Molecular study of Neanderthal adenylosuccinate lyase provides insights in catalysis and reveals a correlation with a human disease-associated mutant

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The advent of genetic information from genomes originating from ancient, sometimes long-extinct species has revolutionised palaeontology and allowed the analysis of the genetic make-up of these species. Thus, the availability of complete genome sequences from archaic hominins permitted the identification of genes which differentiate them from modern humans, information which might be used to provide a deeper understanding of how they differed from modern humans. Genome comparisons can identify differences in DNA and protein sequences between archaic and modern humans but it is difficult, if not impossible, to predict the effect these differences have on the corresponding proteins or on the human phenotype as a whole. We provide a biochemical and biophysical comparisons of a protein, adenylosuccinate lyase (ADSL), which differs between modern humans and Neanderthals by a single amino acid substitution (Ala/Val429). Mutations in this enzyme involved in the purine metabolism can cause ADSL deficiency in modern humans, a disorder associated with psychomotor retardation, epilepsy or autistic features. We detected a decreased stability for the human isoform as compared to the Neanderthal protein and found a mutant human ADSL protein associated with ADSL deficiency to display an even further decrease in stability. Furthermore, our work reveals that ADSL undergoes conformational changes during catalysis and that the structural difference between Neanderthal and modern human ADSL is confined to the dynamics of the associated domain movement. This difference is not translated in a measurable alteration in the enzymology of the purified protein but we speculate that interactions of ADSL in the purinosome can augment the effect of the Ala/Val429 substitution. Cryo-electron microscopy studies could be used for testing this hypothesis and can provide more insights in the conformational flexibility of the Neanderthal and modern human ADSL proteins.