HUMAN GENETICS RESEARCH AND EDUCATION IN KOLKATA

(2008)
PREFACE

The members of Calcutta Consortium on Human Genetics thought it appropriate to share the research carried out by human genetics groups working in various institutions. References to our publications are primarily confined to those published after 2000; however, even among these we have been selective. We are pleased to ‘rediscover’ the strength in human genetics that we have in Kolkata, which should provide us with a renewed enthusiasm to harness this potential through more effective collaboration and attempt to reach greater heights.

We are sharing this document widely in order to collect positive criticism of our work and to forge alliances, both nationally and internationally.

We have tried to be inclusive in preparing this document. However, we do sincerely apologize for our omissions, if any.

September 25, 2008

Members of Calcutta Consortium on Human Genetics
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1. BRIEF HISTORY OF HUMAN GENETICS RESEARCH & EDUCATION IN KOLKATA

Kolkata (formerly, Calcutta) was the citadel of clinical research in India. Pioneering studies on epidemiology of malaria (conducted by Ronald Ross at the Presidency General Hospital), natural history of kala-azar or leishmaniasis and the discovery of a new drug (urea stibamine) for its effective treatment (by U.N. Brahmachari), discovery of the cholera toxin and its role in pathogenesis (conducted by S.N. De), etc., were a prelude to the conduct of genetic studies on various diseases. Pioneers such as Prafulla Chandra Roy ensured strength of teaching and research in Chemistry in Calcutta. An indigenously developed electron microscope at Saha Institute of Nuclear Physics by N.N. Dasgupta facilitated ultrastructural characterization of micro-organisms and early detection of *Mycobacterium leprae*, *Leishmania donavani*, etc. in clinical cases. Introduction of radioactive tracer technology in this Institute further facilitated clinical research in cancer, thyroid malfunction, etc. Clinicians, such as Mahendral Lal Sircar, ensured that basic research gained ground, by setting up research institutions. Thus, even before human genetics was introduced in India, the untiring efforts of these pioneers were vital to the success of the new discipline of human genetics in Kolkata. One of the earliest series of studies, with an explicit genetic view, was on thalassaemias conducted by J.B. Chatterjea at the Calcutta School of Tropical Medicine.

Since human genetics is one of the most quantitative disciplines of biology and involves explicit use of probabilistic and statistical concepts, the Indian Statistical Institute, Kolkata — founded by P.C. Mahalanobis — played a pivotal role in the development of human genetics in India. Mahalanobis undertook large-scale surveys of anthropometric diversity and affinities among ethnic groups of United Provinces (now, Uttar Pradesh) in the 1940s, and later in the late 1950s and early 1960s, among those of Bengal. In the Bengal anthropometric survey, in which C.R. Rao played an active role, in addition to anthropometric measurements, data on ABO blood groups were collected. These surveys led to the development of the Mahalanobis $D^2$ statistic. Many of the conclusions of these two surveys have stood the test of time; later surveys based on genomic data have validated many of the inferences of these surveys. Mahalanobis also sowed the ideas of estimating the extent of contributions of ancestral populations to an admixed population, by initiating studies among the Anglo-Indians of Kolkata. Unfortunately, because of the lack of appropriate biological markers (Mahalanobis could only use anthropometric and morphological markers) these studies did not yield reliable estimates, but at least laid the relevant conceptual foundations.

R.A. Fisher, a founder of statistical genetics and a close friend of Mahalanobis, was instrumental in the organization of the Indian Statistical Institute (ISI). He visited ISI regularly. Upon Mahalanobis’s invitation, J.B.S. Haldane joined the ISI in the late 1950s. This was a landmark, not only in the development of human genetics in Kolkata, but all over India. Haldane initiated a series of studies on theoretical population genetics in ISI, primarily with S.D. Jayakar; large-scale surveys on inbreeding, with K.R. Dronamraju and P. Meera Khan, that later — upon Haldane’s inspiration — resulted in the collection of data on inbreeding at the all-India level during the 1961 decennial Census of India. These studies provided largest global data set on the nature and extent of inbreeding in human populations and its impact on prevalence of recessive disorders, which attracted the attention of many leading human geneticists. R. Ruggles Gates and Curt Stern visited and worked in India on inherited traits; they went on to publish papers with their Indian collaborators, for example, Curt Stern with S.S. Sarkar of the University of Calcutta. The *Journal of Genetics* was brought over by Haldane from London to Kolkata.
R.L. Kirk from the John Curtin School of Medical Research, Canberra, spent many years in Kolkata and established the first leading biochemical genetics laboratory at the ISI. A large number of population genetic studies were conducted using classical genetic markers after this laboratory was established. Many international collaborative projects, particularly with the Soviet Academy of Sciences, were undertaken. A major study on genetics of susceptibility to leprosy was undertaken in West Bengal; the report of this study is now a classic. Cytogenetics also developed in Kolkata, not explicitly in conjunction with human genetics, but in connection with research on flies and plant genetics. S.P. Roychoudhury and A.K. Sharma established state-of-the-art cytogenetics laboratories in Kolkata that paved the way for the conduct of cytogenetic research on human diseases.

