The restless legs syndrome (RLS) is a sensomotor disoder characterized by urge to move lower extremities and this urge is usualy associated with unpleasnat sensations. The symtoms of RLS are alleviated with movement and, on the contrary, worsen during rest. The urge presents circadian rhytmicity peaking in the evening and the first half of night. The diagnosis of RLS is set according to patients' history fulfilling the essential criteria. The prevalence of RLS is quite high in western countries about 11%, women being affected twice as often as men. The disease has two forms, secondary and idiopathic. In the idiopathic RLS, positive family history is observed at about 50% of cases. There are already 3 genetic susceptibility loci on chromosomes 12, 14 and 9 published to be linked with RLS (RLS1, RLS2 a RLS3). Furhter 2 new loci were identified on chromosomes 17 and 4 insofar unpublished study. The current opinion suggests a complex model of inheritance in RLS. The aim of this project was to compare clinical and laboratory parameters in sporadic to familiar RLS and in families affected by RLS to confirm linkage previously detected loci, and eventually discover new susceptibility loci.

The RLS patients were appart clinical evaluation examined with a set of hematological and biochemical tests, incuding erythropetin serum levels and levels of soluable transferin receptor. DNA was collected in families with 2 and more members affected and centralized within the scope of multicentric European project called EU-RLSGENE. The families of Czech origin were tested for linkage in known loci using both parametric and non-parametric tests. In other four families out of the EU-RLS-GENE a genome-wide scan was performed. Furhter we have conducted a family-based asociation study in trios (a family with one affected offspring and both parents genotyped) from the EU-RLS-GENE sample in the loci, where originály linkage was observed. The trios were divided into three groups according to their ethnical origin. Trasmisson disequilibrium test (TDT) detecting both association and non-parametric linkage was employed to analyze the trios. Individuals were genotyped using micosatellite markers and the genome wide scan was performed using single nucleotide polymorphisms (SNP).

In 228 clinically examined patients we have proven a significantly lower age-at-onset of RLS in familier cases as an only difference from the sporadic ones. In 183 patient with laboratory test available we have observed only marginaly signicant lower absolute count of red blood cells in sporadic as compared to familial RLS. The median of erythropoetin level was significantly lower in patients with familial RLS than in the reference population. This finding represents the first observation of erythropoetin level in familial RLS. In 10 RLS pedigrees of Czech origin, signs of linkage at tested loci were observed neither by parametric nor non-parametric tests. However, TDT has detected a significant association with marker D12S78 with in RLS1 locus at $p<0,05$. This result further corroborates the impact of this locus upon RLS ethiology in the central European population. The genome-wide scan has revealed further locus on chromosome 19 in an Italian family by means of both non-parametric and parametric linkage. A family-based association study has confirmed significant impact in the RLS2 locus in the whole group and the same significance level was present for loci on chromosomes 17 and 19 confirming their relevance in RLS etiology. For RLS3 a significant association was observed only in trios of central European origin and for different markers in south europen trios. This result suggests a genetic heterogeneity even in the same locus. On chromosome 4 an asociation was observed with only one marginal marker in subset of trios of north European origin. The impact of this locus could not be confirmed.