Review

Population Genetics in Sudan

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Introduction:

When M. H. Satti embarked on a reconnaissance mission to monitor the visceral leishmaniasis (VL) outbreak in the Blue Nile district in mid 1940s, he immediately realized the gravity of the situation. The epidemic inflicted heavy toll on a small tribe called Jum Jum and almost decimated the very presence of their existence(1). More than sixty years later pertinent questions are still justifiable on why the disease would heavily affect a certain population but not others like the Jum Jum and Nuer who bore the brunt of the 1980s and 1990s outbreak,(2) why a deadly disease becomes endemic to certain territory? why epidemics suddenly erupt in a specified location? and why certain households and individuals are more prone to encounter certain ailments?

During Satti's time population genetics was a fairly new science then, pioneered by outstanding scientists like J B Haldane - a Briton also notorious of being an ardent socialist activist. Haldane not only pioneered population genetics but demonstrated the first examples of human adaptation through haemoglobinopathies that are still the favourite show case of population genetics even today. We know now that, the fate of an allele since its birth in the form of a novel mutation/polymorphism is decided by a number of factors that includes beside natural selection, a well-established paradigm by the 1930, other factors like migration, and genetic drift. Drift was proposed by the Japanese mathematician Muto Kimura and Luca Cavalli Sforza an Italian American geneticist. A similar situation faced A. M. Elhassan and his colleagues when they first set foot on the Rahad region during early 1990s.(2) Elhassan was abhorred by the amount of suffering and misery caused by the disease. The incidence was higher among certain ethnic groups, an observation also seen among game wardens in the adjacent Dinder National Park.(3) The fact that the most vulnerable groups were mainly of Nilo-Saharan speaking background from southern and northern Sudan, was irreconcilable with published evidence that VL caused by *Leishmania donovani*, first emerged and crossed the species barrier in eastern Sudan possibly around 3040- kYBP.(4) The general dictum of host parasite coevolution is that parasites become less virulent the more they coexist with their host. Nilo-Saharan speakers were shown in independent genetic analysis to be the oldest inhabitants of the Sudan and the most ancestral populations. Then what is the explanation for the fact that the Jum Jum and the situation in southern Sudan and Rahad River that they fell easy prey to VL? Explanations could be sought within the realms of population genetics and genetic epidemiology in both cases. Both groups might possess higher frequencies of VL susceptibility alleles. The severity of the VL epidemic among the Nuer and JumJum could be speculated in the light of these groups being naive to the parasite i.e. moving recently into the endemic Upper Nile and Blue Nile areas and progressively encountering the peripheral transmission of the disease sylvatic cycle as more forest areas are being cleared and inhabited by migrant populations. Oral tradition and archaeological evidence suggests migration of the Nilotic groups into the area from further north in the past few millennia. The gravity and high death toll among particular ethnic groups could be interpreted in the light of genetic drift (see below). The force of drift operates more effectively in situations of isolation or inbreeding hence leading to lower effective population size (Ne) and excess susceptibility/resistance alleles that may end in the tragic situation described earlier. The scene of the VL investigation in the Rahad River centred on Koka and Um-Salala

two villages located in Eastern Sudan along the bank of the Rahad River. They are inhabited by Hausa and Massalit tribes respectively who settled the area during the 1950-and 1960 in successive migration waves form the west. In the mid-1990s, the leishmaniasis research team shifted their interest towards studying the role of genetic susceptibility to visceral leishmaniasis. Many studies worldwide reported association of candidate genes with the susceptibility and severity of visceral leishmaniasis (reviewed in[5] and subsequently reported herein). The team focused their attention on candidate genes including the 5q31 a chromosomal region harbouring cluster of genes for interleukins IL-4, IL-5, IL-9, IL-13 and other immune related genes.[6] The team collected samples from villagers of both tribes for allele and genotype frequency. Alleles were single nucleotide polymorphisms (SNPs) which are variations in the nucleotide sequence of the respective genes. 5q31 alleles and genotypes frequencies of Hausa and Massalit tribes differed greatly from alleles and genotypes frequencies encountered in other parts of the world; areas that are endemic with neither malaria nor visceral leishmaniasis. Heterozygotes of each SNP outnumbered both homozygotes put together[6]. In population genetics terms we say that allele and genotypes frequencies deviated from Hardy-Weinberg equilibrium. There are generally five factors that can cause such deviation from Hardy-Weinberg equilibrium; which correspond more or less to those causing allele frequency change mentioned earlier we will discuss each in detail.

