

Monday November, 13
10.30am – 12.30pm
Poster Session 1
Comparative Sequence Analysis Pages
Posters P1 – P14

- P1 EXPRESSION PROFILING OF LEPTOTENE AND PACHYTENE SPERMATOCYTES IN MICE HETEROZYGOUS FOR T(16;17)43H TRANSLOCATION**
D Homolka, P Jansa, R Ivánek, J Capková, J Forejt
Institute of Molecular Genetics, Acad. Sci., Prague, Czech Republic
- S11/P2 EVALUATING THE DISEASE RELEVANCE OF NON-CODING CONSERVED SEQUENCES AT RET**
EA GRice, A Chakravarti, AS McCallion
Johns Hopkins University, McKusick-Nathans Institute of Genetic Medicine, Baltimore, MD, United States
- P3 SENSE RECEPTORS OF MARINE MAMMALS: EVIDENCE FOR REDUCTION OF THE FUNCTIONAL OLFACTORY RECEPTORS**
T Kishida, S Kubota, Y Shirayama, H Fukami
Kyoto University, Wakayama, Japan
- P4 HCOP: THE HGNC COMPARISON OF ORTHOLOGY PREDICTIONS SEARCH TOOL**
MW Wright, MJ Lush, S Povey, EA Bruford
HUGO Gene Nomenclature Committee (HGNC), London, United Kingdom
- P5 BICC1 ZEBRAFISH MODEL FOR POLYCYSTIC KIDNEY DISEASE (PKD)**
DJ Bouvrette, A Chandrasekhar, EC Bryda
University of Missouri-Columbia, Columbia, MO, United States
- P6 HOMOLOGOUS RECOMBINATIONS OBSERVED WITHIN THE HEMOGLOBIN BETA ADULT GENES OF THE WILD DERIVED HOUSE MOUSE, MUS MUSCULUS, IN EAST ASIA**
JS Sato¹, YY Yamaguchi¹, JU Ueta¹, HS Suzuki², WC Wang³, AK Kryukov⁴, KM Mekada⁵, NT Takahata⁶, KM Moriwaki⁵
¹Faculty of Life Science and Technology, Fukuyama University, Fukuyama, Hiroshima, Japan, ²Graduate School of Environmental Earth Science, Hokkaido University, Sapporo, Hokkaido, Japan, ³Lanzhou Institute of Biological Products, Lanzhou, China, ⁴Institute of Biology and Soil Science, Far East Branch of Russian Academy of Sciences, Vladivostok, Russia, ⁵RIKEN Tsukuba Institute, Bioresource Center, Tsukuba, Ibaraki, Japan, ⁶Department of Biosystems Science, Graduate University for Advanced Studies, Hayama, Kanagawa, Japan
- P7 RAT RESOURCE AND RESEARCH CENTER**
BA Bauer, EC Bryda, CL Franklin, RK Riley
University of Missouri, Columbia, MO, United States
- P8 MUT-POWER: A HIGH-THROUGHPUT DNA SCREENING METHOD FOR DETECTING ENU-INDUCED MUTATIONS**
T Mashimo¹, S Tokuda¹, S Nakanishi¹, R Nakajima², T Kuramoto¹, K Yanagihara², T Serikawa¹
¹Institute of Laboratory Animals, Graduate School of Medicine, Kyoto University, Kyoto, Japan, ²Horizontal Medical Research Organization, Graduate School of Medicine, Kyoto University, Kyoto, Japan
- P9 THE ORIGINS OF SEX SPECIFICITY OF RECOMBINATION**
PM Petkov¹, KW Broman², J Szatkiewicz¹, K Paigen¹
¹The Jackson Laboratory, Bar Harbor, ME, United States, ²Johns Hopkins Bloomberg School of Public Health, Baltimore, MD, United States
- P10 PHYLOGENETIC AND COMPARATIVE ANALYSES OF THE ALDOLASE GENE FAMILY AND RELATED PSEDOGENES**
TA Bell, S Vegumanti, DA O'Brien, F Pardo-Manuel de Villena
UNC-CH, Chapel Hill, NC, United States
- P11 THE RAT GENOME DATABASE: INTEGRATED DATA PLATFORM**
M Shimoyama, D Li, R Nigam, A Patzer, V Petri, W Rood, J Smith, R White, S Twigger, A Kwitek, H Jacob
Medical College of Wisconsin, Milwaukee, WI, United States

