Update on Ongoing Projects: Sequence Analysis in the RLS3* Region

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We have recently identified a likely new RLS locus, designed RLS3*, in a large German family with onset of RLS in childhood or early adulthood. A haplotype on chromosome 9p was shared by all 12 investigated affected family members.[1] This haplotype did not overlap with the previously published RLS3 locus.[2]

According to the latest version of the Human Genome Sequence, there are 33 genes located in the RLS3* region, including 12 pseudogenes. We have sequenced all genes but the pseudogenes and two micro RNAs in this region to detect the disease-causing mutation in our RLS family. We found 75 known polymorphisms that are reported to occur with a frequency of >15% among controls. In addition, we found three unpublished heterozygous variants. Two of these changes are located in the TUSC1 gene and we found them in >20% of 40 control chromosomes. The third variant was rare among controls (12/291; 4%). This variant segregated with the disease in the RLS3* family. We found the same variant in another 4/53 (8%) German RLS patients. Three of the patients had an age at onset before the age of 20 years. For one patient, three affected family members were available but the variant did not segregate with the disease.

Taken together, we failed to identify a clear monogenic cause of RLS in the RLS3* family. Further investigations will elucidate the role of a rare variant in the RLS3* region as a potential susceptibility factor for (early onset) RLS.

References

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2. Chen S, Ondo WG, Rao S, Li L, Chen Q, Wang Q. Genomewide linkage scan identifies a novel susceptibility locus for restless legs syndrome on chromosome 9p. American journal of human genetics 2004;74(5):876-885.