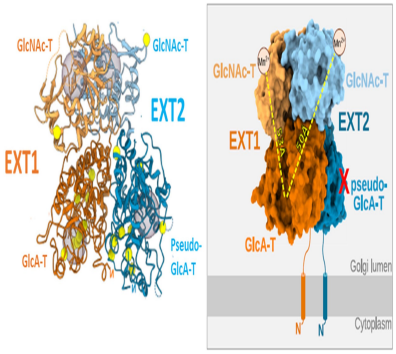
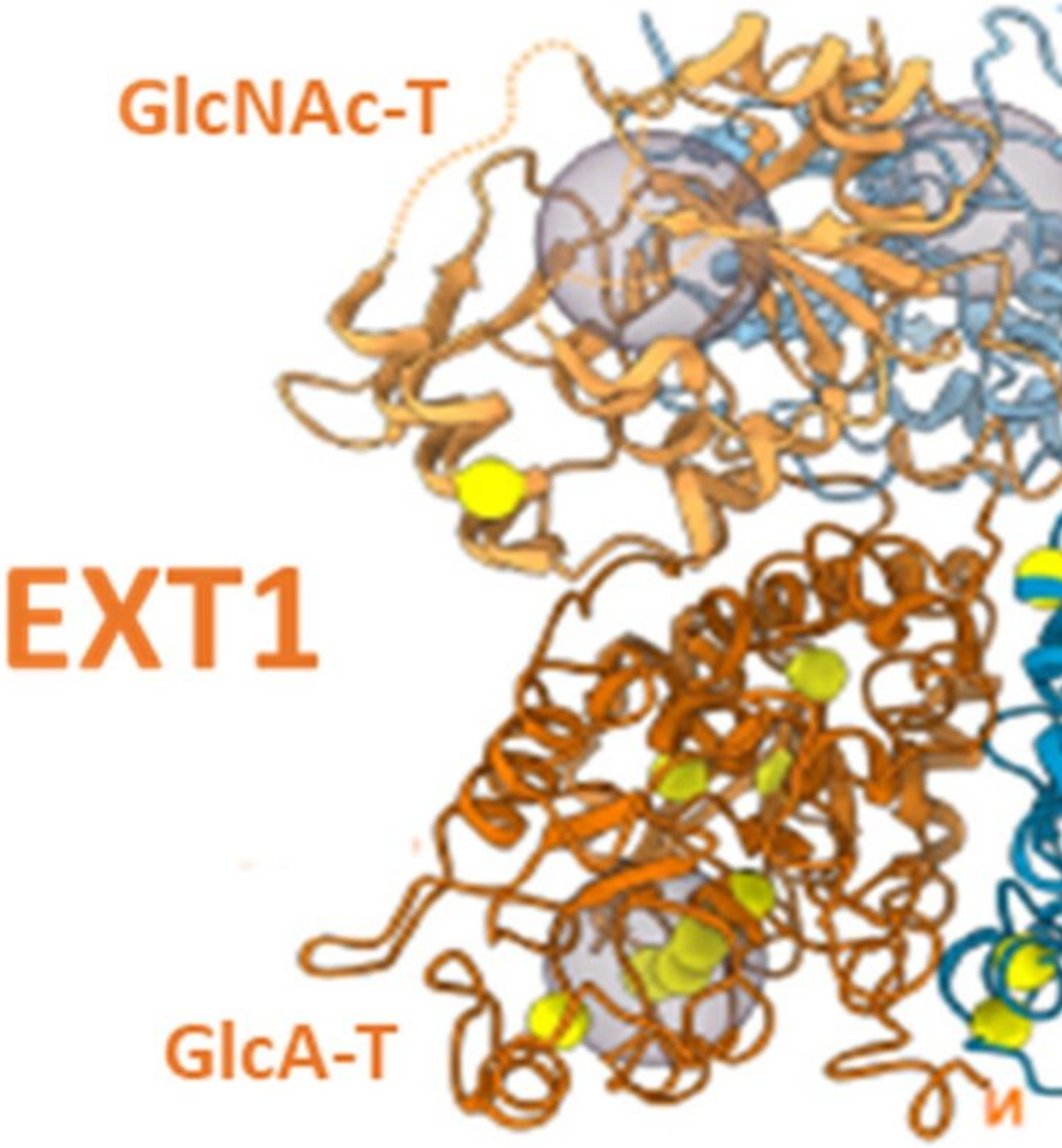



Structure of the Human Heparan Sulfate Polymerase complex EXT1-EXT2

## Description

Heparan sulfates are complex polysaccharides that mediate the interaction with a broad range of protein ligands at the cell surface. A key step in heparan sulfate biosynthesis is catalyzed by the bi-functional glycosyltransferases EXT1 and EXT2, which generate the glycan backbone consisting of repeating N-acetylglucosamine and glucuronic acid units. The molecular mechanism of heparan sulfate chain polymerization remains, however, unknown. The article reports the results of a cryo-electron microscopy structure of human EXT1-EXT2. (PDB accession code 7ZAY) They reveal the formation of a tightly packed hetero-dimeric complex harboring four glycosyltransferase domains. A combination of *in vitro* and *in cellulo*

mutational studies reveals the functional role of the four catalytic sites.



While EXT1 can catalyze both glycosyltransferase reactions, the results indicate that EXT2 might only have N-acetylglucosamine transferase activity. These findings provide mechanistic insight into heparan sulfate chain elongation as a non-processive process. They lay the foundation for future studies on EXT1-EXT2 function in health and disease.

**Category**

1. News