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Non-recurrent *SEPT9* duplications cause hereditary neuralgic amyotrophy

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ABSTRACT

Background Genomic copy number variants have been shown to be responsible for multiple genetic diseases. Recently, a duplication in septin 9 (*SEPT9*) was shown to be causal for hereditary neuralgic amyotrophy (HNA), an episodic peripheral neuropathy with autosomal dominant inheritance. This duplication was identified in 12 pedigrees that all shared a common founder haplotype.
Methods and results Based on array comparative genomic hybridisation, we identified six additional heterogeneous tandem *SEPT9* duplications in patients with HNA that did not possess the founder haplotype. Five of these novel duplications are intragenic and result in larger transcript and protein products, as demonstrated through reverse transcription-PCR and western blotting. One duplication spans the entire *SEPT9* gene and does not generate aberrant transcripts and proteins. The breakpoints of all the duplications are unique and contain regions of microhomology ranging from 2 to 9 bp in size. The duplicated regions contain a conserved 645 bp exon within *SEPT9* in which HNA-linked missense mutations have been previously identified, suggesting that the region encoded by this exon is important to the pathogenesis of HNA.
Conclusions Together with the previously identified founder duplication, a total of seven heterogeneous *SEPT9* duplications have been identified in this study as a causative factor of HNA. These duplications account for one third of the patients in our cohort, suggesting that duplications of various sizes within the *SEPT9* gene are a common cause of HNA.

Hereditary neuralgic amyotrophy (HNA) is a rare autosomal dominant disorder characterised by recurrent episodes of sudden-onset, severe pain, weakness and sensory impairment, primarily affecting nerves in a brachial plexus distribution.[1] Episodes can last for weeks to months, and are often followed by residual weakness and sensory deficits in the affected limbs or muscles. Dysmorphic features, including hypotelorism, circumferential skin folds seen in infants or toddlers, and cleft palate have also been associated with HNA.[2 3] The pathophysiology of HNA is poorly understood. At least half of the pain attacks are precipitated by events such as immunisations, infections, trauma, pregnancy and stress, implying a potential autoimmune aetiology.[4]

A locus for HNA was previously mapped to chromosome 17q25,[5–9] and three point mutations were found in the *SEPT9* gene in patients with HNA.[10] Two missense mutations reside in a conserved region of *SEPT9*, are present in 22% (12/55) of the families in our HNA cohort and have been identified in additional cohorts.[1 2 5 11 12] In our initial study, large duplications or deletions in *SEPT9* were not detected through microsatellite genotyping or semiquantitative PCR analysis. However, using array comparative genomic hybridization (CGH), we recently identified a 38 kb intragenic microduplication within *SEPT9* in 12 pedigrees with HNA that were known to harbor a common founder haplotype. These pedigrees account for an additional 22% (12/55) of the families in our cohort.[13]

SEPT9 is a member of the large family of septin proteins that interact with the cytoskeleton, including microtubules and actin, functioning in cellular processes such as cytokinesis, motility and cell polarity.[14] *SEPT9* produces multiple mRNA transcripts through alternative 5′ splicing.[15] The three longest transcripts, *SEPT9*_v1, *SEPT9*_v2 and *SEPT9*_v3, produce proteins containing a proline-rich region and unique N-termini of 25, 18 and 7 amino acids, respectively. The majority of the proline-rich region is encoded by a 645 bp exon in which the two missense HNA-linked mutations are located. Also, the previously published intragenic microduplication results in an in-frame tandem duplication of this exon predicted to generate protein products with two proline-rich regions, suggesting that this region is important in the molecular pathology of HNA.

Here, we report six additional HNA pedigrees (K4001, K4013, K4023, K4032, K4040 and K4045) containing duplications within the *SEPT9* gene. These duplications are heterogeneous in nature, varying in size and location. However, all of the duplications encompass the 645 bp exon, and lymphoblastoid cell lines from affected individuals express modified protein products similar to those previously observed in the founder pedigrees.[13] These data further support the hypothesis that alterations of the proline-rich region of SEPT9 play a role in the pathogenesis of HNA.

PATIENTS, MATERIALS AND METHODS

Patients

The clinical presentation of HNA patients in this study was consistent with the classic phenotype previously reported.[3 5] Blood samples were obtained by venipuncture under a protocol of informed consent (Human Subjects Division, University of Washington, Seattle, Washington, USA) that was approved by the institutional review board.

