Centre for Brain Research

An autonomous Centre of the Indian Institute of Science

ANNUAL REPORT
2018-19

CONTENTS

CBR at a Glance

The Centre for Brain Research (CBR) was established in 2014 at IISc to focus on research on ageing brain with a goal to identify risk and protective factors that contribute to healthy aging. Research at CBR represents an integrative approach encompassing genetic, imaging, molecular, functional, computational method, while bringing together large groups with diverse expertise to address the complex challenges of understanding brain functioning in health and disease. We aim to develop the foster large-scale research programs and build capacity focused large scale research programs and build capacity focused at inter disciplinary neuroscience research in India thereby setting the stage for our scientists to contribute significantly to the endeavor of understanding the human brain and discovering rational therapies and cures for brain disorders, in addition to gaining insight about the complex cognitive and behavioral functions executed by the brain.

CBR is funded by Pratiksha trust set up by Mr. Kris Gopalakrishnan, co-founder of Infosys and Mrs. Sudha Gopalakrishnan. The trust funds education, research, innovation and entrepreneurship. The Centre also received a generous endowment from ex-IAS officer Ms. Sharwaree Gokhale who passed away on 15th January 2016. Her contribution could help progress our understanding of the human brain. CBR is immensely thankful for the philanthropic support and aims to build capacity for interdisciplinary neuroscience research in India.

Mandate and Vision

- Carry out basic research to understand brain function in health and disease.
- Foster focused research programs for inter-disciplinary neuroscience research to discover rational therapies for dementia and other age-related brain disorders.
- Networking of neuroscientists among institutions across the country, with emphasis on neurodegenerative disorders.

1. RESEARCH PROJECTS

Srinivaspura Aging, Neuro Senescence and Cognition (SANSCOG) study

CBR, in collaboration with National Institute of Mental Health and Neurosciences (NIMHANS), Sri Devaraj Urs Medical College, Kolar and the Indian Institute of Science (IISc) has started the Srinivaspura Aging Neuro Senescence and COGnition (SANSCOG) study. The SANSCOG study is envisioned as a prospective community-based cohort study with long term follow-up over many years for comprehensive evaluation of risk and protective factors associated with cognitive changes due to normal ageing, Alzheimer's disease and other related disorders. This will be a cohort of 10,000 individuals from the Srinivaspura taluk of Kolar district in the state of Karnataka aged over 45 years. The pilot study has been completed with 1,000 individuals in March 2019, the details are given below. The next phase has been taken up in an accelerated mode,

Total No. of Awareness Programs	**18**
No. of attendees	**750+**
Total Number of Baseline Assessments completed	**1054**
Brain MRI completed	**100**
No. of villages recruited from	**9**
Yet to visit the centre (Appointment given)	**25**
Total telephonic follow ups completed	**120**
Total No. of Follow up Assessments completed	**39**
Follow up appointments given	**50**
No. of blood sample collection camps conducted	**23**
Number of subjects that attended the camps	**972**
Distribution of Reports completed for	**972**
Feedback/consultation session attended by	**952**
Villages where survey has been completed	**9**
Street Plays conducted in villages	**4**

The GenomeIndia Project

CBR leads the consortium of 22 national institutes and hospitals across the country for GenomeIndia project which is aimed at cataloguing the common and low frequency genetic variations in Indians by Whole Genome Sequencing (WGS) of 10,000 Indian individuals in the first phase. These individuals are sampled from diverse ethnicities and linguistic communities across the length and breadth of the country. Genetic variations in individuals, which is mostly geographic and ethnicity-specific, play a major role in determining our health conditions and susceptibility to diseases. Populations across the world differ in their genetic makeup in terms of allele frequency and haplotype structure that could determine, with contributions from environmental factors, their susceptibilities to complex genetic diseases. India is a country of remarkable diversity given the presence of thousands of ethnic groups and distinct linguistic communities. And these communities have largely adhered to endogamous marriage practices for centuries which has created several pockets of various mutations or highly prevalent genetic variations in the country, which influences disease susceptibilities of our population. However, we are yet to identify the genetic variations in our population that result in the manifestation of complex diseases such as diabetes, cardiovascular diseases, and mental illness, among others.

The GenomeIndia project will identify these genetic variations (common, low frequency, rare, SNPs and structural) in the diverse Indian population. This will lead to the development of a genome wide association chip specific for Indian population and facilitate large scale genetic studies in the future. The comprehensive list of genetic variations obtained from healthy individuals will serve as filter for non-causal mutations and help perform genetic studies on monogenic disorders. The second phase of the project will focus on whole genome sequencing of additional 10,000 individuals sampled from cohorts of particular diseases, for example cardiovascular, cerebrovascular, and dementia in the country. The results from this project would thus be a valuable national resource for the country and will be made publicly available through an interactive web portal. This project has initiated national level capacity building in sequencing and computation for high throughput human genomics, and several dovetailed efforts of additional whole genome sequencing would happen that will facilitate greatly our understanding of diseases in the Indian population and open up avenues for precision medicine in the country.