Today, major research on genetical aspects of human diseases is carried out in Kolkata in various institutions and hospitals, including Indian Statistical Institute, Indian Institute of Chemical Biology, Saha Institute of Nuclear Physics, Chittaranjan National Cancer Institute, S.S.K.M. Hospital, School of Tropical Medicine, Calcutta Medical College, Bose Institute, University of Calcutta and Vivekananda Institute of Medical Sciences.
2. RECENT RESEARCH

2.1 Molecular Population Genetics and Evolution

With a view to reconstructing the processes of peopling of India, three Institutes in Kolkata – Indian Statistical Institute, Indian Institute of Chemical Biology and Saha Institute of Nuclear Physics – embarked on molecular genetic studies among ethnic groups of India on a pan-India level in 1999. Subsequently, the Central Forensic Science Laboratory, Kolkata, has contributed to this effort. Their sustained efforts have resulted in quantifying the nature and extent of genomic diversity in ethnic groups of India, dispersed geographically and socio-culturally. A clear picture of peopling of India, with reasonable estimates of dates of major migration events, has emerged from these studies. Many of the original findings of this Consortium (such as, low mitochondrial, but not autosomal or Y-chromosomal, genome diversity in Indian ethnic groups compared to that found among ethnic groups of many other geographical regions) have been validated by others. In addition, these studies have shown how various social customs have left their imprints on genomic structures of ethnic groups (for example, through the higher female mobility connected with the social custom of females moving to the geographical regions of residence of males after marriage, resulting in greater dispersal of mitochondrial DNA but not Y-chromosomal DNA). Most recently, many of the scientists involved in these studies have also been actively involved in a national human genome variation consortium study, sponsored by the Council of Scientific & Industrial Research, Government of India.

Relevant publications


2.2 Genetic Epidemiology of Mendelian Disorders

Thalassaemia

Thalassaemias are a major public health burden in eastern India. Several groups in the city are engaged in the estimation of prevalence and identification of the major mutations that cause thalassaemia, especially β-thalassaemia, in populations of eastern India. The major groups engaged in thalassaemia research in Kolkata are:

1. Department of Biophysics, Molecular Biology and Genetics, University of Calcutta
2. Thalassaemia Counseling Unit, Ramakrishna Mission Seva Pratishthan
3. Haematology Departments of Sir Nil Ratan Sircar Medical College and the Calcutta Medical College

The long and sustained work of the thalassaemia researchers in Kolkata have revealed that of the large spectrum of mutations in the beta-globin genes that cause β-thalassaemia, only about five or six mutations explain over 90% of the β-thalassaemia cases found in eastern India. Since HbE is also very common in eastern India, a large number of HbE/β-thalassaemia cases are also found. These individuals have haematological and clinical profiles that are intermediate between β-thalassaemia minor and major. Because of the high prevalence of this haemoglobinopathy, a large number of coalition groups of patients’ families have formed in eastern India, who play a major role in helping patients obtain blood transfusion and procure iron-chelation medicines. Scientists and patient coalition groups in the city have played a major role in increasing public awareness towards thalassaemia, as a result of which the demand pre-marital and pre-natal genetic testing have increased in eastern India. Unfortunately, the demand for genetic testing is only partially met by laboratories in the city; more laboratories offering genetic testing services are required in the city. Various laboratories in the city are also engaged in basic research on different aspects of thalassaemia.
Relevant publications


Bhattacharyya D., Mukhopadhyay D Chakrabarti A (2007) Hemoglobin depletion from red blood cell cytosol reveals new proteins in 2-D gel-based proteomics study, *PROTEOMICS - Clinical Applications* 1, 561-564


Sickle cell anaemia

Sickle cell disease (SCD) is highly prevalent in many tribal and some non-tribal ethnic groups of eastern India. Of the various haplotypes associated with sickle cell disease, one haplotype – called the Arab-Indian haplotype – is common in India. Patients with this haplotype have the high levels of haemoglobin F and low reticulocyte count. Studies on this disease have been carried out at Indian Statistical Institute; Department of Pathology, Medical College; and Department of Medicine, Nil Ratan Sircar Medical College.

Relevant publications


Hemophilia

This X-linked disease is caused independently by defects in Factor VIII and Factor IX genes resulting in Haemophilia A and Haemophilia B, respectively. Scientists of Indian Institute of Chemical Biology in collaboration with Haemophilia Federation of India have identified mutations in Factor IX gene in eastern Indian patients. They have also detected informative markers for carrier detection in these population groups. This group has also examined the effect of point mutations on the crystal structure of the native factor IX by measuring the change in the hydrogen-bonding pattern and electrostatic potential and has explored the possibility of any correlation of the clinical severity of Haemophilia B with the structural perturbation, by plotting the mutations of varying phenotype (severe and mild) on the crystal structure of FIX. Their data suggest that there is a statistically significant correlation between the two groups of mutations associated with severe and mild phenotypes as measured by change in the hydrogen-bonding pattern. The group also examined variations of single nucleotide polymorphism (SNP) in Factor VIII gene in the Indian population and established the utility of a combination of SNP and microsatellite markers for the successful identification of carriers in the affected families.

Scientists at Saha Institute of Nuclear Physics have recently developed an EBV vector for gene therapy that express human factor VIII and von Willebrand factor in cultured B-cells.

Relevant publications:


Wilson’s Disease

Wilson’s disease (WD) is an autosomal recessive disorder caused by defects in the copper-transporting Ptype ATPase gene (ATP7B) resulting in the accumulation of copper in the liver and the brain. WD can be thwarted if detected at a presymptomatic stage. Studies conducted at Indian Institute of Chemical Biology in collaboration with clinical collaborators at the Bangur Institute of Neuroscience and Psychiatry identified prevalent mutations in the ATP7B of Indian WD patients (n>100) and have correlated those with severity of the disease. Interestingly, homozygotes for different mutations that would be expected to produce similar defective proteins showed significant disparity in terms of organ involvement and severity of the disease. It was also observed that WD patients with neurological symptoms had little or no manifestation of hepatic pathology. In one WD family, the proband and a sib had remarkably different phenotypes despite sharing the same pair of mutant chromosomes, indicating the existence of unidentified modifier loci. Dr. Ray’s group also has provided a comprehensive strategy for determining presymptomatic and carrier siblings of WD patients by screening for different subsets of SNPs.

