

CHAPTER 6

Summary and Conclusion

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6.1 Population- based study

Selection and convergent evolution are the two main forces which shape the TLR genes in their respective environment. Populations, which share their environment and inhabited in a particular region face a strong selection pressure due to the presence of pathogen in their surrounding environment. Also the Muslim population, very close to Gurkha in respect of the presence of TLRs, faces the same environmental condition. As a result, selection of specific TLR genes of the immune system shaping the population in respect of their ethnicity. On the other hand, convergent evolution of TLR genes has occurred due to the sharing of similar environment. Although Gurkha and Muslim belong to two different lineages, but their TLR distribution is same due to the sharing of similar environmental conditions. Rajbanshi, Gurkha and Rabha belong to the same East-Asian lineage, but considerably differ in their TLR distribution. This striking observation may infer the impact of environmental selection on the distribution of TLR genes. Such influences of the environment on TLR distribution may depend on the constant presence of specific pathogens in respective environment. Thus, it may be assumed that TLR genes play a significant role in shaping the genetic ancestry of the above mentioned populations from North Bengal region of India as well as in determining the disease exposure in these populations.

Among Rajbanshi population, high frequency of TLR8 and TLR9 is observed. So, it can be inferred that this population, mainly inhabited in the tea garden areas of Terai and Dooars region of North Bengal, may be susceptible to some viral diseases. In Gurkha population, mainly inhabited in the hilly region of North Bengal, TLR4 and TLR5 are present with high frequency. It means that they might come in contact with the bacterial infections. A survey report on this population conveys their susceptibility for bacterial infections. On the other hand, TLR3, TLR5, and TLR7 are present with high frequency. Probably they get infected both with bacterial and viral diseases as we have found that occurrence of HIV infection among Muslim population is much higher than other populations in this region. In Rabha population the frequency of TLR4 is highest, which indicates that the population is susceptible to LPS and other bacterial antigens. A report is

already published out of the present work on the susceptibility of chronic gastro-intestinal diseases among Rabha population.

Phylogenetic and genetic distance assessment based on ten human TLR loci revealed that Muslim and Gurkha population are close to each other. Rabha is distantly related with the other three populations. Genetic distance analysis also proves the closeness of Gurkha and Muslim. The distances between Rajbanshi -Gurkha and Rajbanshi- Muslim are also close.

Conclusively, the combined picture represented the result of the analysis of TLR genes infer that:

1. The studied population now-a-days is very much a mixed population in this region.
2. The substantial variation of the studied population has been seen in this region in respect of their TLR genes.
3. Environmental selection acts on this population in respect to their TLR genes. Due to the sharing of the same environmental conditions it is very much conclusive to say that they come close not due to their ethnicity but in respect to their TLR genes which is very interesting.
4. On the other side, it has also been quiet interesting that convergent evolution occurs among the four populations in this region. Convergent evolution occurs in the TLR genes shapes the population irrespective of their ethnicity.
5. Gurkha, Muslim and Rabha belong to the Mongoloid origin as it has been reported in various studies on other markers like HLA and KIR. The deviation of this finding occurs in respect of the TLR genes, because TLRs are considered as the main markers of the innate immunity. It also depends on the environmental pathogen for their proper functioning. This is the main reason why the populations irrespective of their ethnicity merge into a common line.

It has been concluded that the population in this region are now a mixed population. They all share their gene pool among each other now- a- days. Genetic structure of Muslim population of this region has received the gene flow from the neighboring country, Bangladesh but there is also a considerable admixture of Tibeto Burman element in Muslim population of this region and that differentiates from the other Muslim population of India. In Gurkha population, gene flow occurs between Nepali speaking Gurkha and the population of other region. The admixture of Rajbanshi

of this region with the local Bengali population cannot be ignored. The Rabha population is restricted in some particular area in North Bengal region and not mixed with the other local population. So, the gene pool is restricted on them because of their endogamous character.

