

**Is localization of DNA replication origins linked to triplet repeat instability?
DNA replication origin mapping in the spinocerebellar ataxia type VII (SCA7)
locus**

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Scientific Abstract

Abnormal expansion of trinucleotide repeats (TNR) is the hallmark of increasing numbers of human pathological conditions, among which are several types of hereditary ataxias. TNR increase most likely arises from the tendency of these repetitive sequences to promote the formation of unusual secondary structures during various DNA transactions, and, in particular, during DNA replication, probably through the formation of a slipped strand in lagging-strand synthesis. In this respect, the localization of origins of DNA replication might in principle affect replication fork progression. No studies to date have directly demonstrated alterations of DNA replication origins location in human disease, most likely as a consequence of the technical difficulty of origin identification in mammalian cells. The purpose of this project is to identify and characterize the origins of DNA replication in the SCA7 locus in various cell types from normal individuals and cell lines from patients with spinocerebellar ataxia, and to establish whether a correlation exists between origin activity and genomic instability at this locus.

The preliminary results obtained using a newly developed DNA library enriched in origins of replication (Todorovic et al, Mol Cell, 2005) have indicated that at least 4 different DNA replication origins are localized in a ~200 kb region encompassing the SCA7 locus, one of which is located very close to the tract containing the TNR expansion. In the context of this project, these origins will now be mapped at high resolution and their activity characterized in replicating human cells of different histological derivation, in both normal conditions or after cell treatment with agents affecting DNA replication fork dynamics, and in cells lines from patients with spinocerebellar ataxia.

Lay Summary

The genetic abnormality underlying SCA7 is an unusually expanded repeat sequence in the part of the DNA which contains the code for ataxin 7. The disorder is part of a group of inherited neurological conditions which are caused by a similar expansion, like a genetic stutter. In these cases, the rest of the DNA sequence is perfectly normal, thus raising the question as to why the expansion occurs in that particular part. Here, the researchers wish to explore the possibility that the genetic defect is caused by a problem during the original replication of DNA. The research will involve looking at the sites where DNA replication starts from and looking for differences between replication in normal cells and in cells from patients with SCA7, both when they are under normal conditions and when the cells have been put under stress



which may cause damage. If the process of DNA replication is recognised as the main determinant of the disorder, the findings may have implications for completely new treatment approaches for other repeat expansion SCAs as well as SCA7.

This research will provide support for a talented PhD student working with Dr Giacca, an internationally recognized investigator in the field of DNA replication and currently serving as the Director of the Trieste Component of the International Centre for Genetic Engineering and Biotechnology (ICGEB), an international organization devoted to advanced research and training in molecular biology and biotechnology.

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