**Relevant publications:**


**Oculo-cutaneous albinism**

Indian Institute of Chemical Biology has undertaken molecular genetic studies on Oculo-cutaneous albinism (OCA) in collaboration with Indian Statistical Institute and National Medical College. OCA, a group of autosomal recessive disorders, is characterized by deficient synthesis of melanin pigment, associated with common developmental abnormalities of the eye. It is one of the major causes of childhood blindness in India. Dr. Ray & Dr. Majumder’s initial study covering thirteen ethnic groups of India, some representing >20 million people, revealed that among 25 OCA families 12 were affected with OCA1, and that these cases were primarily due to founder mutations in tyrosinase gene. Haplotype analysis suggested a few founder chromosomes causing the disease in the majority of the patients. Their study also demonstrated that a large number of publicly available nucleotide variants of TYR in this region are same as the bases present in the identical locations in the pseudogene. PCR amplification of these regions using primers with sequences common to both loci may result in coamplification of TYR and TYRL, and may lead to misinterpretation of the results which is particularly important for carrier detection in the OCA affected families. The study reveals that 10% of the total OCA cases from eastern and southern Indian ethnic groups carry mutations in *SLC45A2*.

**Relevant publications:**


**2.3 Host Genome Variations in Modulation of Susceptibility to Infectious Disease and Variability in Host-Response to Vaccines against Pathogens**

**Novel strategy for correction of mitochondrial diseases**

Mitochondria are now recognized to be at the epicenter of a wide variety of human diseases, as well as in the ‘normal’ process of aging. Mitochondrial dysfunction, leading to reduced ATP generation, causes progressive degeneration of various tissues, especially the nervous and muscular systems, as well as sensory and endocrine defects. A subgroup of these disorders is caused by mutations in human mitochondrial tRNA genes. In this context, scientists at Indian Institute of Chemical Biology have made a seminal observation that the *Leishmania* RNA Import Complex
(RIC) induces import of cytosolic tRNAs into human mitochondria, and that imported tRNALys is functional in supported translation of mRNAs in mitochondria containing a patient-derived mutation in the organellar tRNALys gene. Importantly, RIC is taken up efficiently by primary as well as cultured mammalian cells and intracellularly targeted to mitochondria, where it induces import of cytosolic tRNAs. The investigators have shown that as a result, the respiratory function of cybrid cells carrying a tRNALys mutation was restored to near-normal levels.

Thus, for the first time, a functional macromolecular complex derived from an evolutionarily distant organism was used to repair an intracellular defect in human cells. This novel concept of ‘complex therapy’ will be the subject of intensive investigations in the laboratory in the coming years.

Relevant publications:


Host - *Vibrio cholerae* interaction: Response of human intestinal epithelial cells

Scientists at the Indian Institute of Chemical Biology are interested to decipher the effect of genomic variation of the host to *V. cholerae* infection by examining response using intestinal epithelial cell model with the intent to use the information for infection in human. Her group has suggested that ND5, a mitochondrial encoded subunit of complex I of the mitochondrial respiratory chain has been found to be upregulated in the human intestinal epithelial cell line Int407 following exposure to *V. cholerae* which is modulated by the adherence, motility and virulence of *V. cholerae*. Although cholera is commonly considered to be a noninflammatory secretory disease, there is substantial evidence suggesting the presence of an inflammatory component to the disease. Identification of the factors of *V. cholerae* that cause inflammation is essential for the development of safe live attenuated vaccines. Her group reported for the first time that both motility and adherence to intestinal epithelial cells are possible triggering factors contributing to IL-8 mRNA expression by *V. cholerae*. The coordinated expression and up regulation of a number of cytokines with chemoattractant and proinflammatory properties belonging to varied cytokine families in human intestinal epithelial cells following *V. cholerae* infection appears to be mediated by NF-kB and is modulated, in part, by some secretory factors and adherence or motility of this organism. The information obtained by the group is expected to positively impact vaccine and antimicrobial drug development for the disease cholera.

Relevant publications:


Helicobacter pylori mediated gastroduodenal diseases

Studies carried out at Indian Institute of Chemical Biology (IICB) in collaboration with Institute of Postgraduate Medical Education and Research (IPGMER) applying the newly gained knowledge on the genetic variation of Indian population to study the association between cytokine and chemokine genes polymorphisms and *Helicobacter pylori* mediated gastroduodenal diseases. They have identified ethnic differences in allele distribution of IL8 and IL1b gene in populations from eastern India. Further they dissected the genomic region with respect to functional studies to reveal interaction between *IL1B* gene promoter polymorphisms in determining susceptibility to *Helicobacter pylori* associated duodenal ulcer.

Relevant publications:


Anti-tuberculosis drugs (ATD) treatment and risk of hepatotoxicity in tuberculosis patients

Scientists at Indian Statistical Institute are also interested to decipher effect of genomic variants on the efficacy of anti-tuberculosis drugs (ATD). It is known for a long time that the treatment of tuberculosis patients by isoniazid, one of the ATDs, plays important role in causing hepatotoxicity in about 5-25% of the patients. Investigators reported that NAT2 slow acetylators are susceptible to ATD hepatotoxicity since toxic metabolites of isoniazid that are excreted slowly from these patients, causes liver damage. The group has identified polymorphisms at *GSTM1* and *CYP2E1* that increase the risk of hepatotoxicity in tuberculosis patients.

