HISTOCOMPATIBILITY

Edited by

Bahaa Kenawy Abuel-Hussien Abdel-Salam

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Contents

Preface

This book is intended as an introductory text for scientists who want to know more about the histocompatability. It attempts to present the field of immunology from a consistent viewpoint, that of the host's interaction with an environment containing many species of potentially harmful microbes.

The book includes the following topics: 1) HLA Polymorphism in Anthropology. 2) Distinctive Immunological Functions of HLA-G. 3) Immune Privilege Revisited: The Roles of Neuronal MHC Class I Molecules in Brain Development and Plasticity. 4) Human Leukocyte Antigen Class II in Stimulated Polymorphnuclear Neutrophils. 5) Dicer Regulates the Expression of Major Histocompatibility Complex (MHC) Class I Chain-Related Genes A and B. 6.) Killer Immunoglobulin-Like Receptors and Their Ligands. 7.) Sequence Analysis of MHC Class II Genes in Cetaceans. 8.) Regulation of MHC Class I by Viruses. 9.) Major and Minor Histocompatibility Antigens to Non-Inherited Maternal Antigens (NIMA). 10.) MHC Class I Quality Control.

This book would not exist without the efforts of the following authors - Sundararajulu Panneerchelvam and Mohd Nor Norazmi; Giada Amodio and Silvia Gregori; Adema Ribic; Bahaa K. A. Abdel-Salam; Kai-Fu Tang; Roberto Biassoni, Irene Vanni and Elisabetta Ugolotti; Wei-Cheng Yang, Lien-Siang Chou and Jer-Ming Hu; Shatrah Othman and Rohana Yusof; Masahiro Hirayama, Eiichi Azuma and Yoshihiro Komada; Gustav Røder, Linda Geironson, Elna Follin, Camilla Thuring and Kajsa Paulsson which were extremely helpful to all of us, and kept the book running.

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1

HLA Polymorphism in Anthropology

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1. Introduction

Humans are the most adaptable species among living organisms. Adaptation is the sum of all processes which allows the organism to cope with environmental stresses, in particular climate and topography, for its survival. All living species continuing through time and space to the present day are endowed with innate biological adaptation. The whole gamut of biological adaptation of human species is dependent on the sum total of anatomical, physiological, immunological and genetic characteristics. But the human species, in addition to biological adaptation, also possess cultural adaptation. Cultures are customs and traditions which help shape the human body and mind. The quest for understanding diversity of his own species and the rest of the species through time and space has promoted the expansion of the science of biological/physical Anthropology [1].

The irresistible urge for understanding the phenomenon of evolution of *Homo sapiens* with a systematic scientific search to decipher the chronological events of the past led researchers to the objective reconstruction of the vanished past, postulating that anatomically similar modern humans had emerged in Africa 200,000 years ago and dispersed to all regions of the world. The accumulated evidences which led to such a suggestion encompasses research from several scientific disciplines viz., hierarchical taxonomy of primates displaying nested groupings; comparative anatomy of all primates exhibiting homologies such as arboreal adaptation and brachiating anatomy of apes and humans; comparative primate embryology exhibiting similar ontogeny; comparative molecular genetics of hominoid chromosome exhibiting 98% similarity between chimpanzees and humans; adaptive anatomical structures such as pelvic structure adapted to erect bipedalism and larynx adapted for speech; presence of vestigial structures mimicking ancient forms, nipples on males; paleogeographical evidences such as distribution of fossils of earlier and later forms of hominoids and their sequence and pattern and chronological sequence of ancient tools, overwhelmingly centred around the African origin of modern humans [2-7].

Biological anthropology, primarily deals with tracing the biological origins by analysing change in gene frequency in a population gene pool over a period of time leading to heritable genetic differences in subsequent generations and ultimately the genetic diversity of the human species. In the process, scientists undertake genetic analysis to find reasons behind the physical differences between people of various groups [1]. The genetic analysis assesses frequency of variant allele relating to genetic markers and comparing genetic variation among populations with a view to trace evolution. In this article a general

appraisal of genetic diversity, the causative factors of genetic diversity, their impact on evolution [7], and the different molecular genetic markers with emphasis on the human leukocyte antigen (HLA) genetic markers, used in the study of tracing past events of human migrations are discussed.