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DNA sequencing and reverse transcription-PCR

Genomic DNA was isolated from permanent lymphoblastoid cell lines established through Epstein–Barr virus transformation and maintained under standard conditions as previously described.[5 16] To identify breakpoint locations, outward facing PCR primers were designed on either side of the predicted genomic breakpoint region and the cDNA duplication junction (additional table 1). Reverse transcription-PCR was performed using Superscript III polymerase (Invitrogen, Carlsbad, California, USA) and an oligo dT_{20} primer, according to the manufacturer's instructions. Junction PCRs were completed for all individuals in the six pedigrees. PCR conditions consisted of an initial 95°C for 2 min, followed by 35 cycles of 95°C for 1 min, 60°C for 1 min and 72°C for 3 min, with a final extension at 72°C for 10 min. Products were sequenced by the DNA Sequencing Facility at the University of Washington, Department of Biochemistry.

Microsatellite genotyping

Genotyping was completed for all individuals from the six duplication pedigrees for which DNA was available using eight short tandem repeat markers (D17s801, D17s802, 7sGT1, GT1, D17s939, D17s937, MSFtri and 380058) spanning *SEPT9* and the surrounding region, as previously described.[5] Reactions were analysed on an ABI 3130xl Genetic Analyser (Applied Biosystems, Austin, Texas, USA).

Array CGH

Array CGH was performed using a custom oligonucleotide array consisting of 385 000 isothermal probes (Roche NimbleGen, Inc., Madison, Wisconsin, USA) as previously described.[13] The array included 1311 probes spanning a 300 kb region encompassing the *SEPT9* gene (chr17: 72 800 000–73 100 000) with approximately one probe every 229 bp. DNA from individuals in K4001

