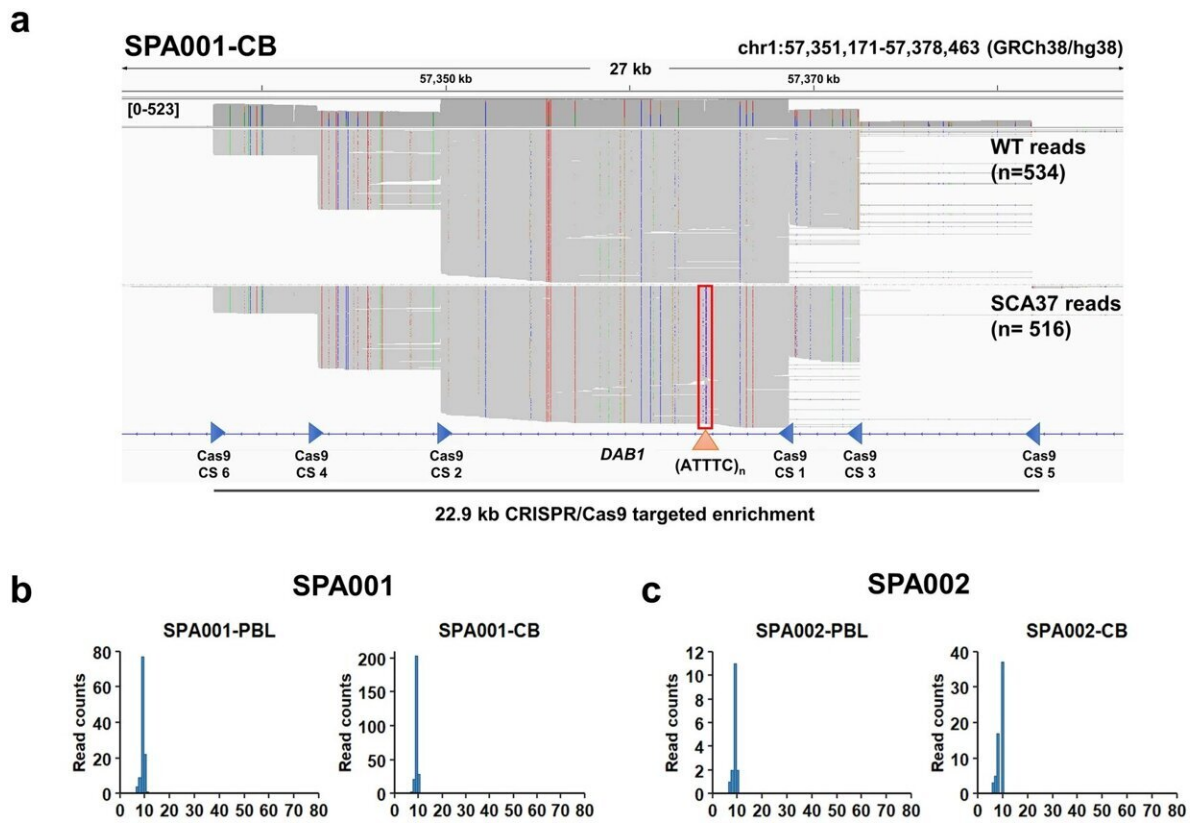
Scientists use an innovative approach to provide relevant insights into a rare neurologic disorder

March 14 2024



Long-read nanopore sequencing of the genomic region including the *DAB1* ATTTT/ATTTC repeat tract enriched by CRISPR/Cas9. **a** The integrative genomics viewer (IGV) showing the entire region of interest within *DAB1* intron 11 enriched by CRISPR/Cas9 successfully captured from SPA001 SCA37 patient's cerebellum. Long sequenced reads were phased using WhatsHap for haplotype reconstruction for wild-type (top) and expanded (bottom) alleles. Read

