

## Genome-wide scanning versus other methods of mapping infectious disease susceptibility loci: A recent study of leprosy

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Infectious disease genetics focuses on approaches that try to map and possibly identify the genes responsible for variable susceptibility to major infectious diseases in humans, such as leprosy, tuberculosis, malaria, schistosomiasis and AIDS. This area has been around for a few decades now and is gaining a fresh impetus from the new and more complete information that has currently been available about human genome. The role of genetic factors in the control of disease phenotype response variability has been generally suggested by twin studies<sup>1</sup>, by strong ethnic differences<sup>2-6</sup> or by the great variability of individual phenotypes within a familial aggregation<sup>2,4</sup>. In this complex biological study, the approaches used to home-in the candidate monogenic/multigenic loci depend essentially on the availability of host-genetic maps and/or genetic polymorphisms associated with putative candidate genes and involve the following strategies:

1. Mapping susceptibility gene homologues in inbred strains of mice through classical genetic methods involving linkage analysis, followed by positional cloning. Due to the homology between the mouse and human chromosome, comparative mapping can be a very effective tool to find the candidate gene involved<sup>7</sup>.
2. Complex segregation analysis of the disease transmission in multigene human families, where specific statistical methods identify one or more candidate genes that strongly segregate with the studied phenotype<sup>6</sup>.
3. More recent human whole genome-wide scanning methods, where a few hundred highly polymorphic microsatellite markers, representative of the whole genome, are scanned for the regions in the genome that are strongly linked with increased sharing of parental alleles in affected sibling pairs. This is because the tested polymorphism is in strong linkage disequilibrium with the dis-

ease allele or is the disease allele itself.

Finally, in all these pursuits, the evidence of a genetic association with the disease will be complete only after a functional analysis of whether the identified candidate gene(s) modifies the gene expression or the gene product in a manner that can affect the susceptibility to the disease.

Leprosy, mainly a disease of skin and peripheral nerves, has afflicted mankind as early as 600 BC. Though one of the oldest diseases, a number of facets of the disease still remain a mystery. It is caused by *Mycobacterium leprae* and often leads to loss of sensation, paralysis and marked physical deformities. WHO reported 8,88,640 cases this year and 70% of the world's registered cases live in India. It is also one of the infectious diseases that has been recognized to have a strong host genetic component influencing the susceptibility to the disease.

A recent study, reported on major susceptibility locus for leprosy conducted with 224 families from South India maps it to chromosome 10p13 and is a landmark achievement that uses the whole genome-wide scanning method discussed above<sup>2</sup>. In this study, at the first stage, 103 independent affected sibpairs were genotyped for 388 highly polymorphic microsatellite markers that cover the entire human genome minus the Y-chromosome, which yielded 28 regions in the genome that weakly associate with leprosy. A further scan of these weakly suggestive loci using additional markers from these regions in an additional 142 sibpairs, revealed a single region on chromosome 10p (D10S548) with a Lod (log of odds). Score of 4.09 ( $P$  value  $< 0.00002$ ), which means that the association of D10S548 with leprosy is about  $10^{4.09}$  times the odd association by an independent assortment. This score exceeds the stringent level proposed for genome-wide scans. Most surprisingly, this region does not house any of the

previously reported leprosy candidate genes such as HLA class II region<sup>5,6,8,9</sup> or NRAMPI locus<sup>10,11</sup>. It is pertinent to note that the associations between HLA-DR2 and susceptibility to leprosy and tuberculosis inferred earlier were on Indian populations. The basis for such a discrepancy is unclear.

It is very likely that susceptibility to leprosy is multifactorial, where it is genetically heterogeneous under multigenic control and susceptibility alleles display high population frequencies. It is remarkable that a single major gene was inferred from earlier studies that seem to influence seemingly highly polygenic nature of infectious disease susceptibility, but does not show up in whole genome scan, which is a more neutral method with respect to how the disease was inherited. Is it due to a situation where complex diseases and traits result mainly from genetic variation that is relatively common in the general population involving a large number of genes, environmental factors and their interactions? If particular clusters of such highly frequent genetic variations are transmitted down as loci affecting disease susceptibility/resistance, it will be relatively hard to pin them down. Then it is all the more perplexing to rationalize the results of strong Lod score at 10p13 for leprosy susceptibility.

