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Editorial

Decoding Population Genetics: Impact on Tuberculosis Control and Treatment

The advent of chemotherapy in the early 1980's was a boon for tuberculosis (TB) afflicted human race and significantly brought down mortality rate. However, an increase in the number of reported cases of TB in recent times combined with the emergence of human immunodeficiency virus (HIV) and multidrug-resistant TB (MDR-TB) was a serious setback for the efforts to eradicate TB worldwide. Presently, as many as one-third of the global population is latently infected with *Mycobacterium tuberculosis* and 5% to 10% of them run the risk of developing active disease in their life-time. What could explain this inter-individual variation in susceptibility and proneness to develop active disease? Apart from the environment and socio-economic factors, genetic predisposition of the host could play a significant role in determining the outcome of the infection. It could be possible that wide variation in the genetic make-up of the human population manifested in the form of gene polymorphisms could lead to such inter-individual variation.

The history of the mankind indicates that TB exerts a strong selection pressure on human evolution. Over the Century, TB significantly wiped out the susceptible population from various parts of the world and by the process of natural selection only those who could develop resistance to TB were selected to survive and multiply. For example, European population are generally less susceptible to TB. It is possible that due to their centuries long association with the bacterium the Europeans have evolved into a more resistant population. In contrast, African sub-Saharan population are highly susceptible to TB probably due to their relatively recent contact with the pathogen.[1] Motulsky[2] suggested that this could have been due to strong selection against susceptibility genes of TB.

Examining the genetic angle of TB susceptibility received impetus from the recent technological advancement in the gene sequencing techniques. Rapid throughput sequencing at a large scale using Sequenom massArray platform (Sequenom Inc.,USA) or Illumina platform have resulted in the complete sequencing of the human genome which led to the identification of a large number of sequence polymorphisms that were previously unknown. This information led to the generation of databases, such as dbSNP[3] and Hapmap[4] which have facilitated the selection and evaluation of yet unexplored sequence variants in the genes of interest.

Given the complexity of the disease TB, it can be assumed that there would be numerous genetic contributing factors. Protection against TB is determined by the potent immune response in any individual. Therefore, susceptibility or resistance to develop TB may be significantly influenced by the variation in the immune response genes and contribute to a scenario where by virtue of their genetic make-up most of the individuals mount an effective immune response and are able to either clear or contain the mycobacterial infection while a certain few fail to do so. Evidence in support of such a notion comes from clustering of TB disease with higher concordance in monozygotic as against dizygotic twins,[5] the ethnic clustering of the disease with higher prevalence of TB in individuals of recent African descent,[6] as well as the demonstration of both common polymorphisms and rare mutations which confer susceptibility to mycobacterial infection in humans.[7] These studies further supports the view that in addition to unique environment and natural selection ethnically governed host genetic factors may play a part in the susceptibility or resistance to TB.

Since TB is primarily a disease governed by the state of the host immune response, the focus of population genetics rested on the extensive analyses of the genes related to innate and acquired immune response. The technological advances as mentioned above together with the tools of bioinformatics facilitated the identification of a range of genetic variations which include polymorphisms in the innate and acquired immune factor related genes capable of identifying persons who are genetically prone to TB. The studies evaluating the involvement of innate immune response have focused on receptors on macrophages, such as toll-like receptors including *TLR1, TLR2, TLR4* and *TLR8, VDR, NOS2, P2X7* receptor, *SP110, SLC11A* (formerly *NRAMP1*), *IRGM* and *DC-SIGN*.[8] On the other hand, the adaptive immune response was characterised mainly by cytokine and chemokine gene polymorphisms. The cytokines of note that have been studied and thought to play a role in susceptibility to TB include variants of interferon-gamma (IFN-γ), tumour necrosis factor-alpha (TNF-α), interleukin (IL)-1β, IL-1RA, IL-18, IL-8, IL-12, and TNF-β.[9]

The impact of genetic variants has also been exemplified in other associated respiratory ailments, such as asthma,[10] and chronic obstructive pulmonary disease (COPD).[11] In both these conditions, selection of genes studied were those related to inflammatory process and are similar to the genes studied in TB. One possible reason for such overlap might be the involvement of an initial inflammatory phase in all the three diseases. As and when more information

will be available the interacting role of these genes contributing to each condition may become clearer.