Relevant publication:


Inter-individual variability of response to vaccines against pathogens

The TCG-ISI Centre for Population Genomics – in collaboration with the National Institute of Cholera and Enteric Diseases, Kolkata; RTI International, USA and Duke University, USA – is conducting a major study on identifying host-genome variations that contribute to inter-individual variability in response to typhoid and cholera vaccines. This study has been funded by the National Institutes of Health, USA. This is a large candidate gene study comprising the screening of over 3000 SNPs in
about 200 genes belonging to innate and adaptive immune pathways. The vaccinees (n=2000) have been recruited from a socio-economically depressed area of Kolkata, where there are annual outbreaks of both typhoid and cholera.

**Relevant publication:**


### 2.4 Genetic Susceptibility to Environmental Toxicants

Scientists of Indian Institute of Chemical Biology have been working on the assessment of genetic damage and genetic variants associated with arsenic toxicity and carcinogenicity in the population exposed to the toxicant through drinking water in West Bengal. Although a large number of individuals are exposed to arsenic through drinking water, only 15-20% individuals showed arsenic induced skin lesions. This indicates that genetic variants play an important role in arsenic induced toxicity and carcinogenicity. The group has been able to identify the best suitable cell type to identify the genetic damage induced by arsenic through drinking water. For the analysis of genetic variants, probable associations of several candidate genes, including arsenic metabolism pathway genes and DNA repair pathway genes have been studied, and variants in some of the genes have been implicated as described in the cited publications below.

**Relevant publications:**


### 2.5 Genetics of Chronic and Late-Onset Diseases

Research groups from several institutions of Kolkata are actively engaged in analyzing the genetic profile and molecular aspects of various cancers. Head and Neck Cancer is most common among all types of cancer in India, while cervical cancer appears to be the most prevalent type among women of lower socioeconomic strata. Recent studies have revealed that breast cancer is also emerging as a major cancer type among Indian population.

**Head & neck cancer and Breast cancer**

Scientists of the Indian Institute of Chemical Biology (IICB) and Chittaranjan National Cancer Institute (CNCI) in collaboration have mapped several chromosomal regions, which possibly harbor multiple new putative tumour suppressor genes implicated in the development of head and neck and breast cancers. Specifically, they identified *SH3GL2* (9p21-22) and *LIMD1* (3p21.31) as novel tumour suppressor genes that may be involved in the head and neck cancer. Their studies on genetic and epigenetic alterations of mismatch repair and spindle assembly checkpoint genes in oral cancer have also provided new insights into the molecular basis of genomic instability.

The human genetics group of the Indian Statistical Institute (ISI) have analyzed SNPs in genes involved in metabolism of tobacco carcinogens such as, Glutathione S-transferases (*GSTM1, GSTT1, GSTM3* and *GSTP1*), N-acetyl transferases (*NAT1* and *NAT2*) and DNA repair loci (*XRCC1, XPC, XPD* and *OGG1*) and determined their association with the development of oral precancer and cancers. The study identified that genotype combinations that imparted disease risk contained at least one carcinogen metabolic locus (say *GSTM3* or *NAT2*) and one DNA repair locus (say *XRCC1* or *XPD*). His work in the area of mitochondrial genetic variations identified that major alleles at mt tRNA\(^{Leu}_{2u}\)(CUN) and ND3 genes enhanced the risk of oral cancer, which was more pronounced in males who were smokers. His group further identified that ~5Kb deletion in mtDNA is a precancerous event whereas mutation at HVS is a late event in carcinogenesis at oral cavity.

Human geneticists of the IICB have also investigated the clinicopathologic and biological significance of *hnRNP* genes as potential biomarkers of oral cancer. Her group observed significant downregulation of human *hnRNP E2* in oral cancer tissues and upregulation of hnRNP K in normal oral tissues. The expression of *hnRNP E2* was correlated with histology, being lower in moderate and poorly differentiated squamous cell carcinoma (SCC) in comparison to well differentiated SCC. Recent studies by her group suggest down regulation of *hnRNP E2* as a novel mechanism to enhance the resistance of cancer cells to apoptosis.

The transmission electron micrograph based studies on Oral submucous fibrosis (OSF) as a precursor of oral cancers, revealed variations in the structure of the fibrillar collagen in such tissues in comparison to control tissues. Analysis based on a computer-aided novel Wavelet-artificial neural network technique could successfully classify the normal and oral precancer stages after getting the image as input. Analysis of the light microscopic histological images also revealed a distinct
quantitative difference between normal oral mucosa (NOM) and OSF with respect to their histological features. Also, incidence of GSTT1 null gene frequencies was significantly higher in such precancerous conditions.

Relevant publications:


Cervical cancer

Scientists of IICB and CNCI have mapped several chromosomal regions that are likely to harbor putative tumour suppressor genes involved in the development of cervical cancer. Their studies also suggest that specific polymorphisms in the p53 gene may confer risk for cervical cancer.

Members of the human genetics group of ISI are involved in studies aimed towards deciphering the role of host pathogen interactions at the genetic and epigenetic levels in the development of cervical cancer. These studies have identified several variations within the host genome that impart risk towards cervical cancer development. Also, the studies have identified mechanisms adopted by HPV16 towards mediating disease risk, involving methylation of the viral promoter and sequence variations in the transcription factor binding sites. This research group has also identified the HPV 16 viral haplotype, which is most often found in cervical cancers in India, and the genetic variations responsible for the transforming potential of this haplotype involving deleterious variations in genes that are implicated in the viral life cycle.

