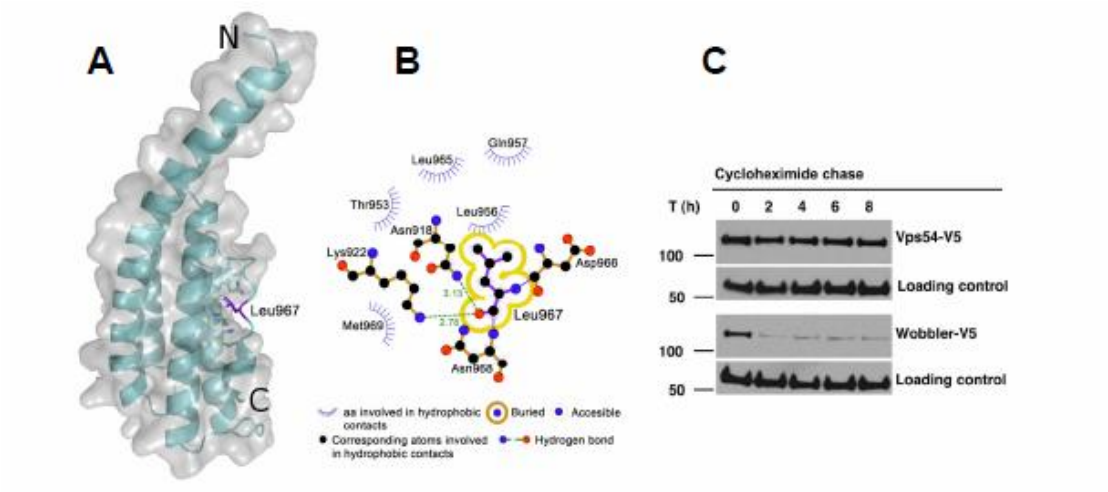
Structural basis for the wobbler mouse neurodegenerative disorder caused by mutation in the Vps54 subunit of the GARP complex

The research, published recently in PNAS (July 6, 2010), was lead by the group of Dr. Aitor Hierro at CIC-bioGUNE, in collaboration with groups from the National Institutes of Health (NIH) and the Neuromuscular Center at the Cleveland Clinic, both in the USA, and the National Centre for Scientific Research (CNRS) in France.

The GARP complex is involved in tethering endosome-derived vesicles to the *trans*-Golgi network. This study sheds light on two important aspects of GARP biology.

Firstly, we report the crystal structure of a C-terminal fragment from the Vps54 subunit of GARP. This structure consists of an α-helical bundle strikingly similar to those of subunits from other multisubunit tethering complexes (MTCs) such as Dsl1, COG and the exocyst. This finding presents the first structural evidence of the ancestral relationship of GARP with other MTCs and is indicative of divergent evolution from common fold.

Secondly, we demonstrate that the leucine-967 to glutamine mutation in Vps54, previously shown to cause a neurodegenerative disorder resembling Amyotrophic Lateral Sclerosis in the “wobbler” mouse, disrupts hydrophobic interactions that are critical for stability and folding of the Vps54 C-terminal domain *in vitro*. We find that this mutation does not prevent integration of Vps54 into the GARP complex but greatly reduces the half-life and levels of the protein *in vivo*. Importantly, we demonstrate that the wobbler phenotype results from destabilization of Vps54 and consequently reduced levels of this protein and of the GARP complex in the mutant mice.



(A) Structure of the C-terminal region of Vps54 highlighting the hydrophobic pocket were Leu967 is located. (B) Diagram showing relevant interactions of Leu967. (C) Stability of Vps54 analyzed by cycloheximide chase.

See the article abstract in:
http://www.pnas.org/content/107/29/12860.abstract