

PREFACE

The fact that living things inherit traits from their parents has been used since prehistoric times to improve crop plants and animals through selective breeding. Many aspects of human and animal behaviors have a strong genetic contribution. Individual variation in different behaviors is also found across animal populations. Animal models are increasingly being used to look for genes underlying these naturally occurring variations in behaviors and the most common species of animals used experimentally are mice and rats. This new and important book gathers the latest research from around the globe in this dynamic field of study with a focus on such topics as: phylogeography of finches and sparrows, pig genomics and transgenesis in biomedical research, epigenetic regulation in bovine cells, understanding the stress response through mouse genetics and others.

Chapter 1 - *Fringillidae* finches form a subfamily of songbirds (*Passeriformes*), which are presently distributed around the world. This subfamily includes canaries, goldfinches, greenfinches, rosefinches, and grosbeaks, among others. Molecular phylogenies obtained with mitochondrial DNA sequences show that these groups of finches are put together, but with some polytomies that have apparently evolved or radiated in parallel. The time of appearance on Earth of all studied groups is suggested to start after Middle Miocene Epoch, around 10 million years ago.

Greenfinches (genus *Carduelis*) may have originated at Eurasian desert margins coming from *Rhodopechys obsoleta* (dessert finch) or an extinct pale plumage ancestor; it later acquired green plumage suitable for the greenfinch ecological niche, i.e.: woods. Multicolored Eurasian goldfinch (*Carduelis carduelis*) has a genetic extant ancestor, the green-feathered *Carduelis citrinella* (citril finch); this was thought to be a canary on phenotypical bases, but it is now included within goldfinches by our molecular genetics phylograms. Speciation events between citril finch and Eurasian goldfinch are related with the Mediterranean Messinian salinity crisis (5 million years ago). *Linurgus olivaceus* (oriole finch) is presently thriving in Equatorial Africa and was included in a separate genus (*Linurgus*) by itself on phenotypical bases. Our phylograms demonstrate that it is and old canary.

Proposed genus *Acanthis* does not exist. Twite and linnet form a separate radiation from redpolls. *Loxia* (crossbills) is an evolutive radiation which includes redpolls also. In North America, three *Carduelis* radiations are found all coming from the Eurasian siskin: 1) that of American goldfinch, 2) the pine siskin one, and 3) the *Carduelis notata* one, ancestor of all South American siskins.

A new group of 'arid-zone' finches is genetically described that includes *Leucosticte arctoa*, *Carpodacus nipalensis*, *Rhodopechys githaginea* and *Rhodopechys mongolica*, at least.

Genus *Rhodopechys* should be redefined.

Pinicola enucleator (pine grosbeak) is the ancestor of bullfinches (genus *Pyrrhula*), forming a single evolutive radiation. Genus *Carpodacus* has been split in several evolutive radiations; American *Carpodacus* form a distinct evolution from Old World *Carpodacus*. *Haematospiza sipahi* is not a single genus, but a radiation together with *Carpodacus erythrurus*. Another evolutive radiation is found: *Uragus sibiricus* (a single species genus) radiated together with *Carpodacus rubicilloides*.

The grosbeak radiation (*Emberizinae*) occurred earlier than that of other *Fringillidae* birds and comprises genera *Coccothraustes*, *Eophona*, and *Mycerobas*. It is not discarded that New World grosbeaks (*Hesperiphona*) is also related.

Old World sparrows (genus *Passer*) conforms a single radiation starting in Africa (with *P. melanurus* and grey-headed sparrows), separated from *Ploceinae* and New and Old World *Emberizinae*. The closest radiation to genus *Passer* is genus *Petronia* (rock sparrows). *Passer hispaniolensis italiae* (brown head) is genetically closer to *P. domesticus* (grey head) than to *P. hispaniolensis* (brown head).

Subfamily *Estrildinae* covers a variety of finches widespread through Africa, Asia, Australia, and Indian and Pacific Ocean islands. Yet, many evolutive radiations are observed within this monophyletic group; they comprise birds from different continents: genetics does not correlate with geography in these birds. A possible origin for them is India since the basal and most ancient evolutive radiation —comprising African silverbill, Indian silverbill and (Australian) diamond firetail— may have started in India.