Relevant publications:


Starting in 1995, the human genetics group at the Saha Institute of Nuclear Physics has been studying various neurodegenerative diseases caused by the expansion of triplet repeats which include Huntington’s Disease (HD), myotonic dystrophy (DM), various subtypes of spinocerebellar ataxia (SCA), Friedreich ataxia (FRDA) etc. This group studied CTG repeats at 3’ UTR of myotonin protein kinase gene in myotonic dystrophy (DM) patients in Indian populations and predicted that the prevalence of DM is likely to be higher in Indian than African populations but lower than the Caucasians. Further, the group studied various subtypes of spinocerebellar ataxia (SCAs), like SCA1, SCA2, SCA3, SCA6, SCA7, SCA8, SCA12 and SCA17. The majority of the clinically diagnosed ataxias (n=1000) belong to SCA2, followed by SCA1 and SCA3. Homozygous expansion of GAA repeats in the first intron of the frataxin gene was identified among several Friedreich ataxia (FRDA) patients. Expansion of CAG repeats at Huntingtin gene (HTT) has been identified in more than 100 Huntington patients. In these diseases, they also identified the origin of mutation by utilizing the linked markers in and around the causal genes. This research was carried out in collaboration with Neurologists from Kolkata as well as various parts of India. Their major collaborators include Bangur Institute of Neurology, Calcutta Medical College, R.G. Kar Medical college, Peerless Hospital, Kolkata, Advanced Diagnostic Center, Ranchi, Bombay Hospitals, Mumbai, Madras Medical College, Chennai.

To identify the role HTT interacting proteins in aggregate formation, a hallmark of HD and apoptosis, observed in the brains of HD patients, this group made a cell model of HD with respect to increased aggregate formation and enhanced apoptosis by exogenous expression of exon1 of HTT gene containing 40 or 83 CAG repeats tagged with green/ red fluorescent protein. Expression of HTT interacting protein alone or together with mutated HTT reveals various important information.
regarding the pathogenesis of the disease. These studies open up possibilities of intervention of HD.

The human genetics group of Biophysics, Molecular Biology and Genetics department of the Calcutta University, have also investigated expansion of mutation in fmr1 gene for identification of patients with Fragile X-mental retardation.

**Relevant publications:**


Basu, P., Gangopadhaya, PK, Mukherjee, SC., Sinha, KK and Bhattacharyya, NP (1998b) Expansion of CTG repeat in myotonin protein kinase gene on Alu ( ins ) - Hinf1-1 background in a myotonic dystrophy patient from India, *Human Mutation*, 13, 79

Basu P., Gangopadhaya PK Mukherjee SC., Das S.K., Sinha KK., and Bhattacharyya NP (2000a) Molecular anatomy of CTG expansion in Myotonin Protein kinase Gene among Myotonic Dystrophy Patients from Eastern India, *Human Mutation*, Mutation in Brief #369 online


Chattopadhyay B., Gangopadhyay, PK, Das SK, Roy T, Sinha SK, Jha DK, Mukherjee SC, Chakraborty, A, Singhal BS, Bhattacharya, AK and Bhattacharyya NP (2003b) Modulation of age of onset in Huntington’s disease and spinocerebellar ataxia type 2 patients originated from eastern India, *Neuroscience Letters*, 345, 393-396


Majumder P, Choudhury A, Banerjee M, Lahiri A, Bhattacharyya NP (2007b) Interactions of HIPPI, a molecular partner of Huntington interacting protein HIP1, with the specific motif present at the putative promoter sequence of the caspase-1, caspase-8 and caspase-10 genes. FEBS J. 274, 3886-3899


Genetic epidemiology of diabetes, metabolic syndrome and mental/behavioral disorders

Indian Statistical Institute through collaboration with multiple centers across India is actively engaged in studies related to many chronic and complex diseases. In particular, human geneticists of this Institute have been engaged in genetic epidemiological studies on diabetes in collaboration with the Madras Diabetes Research Foundation, Chennai; and on genetics of alcoholism as a partner of the Collaborative project on Genetics of Alcoholism (COGA), in collaboration with Washington University School of Medicine. The diabetes (T2DM) study has revealed several interesting features that are significantly different from those in other global regions, including lack of association of some SNPs that have shown strong association with T2DM in western populations. The COGA collaboration has resulted in the formulation of some statistical methods for quantitative locus mapping. Their applications have resulted in the discovery of loci linked to quantitative endophenotypes of alcoholism. The TCG-ISI Centre for Population Genomics has been engaged in a gene-mapping study on coronary artery disease in a specific ethnic group that has high prevalence of hypertension and cardiovascular diseases. Body growth and dimensions, especially fatness, are important contributors to various chronic diseases. The Indian Statistical Institute and Calcutta University researchers have undertaken twin and family studies to estimate genetic and environmental variances for body measurements, familial resemblance in body measurements, and genetic and environmental contributions to human growth.

Relevant publications:


Movement disorders
S N Pradhan for Neurosciences at Calcutta University is interested in molecular pathogenesis of movement disorders including Parkinson’s disease and dystonia. The team at Calcutta University is investigating the genetic basis of these diseases with the intent of genotype-phenotype correlation in collaboration with Bangur Institute of Neuroscience and Psychiatry and Indian Institute of Chemical Biology.
**Parkinson's disease (PD)**, the second most common neurodegenerative disorder, affects at least 1% of the population over the age of 50. However, very little information is available regarding the molecular basis of PD among Indians. Since the largest number of mutations has been detected in the Parkin gene among all known PD loci, The group aims to use Parkin as the candidate gene to assess its role in PD-related pathogenesis in Indian patients. Among eastern Indian PD patients, mutation in Parkin was identified in 7.24% cases. In addition they reported association of two SNPs (Ser167Asn & Val380Leu) for association with PD, and their frequencies are greatly influenced by ethnic origin. This study also provides an opportunity to correlate genetic variation with epidemiological data in Indian population.

