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A 7.5Mb duplication at chromosome 11q21-11q22.3 is associated with a novel spastic ataxia syndrome

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Abstract

Background—The autosomal dominant spinocerebellar ataxias are most commonly caused by nucleotide repeat expansions followed by base-pair changes in functionally important genes. Structural variation has recently been shown to underlie Spinocerebellar ataxia types 15 and 20.

Methods—We applied single-nucleotide polymorphism genotyping to determine if structural variation causes spinocerebellar ataxia in a family from France.

Results—We identified an approximately 7.5 megabasepair duplication on chromosome 11q21-11q22.3 that segregates with disease. This duplication contains an estimated 44 genes. Duplications at this locus were not found in control individuals.

Conclusions—We have identified a new spastic ataxia syndrome caused by a genomic duplication, which we have denoted as Spinocerebellar ataxia type 39. Finding additional families with this phenotype will be important to identify the genetic lesion underlying disease.

Keywords

whole-genome genotyping; genomic duplications; spinocerebellar ataxia; structural variation; SCA39

Introduction

Since the discovery of the first genetic linkage for spinocerebellar ataxia (SCA) in 1990, numerous genetic defects underlying the hereditary SCAs have been identified. There are now 30 known loci, for which over half of the causative genes have been identified, and the list continues to expand. The mechanisms that lead to neurodegeneration include polyglutamine repeat expansions (SCA1, 2, 3, 6, 7, 17, DRPLA and in part SCA8), intronic expansions (SCA10, 31), point mutations (SCA5, 11, 14, 15, 27, 28), and structural genomic rearrangements (SCA15, 20) in genes of ostensibly divergent functions. It is unclear whether the respective pathways function independently or if they converge (1, 2).

The current genome-wide SNP genotyping technologies allow direct detection of structural variation across the genome, and have shown that rearrangements such as large deletions and duplications are more common than expected. These platforms have facilitated the investigation of the role of genomic copy number variation in disease (3). SCA15 and SCA20 are caused by such rearrangements (4, 5). Given that the SCAs have recently been attributed to structural rearrangements, we employed genome-wide SNP genotyping of five affected members of an autosomal dominant spinocerebellar ataxia family to assess whether structural variability is associated with this disease. Here we provide a detailed clinical description of this family and provide evidence to suggest a novel genetic cause of disease in affected family members.

Methods

The family was collected at the University Hospital Salpêtrière in Paris (index case) and at their home (other family members). This study was approved by the local Bioethics committee (approval No. 03-12-07 of the Comité Consultatif pour la Protection des Personnes et la Recherche Biomedicale Paris-Necker to Dr. Dürr and Dr. Brice). Written informed consent was obtained from all participating members of the families before blood samples were collected for DNA extraction. DNA was stored in the DNA and Cell Bank of the CR-icm at the Pitié-Salpêtrière hospital in Paris.

SNP genotyping was carried out on family members 277-10, 277-015, 277-014, and 277-011, and 277-05 using Illumina Infinium HD 610quad Bead Chips as per the manufacturers instructions (Illumina Inc, CA). As previously described, the B Allele frequency and Log R Ratio were used to identify genomic deletions and duplications (3, 6).

These two metrics were viewed within the Genome Viewer tool of Bead Studio (Illumina Inc, CA); these data on each chromosome were viewed in all genotyped family members by an experienced user (JOJ).

We examined the region on chromosome 11 containing the segregating duplication in Illumina Infinium genotyping data (HumanHap550 arrays) from 605 neurologically normal Caucasian individuals from North America genotyped as a part of a separate genome wide association study (7).

Results

Family SAL- 277, from Northern France (See Supplementary Figure 1), has been examined by A.D. at the University Hospital Pitié-Salpêtrière in Paris (Figure 1A). Polyglutamine expansions in SCA genes, SCA10 and SCA12 expansions as well as conventional mutations in SCA5, 13, 14 and 28 have been previously excluded in the index patient.

Patient 277-10 (index case): Onset of symptoms in this 46-year-old man was difficult to assess, but at infancy he already had difficulties running and learning. He had to use a cane at age 30 and became wheelchair-bound at age 41. He presented with moderate spasticity of the lower limbs, and cerebellar dysmetria in the upper limbs and moderate dysarthria. Reflexes were increased with ankle clonus and positive Hoffmann and Babinski signs. Vibration sense was abolished up to the hips, and there was distal lower limb muscle wasting. In addition to a strabismus, oculomotor signs included saccadic pursuit and horizontal gaze palsy. There was a clinical impression of mild mental retardation with normal Mini Mental Status (28/30). Cerebral MRI showed cerebellar atrophy with periventricular white matter hyperintensities (Figure 2). Electroneuromyography showed a neurogenic pattern and normal conduction velocities. Auditory evoked brainstem potentials were prolonged.

The index case displayed the general phenotype observed by patients in the family. Additional features observed in patients include hearing impairment, thoracic deformation, and foot deformation.

