SUMMARY AND CONCLUSIONS
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The inability of geneticists to easily identify genes involved in adaptation to the extreme environment of high altitude (HA) or disorder is seen as a vindication of the importance of nature. Considerable progress has been made in understanding the HA genomics in relation to physical performance or health and disorder in the past decade. With every new example that is uncovered, our previous assumptions about the association of the gene and its variants with routine physical activity or disorder are challenged. This has happened with the discovery of the possible involvement of the ACE I allele in physical performance of athletes, mountaineers and even HA natives, which rectified the previous observation that the same allele is associated with high altitude pulmonary hypertension.

The work carried out as part of this thesis is an initiation of research on HA genomics in our country. This is the first report of association of polymorphisms in blood pressure related candidate genes like ACE, AGT and AT1 receptor with adaptation or routine physical activities and disorders in HA natives and sojourners of Indian subcontinent. The knowledge gained from these studies is not only of benefit for the development of suitable diagnostic tests and to predispose individuals to mountain disorders, but also to elucidate the underlying mechanisms of HA adaptation that facilitate physical performance and the pathogenesis of HA disorders. In the light of these facts, the population based polymorphism screening approach for identifying functional polymorphisms associated with routine physical activities or disorders in HA populations is of significance and perhaps will provide guidelines in modulating the future strategies for HA assignment that can be even used for recreational climbers like mountaineers and trekkers.
The major results and conclusions are:

- The analysis of distribution of the RAAS gene polymorphisms in HLs and LLs revealed the role of ACE I allele and AGT T174 allele in HA adaptation and routine physical activities of HA natives and sojourners. As we observed a trend of over-representation of wild type alleles in HLs, we hypothesize that the preponderance of these alleles favors the natural selection on the basis of environmental influences. As ACE, AGT, and ATI receptor genes are the components of same pathway (RAAS), it may be possible that the ATI receptor (A1166C and G2228A) and AGT gene (M235T and GT repeats) polymorphisms are indirectly involved in HA adaptation by having synergistic effects.

- To discover novel disease mechanisms, one needs to combine the power of the human genome sequence and a study of both normal and diseased human populations. We have tried to implement such an approach in understanding and discovering new mechanisms involved in the pathogenesis of HAPE caused by HA extreme environment. We conclude that the susceptibility to HAPE is associated with the presence of ACE D and AGT M174 alleles. The wild type ACE I and AGT T174 alleles may be associated with lower incidence of HAPE in HA natives and sojourners. Therefore, ACE and AGT gene polymorphisms may act as genetic markers for the predisposition to HAPE.

- On analyzing the role of ACE, AGT and ATI receptor gene polymorphisms in the pathogenesis of systemic hypertension in HA native...
population, we ended with negative association. We hypothesize that the possible reason may be the gene-gene interactions, which explain the interaction of the studied genes with the genes of the same or the other related pathway that contributes to the pathogenesis of the disorder. To an extent, cultural, demographic as well as dietary habits like high salt intake of HA natives may also be involved.

- Genotype-phenotype correlations in HA adaptation and disorders continue to provide key features of the relationship of the genetic factors with environmental influences. We hypothesize for the first time that repeated exposure to extreme environment of higher altitudes, such as in the case of HAM, increases and stabilizes the SaO₂. It strongly suggests that a population or an individual who is less hypoxic than their counterparts, who are less exposed to the same environment, may have a selective advantage in an extreme environment to maintain routine physical activities such as required under the strategic assignments especially to our country. Nevertheless, the comparison of the genotypes of ACE, AGT and ATI receptor genes with SaO₂ level revealed no association suggesting that the mechanism by which the wild type alleles may confer a selective advantage at HA, is possibly not via improved oxygen saturation. In other words, the SaO₂ level may be independent of ACE, AGT and ATI receptor genotypes in HA natives or the sojourners.

By implementing a population polymorphism screening approach we have not only been able to gain insight into the mechanisms involved in HA adaptation or the
pathogenesis of the HA disorders but have been able to identify certain functional
variants associated with the same. The work presented in this thesis provide just a
glimpse as to how powerful such an approach can be in understanding and
discovering new mechanisms involved in the regular physical activities and incidence
of disorders in sojourners. In the coming years, one can only speculate that the use of
population based approaches to answer complex trait will become increasingly
commonplace. Ours has been the initiation, the genome journey seems longer.
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