A clear example of convergent evolution is the case of American *Carduelis dominicensis* and African *Linurgus olivaceus*, which are very similar and acquire black head and greenish / yellow plumage in equatorial forests. Another fine example of phenotypic adaptation to environment is that of *Serinus alario*, the one black and white canary, because it nests on land or land / rocks. Finally, Eurasian goldfinch ancestor, mainly-green *Carduelis citrinella*, shows how plumage can change in relatively short times, as postulated.

In summary, some examples of evolution details and misclassification of songbirds are shown and put in a paleoclimatic and geographical context. This is now possible because of the existence of powerful computation methodologies for constructing molecular phylogenetic trees which are changing both our view of evolution and classification of living beings.

Chapter 2 - Many aspects of human and animal behaviours have a strong genetic contribution. Twin studies have demonstrated that half of the variance in our behaviours can be attributed to genetic factors. Individual variation in different behaviours is also found across animal populations. Animal models are increasingly being used to look for genes underlying these naturally occurring variations in behaviours and the most common species of animals used experimentally are mice and rats. Currently there are a number of different genetic approaches being employed to identify these genes including conventional breeding crosses, analysis of heterogeneous stock populations, mutagenesis and the use of congenic strains. In this review we will discuss the advantages and disadvantages of these different approaches used for gene identification. We will then review the growing number of studies which have used congenic strains of animals and their progress in the identification of genes

responsible for different behaviours. These include behaviours such as fear, anxiety, aggression, depression, addiction and behaviours associated with learning and memory impairments.

Chapter 3 - Common carp *Cyprinus carpio* L. is of one of the major farmed freshwater species. In 2004, production of the farmed common carp was approximately 13% (3.39 million tons) of the world freshwater aquaculture production. China is the main producer of the farmed common carp accounting up to almost 70% of the 2004 world production. However, despite of its great economic value in world aquaculture, genetic knowledge about common carp is relatively poor compared to other cultured fish such as rainbow trout, Atlantic salmon, European sea bass, gilthead sea bream, medaka, channel catfish, and tilapia. To date (November, 2008), the GenBank nucleotide database contains more than 1500 annotated full and partial sequences from genomic and mitochondrial DNA and around 32,000 expressed sequence tags. The SwissProt protein database comprises data about 1350 common carp amino acid sequences. To date, no linkage map specific for the common carp *C. carpio* is built although the linkage map for a hybrid cross between the common carp and Bochi carp *C. pellegrini pellegrini* was constructed in China (2003).

Compared to other cyprinids, common carp is tetraploid because it has a double number of chromosomes ($n=50$ or 52). The genome duplication is estimated to happen about 12 million year ago and, therefore, is one of the most recent genome duplications among vertebrates. The second wave of genomic rearrangements is estimated to occur between 2.3 and 6.8 million years ago and resulted in segmental duplications. Farmed common carp was subjected to all kinds of chromosomal manipulations including generation of monosex cultures; rearing the female monosex stock enhanced production by 7-8% (females being 15% heavier than males). Since most phylogeographic and population genetic studies were done on farmed stocks, the genetic structure of wild populations is very poorly understood. Population genetic studies with allozymes and/or microsatellites revealed lower variability of domesticated breeds compared to wild populations and low genetic distance between breeds. Most of the world production is carried out using unselected strains. When they exist, breeding programs are mostly based on crossbreeding as it brings quick improvement of growth performance (heterosis effect) in F1 generation.

A survey of farmers' needs is required to identify breeding goals and to make sure an improved stock will be well accepted. The construction of a medium- or even high-density linkage map for common carp is strongly recommended in order to produce a useful genetic tool for mapping economically important quantitative traits. The genetic map also provides an essential prerequisite for marker-assisted selection towards breeding strains with higher resistance to multiple pathogens, enhanced production traits and other benefits.

Chapter 4 - Ninety three years after Siedamgrotzky first reported cases of bovine lymphocytic malignancies in Germany in 1876, bovine leukemia virus (BLV) was identified in cultured neoplastic cells from affected cattle. Epidemiological studies carried out in herds with a high frequency of mature B-cell lymphoma/leukemia proved that BLV was the causative agent of these diseases and also of persistent lymphocytosis (PL). This latter condition results in the benign expansion of BLV-infected peripheral blood B-cell lymphocytes.