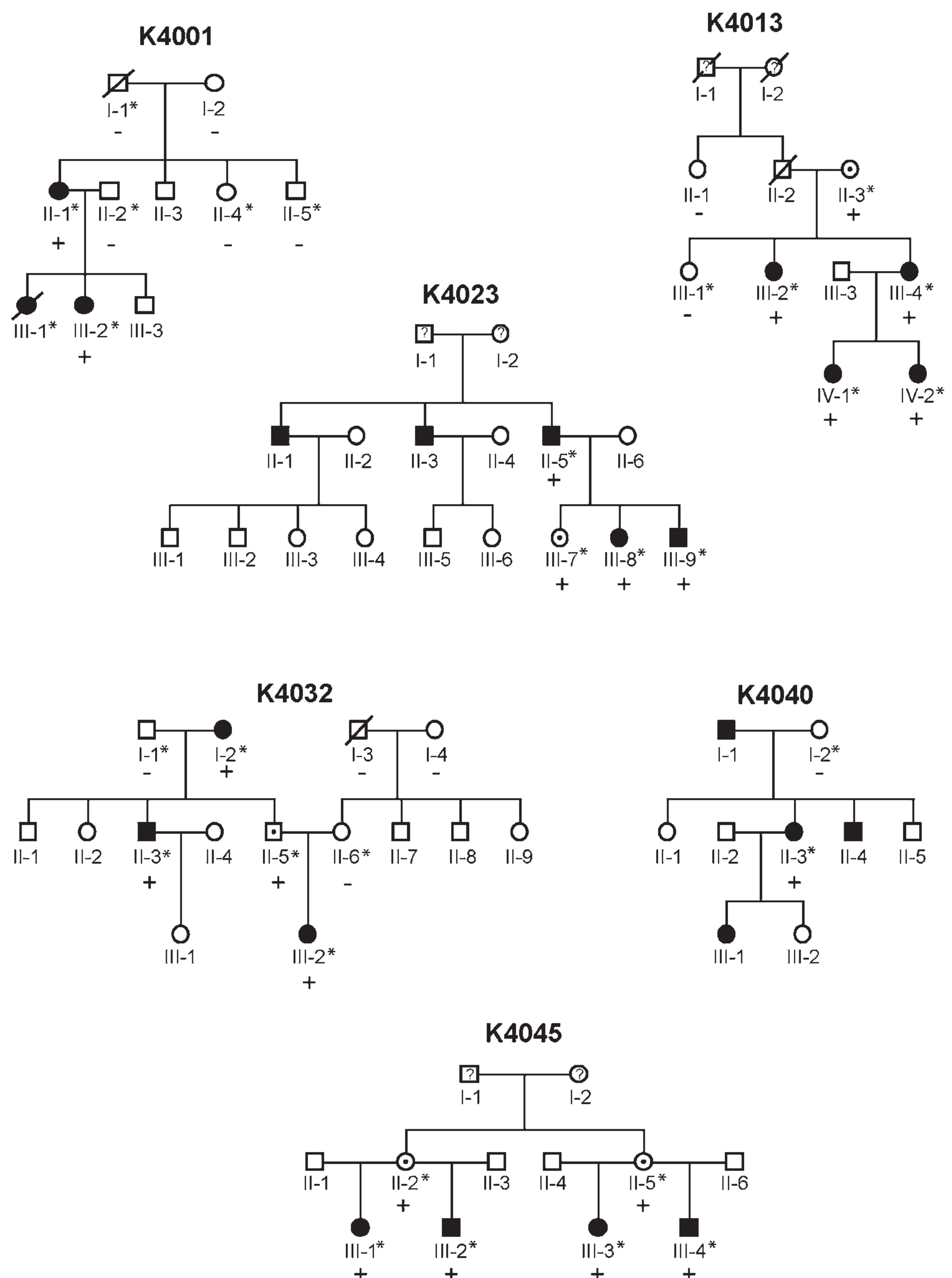

Figure 1 Six hereditary neuralgic amyotrophy (HNA) pedigrees possess duplications within *SEPT9*. Pedigrees for K4001, K4013, K4023, K4032, K4040 and K4045 are shown. Junction PCR analysis on available samples demonstrates that the duplication segregates with disease in each family. The presence or absence of a duplication is shown as positive (+) or negative (−) for each individual. Circles represent women. Squares represent men. Filled symbols represent HNA-affected individuals. Empty symbols represent unaffected individuals. Dotted symbols represent non-penetrant individuals. Cross-slashed symbols represent deceased individuals. Question marks represent individuals for whom no clinical data was available. Asterisk indicates individual was genotyped (additional figures 1 and 2).

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and K4045 were also analysed on a whole-genome tiling array (Roche NimbleGen) containing 2.1 million probes with a median probe spacing of 1169 bp.

Western blots

Western blots were completed using lymphoblastoid cell lines from HNA-affected patients and unaffected family members. Blots were probed with anti-SEPT9 isoforms 1–3 and 5/6-reactive antibodies or an anti-SEPT9_i1-specific antibody as previously described.[13 17] An anti-actin antibody (Sigma, St Louis, Missouri, USA) was used as a control to verify equivalent loading.

RESULTS

To date, sequence analysis of *SEPT9* in larger cohorts of HNA families has not identified any additional mutations beyond those previously reported.[10 12] After identification of the founder duplication, probands from pedigrees lacking *SEPT9* mutations were screened for duplications within *SEPT9* using array CGH. Individuals with HNA in pedigrees K4001, K4013, K4023, K4032, K4040 and K4045 (figure 1) carried *SEPT9* duplications; however, the size and breakpoints were different in each pedigree, ranging from approximately 30 to 110 kb in size (figure 2A and table 1). The duplications in K4001 and K4045 were further characterised using a whole-genome tiling array as the 5′ breakpoints extended outside the region covered by the custom array (figure 2B). These duplications were 200 and 330 kb, respectively. The 330 kb duplication in K4045 included a portion of the gene 5′ to *SEPT9*, *SEC14L1*. The smallest common region shared by all of the duplications encompasses the 645 bp exon in which HNA-linked mutations have been identified, providing further evidence that this region is involved in the pathogenesis of HNA.

To identify the location of the breakpoints, PCR was carried out using primers flanking the array-predicted breakpoint regions (figure 3 and additional table 1). These breakpoint PCRs confirmed that the tested individuals in each pedigree have tandem genomic duplications similar to that observed in the founder haplotype, although they vary in duplication size and breakpoint location (figure 2 and table 1). The six pedigrees appear to have simple duplications, yet the possibility of complex rearrangements, with duplicated regions separated by