2. Genetic diversity

Humans across the world exhibit remarkable phenotypic variations coupled with behavioural attributes. These variations are due to the combined effect of genetic and environmental factors. Researchers assess genetic variation by comparing variation between individuals in a group and by comparing variation between individuals in different groups (intra and inter population differences). The sources of individual variation are due to recombinant events in the genome and mutational events in meiosis leading to polymorphic alleles. Variation between groups is due to selective pressure on the genome due to differences in the environment and due to the combined outcome of founder effect and genetic drift. These differences are the source to trace/validate migration patterns in populations [8-15]. There are four major causes for genetic diversity in populations. They are (1) random sampling of gametes, (2) mutation, (3) subdivision, migration and genetic exchange and (4) natural selection.

3. Random sampling of gametes

In finite populations in the absence of any selection, random sampling of gametes effects a change in the gene frequency from the previous generation by chance. Random sampling is better visualised in finite populations. In real life, all populations are finite. For some populations (bacteria), the assumption of infinite size is a good approximation. For some, this is completely unrealistic. Hardy–Weinberg equilibrium (HW) assumes that the population is infinite. When a population is finite, random genetic drift produces a more pronounced effect. Random genetic drift is the random fluctuation of allele frequencies resulting in fixation or loss of an allele [10-16]. Wright-Fisher model explains the random change of frequency in finite populations. This model assumes a constant number of small panmictic populations producing infinite number of gametes evolving through non-overlapping discrete generations without mutation and without selection. This concept of random selection resulting in random genetic drift is explained in Fig.1. Consider that the parents are heterozygous for a locus, say, A and a. The parents produce a large number of gametes of which A and a will be 0.5 in proportion approximately. This proportion may not be 0.5 since reproductive cell death may occur at any stage of the gamete formation and besides, in females ¾ of the products are lost as polar bodies. In Fig. 1, the population is shown as consisting of 10 (3 AA homozygote; 4Aa heterozygotes and 3 aa homozygotes) individuals at t_0 generation with (allele frequency) of A = 0.5 and a = 0.5, producing infinite gametes and 10 individuals by random selection of gametes in each generation. At generation t_{20} (Fig.1) the gene frequency of A=0.55 and a=0.45 (3 Aa heterozygous 4 AA homozygous and 3 aa homozygous) and over generations, the finite sampling process erase the heterozygosity in the population. The end result of the random change will be that the frequency of A will eventually be 1 and a = 0; - that is the population is becoming homozygous [Fig.1].