P12 A LINEAR MIXED MODEL APPROACH TO IDENTIFYING EXPRESSED SINGLE FEATURE POLYMORPHISMS

SR Bischoff¹, S Tsai¹, B Freking², D Nonneman², G Rohrer², J Piedrahita¹

¹Department of Molecular Biomedical Sciences, College of Veterinary Medicine, North Carolina State University, Raleigh, NC, United States, ²ARS, USDA, U.S. Meat Animal Research Center, Clay Center, NE, United States, ³Center for Comparative Medicine and Translational Research, Raleigh, NC, United States

P13 COMPARATIVE GENOMIC MAPPING OF THE DEERMOUSE (PEROMYSCUS MANICULATUS) REVEALS MUCH GREATER SIMILARITY TO RAT (R. NORVEGICUS) THAN TO THE LAB MOUSE (M. MUSCULUS)

CM Ramsdell, JL Weston, EL Thames, AA Lewandowski, TC Glenn, MJ Dewey

University of South Carolina, Columbia, SC, United States

P14 IDENTIFICATION OF REGULATORY ELEMENTS RESPONSIBLE FOR NEURONAL RESTRICTION OF RAB3A EXPRESSION

R Liu, S Hannenhalli, M Bucan

¹Department of Genetics, University of Pennsylvania, Philadelphia, Pennsylvania, United States, ²Penn Center for Bioinformatics, University of Pennsylvania, Philadelphia, Pennsylvania, United States

P1

EXPRESSION PROFILING OF LEPTOTENE AND PACHYTENE SPERMATOCYTES IN MICE HETEROZYGOUS FOR T(16;17)43H TRANSLOCATION

D Homolka, P Jansa, R Ivánek, J Capková, J Forejt
Institute of Molecular Genetics, Acad. Sci., Prague, Czech Republic

Certain mouse and human chromosomal rearrangements in heterozygous state lead to spermatogenic failure. These rearrangements share several common features: 1) male-limited character of sterility, 2) incomplete spermatogenic arrest at pachytene level, 3) incomplete synapsis of rearranged chromosomes and 4) nonrandom association between rearranged chromosomes and sex chromosomes. Although the mechanism of the spermatogenesis breakdown is not clear, these features imply that such chromosomal rearrangements might interfere with meiotic sex chromosome inactivation¹ (MSCI). To assess the influence of these rearrangements on MSCI we have performed whole-genome expression profiling of leptotene and pachytene spermatocytes of mice heterozygous for the male-sterile T(16;17)43H translocation. The results of expression profiling were compared with synaptic status of individual chromosomes and their chromatin modifications.

¹Forejt, Trends Genet. 12:412, 1996.

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P3

SENSE RECEPTORS OF MARINE MAMMALS: EVIDENCE FOR REDUCTION OF THE FUNCTIONAL OLFACTORY RECEPTORS

T Kishida, S Kubota, Y Shirayama, H Fukami
Kyoto University, Wakayama, Japan

Terrestrial mammals have well developed sense of smell and taste. These abilities relies on the olfactory receptor (OR) and taste receptor multigene families. These sense receptor genes were known to have diverged in the terrestrial environment after fish-tetrapod split, suggesting that these receptors in mammals are essential to survive in the terrestrial environment. We cloned OR genes in baleen and toothed whale genome, and revealed that few cetaceans-specific gene duplications were observed and that the fraction of pseudogenes was significantly larger than that of terrestrial mammals. We also tried to clone bitter taste receptor (T2R) genes in cetaceans, but could find little T2R sequences - all of them were revealed as pseudogenes. These findings suggested that senses of smell and taste acquired in the terrestrial environment were not essential to survive in the marine environment.