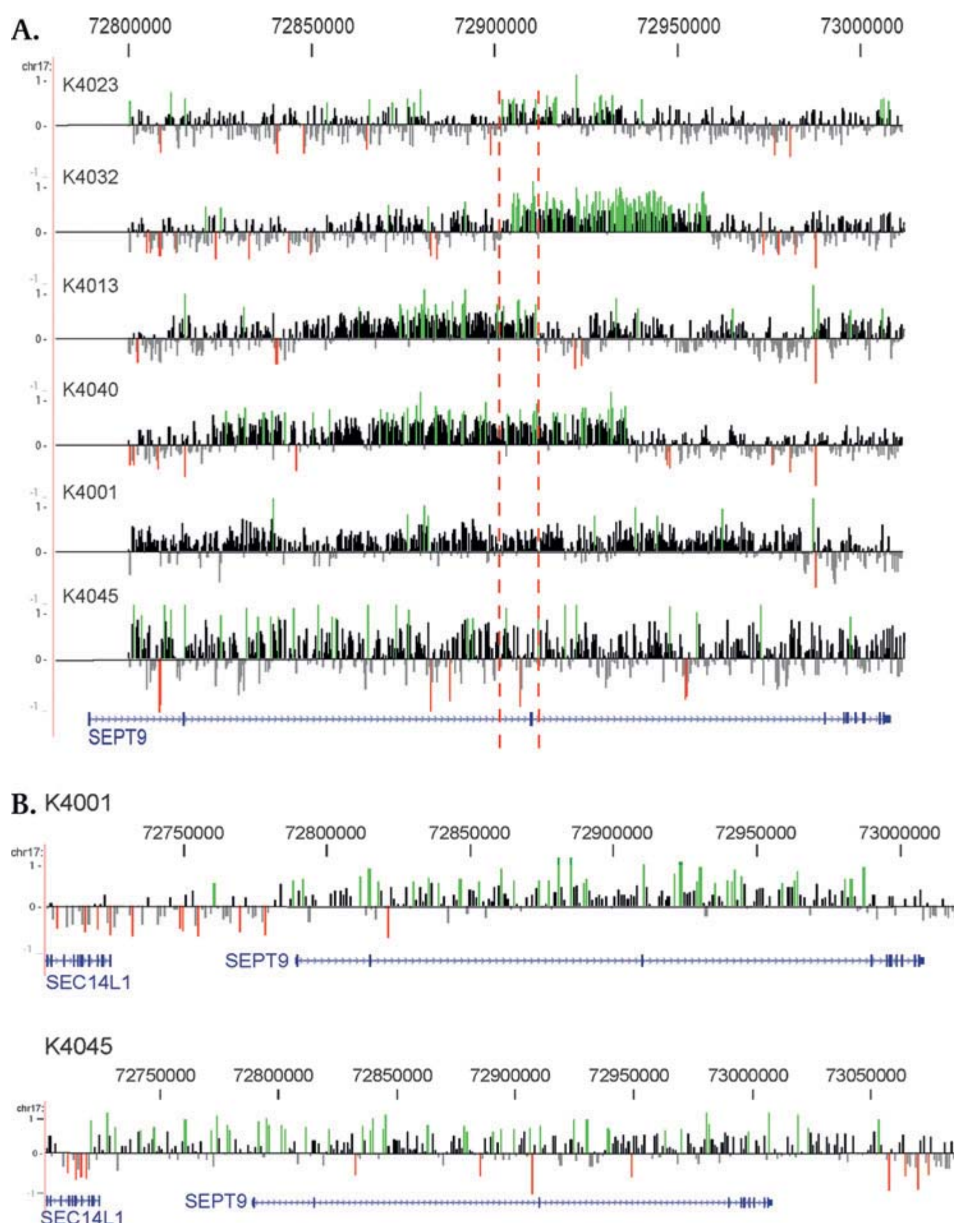

Figure 2 Hereditary neuralgic amyotrophy (HNA) duplications in *SEPT9* are heterogeneous. (A) Array comparative genomic hybridization targeted to *SEPT9* shows that the duplications identified in pedigrees K4023, K4032, K4013, K4040, K4001 and K4045 are heterogeneous in size and location. (B) Two duplications, K4001 and K4045, extended beyond the *SEPT9*-specific array and were further analysed using a whole-genome array. All six duplications showed increased copies of the 645 bp exon (red dotted lines) in which previous point mutations and a founder duplication have been identified.

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Table 1 *SEPT9* duplication characteristics

Families with duplication	Duplication size (kb)	Proximal breakpoint location*	Distal breakpoint location*	Breakpoint sequence
Founder haplotype duplication†	38	72876638	72914241	G
K4023	33	72901921–5	72934912–6	GAAGA
K4032	54	72904532–3	72958680–1	CA
K4013	65	72846731	72912123	CTC(C)AC
K4040	111	72824925–6	72935850–1	CT
K4001	201	72783590–2	72984253–5	AGG
K4045	329	72722677–85	73051609–17	TCAGGGTGG

*Numbering refers to hg18/Build 36.1.
†Previously reported by Landsverk *et al*.[13]

non-duplicated regions, cannot be excluded. Additional potential junction PCRs were attempted and did not reveal evidence for complex duplications (data not shown). Examination of the duplication breakpoints revealed possible microhomology of 2–9 bp (table 1).

Although there are multiple Alu sequences and other repetitive sequences near the duplication breakpoints, no duplication had the same repetitive sequence at its distal and proximal breakpoints. The 5′ and 3′ breakpoint sequences of K4013 are not an exact match — the 5′ sequence contains an additional C (figure 3). In addition, the 5′ sequence of the duplication appears to have been inverted across the breakpoint, and an AAAA was inserted.