The project has undergone several rounds of reviews by experts appointed by Department of Biotechnology (DBT), Government of India and has been scientifically approved. At present, it is under active consideration for funding by finance committees.

Specific Aims

I) Create an exhaustive catalog of genetic variations (common, low frequency, rare, single nucleotide polymorphisms or SNPs and structural variations) in Indians.

II) Create a reference haplotype structure for Indians. This reference panel can be used for imputing missing genetic variation in future GWA studies.

III) Design genome wide arrays for research and diagnostics at an affordable cost.

IV) Establish a biobank for DNA and plasma collected for future use in research.

The 22 institutions forming the consortium for this project with responsibilities involved for sample collection, whole genome sequencing, data processing and analysis to obtain genetic variants, and novel methods development using this data are:

i) AIIMS Jodhpur;

ii) Centre for Brain Research, Bangalore;

iii) CSIR- Centre for Cellular and Molecular Biology, Hyderabad;

iv) Centre for DNA Fingerprinting and Diagnostics, Hyderabad;

v) CSIR - Institute of Genomics & Integrative Biology, New Delhi;

vi) Gujarat Biotechnology and Research Centre, Gandhinagar;

vii) Indian Institute of Information Technology, Allahabad;

viii) Indian Institute of Science, Bangalore;

ix) Indian Institute of Science Education and Research, Pune;

x) Indian Institute of Technology Madras, Chennai;

xi) Indian Institute of Technology, Delhi;

xii) Indian Institute of Technology, Jodhpur;

xiii) Institute of Bioresources & Sustainable Development (IBSD), Manipur;

xiv) Institute of Life Sciences, Bhubaneshwar;

xv) L V Prasad Eye Institute, Hyderabad;

xvi) Mizoram University, Aizawl;

xvii) National Centre for Biological Sciences, Bangalore;

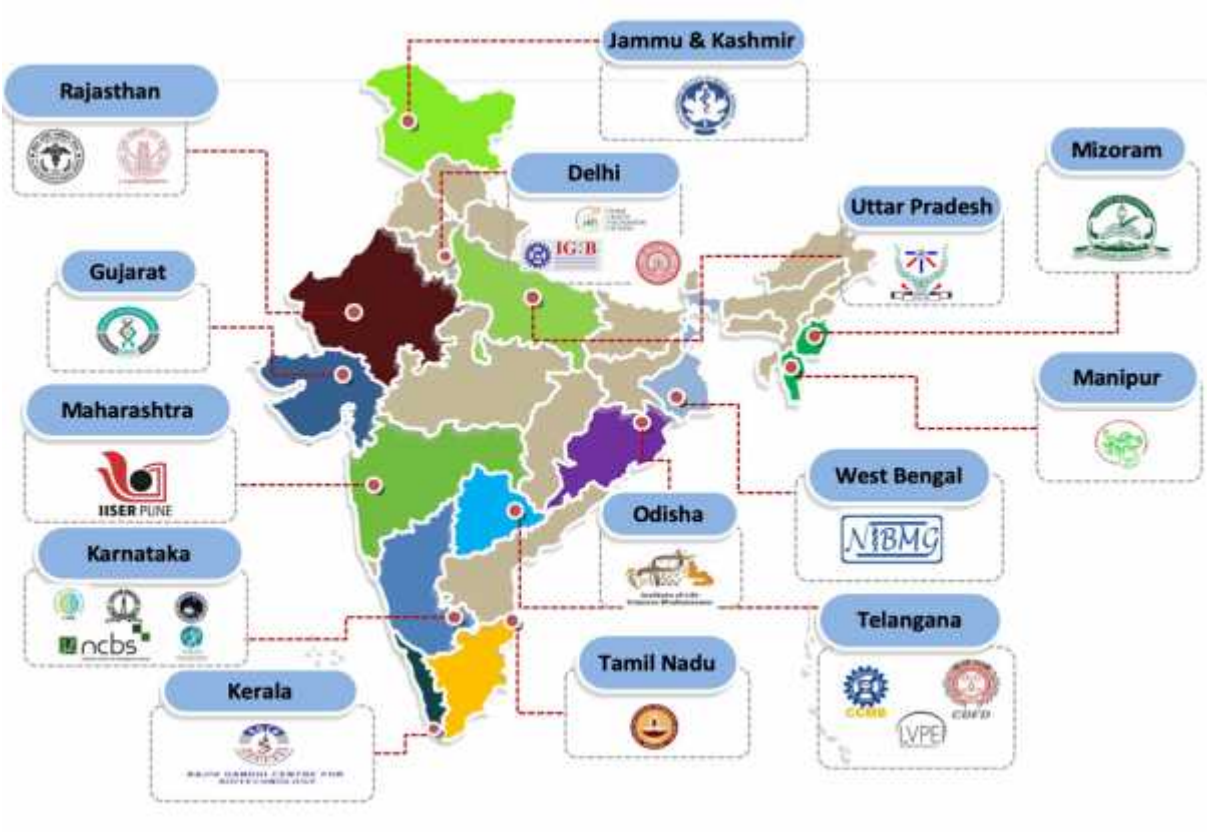
xviii) National Institute of Biomedical Genomics, Kolkata;

xix) National Institute of Mental Health & Neurosciences, Bangalore;

xx) Public Health Foundation of India;

xxi) Rajiv Gandhi Centre for Biotechnology, Trivandrum;

xxii) Sher-e-Kashmir Institute of Medical Sciences, Srinagar;



Working group meetings are regularly held among the institutes to discuss the execution modalities and troubleshooting issues related to the project. Nine working group meetings has been held over the course of two years, since the initiation of the project at the Indian Institute of Science on June 30, 2017.