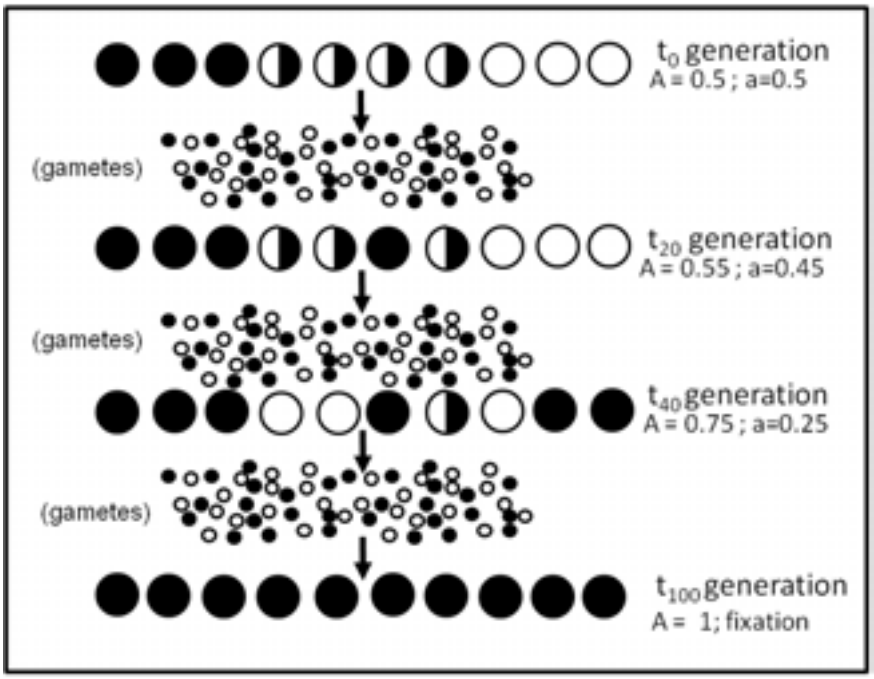


Fig. 1. Random Selection of Gametes
Illustration of random selection of gametes in a finite population represented by 10 circles, producing infinite number of gametes evolving through non-overlapping discrete generations without mutation and without selection. Solid circles (homozygous AA), open circle (homozygous a a) and semi-solid circles (heterozygous individuals A a)

The rate of genetic drift has an inverse relationship to the size of the population. This is to say that in an infinite population the loss of heterozygosity is extremely minimal. One reason for this is that the pool of reproductive individuals is always smaller than the total population. There are other reasons, including individual differences in expected fertility and changes in population size. Basic principles show that if the population size fluctuates, genetic diversity (heterozygosity) is lost at a rate related to the smallest size. There are two specific circumstances that greatly accelerate genetic drift. The first, called a bottleneck, occurs when a population size is reduced for a protracted period of time and then rebounds. The second, called a founder effect, occurs when all individuals in a population are traced back to a small number of founding individuals. Genetic diversity is lost very slowly in large populations. Like selection, drift is a process of differential reproductive success; however, the key element of genetic drift is that which individuals survive and reproduce is unrelated to their phenotype and genotype and it is random.

4. Mutation

Mutation is the ultimate source of all variations in a population. Mutations can be beneficial, neutral, or harmful for the organism, but mutations do not try to supply what the organism

needs. In this respect, mutations are random. Many mutations are functionally silent either due to their presence outside the protein coding region of the genome or when present within the coding region does not alter the final protein product [17]. These silent mutations are used in deciphering genetic ancestry and demography of populations. Random genetic drift due to finite sample size which results in loss of genetic variation is offset by mutations generating genetic variation. The balance between these two opposing forces is assessed by using Coalescent modelling [18, 19].

Coalescent theory states that all genes or alleles in a given population are ultimately inherited from a single ancestor shared by all members of the population, known as the most recent common ancestor (MRCA) [19-21]. If the inheritance relationships are displayed in the form of a phylogenetic tree (termed a gene genealogy), the gene or allele of interest is said to undergo coalescence to the common ancestor (sometimes termed the coancestor to emphasize the coalescent relationship) [Fig 2]. Basic coalescence theory assumes that genes do not undergo recombination and models genetic drift as a stochastic process. Because the process of gene fixation due to genetic drift is a crucial component of coalescence theory, it is most useful when the genetic locus under study is not under natural selection. Coalescent modeling helps to understand the structure of whole population by assessing a small sample of descendents. It allows quantitating expected sequence diversity, the expected number of segregating sites, expected heterozygosity etc. Though the coalescent model addresses complex issues of population genetics there underlies the following basic components viz., the expected time back to the MRCA, the mutation rate and the outcome of the mutation [16-21].