To further characterise the duplication mechanism, microsatellite genotyping spanning *SEPT9* and the surrounding region was carried out in the six duplication pedigrees as previously described.[5 10] All pedigrees demonstrated segregation of a family-specific disease chromosome (additional figures 1 and 2). Pedigrees K4023 and K4032 showed segregation of the diseased chromosome, although no microsatellite markers were located within the duplicated regions. K4013 and K4040 show segregation of three markers within their respective duplications, implying that the duplications were intrachromosomal. However, the number of individuals genotyped in K4040 was

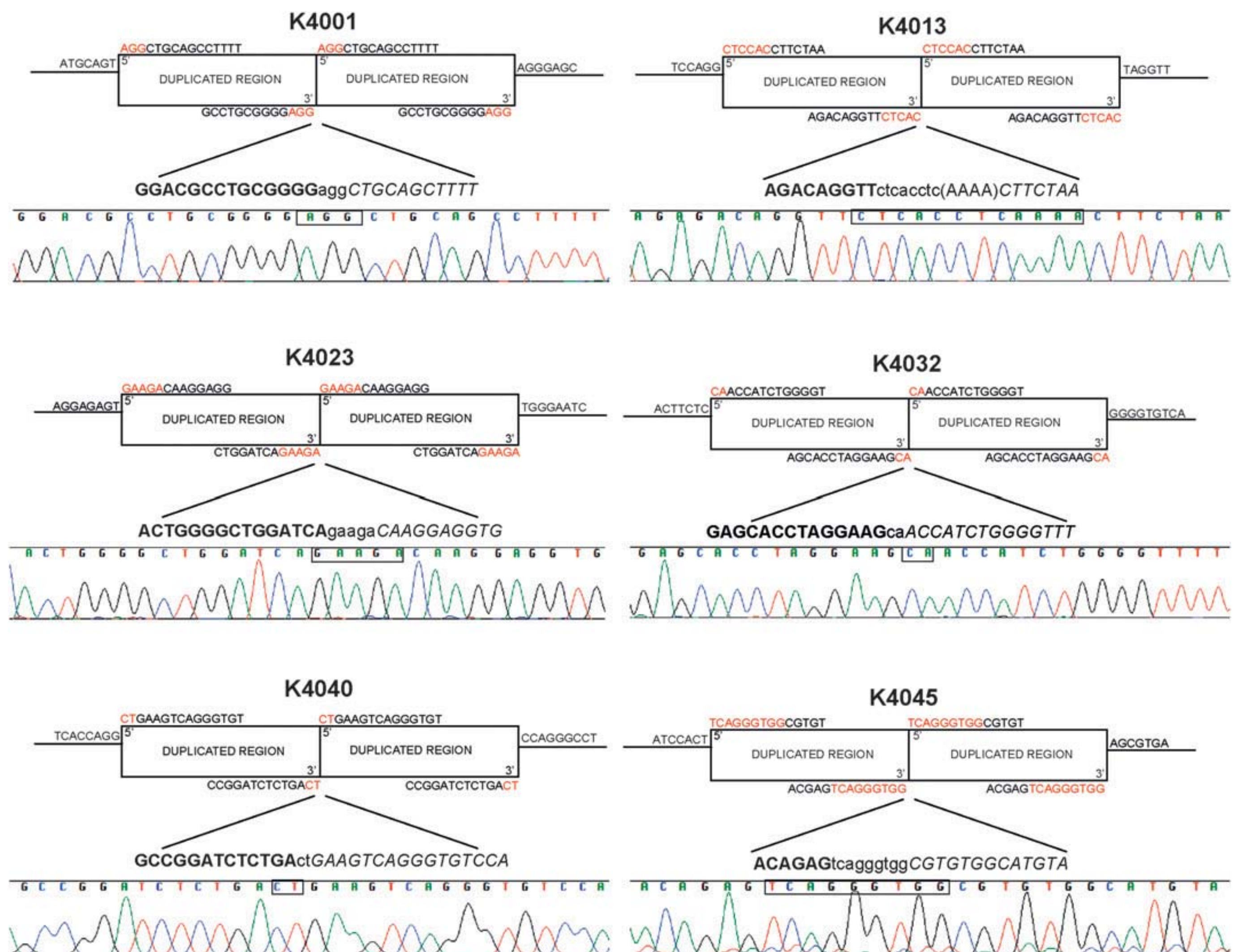

Figure 3 Characterization of *SEPT9* duplications. To further refine the *SEPT9*-duplicated regions, primers were designed to span the duplication junctions. Genomic DNA from pedigrees K4023, K4032, K4013, K4040, K4001 and K4045 was screened for the presence of intragenic duplications. The shared regions at the proximal and distal ends of the duplicated regions are shown in red. In sequences across the breakpoints, the 3′ sequence of the duplicated region is shown in bold, the 5′ sequence in italics and the shared region in lowercase. Duplicated regions are not shown to scale. The overlapping regions of K4013 are not exact (the 5′ sequence contains an extra C) and there appears to be an inversion of the sequence at the breakpoint in addition to an AAAA insertion. Sequence analysis shows that the breakpoints of the duplications are unique. Shared regions are boxed in sequence traces.