The human ethics protocols and informed consent for sample collection has been formulated based on suggestions of DBT expert committee, and institutional human ethics committee of CBR. This includes clause for re-contacting in the scenario of incidental findings for study participants, and inclusion of proper protocol for biobanking of blood, plasma, serum, DNA samples for future research. This will be used for sample collection by all institutes participating in the project. Standard operating procedures (SOP) for sample collection, DNA isolation and questionnaires have been finalized by the group.

A strategy for sample collection has been adopted by the group based on the genetic studies on large and small population groups identified by Indian Genome Variation Project earlier. The sample collection grid is optimized based on genetic clusters, ethnic groups, population size, social status and linguistic preference of the Indian population. All samples will be freshly collected with detailed socio-demographics data along with anthropometry and blood biochemistry for obtaining background information of the samples. 67 samples have been collected so far.

Next generation sequencing platform (Illumina Novaseq 6000 for WGS) and Affymetrix high-throughput whole genome genotyping facility has been established at IISc through funding from Tata Trusts. These equipment are fully functional currently. Three runs have been completed using S4 and S2 flow cells.

The data analyses pipeline for WGS has also been optimized. The analysis of base calls from the sequencing raw output in order to obtain genotype variant calls has been executed by CBR with computing architecture of Supercomputer Centre (SERC) at IISc. The analysis has been implemented through extensive parallelization in CRAY XC40, which is an Intel Haswell 2.5 GHz based CPU cluster; with 128GB RAM at each node and nodes connected using Cray Aries interconnect.

Strategic international partnerships have been formed with acclaimed research groups already doing large scale WGS projects, namely, the BROAD institute of MIT and Harvard, Alzheimer's Disease Sequencing Project, JCVI and University of Pennsylvania.

Project personnel: Krithika Subramanian, Abhishek Panda, Anupriya Sadhasivam.

Faculty Research:

Dr. Ganesh Chauhan

Project title: Joint analysis of GWAS of stroke subtype to identify new loci for stroke

Funding : DBT-Ramalingaswami Re-entry Fellowship

Project personnel : Dr. Devendra Meena (post-doctoral fellow), Mr. Shrihari A (PhD student), Ms. Soumi Chowdhury (PhD student).

Genome-wide association studies have successfully reported hundreds of novel genetic variants associated with many complex genetic traits including Stroke, Alzheimer's and cardiovascular diseases. These variants each with small effect size explain only a fraction of trait heritability in most cases therefore leaving the remaining heritability unexplained. A number of studies using novel statistical methods applied to GWAS summary statistics (without individual-level data) have shown that joint-analysis of multiple GWAS results in increased statistical power to capture novel genetic variants.

Here, we applied multi-trait analysis of GWAS (MTAG) to MEGASTROKE summary statistics to uncover novel SNPs associated with stroke and stroke subtypes. MEGASTROKE is the largest project on GWAS of stroke that has analyzed close to half a million of subjects across the world. MTAG is essentially a fixed-effect meta-analysis method (inverse-variance-weighted) assumes that each risk allele shares same effect size across traits but novel in the approach that it considers genetic correlation between phenotypes to estimate phenotype-specific effects. This has led to the identification of four novel loci for stroke which were identified for association with stroke for the first time through this study (*PITX2, PRDM16, F11 & STIM2/PCDH7*). Some of the loci have been previously implicated in stroke or related pathophysiology but never identified through the stringent GWAS approach. These loci also are part of pathways which play an important role in predisposition to stroke, however we could like to validate these novel loci in an independent study. A detailed literature review of these novel genes identified is listed below.

PITX2: This locus has been previously shown to be associated with stoke though large scale GWAS. The SNPs identified through this study are independent of previously reported SNPs thus suggesting two independent SNPs in the same region. This locus is also associated with cardiac disorders and atrial fibrillation.

PRDM16: PRDM16 (PR-domain containing 16) acts as a molecular determinant of the brown fat cell phenotype; that induces brown fat genetic program including the expression of PGC-1α , UCP-1 in brown and beige adipocytes activating uncoupled respiration by working as a transcriptional co-activator of other mediator molecules. It is a known locus for migraine a phenotype which has strong genetic overlap with stroke. Knock down is zebrafish has shown to cause arterial vascular defects which can lead to stroke like phenotype.