P4**HCOP: THE HGNC COMPARISON OF ORTHOLOGY PREDICTIONS SEARCH TOOL**

MW Wright, MJ Lush, S Povey, EA Bruford
HUGO Gene Nomenclature Committee (HGNC), London, United Kingdom

The HUGO Gene Nomenclature Committee (HGNC) maintains a close collaboration with the Mouse Genomic Nomenclature Committee (MGNC) and together we make every effort to reduce interspecies nomenclature confusion by assigning the equivalent gene symbol to orthologous human and mouse genes, where possible.

Various groups report orthology information, but a single tool for comparison of these data to identify a consensus of the orthology predictions has not previously been available. The HGNC Comparison of Orthology Predictions search tool, HCOP (<http://www.gene.ucl.ac.uk/hcop.pl>), enables users to compare ortholog predictions for a specified human gene, or set of human genes. HCOP was originally designed to show orthology predictions between human and mouse, to identify discrepantly named orthologs, but has recently been expanded to include rat and chicken genes.

HCOP currently includes orthology data from the Ensembl, HGNC, HomoloGene, Inparanoid, MGI and PhIGs databases. Users can assess the reliability of the prediction by the number of these different sources that identify a particular orthologous pair. Each HCOP search returns the official nomenclatures, sequence accessions, database identifiers, aliases, and chromosomal locations for each putative ortholog pair. In the future this resource could potentially be further expanded, to include orthology information from other orthology prediction databases and for other species.

Further information on the work of the HGNC can be found on our website (<http://www.gene.ucl.ac.uk/nomenclature>). Please contact us directly if you have any orthology or gene nomenclature queries at nome@galton.ucl.ac.uk

P5**BICC1 ZEBRAFISH MODEL FOR POLYCYSTIC KIDNEY DISEASE (PKD)**

DJ Bouvrette, A Chandrasekhar, EC Bryda
University of Missouri-Columbia, Columbia, MO, United States

Polycystic kidney disease (PKD) is an inherited disorder affecting nearly 600,000 Americans. Clinical manifestations include renal enlargement, progressive cyst formation, abnormal tubular development and ultimate progression into end-stage renal disease. Several genes, when mutated, have been shown to cause a PKD phenotype, however, the molecular mechanisms and pathways involved in cystogenesis remain unclear. *Bicaudal-C* (*Bicc1*) is the PKD disease-causing gene in the juvenile congenital polycystic kidney (*jcpk*) mouse model. The function of *Bicc1* in the kidney is unknown; however there is a high degree of conservation at both the nucleotide and protein levels across species. In this study, we use the unique characteristics of zebrafish to further investigate *Bicc1* function in the kidney. Early kidney development in zebrafish parallels that of the mammalian system to the mesonephros stage. The zebrafish pronephros forms between 12-72 hours post fertilization (hpf) and can be visualized easily in the transparent embryos. The expression of *Bicc1* in zebrafish was evaluated by RT-PCR and *in situ* hybridization, demonstrating that *Bicc1* is expressed from the 2 cell stage through 48 hpf. An antisense morpholino was used to knockdown *Bicc1* expression in zebrafish to determine the effects of loss of *Bicc1* function. Histological analyses of the morphants reveal large, epithelial lined cysts throughout the tubules of the pronephric kidney, closely resembling the cystic phenotype in the mouse. Rescue experiments utilizing the mouse *Bicc1* gene in the zebrafish *Bicc1* morphants will provide further evidence that *Bicc1* has a similar functional role in both the mouse and zebrafish. Our preliminary work supports the validity of using a zebrafish model to study *Bicc1* function in the kidney.

