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Neanderthal adenylosuccinate lyase: insights in catalysis and link with disease-causing mutation

Bart Van Laer[1], Ulrike Kapp[1], Montserrat Soler-Lopez [1], Kaja Moczulska[2], Svante Pääbo[2], Gordon Leonard [1], Christoph Mueller-Dieckmann [1]

1. Structural Biology group, European Synchrotron Radiation Facility (ESRF), Grenoble, France
2. Max Planck Institute for Evolutionary Anthropology, Leipzig, Germany

email: bart.van-laer@esrf.fr

Adenylosuccinate lyase is a conserved enzyme involved in purine metabolism for which several mutations in the human enzyme (hADSL) are known to affect intelligence and behaviour. During evolution modern humans acquired a specific substitution (Val429Ala) in ADSL distinguishing it from the ancestral variant present in Neanderthals (nADSL). I will present a structural, biophysical and biochemical comparison of hADSL and nADSL aimed at determining whether this substitution is functionally relevant and could be responsible for phenotypical differences between these species. This work shows that hADSL and nADSL differ in thermal stability but not in enzymatic activity. Similar observations are made when comparing native hADSL with hADSL containing the nearby disease-causing Arg426His substitution hinting towards a phenotypical effect. In addition the combined X-ray crystallography and SAXS data reveals that ADSL undergoes conformational changes during catalysis which together with the structure of a hitherto undetermined product bound conformation helps explain the effect of several human disease-causing substitutions.

Keywords: Neanderthal, Human disease.