F11: This gene codes for coagulation factor XI. Although mutations in this gene mainly leads to several bleeding disorders; earlier reports stated that patients with severe factor XI deficiency have showed reduced incidence of ischemic stroke, lower risk of cardiovascular and venous thromboembolism events. F11 levels are associated with Corornary Heart Diseases and Stroke. Candidate gene studies of F11 polymorphisms have shown association of stroke.

STIM2/PCDH7: The stromal interactive molecule 2 (STIM2) is an ER resident calcium sensor protein that regulates the store operated calcium entry (SOCE) along with its homolog STIM1. STIM1 and Orai have been implicated to take part in stroke pathophysiology and as novel target for vascular diseases. SOCE being a contributor in platelet physiology and thrombosis process can be therapeutically targeted to treat or prevent thrombo-inflammatory diseases states such as ischemic stroke. STIM2 protein have implications in neurodegenerative disorders like Huntington Diseases.

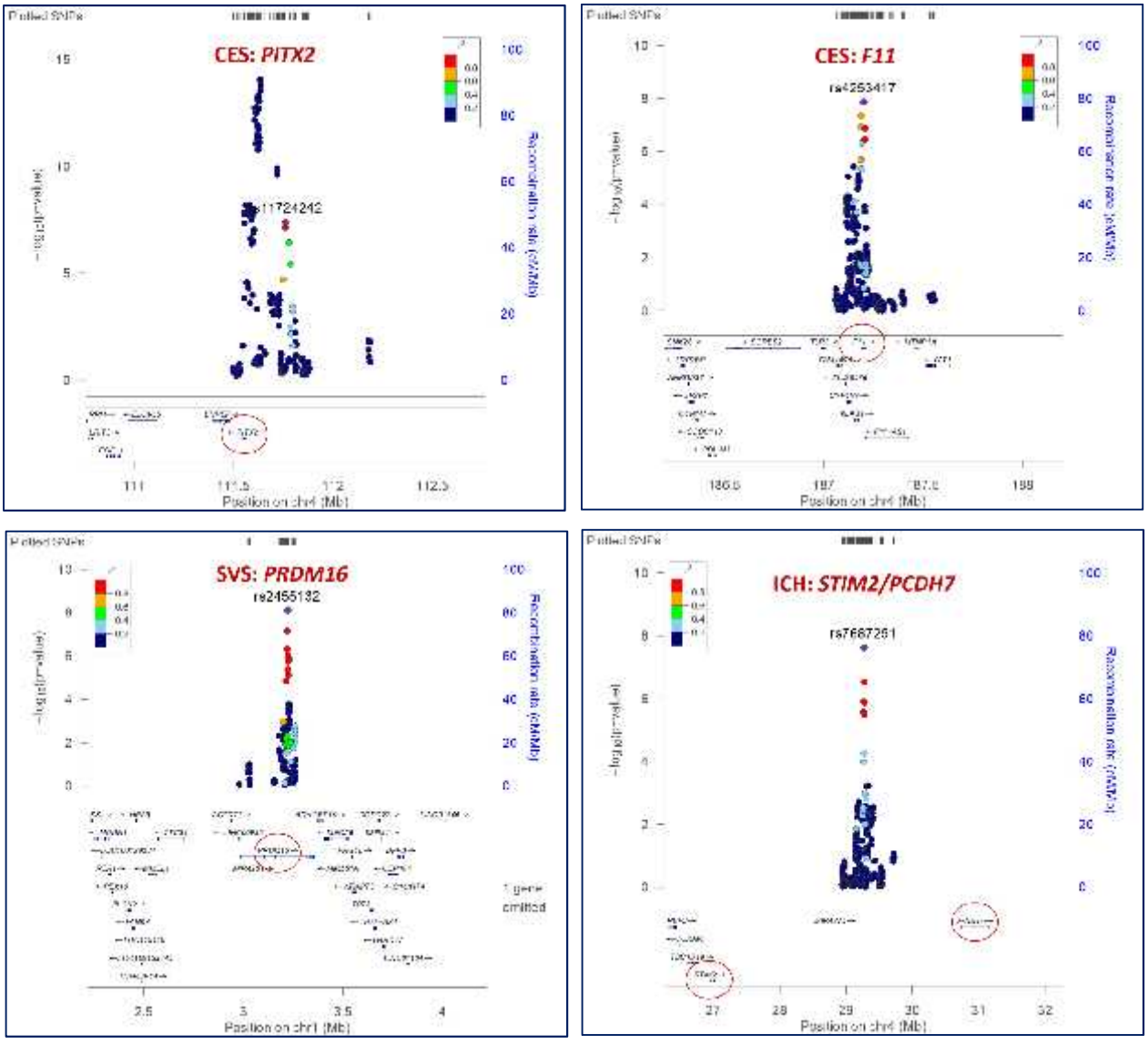


Figure : Regional plots of the four loci identified for stroke subtypes.

Dr. Bratati Kahali

Project Title: Optimizing Machine Learning algorithms for cognitive impairment classification

IISC undergraduate student Abhay Gupta has been working on this project with publicly available data.