P6**HOMOLOGOUS RECOMBINATIONS OBSERVED WITHIN THE HEMOGLOBIN BETA ADULT GENES OF THE WILD DERIVED HOUSE MOUSE, *MUS MUSCULUS*, IN EAST ASIA**

JS Sato¹, YY Yamaguchi¹, JU Ueta¹, HS Suzuki², WC Wang³, AK Kryukov⁴, KM Mekada⁵, NT Takahata⁶, KM Moriwaki⁵
¹Faculty of Life Science and Technology, Fukuyama University, Fukuyama, Hiroshima, Japan, ²Graduate School of Environmental Earth Science, Hokkaido University, Sapporo, Hokkaido, Japan, ³Lanzhou Institute of Biological Products, Lanzhou, China, ⁴Institute of Biology and Soil Science, Far East Branch of Russian Academy of Sciences, Vladivostok, Russia, ⁵RIKEN Tsukuba Institute, Bioresource Center, Tsukuba, Ibaraki, Japan, ⁶Department of Biosystems Science, Graduate University for Advanced Studies, Hayama, Kanagawa, Japan

Since the onset of considerable samplings in 1970s, many individuals of the wild derived house mouse, *Mus musculus*, in East Asia have been examined with morphometric, chromosomal, biochemical, and genetic data. Several variants of the hemoglobin beta chain (*Hbb*) have also been characterized by polymorphisms of the protein electrophoresis and nucleotide sequences. There are five *Hbb* haplotypes, *s*, *d*, *p*, *w1*, and *w2* in the wild populations of the house mouse and the establishment of these haplotypes are closely associated with the diversification process of the main four subspecies groups, *baccarionus*, *castaneus*, *domesticus*, and *musculus*. In this study, by determining the nucleotide sequences of the b1 and b2 genes, we show that the *p* haplotype is the recombinant carrying the b1 gene of the *d* haplotype and the b2 gene of the *w1* haplotype, and the *w2* haplotype is likewise the recombinant between the *w1* and unknown haplotypes. The recombination points were also specified within the intergenic spacer region between b1 and b2 genes, and it was suggested that the recombination events are possibly caused by tandem repeat sequences. We discuss more about the differentiation of the mouse subspecies groups, the recombination events caused by hybridizations among different subspecies groups, and the role of the repeat sequences on the recombination mechanism within the genome.

P7**RAT RESOURCE AND RESEARCH CENTER**

BA Bauer, EC Bryda, CL Franklin, RK Riley
 University of Missouri, Columbia, MO, United States

The Rat Resource and Research Center (RRRC) was established in 2001 with funding from the National Institutes of Health (NIH) National Center for Research Resources (NCRR). The goals of the RRRC are to (1) provide the biomedical community with a repository and distribution center for valuable rat strains, and (2) to shift the burden for maintaining and distributing unique rat models from investigators to a National Resource Center. Currently, the RRRC has imported more than 300 rat lines through donations from investigators who have created rat models, active recruitment of valuable rat models, and assuming responsibility for previous archival collections of rat models. Gametes and embryos are cryopreserved from all rat models to insure against future loss of the model. Rat models are available for distribution as live animals, tissues or cryopreserved gametes and embryos. Additionally, an international network of rat repositories has been established linking the United States, Europe and Japan. Through this international network the RRRC can provide rat models that are available worldwide to biomedical researchers using the RRRC on-line ordering system. In addition to repository and distribution functions, the RRRC also conducts research. To date, research efforts by the RRRC have significantly advanced cryobiology, infectious disease detection and assisted reproductive technologies (ART) for the rat. The RRRC (www.nrrrc.missouri.edu) is a valuable resource to the community of rat users as it continues to expand the rat models available and services available to the biomedical community