Mutation:

One process that can alter the frequencies of alleles within a population is mutation. Gene mutations consist of heritable changes in the DNA that occurs within a locus. Usually a mutation converts one allele form of a gene to another. Mutation is the source of all new genetic variation. Most mutations are neutral and do not affect the reproductive fitness of the organism. Other mutations are detrimental and are eliminated from the population. However, a few mutations confer some advantage to the individuals that possess them and spread through the population. The nucleotide polymorphisms in the studied interleukins genes originally arose as mutations in ancestral populations. Whether a mutation is neutral, detrimental, or advantageous depends on the specific environment, and if the environment changes, previously harmful or neutral mutations may become beneficial.[7]

Inbreeding:

Inbreeding is the sexual reproduction of offspring from the mating or breeding of individuals that are closely related genetically. Inbreeding results in homozygosity, which can increase the chances of offspring being affected by recessive or deleterious traits. This generally leads to a decreased biological fitness of a population. The excess heterozyosity level in Hausa and Massalit tribes is more consistent with out-breeding rather than in-breeding, despite more than 90% of marriages occurred within the village. This was speculated to be due to the large Ne of these groups particularly Hausa.[6]

Migration:

One assumption of the Hardy–Weinberg law is that the population is isolated and not influenced by other populations. Many populations are not completely isolated, however, and exchange genes with other populations of the same species. Individuals migrating into a population may introduce new alleles to the gene pool and alter the frequencies of existing alleles. Thus migration has the potential to disrupt Hardy–Weinberg equilibrium and may influence the evolution of allele frequencies within populations. Hausa tribe originally migrated from northern Nigeria (mainly from the towns of Kanu and Sakatu); the majority of the present inhabitants can therefore be expected to have been born in the village. Um-Salala on the other hand was founded in 1969 by members of the Massalit tribe who migrated from western Sudan (Darfur State, near El-Geneina town). The migration to the Um-Salala village increased dramatically after the drought that hit Darfur in 1984. There is no evidence of significant migrations in or out of Koka and Um-Salala villages; hence migration alone cannot explain the deviation from HWE.

Genetic Drift

Another major assumption of the Hardy–Weinberg law is that the population is infinitely large. Real populations are not infinite in size, but frequently they are large enough that chance factors have small effects on allele frequencies. Some populations are small, however, and in this case chance factors may produce large changes in allele frequencies. Random change in allele frequency due to chance is called random genetic drift, or simply genetic drift.[7] Genetic drift can partly explain the resultant deviation of HWE because population sizes of both villages remained relatively small over time (Koka village population is ~1800 individuals and Um-Salala village population is ~1450 individuals). However the intergeneration difference and the fluctuation in heterozyosity encountered in the study are more in line with the strongest force that can possibly deviate alleles and genotypes frequencies away from HWE; Natural Selection.

Natural Selection

Natural selection is the process by which traits evolve in a way that make organisms more suited to their immediate environment; these traits increase the organism's chances of surviving and reproducing. Natural selection is most likely the cause of HWE deviation because of the well documented high fatality rate of visceral leishmaniasis among children in the area.[3,5] There are many types of selection; Directional selection occurs when a certain allele has a greater fitness than others, resulting in an increase in frequency of that allele. Stabilizing selection, which lowers the frequency of alleles that have a deleterious effect on the phenotype, and finally balancing selection or over dominance, in which the heterozygous genotype has the greatest fitness. The best-known example is the malarial resistance observed in heterozygous humans who carry only one copy of the gene for sickle cell anaemia. The excess heterozyosity in 5q31 is best explained with over-dominance selection between malaria and visceral leishmaniasis since malaria favours high cytokine TH2 response - high level of IL-4, IL-5, IL-13 are associated with malaria parasite clearance,[8] while the same response is associated with disseminated leishmaniasis.[9] We used in-silico technique to show that SNP alleles differ greatly in their expression, activity, stability and regulation.[10] The leishmaniasis Research Group at the Institute of Endemic Diseases initiated an extensive intervention program in the form of introducing modern diagnostic techniques, and drug availability. They established a modern hospital (Kasab hospital) and a research center (Professor Elhassan Research Centre) in the area. As a result of that, incidence of visceral leishmaniasis remarkably dropped in the area and the trials are now directed towards developing an effective vaccine against visceral leishmaniasis. This was even manifested in allele frequency differences between generations, where the intervention of the 1990 led to restoration of HWE in younger generations.[6] The utilities of population genetics extends beyond the examples of VL and other infectious and chronic diseases, forming an important bridge between universal approaches in medicine and burgeoning new paradigms of individualized and precision medicine like the following example on Lactase persistence. Lactase persistence (LP) is one of the clearest examples in humans in which organisms evolve in a way that suits their mode of lifestyle. Lactase is the enzyme responsible for the digestion of the milk sugar lactose and its production decreases after the weaning phase in most mammals, including most humans. Some humans, however, continue to produce lactase throughout adulthood, a trait known as lactase persistence.[11] The origins of lactase persistence-associated alleles were dated back to the time of animal domestication and the ingestion of dairy milk.[11] Thirty five per cent of adults living in the world today have LP[12,13] but varies widely among human populations. The highest frequencies of LP are observed in the British Isles and Scandinavia; 89–96% of population.[15,16] In Africa, high frequencies of LP are witnessed mainly in traditionally pastoralist populations.[14,17,18] In Sudan, LP reaches 64 per cent in Beni Amir pastoralists, whereas in Dounglawi, a neighbouring non-pastoralist population, LP frequency is around 20 per cent.[11] This example illustrates the need for collapsing the wall that separates clinical practice

from the science of population genetics built in most physicians' minds. The future of medicine will certainly be directed according to the genetics of population within the field of population genetics.

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