Dementia is a neurological syndrome which is projected to affect more than 48 million people in 2020 with doubling of numbers every 20 years. More and more cases are being reported from low- and middle-income group countries like India and China in recent years. Alzheimer's disease (AD) represents the primary cause of neurodegenerative dementia. AD pathology is defined by cognitive impairment, behavioural disturbance, and functional disabilities, which have a great impact on the quality of daily life of the patient and is major problem for families and caregivers too. Neuropsychological assessment plays a crucial role in detecting loss of cognitive functions and change in behavioral and functional state compared to normal conditions. Neuropsychological tests can measure different cognitive domains (e.g., language, learning, and memory) and subdomains (e.g., long-term memory and recognition memory), and is often a large battery of tests that has to be undertaken by the individual. However, subjective judgement exists in this diagnostic process.

The aims of this project are to use neuropsychological and demographic data to predict cognitively healthy, MCI, AD through the implementation of machine learning models and to determine a best combination of attributes in the entire battery of neuropsychological tests that can be used to reliably classify and diagnose individuals with cognitive impairment that can be implemented easily in the community. This variable selection process would avoid data over-fit, improve classification accuracy, provide faster models, and gain deeper insight into the underlying processes that generate the data.

Cognitive function was assessed with a battery of neuropsychological tests encompassing logical memory, visuospatial abilities, attention, language, measures of orientation and other related aspects administered by neuropsychological test technicians in the two studies: Religious Orders Study and Memory and Aging Project (ROSMAP), and National Alzheimer's Coordinating Center (NACC), USA. The dataset is comprised of participants falling within one of three diagnostic classes: healthy volunteers, MCI, and AD.

We have applied different machine learning algorithms: Random Forest, Linear and Radial Support Vector Machine on these multi-class datasets and inferred which of them correctly predict the clinical diagnoses of cognitively healthy, mild cognitive impaired, and Alzheimer's disease based on these neuropsychological test measures. During the testing phase, the trained models are blind to the response variable for each data point and forced to predict the target response variable based on assumptions made during the training phase. We observe that Random Forests perform better for multi-class data sets than SVM.

Moreover, we also implemented feature selection methods, and observed that a subset of 6-8 neuropsychological tests in the entire battery can accurately predict (95% accuracy) the cognitive status of an individual when compared to the whole battery of tests. These 8 tests belong to the domains of episodic and semantic memory, perceptual orientation, executive functioning, and are sufficient to accurately predict the cognitive status of an individual. These results are promising for large scale implementation in communities.

For large scale studies conducted at multiple locations across the country, we do not have affordable and accurate diagnostic measures for imaging or blood biochemistry to correctly predict the study subjects as cognitively healthy, mild cognitive impaired or affected with Alzheimer's disease. This machine learning approach for multi-class prediction based on just 8 neuropsychological tests, would enable larger community based studies of aging at diminished costs, without comprising on the accuracy of the end results of prediction, and maintain diagnostic consistency across time, centres, and different testers, and importantly reduce subject burden.

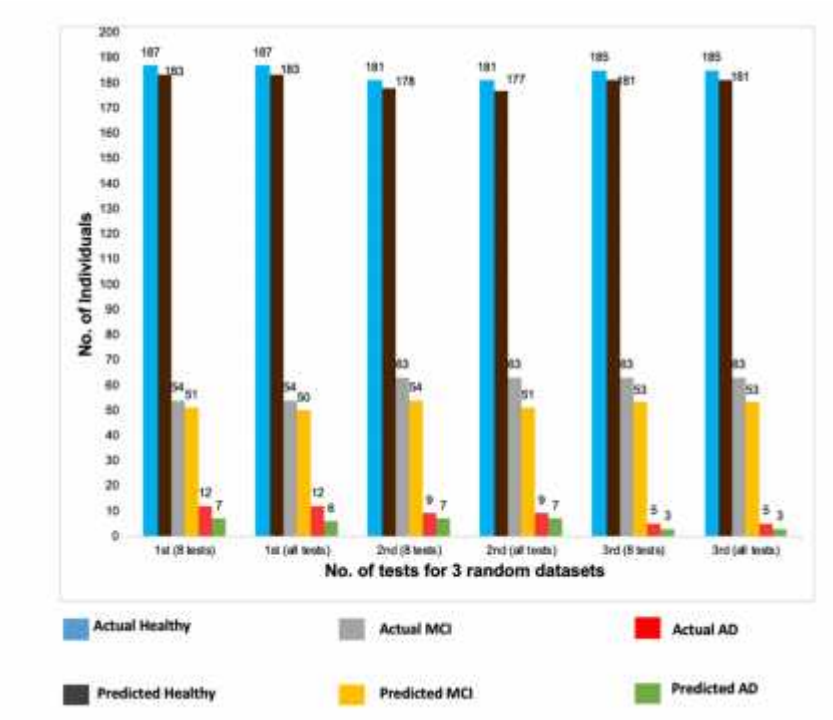


Figure : Performance Comparison of subset of tests to the whole battery for ROSMAP study. It shows the number of actual and predicted healthy, MCI and Alzheimer's individuals for3 testing data sets comparing results for 8 neuropsychological tests vs all 24 tests using Random Forests.