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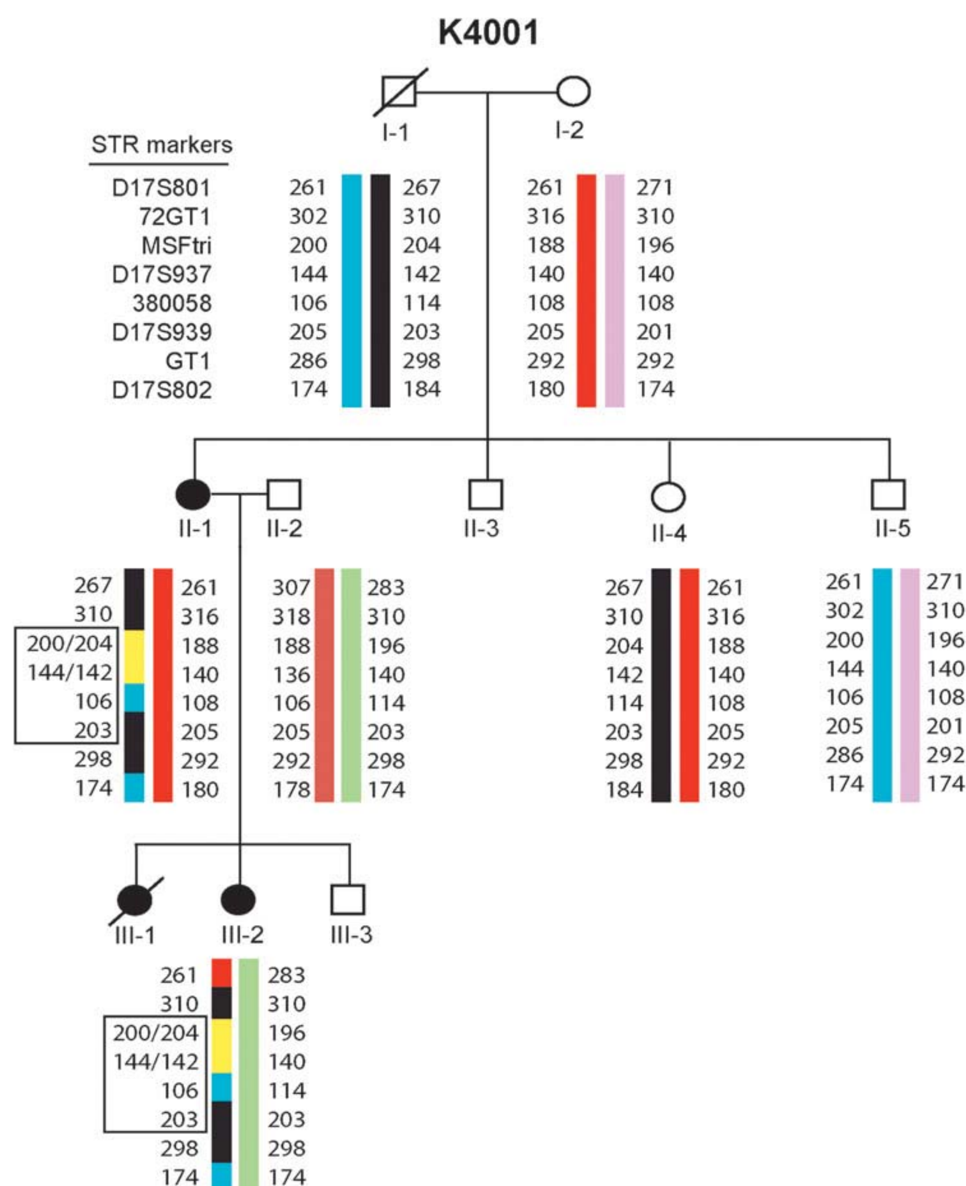

Figure 4 Hereditary neuralgic amyotrophy (HNA) pedigree K4001 contains a de novo duplication in *SEPT9.* Genotyping was completed for pedigree K4001 using short tandem repeat markers (D17S801, 72GT1, MSFtri, D17S937, 380058, D17S939, GT1 and D17S802) spanning *SEPT9* and the surrounding region, as previously described.[5 10] Microsatellite PCR product lengths are shown in order of chromosomal location. K4001 II-1 represents a de novo mutation involving duplicated regions from both of the paternal chromosomes. The duplicated region is noted by a box. Yellow indicates the chromosomal region inherited from both paternal alleles.

limited. For pedigree K4045, the markers in the duplicated region represent two alleles from one parent and a single allele from the other, indicating an interchromosomal insertion of the region from the homologous chromosome. The duplication in K4001 II-1 results from a more complex chromosomal rearrangement (figure 4). While a single allele is inherited from the mother for each of four markers in the duplicated region (MSFtri, D17S937, 380058 and D17S939), both paternal alleles are inherited for markers MSFtri and D17S937. In contrast, only a single allele from one paternal chromosome is inherited for marker 380058, while a single allele from the other paternal chromosome is inherited for marker D17S939. These data provide evidence for a combination of interchromosomal and intrachromosomal rearrangements leading to *SEPT9* duplications in HNA.

