論 文 の 内 容 の 要 旨

獣医学　専　攻
平成２１年度博士課程　入学
氏　　名　パベル　プロセルコフ
PAVEL PROSSELKOV
指導教員名　糸原　重美

論文題目　Evolution of the Cognitive Complement as a product of subneofunctionalization among the Netrin-G family members
（ネトリン Ｇファミリーメンバーの機能分化による認知機能の進化）

More than half a billion years ago a dramatic event happened in the evolution of Earth: a whole genome duplication of the jawless fish resulted in the appearance of vertebrates carrying a double load of genes. Ability to simultaneously integrate both sensory (bottom-up) and higher cognitive processing (top-down) stimuli of the complex milieu had being given a boost and had successfully evolved into the emergence of mammals and subsequently into humanoid-like creatures claiming to possess a higher cognitive abilities than their precedents and other close evolutionary related species. And this is likely how the subneofunctionalization of several paralogue genes had started with the Netrin-Gs among them. Originally derived from the cell adhesion (laminin) and guidance cue superfamilies (netrins) Netrin-G1 (G1) and Netrin-G2 (G2) are both unique in their ability of being attached to the presynaptic membrane and brain-restricted appearance. Their self-exclusive pattern of expression in the brain areas and participation in the brain laminar structure formation points towards a discernable dissociation of their function in the information segregation flows.

Both, G1 and G2 show an extraordinary level of protein conservation among the vertebrates with 100% and 99% identity between the human and apes, 97% and 88% between the mice and humans, 67% and 57% between the human and tetrapod fish coelacanth, respectively. Two coding areas within the both genes (Ukd domain and GPI-link) underwent an accelerated evolution with the simultaneous great expansion of the preceding introns. Single nucleotide substitutions from them are seemed to play a key role in the Netrin-Gs subneofunctionalization and, as a result, adopting the *de novo* evolving cognitive features. To test this, schizophrenic patients (G1: n=61, G2: n=59, controls: n=143) carrying SNPs for either G1 or G2 genes underwent IQ tests (WAIS-III). The results unequivocally demonstrate a dramatical effect of a single SNP for each gene on the cognitive subdomain performance with G1 SNP affecting verbal comprehension (p = 0.0037) and G2 working memory (p = 0.0031) information flow.

Human psychogenetics data fully corroborate the observations in the mice cognitive phenotype abnormality, with G2 but not G1 upregulated by the cognitive task and a smaller brain size for the both KO mice upon the life-time intensive cognitive training comparing to the wild-type. Despite G1 and G2 have an identical gene and protein domain structures the function they perform is definitely not the same but rather complementary to each other comprising the unit of cognition.