We observed a single structural genomic variant that was present in each of the five affected family members tested. B allele frequency and log R ratio indicated that this variant is an intrachromosomal duplication that lies between rs11021461 and rs10488755 on chromosome 11. This spans 7.5Mb, containing an estimated 44 individual transcripts [Figure 1]. We failed to identify this duplication, or any duplication greater than 451Kb in size at this locus, in 605 control individuals. No other genomic structural variant was observed in all affected family members in other regions of the genome.

Discussion

Development of recent technologies has facilitated a greater understanding of the contribution of genetic variation to disease. It has long been known that the human genome is highly polymorphic at the individual base pair level, and techniques such as next generation sequencing have made it possible to study the genome at this level with considerable depth. Next generation sequencing is novel, and algorithms are being developed to best assess the genome at the level of structural variation (8). However at present, detection of structural variation is more effective on established platforms such as genome-wide SNP genotyping arrays. The extent of structural variation has only more recently been realized. Large deletions, insertions, and duplications may occur in up to 12% of the genome, and the presence of functional sequences within and around these copy number variants (CNVs) suggests that they make a substantial contribution to phenotypic variability (9). We did not identify single base pair mutations in Family 277 in known spinocerebellar ataxia genes. Therefore, in the assessment of Family 277, we considered that a structural change might account for the presence of the spinocerebellar ataxia syndrome. We identified an approximately 7.5Mb chromosome 11 duplication now denoted SCA39 (Submitted to the HUGO Gene Nomenclature Committee, Hinxton, UK).

The duplication is shared by all affected members of the family and absent in more than 1200 control chromosomes. Non-affected individual DNA was not available for structural assessment. While it is a possibility that this is simply a rare benign CNV, the presence of the duplicated segment with those affected with early-onset disease in this family, the absence of a similar, overlapping duplication in control individuals, and the fact that the multiplication contains a dense array of functional sequences strongly supports the notion that this will have phenotypic consequences. It is conceivable that increased genetic load of individual transcripts underlies this disease, as in other neurodegenerative disorders (10, 11), but it is also possible that disruption of the genes at the breakpoints of the duplication may produce the phenotype. While examination of the B allele frequency in affected family members suggests intergenic breakpoints on both the centromeric and telomeric sides of the duplication, this method only provides an approximate interval for the breakpoint and thus further delineation of the breakpoints may be necessary.

Chromosomal rearrangements have been associated with several disorders where the causative gene is unknown (12, 13). Given the variety of pathways to spinocerebellar ataxia syndromes, any of the genes in this interval are potential candidates. In this family, spastic ataxia was the main clinical feature but the phenotype is complex. Intellectual disability is also present in at least 3 of the 5 patients examined, while such impairment is suggested

anecdotally for the remaining 2. Moreover, several patients have hearing impairment and reduced visual acuity. The brain MRI of the proband, who essentially displays the overall clinical picture of the family, shows both atrophy and developmental abnormality of the brain (e.g. white matter hyperintensities and dysgenesis of the corpus callosum).

Interestingly, the phenotype and imaging of Family 277 patients are reminiscent of SPG11, an autosomal recessive subtype of hereditary spastic paraplegia. The genetic causes of SPG11 are single base pair and frameshift mutations in KIAA1840 on chromosome 15q21.1, which encodes spatacsin (14). It is possible that disease is caused by a single gene defect with a wild type function similar to that of KIAA1840. Alternatively, this disorder may be caused by the aggregate effects of multiple genes at the SCA39 locus. The contiguous gene syndrome is not a concept uncommon to disorders where very large chromosomal rearrangements are involved (15), and is more likely with broad, early-onset phenotypes. In summary, we present here a new form of spastic ataxia segregating genomic duplication, which we have denoted as SCA39. There are several plausibly relevant genes across the critical interval. Clearly, finding additional families or individuals with a spastic ataxia phenotype and interval overlapping SCA39 will be key to isolating the critical gene/genes in this region.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Figure 1.

Duplication of ~7Mb on chromosome 11 associated with SCA39. The upper panel shows genotyping data from affected family member 277-14, generated using Illumina HumanHap610quad Bead Chips. Shown is B Allele frequency for each SNP assayed, where a value of 0 indicates a homozygous A/A genotype, a value of 1 indicates a homozygous B/B genotype and a value of 0.5 represents a heterozygous A/B genotype. The boxed region delimits the duplicated segment; within this region there are a lack of heterozygous calls and clusters of points at a B allele frequency of ~0.33 and ~0.66, which coupled with increased signal (not shown), are indicative of A/A/B and A/B/B genotype calls respectively. Figure plotted using R.

Figure 2.

Brain MRI images of proband SAL-277-010 (A) T1-weighted sagittal image showing mild atrophy of the upper part of the cerebellar vermis and thin corpus callosum (B) T2-weighted axial image showing mild periventricular white matter hyperintensities.