Previous studies have shown that a duplication within *SEPT9* leads to altered protein products of increased size.[13] To determine if SEPT9 protein was altered in these pedigrees, we examined the expression of SEPT9_i1, i2, i3 and i5/6 (also known in the literature as i4[18]) by immunoblotting of lymphoblastoid cell lines with anti-SEPT9 antibodies.[13 17] In addition to wild-type bands, pedigrees K4001, K4013, K4023 and K4040 all expressed SEPT9-reactive bands migrating at around 100 and 80 kDa, consistent with those previously observed in the founder haplotype pedigrees (figure 5A).[13] Additional SEPT9-reactive bands migrating at approximately 70 and 55 kDa were observed in pedigree K4001. The identity of these bands is unknown, yet they are similar in size to those observed when SEPT9 protein isoforms are overexpressed in cell culture, indicating possible protein degradation products.[19] However, these bands are not SEPT9_i1 reactive, suggesting that other SEPT9-reactive transcripts may be expressed in this family. Interestingly, SEPT9 protein expressed in K4045 is indistinguishable from that expressed in unaffected control samples (figure 5B). Tandem duplication of the 645 bp exon leading to altered protein products was confirmed by junction PCR of cDNA from these pedigrees (figure 5C and additional table 1). Duplication of the 645 bp exon was not observed in K4045, confirming the lack of additional protein products, and sequence analysis revealed no missense mutations. Therefore, these data indicate that a duplication of the entire *SEPT9* gene leads to the same clinical phenotype as do duplications limited to the 645 bp exon and single missense mutations within this exon.

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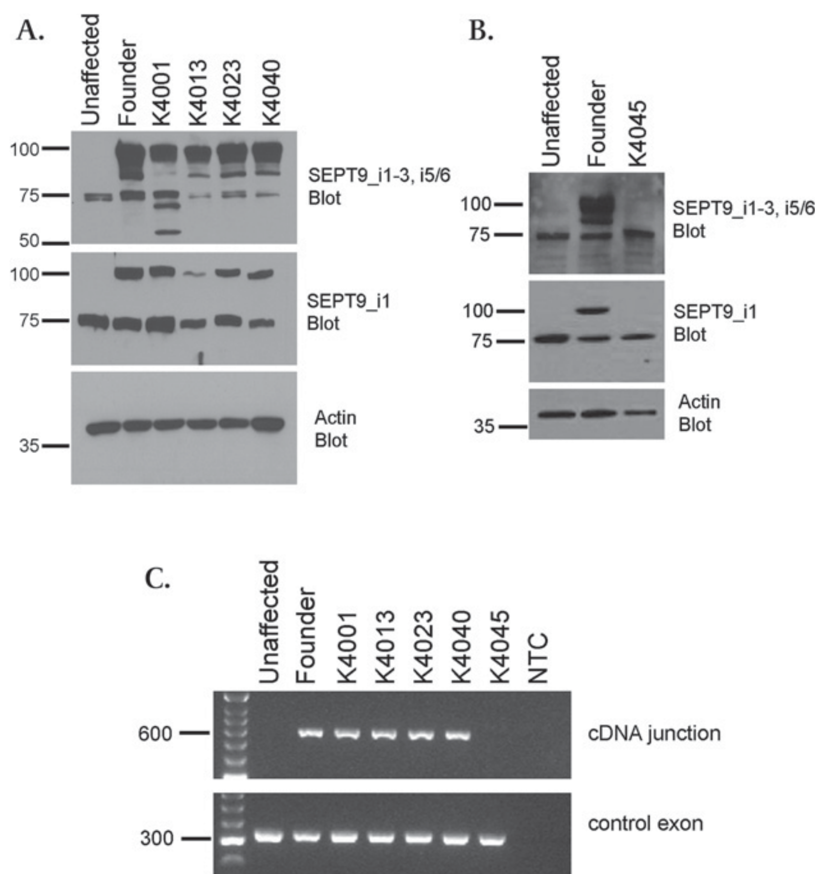

