Thesis: **Variability in *LPA* gene transcription regulatory sequences**

Name: **Mgr. Kateřina Zídková**

Thesis Adviser: **Prof. Richard Češka, M.D., Ph.D.**

Consulting Thesis Adviser: **Assoc. Prof. Milada Kohoutová, M.D., Ph.D.**

Summury of Doctorate thesis

Increased Lp(a) concentration is an independent risk factor for premature atherosclerosis. The Lp(a) concentration is almost entirely genetically determined with an exclusive linkage to a unique locus, the gene for apo(a), so called *LPA* locus. Nevertheless Lp(a) concentrations varies widely between individuals in all populations studied so far. There is a *LPA* gene size heterogeneity (K_{LPA}IV type 2 repetition) accounting for 40-60% of the variance. Some of the variance could be additionally related to polymorphic sites either in the coding sequence or in transcription regulatory regions of *LPA* gene.

We had scanned the *LPA* gene transcription regulatory regions (promoter, DHII, and DHIII enhancers) for variabilty. None of them was revealed to be extremely polymorphic. However significant linkage disequilibrium was detected even between polymorphic sites from far regulatory sequences. We have investigated if certain compound genotypes of apo(a) gene regulatory sequences could be associated with a narrow range of Lp(a) levels at least in part due to linkage with restricted range of apo(a) gene K_{IV} type 2 length variants. In contrast with the persistent genetic linkage all major 5-polymorphic compound genotypes were distributed in a broad range of Lp(a) levels.

Considering the low recombination rate that tends to preserve the ancestral chromosome segment composition we suggest the unequal sister chromatid exchange and gene conversion as possible mechanisms of a new apo(a) isoform evolvement and redistribution of polymorphic sites without disrupting linkage disequilibrium. Thus, combined effect of all polymorphic sites from the whole *LPA* gene locus, including the gene length polymorphism, should be considered when dealing with high population variability of Lp(a) levels.