P8

MUT-POWER: A HIGH-THROUGHPUT DNA SCREENING METHOD FOR DETECTING ENU-INDUCED MUTATIONST Mashimo¹, S Tokuda¹, S Nakanishi¹, R Nakajima², T Kuramoto¹, K Yanagihara², T Serikawa¹¹Institute of Laboratory Animals, Graduate School of Medicine, Kyoto University, Kyoto, Japan, ²Horizontal Medical Research Organization, Graduate School of Medicine, Kyoto University, Kyoto, Japan

Although the laboratory rat is an increasingly used mammalian model in biomedical research, no technology exists so far in this species for the production of *in vivo* genetically engineered mutations equivalent to knockout or knock-in mice. The aim of our project is to generate a large repository of ENU induced mutations identified in the heterozygous carriers by structural changes at the DNA level. For the development of this technology we used the Mu-transposition technique as recently reported by Yanagihara et al; (*PNAS* 2002). Mu transposition exhibits a strong target site preference for single-nucleotide mismatches. We combined Mu transposition with DNA pooling to develop a high-throughput DNA screening method, so called MuT-POWER.

Male F344/NSlc rats were treated with a split dose of ENU (2 x 40 mg/kg) and were mated with F344/NSlc females to generate G1 offspring. Phenotypic variant pups were visually inspected in the G1 rats checking for obvious anatomical malformations or behavioral abnormalities. Genomic DNA of these G1's were pooled eightfold to maximize the efficiency of mutation detection. PCR amplifications were performed with 42 primer sets (12 epilepsy related genes), followed by Mu transposition reaction at 20 degree for 5 min. DNA products were then capillary-electrophoresed using an ABI3100 DNA sequencer. The MuT-POWER technology proved to be a very powerful tool to detect point mutations in ENU mutagenized G1 animals, reducing the cost performance ratio to about one tenth compared to standard sequencing analysis as well as it leads to a drastic reduction of sequencing time.

P9

THE ORIGINS OF SEX SPECIFICITY OF RECOMBINATIONPM Petkov¹, KW Broman², J Szatkiewicz¹, K Paigen¹¹The Jackson Laboratory, Bar Harbor, ME, United States, ²Johns Hopkins Bloomberg School of Public Health, Baltimore, MD, United States

The reasons why mammalian recombination frequencies are significantly higher in females than in males (1.7x in humans, 1.3x in mice) have remained elusive. Although we know that meiotic recombination is restricted to special sites termed hotspots, it has been unclear whether females and males use different hotspots or vary the activity of the same set, and whether these sex differences are uniform along chromosomes or subject to regional variation.

To address this problem, we studied the recombination frequencies along mouse Chr 1 in 3000 offspring each of C57BL/6J x CAST/EiJ F1 females and males. Recombinants over the entire chromosome were mapped at 5-Mb resolution, and those in the distal 25 Mb were mapped at 3-50 kb resolution to provide detection of single hotspots. Our results lead to several conclusions.

At high resolution, both sexes generally used the same hotspots, and only a few hotspots could be considered truly sex-specific. There were, however, significant differences between the two sexes in activity of many hotspots, both on a regional basis (long stretches where female or male recombination predominated) and, within these regions, substantial variation at individual hotspots.

Over the entire Chr 1, meiosis in females resulted in 1.25x more recombination than in males, which is similar to the genome-wide ratio of 1.3. Both sexes showed the same frequencies of single recombinants. The difference was entirely due to the increased number of double (1.53x) and triple (23.4x) crossovers in females. This resulted from the fact that the minimal interference distance between crossovers (the distance within which double crossovers are excluded) was substantially greater in males (90Mb) than in females (60Mb), thus reducing the possibility of double crossovers.

We conclude that crossover interference mechanisms play a major role in determining the higher recombination rates in females compared to males. This fact may bring new insights in our understanding of the fine details of processes occurring in prophase I of meiosis.