counts and repeat size for WT-(ATTTT)n and SCA37-(ATTTC)n from SPA001 **b** and SPA002 **c** blood lymphocytes and cerebellar samples. **d** No allele dropout was observed in read counts of expanded alleles compared to normal alleles (two sample *t* test; *p* value = 0.63, *n* = 14). Dot point indicates outlier WT read counts for the HMW extracted SPC0001 fibroblasts. Waterfall plots generated using Guppy Sup base calling mode showed pure (ATTTT)n and (ATTTC)n repeat tracts for SPA001 and SPA002 PBLs (**e** and **g**) and cerebella **f** and **h**. No interruptions were identified in any 5′(ATTTT)n–(ATTTC)n–3′(ATTTT)n repeats tract (Suppl. Figure 5). Relevantly, SCA37 alleles sequenced by long reads showed an ATTTTTTT sequence preceding the 5′(ATTTT)n in SCA37 alleles in contrast to the ATTTATTT sequence preceding the WT-(ATTTT)n alleles. Credit: *Human Genetics* (2024). DOI: 10.1007/s00439-024-02644-7

Researchers from the Germans Trias i Pujol Research Institute (IGTP) and the Barcelona Supercomputing Center-Centro Nacional de Supercomputación (BSC-CNS) have discovered new genetic mechanisms related to spinocerebellar ataxia type 37.

Their research, published in the journal *Human Genetics*, employed advanced techniques such as CRISPR/Cas9 gene editing, real-time large DNA sequencing, and machine learning. The study deepens our understanding of this inherited disease, leading to more precise diagnoses and improved genetic counseling for patients.

Spinocerebellar ataxia type 37 is a rare neurological disorder originally found in patients from the Iberian Peninsula. It starts in adulthood and gradually worsens, causing speech difficulties, imbalance, and uncoordinated movements, among other symptoms. Over time, this often results in increased mobility issues, and many individuals may need to use a wheelchair.

This condition was first described in 2013 by IGTP's Neurogenetics

Group, led by Antoni Matilla. It stems from the degeneration of cerebellar neurons, triggered by a genetic mutation in the Disabled-1 (DAB1) gene. This mutation involves a complex repetitive DNA sequence that leads to the disruption of normal cerebellar function, central to controlling movement and balance.

Matilla's group has continued to study the disease and has now published their *Human Genetics* study with new insights into the disease's genetic mechanisms, in collaboration with BSC-CNS. The team used, for the first time, gene editing with CRISPR/Cas9 and real-time nanopore sequencing, along with machine learning, to precisely analyze the DNA mutation causing spinocerebellar ataxia type 37.

This innovative approach has led to a better understanding of how nearby DNA sequences and specific methylation sites impact the disease's symptoms.

"Our team has generated predictive models using machine learning, which define the genetic and clinical correlations of how the disease progresses and its severity. These models are instrumental in foreseeing how the condition might develop in patients, offering valuable insights for treatment and management," Matilla states.

He adds, "We hope these findings will help provide more accurate diagnoses and better genetic counseling for patients with this type of ataxia." The study also made a significant discovery: tracing the disease's mutation back to a common origin 859 years ago in the Iberian Peninsula by studying Spanish and Portuguese ataxia patients.

This historical perspective adds a new dimension to our knowledge, underscoring the disease's longstanding presence in the region. However, Matilla does not rule out a possible non-European origin of the DNA mutation in this type of inherited ataxia, because at that time, the south

of the Iberian Peninsula established important migration from the African continent.

Overall, this research represents a notable advance in determining the size and structure of the spinocerebellar ataxia type 37 mutation, essential for precise genetic diagnosis. The study uncovers important connections between genotype and phenotype and distinct cerebellar methylation patterns, which deepen our understanding of the underlying causes of the disease.

More information: Marina Sanchez-Flores et al, Novel genotype–phenotype correlations, differential cerebellar allele-specific methylation, and a common origin of the (ATTTC)n insertion in spinocerebellar ataxia type 37, *Human Genetics* (2024). DOI: 10.1007/s00439-024-02644-7

Provided by Germans Trias i Pujol Research Institute