Project title : Decoding genetic basis of metabolic disorders and its shared genetic etiology with dementia in Indian population

Funding: Ramalingaswami Fellowship

Project personnel: Abhishek Panda, Diksha Chaudhary

Polygenic and complex human disease like, dyslipidemia, type 2 diabetes (T2D), cardiovascular disease, fatty liver disease and Alzheimer's dementia, are caused by genetic variations in more than one gene as well as environmental contributions, and obesity is a precursor to these complex diseases in the general population. Large scale comprehensive genetic analyses for such complex disorders are lacking in India. Similarly, numerous genetic variants have been found to be associated with Alzheimer's in Europeans, but none exclusively from Indian population. Additionally, obesity (measured as body mass index), and abdominal fat depots in particular (measured as waist to hip ratio adjusted for BMI, fat accumulation in liver) is a growing health problem, and predisposes to the above mentioned metabolic and neurodegenerative diseases. This project is aimed at understanding the genetic basis of obesity and uncovering the causal relationship of obesity to the other metabolic and neurodegenerative disorders. The particular aims of this project are to develop a pipeline for accurate and efficient genotype imputation that can be used across SANSCOG and TLSA; to measure the phenotypic correlation between Alzheimer's and the hallmarks of metabolic traits, to estimate the respective genetic correlations, and to detect the shared genetic architecture of metabolic and neurodegenerative diseases.

CBR have already established prospective community-based cohort studies with long term follow-up over many years for comprehensive evaluation of normal age-related disorders in urban Bangalore and Kolar district in Karnataka. The study cohorts (N ~ 10,000) comprising of cognitively healthy individuals in the age group 45 years and above will be evaluated with detailed clinical, neurocognitive, lifestyle, anthropometric, biochemical and genetic assessments in the baseline as well as during periodic follow up, and this data will be used to assess the shared genetic architecture of metabolic and neurodegenerative diseases when obesity is a precursor.

About 60 samples have undergone Whole Genome Sequencing, and we have processed and analyzed the sequencing data to obtain genetic variation information from these South Indian samples. Currently, we are pursuing the regression models for the UK BIOBANK dataset, and after standardizing the methods we will apply them appropriately to the Indian dataset in SANSCOG and TLSA when adequate genetic data has been generated. The completion of this project would yield robust results about the shared etiology of obesity associated metabolic and neurodegenerative disorders.

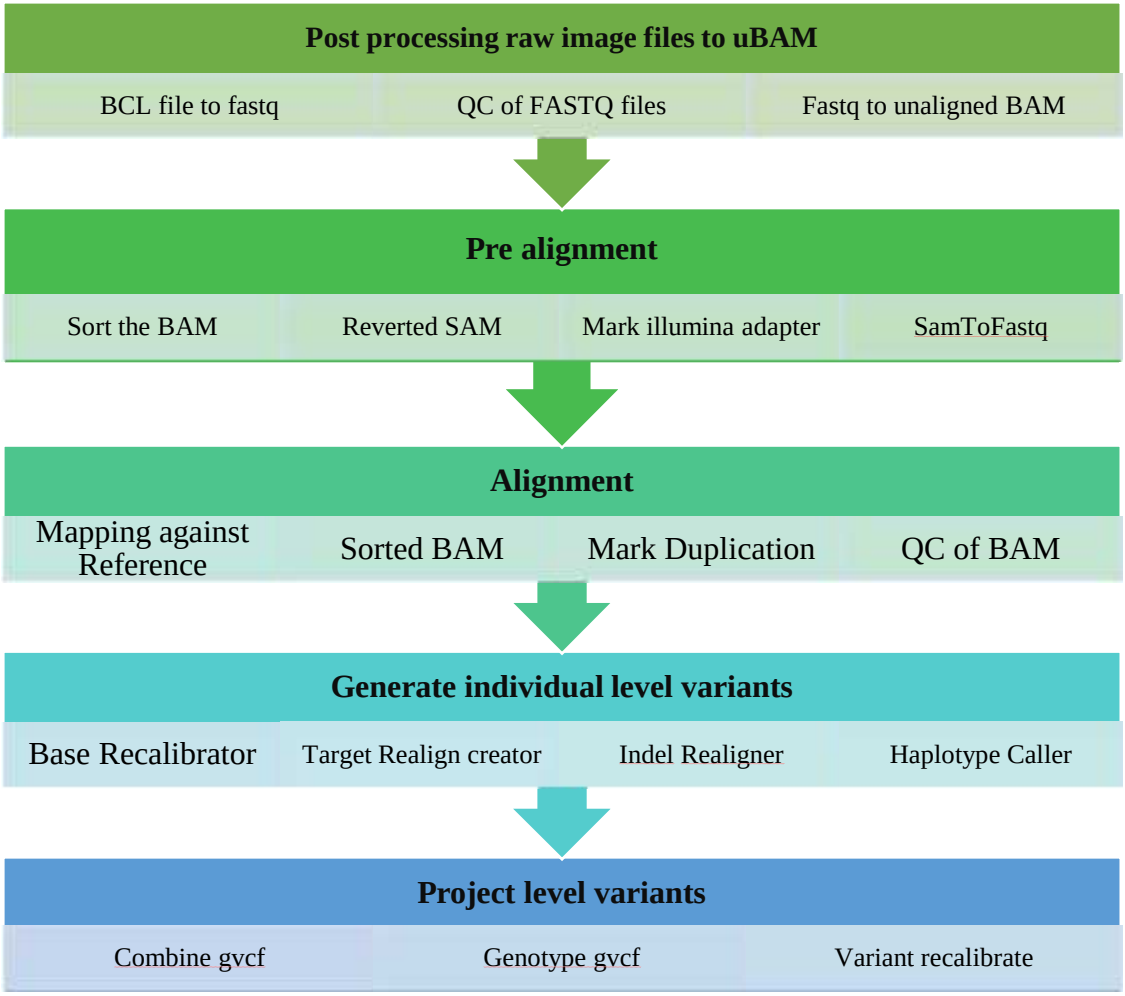
Project title: Establishing standardized data analysis pipeline for Indian whole genome sequencing