The present study on these four populations unveiled the curtain of the frequency and distribution in respect of their TLR genes. Environmental selection of some specific TLR genes among different population and convergent evolution shapes the population of this region into a peculiar nature irrespective of their ethnicity. This study is one of the primary and first hand report on population based study of TLR genes. So, further study is needed to reveal their genetic background in respect of their TLR genes and to know how TLR genes act on them in different conditions. One needs to lift up the curtain and try to find out their immune status and other polymorphic variation in the TLR genes which might help to build the knowledge how TLR helps to fight against various diseases.

6.2 Rheumatoid arthritis- based study

Rheumatoid arthritis is a systemic inflammatory autoimmune disease, characterized by chronic, erosive polyarthritis and by the presence of various autoantibodies in serum and synovial fluid. The main diagnostic tests are anti-CCP and RF titre assay for RA. The disease is caused due to the genetical and environmental factors. Different study suggested the association of toll like receptor with RA. Various polymorphic varieties present in the TLR genes in different population worldwide demonstrate their association with RA.

The findings of this study can be summarized as below:

1. The concentration of anti-CCP and the titre are very high in majority of the patients.
2. The frequency of TLR1, TLR6 and TLR8 are highest among patients compared to the control group. Low frequency is observed for TLR2, TLR5 and TLR10. It is evident from the study that the TLRs, those are present in high frequency mostly related with the RA , also recognize the antigens produced during inflammation in the joints.
3. The high odd ratio for TLR1, TLR4, TLR6, TLR8 and TLR9 determines the association with the disease which is also very much significant.

4. Relative risks are also very high for TLR4, TLR6, TLR7, TLR8 and TLR9. Door line association has been found for TLR1 and TLR3. It also signifies the positive relationship of TLRs with the disease.

5. High level of sensitivity for some of the TLRs deciphers the positive association with the disease.

6.3 Typhoid –based study

Typhoid fever is one of the most common diseases among the tea garden areas of this region due to the unhygienic conditions, lack of sanitization and lack of proper drinking water in this region. The disease is not very common in urbanized areas but frequently found in the rural especially in the tea garden areas. One needs to study the genetic nature of TLR genes and their frequency distribution in Siliguri and adjoining areas.

The findings of this study can be summarized as below:

1. The frequency graph clearly indicates that TLR1, 5 and TLR6 are highly up regulated, more or less consistent with the previously published reports. Widal test result is also very high in majority of the samples.
2. The door line association found for the respective TLRs indicates the positive association of the disease with the TLRs.
3. The sensitivity factor also high for TLR 1, 5 and 6 which shows the positive association of the disease among the population of the area.
4. Odd ratio among the groups also very high which indicates the susceptibility for the predisposition of the disease.

6.4 HIV –based study

Human immunodeficiency virus is a major causative agent for the acquired syndrome disease worldwide which demolish the immune system of individuals. There are no proper medications or vaccine to cure the disease because of the frequent mutation in the genome of the virus. Present study investigated the association of HIV+ patients with TLR variants in Siliguri region.

The findings of this study can be summarized as below:

1. The frequency graph clearly indicates that TLR8 and 9 are highly up regulated which are more or less in agreement with the previously published reports.
2. The positive associations in case of their relative risk are also found for the respective TLRs, indicates the positive association of the disease with the TLRs.
3. The sensitivity factor also high for TLR4, 8 and 9 shows the positive association of the disease among the population of the area.
4. Odd ratio among the groups also highly up-regulated indicates the susceptibility for the predisposition of the disease.

In this present work, the main goal was to determine the genetic predisposition in three main diseases and the role of TLR genes in the disease pathogenesis in multi ethnic populations in Siliguri and adjoining areas. Current findings on the risk factor of three diseases based on TLR gene profile provide a compact knowledge on the genetic basis of the diseases. Further study is needed to illuminate the role of single nucleotide polymorphism of TLR genes and susceptibility/resistant for the diseases in Sub- Himalayan region of West Bengal.