The group is also interested in understanding the molecular basis of Dystonia which is a common movement disorder. The purpose of this study is to examine the relative distribution of the primary dystonia subtypes and identify mutation(s) in the DYT1 gene in Indian patients. Primary dystonia patients (n=178) and controls (n=63), lacking any symptoms of the disease, were recruited for the study from eastern India. Three reported and two novel changes were identified in this gene. The homozygous genotype (G,G) for a missense variant (c.646G > C; Asp216His) was significantly over-represented in the patients compared with controls (P < 0.05). However, the commonly reported 3 bp deletion (904–906delGAG) was not detected. The study suggests that the DYT1 gene might have a limited role in causation of dystonia in the Indian population.

**Relevant publications:**


**Diseases related to mental retardation**
The Manovikas Kendra Rehabilitation and Research Institute for the Handicapped in Kolkata aims to improve the quality of life of children affected with sensory, motor or cognitive disability. Accordingly, the institute is focused on deciphering the molecular genetic basis of mental retardation in Down syndrome, genetic susceptibility to Attention-deficit-hyperactivity disorder (ADHD) and other related disorders in children. The research program is based on biochemical, molecular, genetic and bioinformatics approaches to identify genetic markers of prognostic value and unravel the molecular pathogenesis underlying the disorders.

In *Down syndrome* patients with cognitive and behavioral impairments, two candidate genes, DRD4 and serotonin transporter, and other reported genetic markers have been examined but no association with the disease phenotype was apparent in the cohort.

**Attention deficit hyperactivity disorder (ADHD)** is one of the most common childhood onset neurobehavioral disorders. Analysis of four dopaminergic genes, and dopamine beta hydroxylase (DBH) in the eastern Indian nuclear families with ADHD
proband revealed transmission of specific alleles to ADHD cases as detailed in the cited references.

In patients with **Idiopathic mental retardation (IMR)** an allele of the Cystathionine beta synthase gene has been reported to be associated with a risk of IMR in their patient cohort. Currently, the investigators are evaluating the variants in folate metabolism system genes for any potential role in causation of the disease.

**Autism** is a behaviorally defined neurodevelopmental disorder. Family and twin studies suggest that the disorder has a high heritability factor. Therefore, the institute has initiated genetic research on autism using a candidate gene approach in the Indian population. Towards this goal, based on location and functional importance, they have selected the genes that code for serotonin transporter, serotonin receptor 2A, reelin and homeobox transcription factors as potential candidates for autism which are currently being investigated.

The long-term goals of the laboratory include working in tandem with the Assessment and Counseling Unit of the Out-Patient Department of Manovikas Kendra to provide services of value to patients and their families.

**Relevant publications:**


Das, M; Das Bhowmik A; Sinha S; Chattopadhyay A; Chaudhuri K; Singh M; and Mukhopadhyay K. (2006) MAOA Promoter Polymorphism and Attention Deficit Hyperactivity Disorder (ADHD) in Indian Children. *Am J Med Genet, Neuropsychiatr Genet* 141B: 637-642.


**Duchenne and Becker muscular dystrophy**

The most common genetic neuromuscular disease of childhood, Duchenne and Becker muscular dystrophy (DMD/BMD), the most common genetic neromuscular disease is caused by deletion, duplication or point mutation of the dystrophin gene located at Xp 21.2. In a recent study conducted by Calcutta University with Bangur Institute of Neurology & Psychiatry and others, reported that deletion of dystrophin gene at 46 patients out of 76 patients.

**Relevant publication**
Glaucoma

Indian Institute of Chemical Biology (IICB) – in collaboration with Regional Institute of Ophthalmology at Kolkata and a private clinic (Dristipradip) – study molecular pathogenesis of glaucoma which affects 67 million people worldwide and about 1.5 million people are blind due to the disease.

On examining multiple candidate genes, it was observed that myocillin plays a major role in causation of the juvenile and adult onset forms of primary open angle glaucoma (POAG). They hypothesized that myocillin might have evolved from two different primordial proteins. Bioinformatic approaches were also used for identification and characterization of olfactomedin-related genes with potential role in pathogenesis of ocular disorders particularly glaucoma. They also observed that on rare occasions CYP1B1 may be primarily responsible for JOAG by possible monogenic association, and this observation emphasizes the importance of screening for mutation in this gene of JOAG patients that are determined not to harbor mutations in previously characterized candidate genes and loci for POAG. The investigating group is currently examining functional implication of the variants identified in the genes examined.

Studies conducted by a collaborative effort between Indian Statistical Institute (ISI) and LV Prasad Eye Institute at Hyderabad reported that CYP1B1 mutations in primary congenital glaucoma are strongly structured by geographic and haplotype backgrounds. Also, ISI participated in collaborative study with WHO to investigate role of Rage gene promoter polymorphisms in diabetic retinopathy in a clinic-based population from South India.

Relevant publications:


2.6 Statistical Genetics

The major group working on statistical genetics in Kolkata is in the Indian Statistical Institute. The focus of this group has been to devise efficient statistical methods for mapping genes, particularly for quantitative traits. A notable contribution of this group has been to propose novel and efficient non-parametric methods for mapping quantitative traits using relative-pair data. In addition, this group has also proposed efficient algorithms for haplotyping.

Relevant publications:


### 2.7 Bioinformatics

Scientists of Indian Institute of Chemical Biology involved in computation biology are also working on *in silico* characterization of the selection forces governing protein composition in human, clustering of protein families & taxonomic distribution of domains, development of novel software tools or algorithms for genome / proteome analysis. Scientists of Bose Institute involved in bioinformatics studies are working towards understanding the structure and folding of proteins and their interactions with other molecules using biophysical techniques (especially, X-ray crystallography) and database analysis. Scientists of the Indian Statistical Institute have been involved primarily in the development of bioinformatics methodologies.