Project personnel: Abhishek Panda, Diksha Chaudhary, Krithika Subramanian.

Discoveries from high throughput whole genome sequencing are dependent on efficient processing, storing, and analyzing this enormous amount of genomic sequencing data, often in the scale of petabytes. We have standardized such a pipeline using IISc SERC CRAY XC40 and lab workstations, which is explained here. We analyse the raw reads from whole genome sequencing (WGS) by adhering to international best practices standards, such as, the international Alzheimer's Disease Sequencing Project, and the 1000 Genomes Project. We mostly use modules of Genome Analysis Toolkit (GATK, https://software.broadinstitute.org/gatk/) for obtaining genetic variants. A schema for WGS data processing that we have implemented for pilot 24 samples' dataset is provided below. We start with converting raw image base calls (.bcl) to analyzable sequence format (.fastq). We convert the fastq to unaligned bam files for preprocessing for alignment of read pairs against current human genome build. We used BWA-mem (https://arxiv.org/pdf/1303.3997.pdf) for alignment. After alignment, we sort the output BAM files and mark duplicates as same DNA sequence can be sequenced several times and downstream GATK tools will then ignore these duplicate reads by default, through the internal application of a read filter. Then we generate the individual level genomic variants (.g.vcf). We call SNP variants, short indels, using standard GATK best practices. The entire process could result in >2000 TB of aligned reads and variant calls. We have developed in-house processes for efficient handling of our study dataset, including, but not limited to developing computational tools for parallel processing different chunks of chromosomes, efficient parsing system for storing, viewing, merging, and analyzing data and integrative analyses for identifying genetic variants. We use parallel programming using MPI/MP prototypes to make analysis of such large scale WGS data highly competent and time- efficient, as has been optimized for pilot dataset in our preliminary work done. All of these operations need to be performed in a highly secure compute environment so that personally identifiable information is never compromised for the individuals participating in GenomeIndia. Joint calling is currently being done for 58 samples. We are using Intel GenomicsDB storage technology for genomic variants and likelihoods for this process, where samples are mapped to rows and genome positions or sites of variants are mapped to columns. This type of storage enables the joint genotyping workflow in GATK to scale to 100,000 samples and beyond. When genotypegvcf variant calls are processed from distinct GenomicsDB datastores, it processes the data in a single process multiple data (SPMD) fashion which leads to increased performance in fetching the genomic data, which is the basic concept for increased efficiency.

The entire processing and analysis pipeline will be accordingly modified as and when new tools become available.

This work is of great impact for GenomeIndia, as it will enable to achieve our target of analysing at least 3333 whole genome sequencing samples in a year with ample time for necessary quality checks and interim joint calling.


Post processing raw image files to uBAM
BCL file to fastq
QC of FASTQ files
Fastq to unaligned BAM
Pre alignment
Sort the BAM
Reverted SAM
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Alignment
Mapping against Reference
Sorted BAM
Mark Duplication
QC of BAM
Generate individual level variants
Base Recalibrator
Target Realign creator
Indel Realigner
Haplotype Caller
Project level variants
Combine gvcf
Genotype gvcf
Variant recalibrate

Dr. Smitha Karunakaran

An essential feature of Alzheimer's disease (AD) is the accumulation of Amyloid-β peptides in the brain, decades before the onset of cognitive symptoms. Establishing a causal link between neuronal circuit dysfunction and particular behavioral traits relevant to the very extended early phase of the disease is crucial to shed new light on the mechanisms underlying the progressive pathology. The overarching goal of our laboratory is to understand the early local neuronal circuit and large-scale network alterations, and how exactly they translate to neurological dysfunction in AD. We are currently focusing on hippocampus and hippocampal projecting neuronal systems that influence hippocampal network activity in a mouse model of AD, APPSwe/PS1ΔE9 (APP/PS1). APP/PS1 is a well-studied mouse model where amyloid plaque deposition occurs at 6 months of age onwards, and this is known to parallel the behavioural decline.