P10

PHYLOGENETIC AND COMPARATIVE ANALYSES OF THE ALDOLASE GENE FAMILY AND RELATED PSEDOGENES

TA Bell, S Vegumanti, DA O'Brien, F Pardo-Manuel de Villena
UNC-CH, Chapel Hill, NC, United States

Glycolytic enzymes are required for sperm motility and male fertility, as demonstrated by targeted deletion of GAPDHS or PGK2, two isozymes in this pathway that are expressed only in male germ cells. In mammals the 11 enzymes that catalyze glycolysis are each encoded by a gene family containing both canonical genes and retrogenes. In addition, there are large numbers of related pseudogenes for many of these gene families. Our preliminary studies indicate that the number of pseudogenes may exceed the number of genes by two or three orders of magnitude. The large number of genes, retrogenes and pseudogenes represents a challenge for the identification of clinically relevant mutations in a trait (infertility) that is rarely studied by pedigree analysis. On the other hand, the large number of genes may facilitate the identification of functionally important amino acid variants through comparative analysis. Detailed genomic comparisons also may provide new insights in the evolution of gene families and in the mechanics of retrotransposition of processed mRNAs. As a test case we have characterized the aldolase gene family in mouse. This family is composed of three canonical genes, two retrogenes expressed in the male germline and over a dozen pseudogenes. Our studies reveal the complex phylogenetic relationships between genes, retrogenes and pseudogenes. We also demonstrate that: 1) there are differences between in retroposition rates among gene family members, 2) there are variations in retroposition rate of a gene during evolution and 3) there are biases among genomic regions in which retroposed sequences lie.

P11

THE RAT GENOME DATABASE: INTEGRATED DATA PLATFORM

M Shimoyama, D Li, R Nigam, A Patzer, V Petri, W Rood, J Smith, R White, S Twigger, A Kwitek, H Jacob
Medical College of Wisconsin, Milwaukee, WI, United States

The Rat Genome Database continues to provide researchers with a comprehensive platform of integrated data and analysis tools. RGD attracts an ever-growing, diverse population of users looking for a one-stop data mining and analysis center. In addition to a comprehensive dataset of genetic and genomic elements, RGD also integrates diverse data types such as biological processes and pathways, disease information and experimental phenotype data. RGD currently houses nearly 24,000 known and predicted genes and frequent integration of emerging data ensures that RGD maintains the most comprehensive, current set of rat genes. QTL and strain data also provide links to disease and phenotype information. Integration of ortholog and complementary QTL data from mouse and human facilitate cross-species investigations. Data mining and visualization tools take full advantage of the four ontologies RGD uses to provide gene function, biological process, pathway, phenotype and disease data to facilitate discovery of connections from the molecular level to that of the whole organism. An overview of recent developments in datasets and tools will highlight RGD's role as a research platform for cross-species and disease studies.

P12**A LINEAR MIXED MODEL APPROACH TO IDENTIFYING EXPRESSED SINGLE FEATURE POLYMORPHISMS**

SR Bischoff¹, S Tsai¹, B Freking², D Nonneman², G Rohrer², J Piedrahita¹

¹Department of Molecular Biomedical Sciences, College of Veterinary Medicine, North Carolina State University, Raleigh, NC, United States, ²ARS, USDA, U.S. Meat Animal Research Center, Clay Center, NE, United States, ³Center for Comparative Medicine and Translational Research, Raleigh, NC, United States

Using Affymetrix Porcine short oligonucleotide microarrays, we developed a novel approach to identifying expressed single feature polymorphisms (SFP) between two breeds of pigs, Meishan and white composite (1/4 each of Large White, Landrace, Chester White, and Yorkshire). Gene specific linear mixed models were fit to each of the log₂ transformed probe intensities on these arrays, using fixed effects for breed, probe, and breed by probe interaction, and a random effect for array. After correcting for average breed effects, we identified 2,452 probes (approximately 1% of all probes represented on the array) with significant probe by breed interactions as putative SFPs at a significance threshold of $q < 0.05$. We developed pyrosequencing assays to confirm the identity of a selection of high confidence SFPs. All working pyrosequencing assays corroborated the existence of polymorphisms within the probe sequence. By this method we detected both transition and transversion single nucleotide polymorphisms, as well as insertions/deletions. These results demonstrate that this approach can sensitively identify polymorphisms between two breeds and/or lines of any species for which a short oligonucleotide array is available, and can be used to rapidly develop markers for genetic mapping and association analysis in species where high density genotyping platforms are otherwise unavailable.