BLV is identified in almost every case of bovine B-cell lymphoma/leukemia; however, less than 10% of BLV-infected cattle develop these diseases, while about 30% of BLV-infected animals develop PL. Early observations of the increased incidence of B-cell

lymphocytic neoplasias or PL in certain bovine pedigrees, but not in others, suggested that host-genetic factors were involved in the development of these conditions after BLV-infection. There were also indications that host-genetic factors influenced the susceptibility to one condition or the other independently. Epidemiological data also indicate that 2/3 of all cases of B-cell neoplasia occur in cattle with pre-existing PL, while 1/3 of cases come from animals with a normal blood profile.

The major histocompatibility complex of cattle, termed Bovine Lymphocyte Antigens (BoLA) was discovered in 1978. The BoLA complex is a multiallelic or polymorphic genetic region located on chromosome 23 at band 22, and is organized into class I, II, and III genes, which encode proteins with different tissue distributions and functions. B-lymphocytic leukemia/lymphoma, PL and even the number of BLV-infected peripheral blood lymphocytes were subsequently found to be associated with certain BoLA-genotypes.

Due to the wide dissemination of BLV among dairy cattle in Argentina and other countries, control and eradication programs based on the serological detection of BLV-infected cattle and the subsequent culling of infected animals has several drawbacks. A new approach to classify BLV-infected Holstein cattle belonging to high prevalence BLV-infected herds was recently reported. Two BLV-infection profiles: low and high proviral load (LPL and HPL, respectively) showed a strong association with certain BoLA-DRB3.2 polymorphisms. LPL was more frequently associated with BoLA-DRB3.2*0902, and HPL with BoLA-DRB3.2*1501 or 03. Further experimentation has indicated that these alleles are good candidates for genetic markers of resistance or susceptibility to BLV transmission, and would serve as powerful tools toward controlling BLV dissemination by marker assisted breeding of genetically-selected cattle. The dynamic between BLV and the BoLA complex should serve as a model for studying the interaction between host and virus. Such understanding should prove important to, not only veterinary medicine, but also to human oncology, wherein human T-cell lymphoma/leukemia virus, a member of the same genus of retroviruses as BLV, causes T-lymphocytic malignancies.

Chapter 5 - Studies of the pathobiology of diseases as well as development and evaluation of therapeutic strategies depend on the availability of appropriate animal models. Rodents are most widely used for basic research. Translational research transfers novel results from basic research to clinical application. For this aim, pigs are suitable models as they share many anatomical and physiological characteristics with humans. The high reproductive performance of pigs is a suitable prerequisite for a model organism. Intense breeding efforts provided pig breeds differing substantially in various phenotypic traits which allows to choose breeds for specific experimental requirements. Pig genome analyses resulted in the availability of several resources of genomic data. In addition, the first pig whole genome sequence will be available in the near future. Efficient and precise techniques for the genetic modification of pigs have been established, facilitating the generation of useful disease models. Transgenic pigs increasingly act as appropriate animal models for human genetic diseases in biomedical research and as promising donor organisms for xenotransplantation.

Chapter 6 - Research on epigenetics and nutrigenetics, the genome-nutrient interface and is in its infancy with respect to livestock species. Ruminant species have evolved to metabolize short-chain fatty acids (VFA) to fulfill up to 70% of their energy requirements. Our studies revealed that VFA, especially butyrate, participate in metabolism as nutrients and as inhibitors of histone deacetylases (HDAC), which are one of the most important types of epigenetic regulators. The detailed mechanisms by which butyrate induces cell growth arrest

and apoptosis were analyzed using global gene expression profiles and the Ingenuity Pathways Knowledge Base. Gene expression profiling with high-density oligonucleotide microarrays indicated that butyrate induces many significant changes in the expression of genes associated with many regulatory pathways that are critical to cell growth, immune response and signal transduction. The functional category and pathway analyses of the microarray data revealed that several canonical pathways (Cell cycle: G2/M DNA damage checkpoint; pyrimidine metabolism; Cell cycle: G1/S Checkpoint Regulation; and purine metabolism; insulin-like growth factor axis components) were significantly affected. Butyrate Induced cell cycle arrest in bovine cells through targeting gene expression relevant to DNA replication apparatus. Our results also suggest that IGF2, not IGF1, along with its receptor (IGF2R) played a critical role in regulating cell cycle progression and programmed cell death. The present findings provide an example of epigenetic regulation of genome at work and basis for understanding the full range of the biological roles and the molecular mechanisms that butyrate may play in human and animal cell growth, proliferation, and energy metabolism.