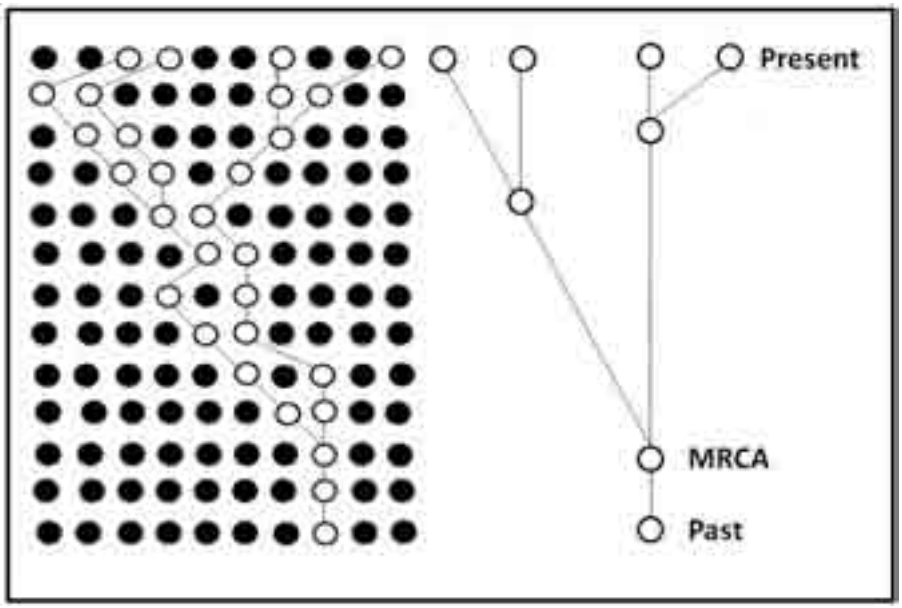


Fig. 2. Coalescent Model
Tracing the gene geneology of the four sub-divided present day population leading back to the MRCA.

5. Subdivision, migration and genetic exchange

The collection of genetically differentiated subpopulations is referred to as population substructure [22, 23]. In a large random mating population the genes with multiple alleles obey HW equilibrium in the absence of natural selection. Migration into and out of a population affects the population genetic structure [23-26]. Consider a hypothetical supposition that immigrants from a large population formed a new population in a different location. The parental population and the new population after hundreds of generations may again subdivide. This gives rise to two additional populations. All the four populations (ie. the parental plus the 3 sub-divided populations) will go through hundreds of generations. Eventually these populations are known as meta populations – regardless of whether they remain completely isolated or they may have been in communication with each other through the exchange of individuals.

Migration between two populations may have effect on genetic variation. However, it will be difficult to identify the boundaries of sub-populations and on genetic analyses one may confront with samples of individuals that may come from one sub-population or from more than one sub-population. The parental and the newly formed sub-populations may genetically be different from each other. Even if each of the subpopulations obeys HW and linkage equilibrium, a pooled sample from these populations may not match the expected and observed data. It is due to the fact that populations are more likely to choose mates living nearby and not in a random fashion. Since individuals that live close to one another tend to be more genetically similar than those that live far apart, the impacts of local mating will mimic those of inbreeding within a single well-mixed population. This is known as Walhund effect [27].

On genetic analysis the copies of a certain genetic locus coexisting in a sub-population do not always coalesce together. With reference to Fig. 3, sub-populations B and C, before coalescing at (MRCA), coalesce with D. If the subpopulations have high frequencies of certain alleles at a locus, the pooled population will show substantial linkage disequilibrium. If all the populations are in contact and random mating takes place it will take a considerable time for attaining linkage equilibrium since the reduction in linkage disequilibrium is by a factor of 1-r per generation, where r is the recombination fraction between two loci, that is the linkage disequilibrium between two linked loci will be reduced by ½ per generation. Continued random mating eventually result in linkage equilibrium. The genetic exchange between the local sub-populations is termed as gene flow.