**Relevant publications:**


3. TRAINING
While the interest on Human Genetics was mounting globally, the small group of human geneticists working in Kolkata in the 1990s felt the need to impart training in human genetics, especially in view of the fact that human genetics was not included in the formal curricula of most Indian universities and institutes. Initiation of efforts to fulfill this need was made with the first winter school on “Human Genetics: concepts, paradigms and methods” with funding from the Department of Biotechnology, Govt. of India, in January 1998, held at the Indian Institute of Chemical Biology (IICB), Kolkata, and organized jointly the Indian Statistical Institute, IICB and Saha Institute of Nuclear Physics. It is comforting to find that many of the attendees of that workshop are active scientists of the country working in the area of Human Genetics & Genomics. Organization of these Workshops gained momentum when the TCG-ISI Centre for Population Genomics, in collaboration with the University of Pittsburgh, obtained a Training Grant from the Fogarty International Center, NIH, USA. Under this training grant, several graduate students, post-doctoral fellows and junior faculty members obtained training in human genetics and genetic epidemiology. Human geneticists of Kolkata, jointly with those of the University of Pittsburgh, have been conducting regular annual workshops in Kolkata on statistical methods in genetic epidemiological analyses of complex human disorders. The beneficiaries of these workshops are spread throughout India, and these training efforts have undoubtedly resulted in the wider spread of the culture and practice of human genetics in India.

4. NATIONAL & INTERNATIONAL COLLABORATIONS AND EXTRA-MURAL FUNDING

Human genetics groups of Kolkata have traditionally collaborated among themselves and with other national and international groups. A Calcutta Consortium of Human Genetics was formed in 1998, comprising groups affiliated with the Indian Statistical Institute, Indian Institute of Chemical Biology, Saha Institute of Nuclear Physics and Chittaranjan National Cancer Institute. The human genome diversity studies among ethnic groups of India were the major initial project undertaken by the Calcutta Consortium. Subsequently, members of this Consortium have continued to collaborate on various genetic disorders, including Huntington disease, ataxias, cancer, etc. This Consortium also formed alliances with various other Indian institutions and universities, especially in connection with the conduct of human genome diversity studies. Notable among these have been (i) Pandit Ravishankar Shukla University, Raipur; (ii) University of Madras, Chennai; (iii) B.J. Medical College, Mumbai; (iv) Guru Nanak Dev University, Amritsar; (v) Institute of Genomics and Integrative Biology, Delhi; (vi) Centre for Cellular and Molecular Biology, Hyderabad; and (vii) Central Drug Research Institute, Lucknow. In connection with studies on genetic diseases, members of the Calcutta Consortium collaborate with (i) Institute of Genomics and Integrative Biology, Delhi; (ii) National Institute of Mental Health & the Neurosciences, Bangalore; (iii) Madras Diabetes Research Foundation, Chennai; (iv) L.V. Prasad Eye Institute, Hyderabad and many other institutions. In view of the fact that human genetics is not included in the formal curricula of most Indian universities, the Consortium felt the need to organize short-term courses and workshops on human genetics for faculty members and graduate students for capacity-building in human genetics. Many such courses and workshops have been organized; these have been very well-attended and participants have found these to be very helpful in their careers.

National Extra-Mural Funding: The funding for the initiation of genome diversity studies was provided by the Department of Biotechnology, Government of India. Subsequently, the Council of Scientific & Industrial Research, Government of India, provided funding to initiate the Indian Human Genome Variation Consortium project. Most human genetic research in Kolkata is funded by the Department of
Biotechnology. Human geneticists of Kolkata have also received sustained funding from other Government of India agencies, including Department of Science and Technology, Indian Council of Medical Research, Council of Scientific & Industrial Research and Department of Environment.

International Collaborations: In addition to forging alliances with various national institutions and universities, members of the Calcutta Consortium on Human Genetics, have also collaborated with and are continuing to collaborate with various international institutions. Notable among these are collaborations with University of Pittsburgh, USA; Hebrew University, Israel; RTI International, USA; Duke University, USA; Washington University School of Medicine, USA; University of Western Australia, Australia etc.

Private-Public Partnership: The Calcutta Consortium has also played a leading role in promoting the formation of a private-public partnership institution in Kolkata. In 2001, a Centre for Population Genomics (CpG) was established in Kolkata – a Government of India recognized centre of excellence in human genetics – as a partnership between The Chatterjee Group (a private investment company) and Indian Statistical Institute. Members of the Calcutta Consortium have collaborated with CpG in conducting research and in organizing courses and workshops in human genetics.

International Funding: The Indian Statistical Institute and Saha Institute of Nuclear Physics have obtained funding from the India-Israel science co-operation, for the conduct of human migration studies and *Intron exonization due to variation in the Alu Sequence in the human genome*. CpG has successfully obtained major funding from the Fogarty International Centre, USA (*training grant in genetic epidemiology*); National Institute of Allergy & Infectious Diseases, NIH, USA (*research grant on population genetics of immune response to vaccines*); India-Australia co-operation in biotechnology (*research grant on mapping genes for primary congenital glaucoma*); and, Indian Council of Medical Research, New Delhi (*research grant for mapping genes for coronary artery disease*).
INSTITUTES IN KOLKATA PURSUING STUDIES RELATED TO HUMAN GENOME AND DISEASES

INDIAN INSTITUTE OF CHEMICAL BIOLOGY

**Susanta Roychoudhury, Molecular & Human Genetics Division**
(susanta@iicb.res.in)
Genetic and epigenetic alterations in oral cancer.
Functional analysis of genetic variants to understand biochemical basis of disease susceptibility