Chapter 7 - Age, gender, feed composition, and genetics can affect beef quality. While farmers can easily manage the first three, specific and usable knowledge of the genetic basis for producing nutritional and flavorful beef is only just becoming a reality. Selective breeding of animals has existed for some time, but when based on phenotypic characteristics rather than known genotypes, the results are sometimes disappointing. Marbling is highly heritable, suggesting that this trait may be influenced by alleles of specific genes. Identification of polymorphisms within genes that affect marbling can help ensure selective breeding strategies are successful. To date, of the polymorphisms identified as having a positive association with marbling in cattle, many are within protein coding regions of genes for hormones, receptors and enzymes. In this review, we argue that polymorphisms in areas of the genome that ultimately affect the expression level of proteins could account for differences in marbling. These polymorphisms would include those in the promoter regions, splice sites as well as the 5' and 3' untranslated regions of genes. A discussion of how polymorphisms could affect possible pathways controlling both muscle metabolisms and hypothalamic control of fat deposition in muscle is presented. Much work is needed to identify possible candidate genes containing these non-coding region SNPs and in understanding these regulatory regions of genes with the potential to influence the marbling phenotype in cattle.

Chapter 8 - For the 21st century a severe increase in world population is expected. As a consequence the need for crop production output will also increase. Additionally, the current energy crisis will require substantial increases in the production of biofuel crops such as sugarcane or maize. These three factors, together with urban expansion, will especially be noticed worldwide but with special relevance in developing countries, most of which are located in the tropics. Other areas less prone to human population increases such as Brazil, Argentina, South Africa, The United States of America and Australia will also be affected by these factors as they are net exporters of agricultural products with special reference to cereals. This last group of countries share a common characteristic which the fact that they are also important producers and exporters of meat, especially beef from range-based production systems. In such a context, it is likely that the general scenario for beef production in coming years is that many of the areas currently being used for commercial beef production will be reconverted for agricultural use. It is therefore likely that in the future, commercial cattle production in the tropics will be made essentially in areas unsuitable for

agricultural use, such as steppes, savannahs, high altitude plateaus, semi-deserts or other marginal lands. These environments have three relevant conditions that will determine livestock breeding: a) scarcity of water and high quality pastures; b) high temperature conditions and c) continuous challenging by disease, parasitism and vector borne diseases. It is highly unlikely that the breeds which are the basis for current commercial cattle production will adequately meet these three requirements. Therefore, a new breed type might be needed, a small sized animal able to adequately cope with nutritional and high temperature stresses and with genetic traits that will allow them to withstand diseases and parasitism. Certain breeds like the N'Dama from West Africa or the Nguni from Southern Africa will surely fit these characteristics. The objective of this chapter is to provide a global insight on commercial beef production in upcoming years and the role that might be expected from low productivity breeds in such a context.

Chapter 9 - Animal experimental models of brain disorders represent a valuable tool in today's biological psychiatry [23, 35, 77, 78, 142, 153, 154, 172, 173]. Various genetic animal models, based on selectively bred, hybrid, gene-targeted or transgenic animals, are widely used in neuroscience research for screening neuroactive drugs, testing neurobiological hypotheses and finding candidate genes for stress-related brain disorders [35, 70, 76, 162, 163].

Numerous data indicate that brain disorders in many cases represent overlapping pathogenetic pathways with common genetic determinants and clinical manifestations (Table 1) [71, 76, 78]. Together, this raises the possibility that a *combination* of several distinct but interacting domains, and their *interplay*, may contribute to clinical and experimental phenotypes. This also implies that a closer in-depth analysis of different domains may be needed for developing new, clinically relevant genetic experimental modeling of neuropsychiatric disorders.

Chapter 10 - Stress helps organisms adapt to the challenges of the environment, however, too much of it can be harmful. High levels of stress have been linked to a number of physiological and psychological conditions including, but not limited to, psychosomatic, immunological, cardiovascular, and affective disorders (Anisman et al., 1998). It is well known that the specific type of stress and stressor characteristics (e.g., controllability, predictability, ambiguity, chronicity, and intermittence) influence the stress response (Anisman and Matheson 2005). While some individuals appear to be susceptible to stress-related disorders, others are not, and there seems to be much variability in response to relatively equivalent stressors. Why do some individuals have stronger biological responses to stress than others? Research indicates that a combination of experiential factors, resource characteristics, and organismic variables (e.g., species, strain, age, and sex) influence the magnitude of the stress response (Anisman and Matheson 2005).