6. F statistics

Walhund effect is the observation of excess homozygotes or deficiency of heterozygotes in a population of pooled subpopulations. Subpopulations fixed for a particular allele in a certain locus, is indicative of homozygous individuals in that population for that allele. Sewall Wright [11,12,28,29] expressed such effect by defining fixation index. Wright defined fixation index (F) as,

$$F=\frac{2\bar{p}(1-\bar{p})-\bar{p}}{2\bar{p}(1-\bar{p})}$$

$\bar{p}$ is the average allele frequency of homozygotes in sub-populations. Wright's F parameter values lies between 0 to 1. If there is no difference in allele frequency between

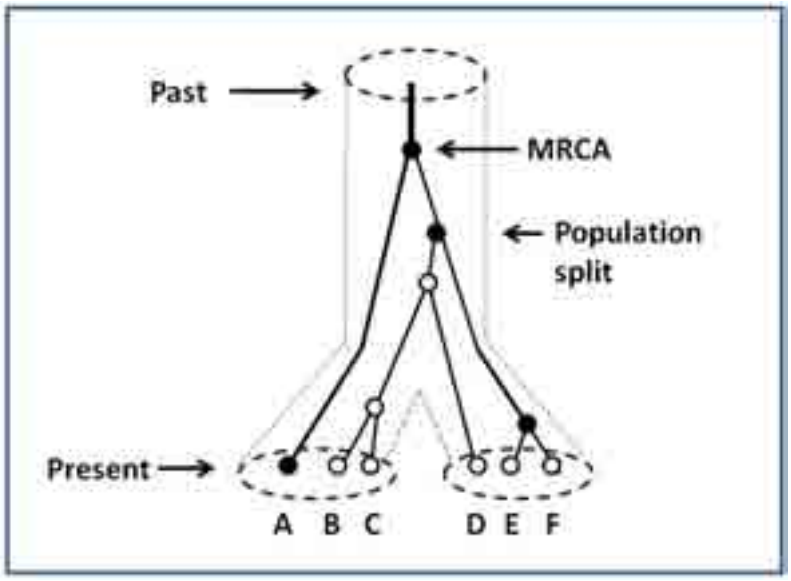


Fig. 3. Coalescent model in a subdivided population. Adapted from (16)
The present day sub-divided populations (also known as meta populations) represented by A, B, C, D, E and F tracing back to one single parent population in the past. Selected genetic locus coexisting in a sub-population do not always coalesce together. For example, the subdivided populations B and C coalesce with sub-divided population D before they coalesce with the MRCA despite sub-divided population D being in another group of sub-divided population. Solid circle represents unchanged allele within the selected gene locus of the parent while open circle represents the alternate allele in the selected locus.

subpopulations, then F = 0 (random population); alternatively if they are fixed for an allele then F = 1 (100% homozygosity). In the absence of selection and mutation, genetic drift is the primary evolutionary force causing differentiation of the population. Mutation and migration may prevent F from reaching 1 by introducing alternative alleles. Low levels of migration leads to moderately high level of F value. If the drift and migration is continuing through many generations and reaching equilibrium then F attains a constant value and can be deduced by the equation,

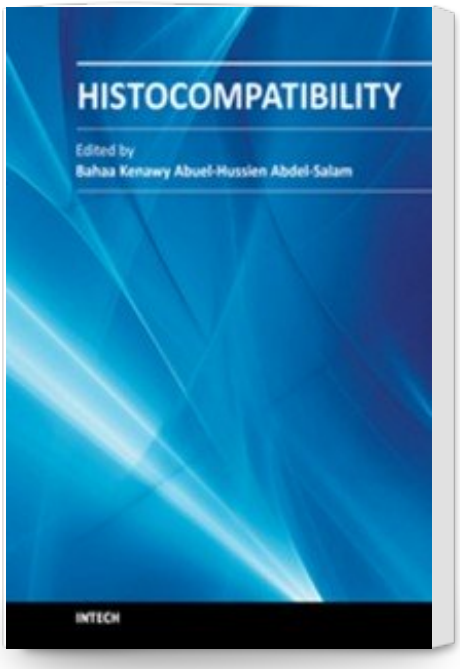
$$F=\frac{1}{4Nm+1}$$

Where N is the effective population size (often referred as N_e) and m is number of migration rate.

7. Natural selection

Natural selection is the fourth primary mechanism which acts as a whole on populations rather than individual organisms that produces changes in the genetic composition of a population from one generation to the next and in due course causes evolutionary change

Histocompatibility



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