The impact of genetic make-up of the host on the development of TB has been studied in Indian population also. Recently a database called the Indian genome variation database (IGVDB)[12] has been developed on the lines of Hapmap database. The Hapmap database includes the variation frequencies typed in five world populations but does not include the Indian population. The IGVDB has typed certain selected sequence polymorphism in samples from all over India and facilitated the classification of the Indian population into structured subgroups. This database has shown that the gene pools of north and south Indians differ significantly in their genetic make-up which means variations posing a risk in south Indians need not be valid for north Indians, as genetic proneness to susceptibility to TB has a ethnicity bias. While some reports are available from south India,[13] till recently not much information was available from north India. Abhimanyu *et al*,[14,15] have recently added to the spectrum of studies on genetic susceptibility to TB from north India. So far, after typing more than 50 variants from 7 cytokine genes, they were able to identify 11 novel variants implicated in TB susceptibility.[14,15] In addition, they have also examined the possible impact of population genetics in lymph node TB, a form of extra-pulmonary TB, for the first time in the north Indian patients. They examined 25 variants of SP110 gene for susceptibility to TB and identified for the first time a variant (rs1427294) that could be a useful marker for lymph node TB susceptibility in north Indians.[16]

The benefit of such studies could be multiple. The information generated would help us to identify the genetic markers to screen people of being "resistant" or "prone" to the disease. Identifying the alleles that impart a risk of developing the disease in the population under study and the identified markers could help in providing appropriate and targeted therapy to the prone individuals. A few evidence in support of this notion stems from the work done with the help of SNPs in other diseases, such as lung cancer,[17] Hutington's disease, etc. Pfister *et al*[18] have designed and validated selective siRNAs for the three SNP sites of Hutington's disease, laying the foundation for allele-specific RNA interference (RNAi) therapy for Hutington's disease. SNPs could also be very useful in giving personalised medicine as shown by Chu *et al*.[17] As outlined by Barnes[19] immunotherapeutic strategies for TB could include administration of Th1 cytokines, such as IL-2 or IFN-γ, or of IL-12 and IL-18, which elicit IFN-γ production which is vital for protection against TB. Alternatively, natural inhibitors of transforming growth factor-β or anti–IL-10 antibodies could be used to downregulate the Th2 response, in patients who could be identified successfully by their susceptible status utilising SNP information to this effect. A personalised medicine on the lines of cancer therapy can also be developed as individuals with TB have been shown to differentially metabolise isoniazid (INH), categorised as slow acetylators or fast acetylators,[20] thereby, affecting the outcome of the treatment. SNPs identified could help us sort those individuals out who are fast acetylators and treat them with some alternate drug.

While a large body of data is being generated globally, there are still conflicts to recognise the relevance of these genetic markers in the context of disease development. The markers reported in a certain population may not be found to be the risk factors in other population. Such observations could be due to lack of carefully planned studies, poor control selection or presence of population sub-structure[21] in the analysed data. These points are of utmost importance and should be taken into account while analysing a genetic dataset to draw a robust and lasting conclusion that would influence the future application of the emerging information in the treatment and control of TB.

At this crucial juncture we find ourselves asking the question: now what? The future direction could be to validate the commonly reported variants throughout the world in the context of Indian regional ethnicity, detecting the changes caused by the identified polymorphisms to conclusively demonstrate the "cause and effect" correlation. In addition, there should be persistent efforts to identify new loci by conducting more carefully planned multi-centre studies. Finally, the "genetic markers" identified must be utilised to develop certain modules that would aid the current approach to diagnosis and treatment.

The quest for genetic polymorphisms translating into population genetics have come a long way and still has a longer path to traverse. But the systematic efforts should continue to facilitate better understanding of the genetic basis of resistance or susceptibility to TB which could be translated into targeted immunotherapy as a preventive measure as well as an effective adjunct to multidrug therapy for TB.

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