**Kunal Ray, Molecular & Human Genetics Division**
(kray@iicb.res.in)
Molecular bases of genetic diseases – Eye diseases (Glaucoma, Oculocutaneous Albinism) Neurological disorders (Wilson's & Parkinson's Disease), Bleeding disorder (Haemophilia)
Genetic basis of Arsenic toxicity

**Keya Chaudhuri, Molecular & Human Genetics Division**
(kchaudhuri@iicb.res.in)
Host- *Vibrio cholerae* interaction
Molecular basis of susceptibility to oral submucous fibrosis and oral cancer
Development of bioinformatics tools and their application to genome analysis

**Chitra Dutta, Structural Biology & Bioinformatics**
(cdutta@iicb.res.in)
In silico characterization of the selection forces governing protein composition in human
Development of novel software tools or algorithms for genome / proteome analysis

**Ashok Kumar Giri, Molecular & Human Genetics Division**
(akgiri@iicb.res.in)
Molecular epidemiology and Environmental health
Genetic basis of toxicity among people of West Bengal resulting from the exposure to arsenic through drinking water

INDIAN STATISTICAL INSTITUTE

**Partha Pratim Majumder, Human Genetics Unit**
(ppm@isical.ac.in)
Genetic Epidemiology, Human Genome Diversity & Evolution, Statistical Genetics

**Bidyut Roy, Human Genetics Unit**
(broy@isical.ac.in)
Gene-environment interactions in diseases with special references to oral cavity cancer, anti-tuberculosis drug induced hepatotoxicity

**Sharmila Sengupta, Human Genetics Unit**
(sharmila@isical.ac.in)
Genetic epidemiology of cervical cancer
**Saurabh Ghosh, Human Genetics Unit**  
(saurabh@isical.ac.in)  
Genetic Epidemiology, Statistical Genetics, Statistical Computing

**B. Mohan Reddy, Biological Anthropology Unit**  
(bmrisi@gmail.com)  
Genome diversity, Genetic Disease

**T.S. Vasulu, Biological Anthropology Unit**  
(vasulu@gmail.com)  
Genome diversity

CALCUTTA SCHOOL OF TROPICAL MEDICINE

**Anusri Tripathi, Department of Biochemistry & Med. Biotech**  
Molecular basis of genetic susceptibility of Mycobacterium laprae infection  
Molecular basis of cancer development

SAHA INSTITUTE OF NUCLEAR PHYSICS

**Nitai P. Bhattacharyya; Crystallography & Molecular Biology Division and Structural Genomics Section**  
(nitai.pada.bhattacharya@saha.ac.in)  
Molecular and functional studies related to triple repeat expansion disorder – i.e. Huntington’s Disease, myotonic dystrophy (DM), various subtypes of spinocerebellar ataxia (SCA), Friedreich ataxia (FRDA) etc

**Abhijit Chakrabarti; Biophysics Division and Structural Genomics Section**  
(abhijit.chakrabarti@saha.ac.in)  
Proteomics in blood disorders (Red cells and B cell proteomics, implications in Leukemia and Thalassemia, analysed by 2DGel Electrophoresis and MALDI-ToF/ToF.

**Subrata Banerjee; Biophysics Division and Structural Genomics Section**  
(subrata.banerjee@saha.ac.in)  
Main area of our interest is to understand how the immune disorder leads to the opportunistic proliferation advantage and differentiation abilities in hematological malignancies and gene therapy

UNIVERSITY OF CALCUTTA

**Jharna Ray; S N .Pradhan Centre for Neurosciences**  
(jharnaray@gmail.com)  
Molecular pathogenesis of movement disorders including Parkinson’s disease and dystonia

**Uma Dasgupta; Dept. of Biophysics, Molecular Biology and Genetics**  
(ubdgh@yahoo.co.in)  
Molecular studies on genetic diseases with special interest in thalassemia

**Sanghamitra Sengupta; Dept. of Biochemistry**
Susceptibility loci identification in Malaria infected individuals

CENTRAL FORENSIC SCIENCE LABORATORY

Anil K. Sharma
(akscfsl@yahoo.com)

WEST BENGAL UNIVERSITY OF HEALTH SCIENCES

Abhijit Chowdhury, Institute of Postgraduate Medical Education and Research
(achowdhury2002@yahoo.co.in)
Studies on potential role of cytokine and chemokine genes in Helicobacter pylori mediated gastroduodenal diseases and liver diseases

CHITTARANJAN NATIONAL CANCER INSTITUTE

Chinmay Panda; Department of Oncogene Regulation
(ckpanda@vsnl.net)
Molecular genetics of carcinomas of head and neck, breast and uterine cervix

VIVEKANANDA INSTITUTE OF MEDICAL SCIENCES

Madhusnata De
Diagnosis and profiling α- and β- thalassaemia in eastern India

MANOVIKAS BIOMEDICAL RESEARCH & DIAGNOSTIC CENTRE

Monaranjan Singh, Dr. Krishnadas Nandagopal (knandago2001@yahoo.com),
Kanchan Mukhopadhyay (kanchanmvk@yahoo.com) and Usha Rajamma
(ushamvk@yahoo.co.in)
Engaged in molecular genetic of mental retardation, autism, fragile X, down syndrome and other disorders

ICMR VIRUS UNIT

Runu Chakravarty; ICMR Virus Unit
(runugc@yahoo.co.uk)
Host response of HBV variants in Eastern Indian Population

ANTHROPOLOGICAL SURVEY OF INDIA

V. R. Rao (drraovr@yahoo.com) Biswanath Sarkar (drbnsarkar@yahoo.com)
Molecular characterization of haemoglobinopathies and beta- thalassaemia in West Bengal