

## W0119

**The Structure of the N-terminal Domain of Lis1 Reveals a Novel and Ubiquitous Dimerization Motif.** David R. Cooper<sup>1</sup>, M.H. Kim<sup>1</sup>, A. Oleksy<sup>2</sup>, Y. Devedjiev<sup>1</sup>, U. Derewenda,<sup>1</sup> O. Reiner<sup>3</sup>, J. Otlewski<sup>2</sup>, Z.S. Derewenda<sup>1</sup>. <sup>1</sup>Univ. of Virginia, Charlottesville, VA, <sup>2</sup>Univ. of Wroclaw, Wroclaw, Poland, <sup>3</sup>Weizmann Institute of Science, Israel.

The crystal structure of the N-terminal domain of Lis1, the product of a causal gene for lissencephaly, has been determined to 1.75 Å. Recent research shows that Lis1 is involved in a myriad of cellular functions, especially dynein-mediated motor functions such as neuronal and nuclear migration and cellular division. Consistent with the proposed role of Lis1 in kinetochore and centrosome formation, homozygous deletions of the Lis1 gene are lethal. Homozygous mutations result in dose dependent defects, notably the debilitating disorder lissencephaly (smooth brain) resulting from abnormal neuronal migration. The Lis1 protein consists of an N-terminal LisH (Lis1 Homology) motif that is found in over 100 proteins, a coiled coil fragment, and a seven-blade  $\beta$ -propeller domain. Structural and thermodynamic characterization reveals that the LisH motif is a very stable homodimerization domain with a large buried interface. Proper formation of the coiled coil region enforces a dramatic asymmetry on the homodimer. The absolute sequence conservation of the disparate fragment suggests that this asymmetry is vital for the function of Lis1.