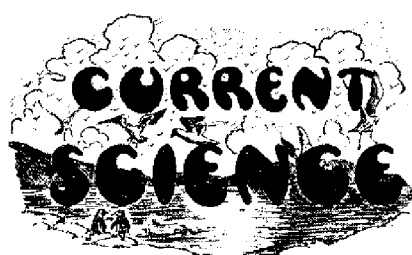
Perhaps future studies involving more robust genome-wide scanning methods involving SNP-markers will unveil many more new loci from where an integrated picture will start emerging<sup>12</sup>. Disease gene studies and population genetics efforts would benefit from knowing the typical distances up to which allelic variations can be expected to be in linkage disequilibrium. SNP maps can also help identify beneficial and deleterious alleles, which dominate in the population and would therefore be important targets of study. That horizon may not be too far off, hopefully.

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### The New Viceroy and Science

Few Viceroys have been called upon to assume the responsibilities of their exalted office in circumstances more critical than those which confront Lord Linlithgow, and the problems which await solution are not, however, beyond his statesmanship.

The welfare and prosperity of the people depend on the extent to which the country is scientifically organized, and our firm conviction is that unless the major industry of the people persistently applies scientific method and scientific knowledge to its problems, it cannot escape from the difficulties with which it is surrounded. In the field of science, therefore, no Legislature can reasonably recommend measures of economy which will sacrifice the efficiency of research organization. The Royal Commission on Agriculture has pointed out that 'in spite of marked progress which has been made in many directions during the last quarter of a

century, it is hardly an exaggeration to say agricultural research in this country is still in its infancy.

It seems to us that simultaneously with the inauguration of constitutional reforms, an announcement should be made in regard to the establishment of the National Advisory Council of Scientific Research for the purpose of co-ordinating all the research organizations in order to promote a steady advancement of the industrial prosperity.

The principal task of such an institution will be to emphasize that no industry can afford in these times to neglect any opportunity for increasing its efficiency and, of all the means to this end, the pursuit of research and the applications of the results obtained are often the most far-reaching and fruitful. If the case for research on the production of Indian commodities is as strong as ever, the need for research into their utilization is stronger still. In nearly every industry to-day, movements are on foot to apply old materials to new uses, and to discover uses for new material. Cotton, wool, rubber, food products and alloys of metals are instances in point. Whether the object in view be to create a wide demand for a commodity and thus reap the advantages of modern methods of production or to discover the most suitable material for a particular purpose, it is equally important that the chemical and physical properties of the materials concerned should be fully understood. For investigations of this

kind, the facilities in the laboratories of the universities and in those of the Indian Institute of Science, if extended and supported by increased grants from the funds of the National Advisory Council of Scientific Research will be found ample for industrial research of the highest quality.

The poverty and backwardness of India can be removed only by investing more money in the promotion of scientific research and if, in the midst of his political concerns and duties. His Excellency Lord Linlithgow could bestow some attention on the imperative need of consolidating the work of the Royal Commission over which he so worthily and ably presided, his contribution to the lasting happiness and prosperity of India would be such as few Viceroys have conceived or achieved. To watch and guide the working of the New Reforms Act is part of the routine programme of the Viceroy's duties, but to devise a scientific organization of this great country 'as a means of assisting the advance of the rural community towards a richer and fuller life, and of awakening the desire in that community for better things and arming each individual member of it against the temptations that beset him, without impairing either his self-respect or his spirit of manly independence', calls for the active and generous exercise of those higher qualities of statesmanship with which Nature and political training have abundantly endowed Lord Linlithgow.