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It Takes 2 (Repeats) to Lose TANGO2

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The sequencing field is rapidly approaching a crossroads. Advances in long read sequencing raise the question: at what point is it economically feasible to start with long-read sequencing to shorten the diagnostic odyssey of patients?

Transport and Golgi organization 2 homolog (TANGO2) deficiency disorder (TDD; OMIM 616878) is an early-onset autosomal recessive neurodegenerative disease with a constellation of symptoms associated with movement defects such as ataxia in addition to muscle breakdown and heart complications.[1-4] Cardiac arrest is the most common cause of mortality.[1,5] Patients often present within the first 1–3 years of life with intellectual disability and microcephaly and are recognized to have TDD after being hospitalized for a metabolic crisis, often triggered by fasting or illness.[1] TDD is also known as recurrent metabolic crises with rhabdomyolysis, cardiac arrhythmias, and neurodegeneration (MECRCN),[6] or less frequently as TANGO2-related metabolic encephalopathy and arrhythmias (TRMEA).[7] Pathogenic variants in *TANGO2* were first described in 2016,[2,4] after which the number of cases attributed to TDD increased dramatically as neurologists gained a better grasp on the patient details and retrospective cohorts were sequenced. A handful of coding and splice altering variants have been detected in TANGO2, but by far the most common variant—accounting for nearly half of cases—is a deletion of exons 3–9.[1,6] This deletion is present at low frequency in the population (minor allele frequency of 0.0013% in European ancestry), although never in homozygous form in unaffected individuals.[3,4] Deletions involving exons 4–6 have also been detected in ∼5% of cases, and other combinations of exon 1–2, 3–5, and 4–9 deletions have been reported.[1]

The function of TANGO2 is not well understood. Cellularly, the TANGO2 protein is localized to the Golgi apparatus and the cytoplasm, with depletion leading to the fusion of Golgi membranes with the endoplasmic reticulum.[2-4,8] Little is known about the function of the TANGO2 protein or its role in metabolic decomposition; however, TANGO2 deficient cells have secondary mitochondrial dysfunction and abnormal trafficking between the Golgi apparatus and endoplasmic reticulum.[3,8] In addition, perhaps owing to the various organs that are affected (*TANGO2* has fairly consistent expression across tissues), it can take time to pin down the corresponding disease. The age at onset is broad (4 months–8 years).[3]

Writing in *Neurology® Genetics*, Sabbagh et al.[9] provide an example of a structural variant in *TANGO2* that becomes clear on long-read sequencing, enabling precise delineation of breakpoints that span several Alu and ERV or Alu and LINE repeats. They identify an exon 3–9 deletion in an individual from one family and an exon 4–6 deletion in 4 siblings from a second family with onset from 2 days to 15 months[9] that were missed with conventional testing approaches. The clinical presentation was quite variable ranging from a slow progression to acute decompensation and metabolic crises in the second family.

Deducing the precise genomic structure of the breakpoints—as is possible with long-read sequencing—can help in understanding how these deletion events occur and what other variability at the breakpoint site could promote deletion and lead to other examples of exon 3–9 loss. Curiously, no microhomology was identified at the exon 3–9 breakpoints.[9] In exon 4–6 loss, there were only 4 base pairs of homologous sequence.[9] This suggests that different mechanisms led to the break and repair events that removed *TANGO2* coding exons, highlighting the importance of investigating the precise repeats that define the deletion. Notably,

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long-read telomere-to-telomere genomes from Human Pangenome Reference Consortium samples[10] reveal variability in the number of Alu repeats at a repeat "graveyard" distal to *TANGO2*.

In theory, a 45 kb homozygous deletion should be readily detected in short read sequence reads because of absence of reads that align to the region. In practice, this is not always obvious, especially when structural variants rely on junction reads that span the deleted region. This underscores the need to have a database of rare structural variants that are important for pathogenicity. Identifying single nucleotide variants in linkage disequilibrium with the deletion could help pinpoint individuals with deletion-by-proxy that warrant follow-up to confirm whether they have a homozygous deletion. Many, if not most, genes have repeats scattered throughout, so it is somewhat surprising that these deletion variants are so prominent in disease. Although the breakpoints identified in the 2 families by Sabbagh et al. appear to be identical to a previous report,[2] not all exon 3-9 junctions are the same, suggesting fragility at the sites and multiple independent events that target the same region.[9] These data highlight the contribution of retrotransposon-mediated recombination for genomic instability at the *TANGO2* locus, which occurs de novo in the most common deletions (exons 3–9 and 4–6), resulting in intergenic deletion sequences across diverse exon pairings.

From a clinical standpoint, TDD-related metabolic crises often emerge after a stressor, such as infection, heat exposure, or fasting.[1,2] Why these particular stressors exacerbate TDD clinical symptoms is not clear and worthy of further investigation. Knowing what individuals are more at risk for serious adverse events could help prioritize aggressive treatment regimens to minimize phenotypic consequences. Clinicians should pay attention to patients presenting with developmental and speech delays and symptoms associated with TANGO2 spells (ataxia, head tilting, exotropia, lethargy, and paroxysmal dyskinesia) in tandem with abnormal laboratory tests including elevated levels of creatinine kinase and corrected QT interval prolongation when admitted for metabolic crisis.[1]

Thus, in examples like these 2 families investigated in Sabbagh et al.,[9] long-read sequencing provides an unambiguous result that was not obvious with previous microarray and exome analysis approaches. In the future, using long-read sequencing early on will help streamline the diagnostic odyssey as costs continue to fall and the approach enjoys a more widespread deployment.

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