Figure 5 Heterogeneous duplications result in in-frame duplication of 645 bp exon. (A) Lymphoblastoid cell lines from an unaffected individual; an affected individual with the founder haplotype; and affected individuals from pedigrees K4001, K4013, K4023 and K4040 were lysed and probed with antibody specific for SEPT9_i1, i2, i3 and i5/6, or SEPT9_i1 alone. K4001, K4013, K4023 and K4040 expressed additional SEPT9-reactive proteins migrating at around 100 and 80 kDa, consistent with the founder individuals previously observed.[13] Additional SEPT9-reactive bands migrating at approximately 70 and 55 kDa were observed in pedigree K4001. An anti-actin antibody was used as a control to verify equivalent loading. (B) Pedigree K4045 expresses wild-type SEPT9 protein and does not express SEPT9-reactive proteins of larger size observed in other duplication families. (C) cDNA from an unaffected individual, founder haplotype individual and affected individuals from the heterogeneous duplication pedigrees (K4001, K4013, K4023, K4040 and K4045) were screened for tandem duplication of the 645 bp exon using primers on either side of the predicted junction. PCR over the cDNA 645 bp duplication junction confirms that an enlarged transcript, seen in the founder individual, is present in all pedigrees carrying intragenic duplications; however, this transcript is not present in K4045. A control region within *SEPT9* was amplified simultaneously to verify template and PCR conditions.

DISCUSSION

The heterogeneous duplications described here are non-recurrent genomic rearrangements without common breakpoints. Also, microsatellite genotyping of the de novo duplication in pedigree 4001 indicates interchromosomal and intrachromosomal rearrangements. Therefore, the duplications observed in our HNA families could be generated by a number of different proposed mechanisms.[20] Non-allelic homologous recombination is generally mediated by low-copy repeats and can occur on the same chromatid, between sister chromatids or between homologous chromosomes.[21] Non-homologous end-joining is a repair mechanism for double-stranded breaks and results in junctions with microhomology of a few base pairs and/or insertion of other sequences.[22] In serial replication slippage or Fork Stalling and Template Switching models, the replication machinery slips backwards along the chromosome, resulting in a tandem duplication, or slips forward, creating a deletion.[20 23 24] This slippage can also create complex rearrangements when repeated, or multiple slippage events occur, creating blocks of deleted or duplicated sequence with intervening single-copy sequence. More recently, this model has been expanded in the break-induced serial replication slippage and microhomology-mediated break-induced replication models to include template breakage.[25 26] The occurrence of one mechanism or another may be dependent on nearby genomic sequence and specialised elements. Interestingly, *SEPT9* was initially identified in acute myeloid leukaemia as a fusion partner of the mixed-lineage leukaemia gene (MLL).[27] cDNA encoding the fusion protein has been examined in several studies and has shown that a majority of the MLL fusions are to the 645 bp exon, indicating that the genomic breakpoints for the fusion protein are in the same genomic region as five of the seven heterogeneous duplications.[28–32]

How point mutations and duplications in the *SEPT9* gene are causative factors of HNA remains unknown. The present data suggest that alterations in the proline-rich region encompassed by the 645 bp exon are linked to HNA. The two missense mutations are located in this exon, and five intragenic duplications generate larger protein products produced by tandem duplication of this exon. This region has also been shown to interact with other proteins[33 34] and possess a number of confirmed phosphorylation sites.[35 36] In contrast, the entire gene duplication in pedigree K4045 apparently does not alter the protein, suggesting that HNA may also be caused by increased dosage of the wild-type protein. Due to the complexity of expression on the various SEPT9 transcripts, we were unable to determine if an increase in genomic copy number leads to a concomitant increase in levels of *SEPT9* mRNA transcripts. However, because *SEPT9* produces so many transcripts that are nearly identical, our results were inconclusive (data not shown). Also, it is possible that the expression of *SEPT9* transcripts in lymphoblastoid cell lines does not represent expression in other tissues. Pedigree K4045 has a known non-penetrant generation before the affected generation, suggesting that there may be other gene modifiers or factors affecting the clinical characteristics of HNA. To date, we have identified *SEPT9* gene defects in 55% (30/55) of our cohort. At least three families in this cohort do not link to 17q25, providing further evidence that additional HNA-linked genes exist.[37] Therefore, it is possible that other genes responsible for HNA are cell-type-specific SEPT9 binding partners. Further work is required to determine the function of the proline-rich region of SEPT9 and to identify additional genes

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that may be involved in HNA in families who do not show linkage to 17q25.

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Competing interests None.

Ethics approval This study was conducted with the approval of the University of Washington.

Contributors AMBC and MLL wish it to be known that, in their opinion, the first two authors should be regarded as joint first authors.

Provenance and peer review Not commissioned; externally peer reviewed.

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