthy unrelated individuals of Swedish origin was used to determine allele frequencies of the three markers, closely linked to the SCA7 disease gene, for which all 15 Swedish and Finnish SCA7 families shared a common haplotype. Allele A for the intragenic polymorphism ^{3145}G/A was present in 31% of the chromosomes (*n* = 96) and allele 10 for marker D3S1228 was present in 34%. In contrast, allele 3 (253 bp) of

D3S1287 was present in only 2.6% (n = 264). This rare allele has so far only been reported on SCA7 chromosomes from one American SCA7 kindred of German origin (labelled allele 5 in the study referred to), but not on disease-bearing chromosomes from 32 other SCA7 families of various origins.[24]

Of the seven control individuals who carried allele 3 for D3S1287, only two also carried allele A for the intragenic polymorphism ^{3145}G/A. As these individuals were heterozgyous for both markers, the maximum frequency for a possible A-3 haplotype in the non-affected Swedish population is as low as 0.75%. Genotyping of the two individuals with a possible A-3 haplotype with respect to the SCA7 CAG repeat, showed that both were homozygous for the common normal allele of 10 CAG repeats. Furthermore, linkage disequilibrium calculations using Fisher's exact test were highly significant both for the segregation of allele 3 for marker D3S1287 ($D = D_{max} = 0.25$, $P = 5.18 \times 10^{-6}$) and for the haplotype A-3 for D3S1287–SCA7 ^{3145}G/A ($D = D_{max} = 0.25$, $P = 1.51 \times 10^{-4}$) on disease bearing chromosomes. These data all support the hypothesis of a strong founder effect for SCA7 in Scandinavia.

Discussion

In this paper we demonstrate that the relatively high frequency of spinocerebellar ataxia type 7 (SCA7) observed in Sweden and Finland is most likely the result of one founder mutation. In other populations studied SCA7 is considered to be one of the most rare forms of autosomal dominant cerebellar ataxia (ADCA), reported to constitute only 4.5 to 11.6% of the genetically verified ADCAs.[27,28] In most populations other forms of spinocerebellar ataxias dominate, as exemplified in a recent study of 48 Portuguese ataxia families where Machado-Joseph disease (MJD) constituted the most common form of ADCA (74%) found.[29] A similar study of 72 Spanish patients with hereditary ataxia instead demonstrated SCA2 and SCA3 to be the most common forms in this population (15% each).[30] Neither of these studies reported any cases of SCA7. In a study of 134 sporadic ataxia cases, only one was diagnosed as SCA7, suggesting a low *de novo* frequency of this mutation.[28]

These studies are in contrast with our results, showing that SCA7 constitutes the major part of the genetically verified dominant ataxias in Sweden and Finland. In Sweden SCA7 is in fact nearly as common as Friedreich's ataxia (FRDA), the latter reported to be the most frequently diagnosed hereditary ataxia in the Caucasian population.[31] Also in Finland, SCA7 appears to be one of the major forms of hereditary ataxia genetically verified. However, in the Finnish population only a few cases of FRDA have been identified by molecular diagnosis. This difference in frequency between Sweden/Finland and other populations studied, suggests that a strong founder effect has led to the relatively high frequency of SCA7 seen in Sweden and Finland today.

We have identified 15 families, eight Swedish and seven Finnish, with SCA7 in a survey conducted in Scandinavia (Sweden, Norway, Finland and Denmark). In Norway and Denmark no cases have been genetically diagnosed, to the best of our knowledge.

All patients with clinical symptoms included in this study carried an expanded CAG repeat upon mutation analysis. Interestingly, as many as nine non-affected relatives also carried the mutation. Eight out of nine non-affected carriers displayed repeat sizes in the lower range of the disease-causing spectrum. Initial reports of mutation analysis in SCA7 families identified few cases of intermediate-sized repeats and no overlap of repeat size between affected/non-affected individuals, indicating that presymptomatic testing of SCA7 should be simple and straightforward.[1–3,5,32] However, in the present study two non-affected carriers with 39 and 40 CAG repeats, respectively, were identified, age 68 and 85 years. In addition, one clinically affected patient with 39 repeats (age at onset 74 years) was identified. This overlap of repeat sizes in affected and non-affected individuals demonstrates the reduced penetrance previously suggested in SCA7.[19]

Stevanin *et al*[24] recently demonstrated multiple origins of SCA7 in 41 families from several different ethnic backgrounds (Korea, Algeria, Morocco, Tunisia, USA, the UK, Italy, Belgium, France, Germany, Israel, South Africa, Brazil, Jamaica and the Philippines). The authors described four major haplotypes for the centromeric *SCA7* region (^{3145}G/A/)/D3S1287/D3S3635) distributed in four distinct geographical areas, indicating regional founder effects. This pattern is very similar to that we observed in the Scandinavian population, where all families tested demonstrated a common haplotype for the region (^{3145}G/A)/D3S1287/D3S1228. However, the haplotype segregating in Scandinavian SCA7 families is clearly distinct from all the four major haplotypes described by Stevanin and co-workers.[24] In the present study all Scandinavian disease-bearing chromosomes harbour allele A for the *SCA7* intragenic polymorphism ^{3145}G/A, in combination with allele 3 (253 bp) for the closely linked marker D3S1287, a rare allele present only in 2.6% of the Swedish population. In the report by Stevanin *et al*[24] the 253 bp allele of D3S1287 is only represented on disease-carrying chromosomes in one American family, of German origin, suggesting a possible kinship between the Swedish/Finnish families and this German family. This 253 bp allele (named allele 5 in the study referred to) was not present on any of the remaining SCA7 chromosomes from 32 other families of various ethnic background.[24] The possibility of kinship between the Swedish and Finnish families and the German family reported by Stevanin *et al* remains to be investigated.

In the present study, the maximum frequency of individuals carrying haplotype A-3 for the intragenic polymorphism ^{3145}G/A and marker D3S1287 is as low as 0.75% in healthy

controls, demonstrating a strong linkage disequilibrium for SCA7 in Sweden and Finland.

We conclude from this study that the relatively high frequency of SCA7 in Sweden and Finland is the result of a founder premutation that apparently arose several hundred years ago. Due to limited migration and the large number of children in the families over the years, this relatively rare mutation has reached the high frequency at which it is found in the Swedish and Finnish populations today.

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