Synonymous mutations inside the coding region which do not alter the amino acid chain are usually considered to have no effect on the protein. However, in recent years it was shown that they may regulate expression levels via various mechanisms, suggesting that they may also play an important role in tumorigenesis.

In the current study, we suggest a pipeline for detecting cancerous synonymous mutations that affect the cancer fitness via regulation of transcription. We demonstrate our approach by reporting for the first time that two adjacent synonymous mutations in the BCL2 gene were detected. All the patients with one of these mutations have DLBCL GCB lymphoma, which indicates a selection in GCB towards these mutations.

Patients who have at least one of these mutations present significantly higher expression of BCL2, a protein responsible for blocking the apoptotic cell-death mechanism.

MSC (Musculin), a transcriptional repressor known to play a role in B-cells, was found to be significantly influenced by mutations in the 600 and 601 zone.

MSC is highly expressed in lymphocytes, the same cells that GCB lymphoma are developed from. It may denote MSC’s main role in lymphocytes’ action mechanism.

There are no alternative binding sites for the MSC repressor in the surroundings of the 600-601 zone of the BCL2 gene, hence damaging it will prevent repressor binding in that region.

A detection method for cancer driver mutations that interfere with transcription factors' regulation mechanisms was developed. By using this method, novel driver cancerous synonymous mutations within the coding sequence of the BCL2 gene were detected.