This work was supported by a National Research Initiative Grant (2005-35604-15343) from the USDA Cooperative State Research, Education, and Extension Service to JP and BF and by a NSF Integrative Graduate Education and Research Traineeship (9987555) to ST.

P13**COMPARATIVE GENOMIC MAPPING OF THE DEERMOUSE (PEROMYSCUS MANICULATUS) REVEALS MUCH GREATER SIMILARITY TO RAT (R. NORVEGICUS) THAN TO THE LAB MOUSE (M. MUSCULUS)**

CM Ramsdell, JL Weston, EL Thames, AA Lewandowski, TC Glenn, MJ Dewey
University of South Carolina, Columbia, SC, United States

Despite the greater degree of morphological similarity to *Mus*, initial results from the deermouse genome mapping project have surprisingly shown a very high degree of synteny and conserved gene order with that of the rat genome. Thus far, markers covering the majority of four rat chromosomes have yielded an almost identical genomic organization in the deermouse when compared to rat and with very similar breakpoints as rat when compared to the *Mus* genome. These results were obtained using a 116 animal *P. maniculatus* x *P. polionotus* backcross panel and a 103 cell-line 5000 rad whole genome radiation hybrid panel, both developed in our lab, and may lend interesting insight into understanding the organization and evolution of the rodent and mammalian genomes.

P14

IDENTIFICATION OF REGULATORY ELEMENTS RESPONSIBLE FOR NEURONAL RESTRICTION OF RAB3A EXPRESSION

R Liu, S Hannenhalli, M Bucan

¹Department of Genetics, University of Pennsylvania, Philadelphia, Pennsylvania, United States, ²Penn Center for Bioinformatics, University of Pennsylvania, Philadelphia, Pennsylvania, United States

Synaptic proteins modulate neurotransmitter transmission and synaptic plasticity, thereby mediating all brain functions ranging from sensory processes to movement and behavior. Expression of genes that encode synaptic proteins is stringently regulated, temporarily and spatially, in relation to neuronal development and synaptic activity. The mechanism underlying the neuronal specific expression of synaptic genes remains largely unknown. RAB3A is the most abundant neuronal protein and a key player involved in neurotransmitter release. Using transient transgenics in mouse, we identified a 6 kb genomic region containing *Rab3a* gene sufficient to drive endogenous *Rab3a* expression. Comparative sequence analysis of orthologous regions in multiple species revealed surprisingly few evolutionarily conserved non-coding sequences (ECSs) in the 6 kb genomic region. Based on luciferase reporter assay, we have confirmed that all ECSs exhibit cis-regulatory roles. Two regulatory regions (E1 -1435 ~ -1261 and E2 -123 ~ -146) in the upstream region of *Rab3a* can upregulate luciferase reporter exclusively in neuronal cell lines, whereas an intronic region (R1 +239 ~ +425) functions as a generic repressor in all tested cell lines. We then identified 129 additional genes potentially regulated by E1 by virtue of having same set of binding sites (or a close relative) in their upstream 5kb regions within a 500 bp window. Next, we tested whether the target genes were over-expressed in specific tissues. For each of the mouse tissues in the Novartis expression dataset, we compared the expression level of target genes against all other genes using Wilcoxon rank sum test. Only one tissue – Cerebellum – reveals over-expression of the 129 genes, with a p-value = 0.028. This work uses a combination of comparative, experimental and computational approach to reveal aspects of regulatory network controlling neuronal specific expression of synaptic genes, specifically *Rab3a*.