Project Title: Hippocampal circuitry in early Alzheimer's disease

Funding: CBR core fund

Project personnel: Ruby Gupta

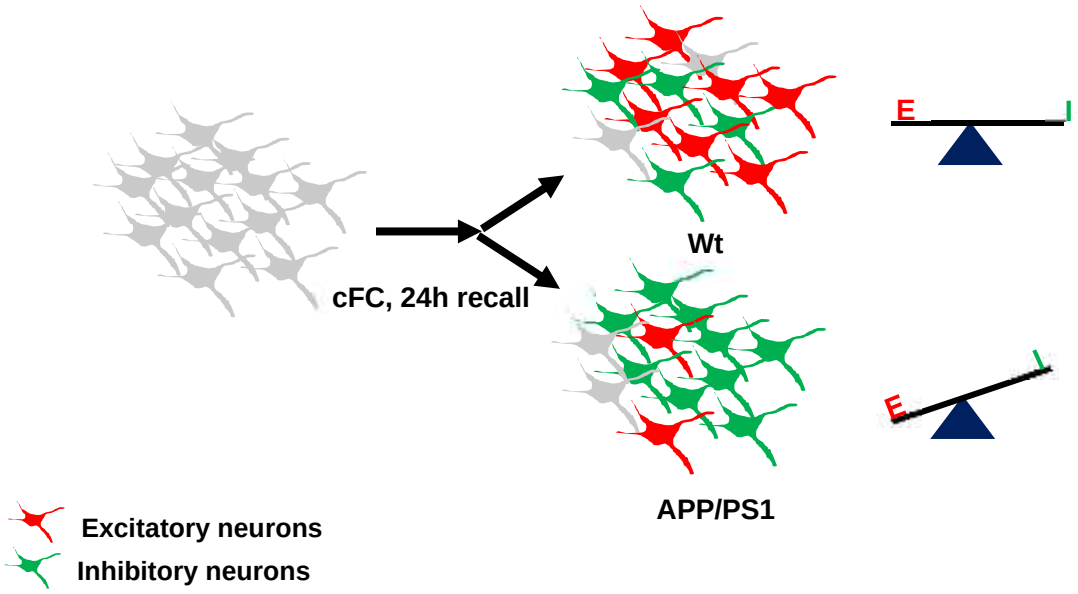
Memory impairment is one of the facets of the much broader mild cognitive syndrome present in early AD patients. We know very little about the nature of memory impairment in preclinical AD. Many studies have recorded memory impairment in general, demonstrating they forget episodic-like memories, spatial-like memories, etc. However, we still do not have an insight into the representational loss these subjects experience during early stages of AD. The neuropsychological test batteries such as stick design test, name recall test etc., though target specific cognitive domains, only help us pick up general memory deficits and do not have strong anatomical correlations at the micro-circuitry level. Therefore, they do not help us to identify the link between distorted memory representations and disease pathogenesis at an early stage. On the other hand, animal models, specially familial mouse models of AD, behavioural assessments normally target anatomical structure such as hippocampus, entorhinal cortices etc., which are known to be involved early on during the pathogenesis of AD, and can be studied without technical or accessing limitations. In this study, we try to understand the representational aspect of memory dysfunction in early AD in 2 month old APP/PS1 – a paradigm shift from volume loss atrophy model to an early dysfunctional model.

Behavioural experiments from our laboratory report that deficits in specific hippocampus dependent memory paradigms can be observed as early as at 2 months of age in APP/PS1. Memory recall deficits were noticed in episodic memory tasks such as Object-place recognition and Object-in-context recognition. Recall deficits were also observed after contextual fear conditioning (cFC), but not in spatial learning paradigm such as Morris Water Maze task (MWM). Therefore, a profound deficit in aversive but not spatial learning was observed in 2m old male APP/PS1 mice. This finding led us to the next question, that is to understand how memory systems involving hippocampus encode importance to a particular memory (aversive v/s spatial) over the other. From our studies, we now know that male APP/PS1 show memory deficits in specific hippocampus dependent memory tasks which has salient (memorable) cues as part of the paradigm at 2 months of age. We report that salience-based behavioural learning is specifically affected during early phases of AD. We carried out hippocampal dependent tasks with

negative salience (shock makes the context salient) as in cFC, and positive salience as in Familiar Object Preference assay (FOP; female odour makes a familiar object salient for a male mice). Neuronal activation pattern was recorded in the hippocampal CA3 region using the immediate early gene c-Fos. At baseline conditions, and where training context alone was introduced to the animal, we did not notice a significant difference in the c-Fos induction both in wildtype and APP/PS1. Context plus shock experience resulted in strong c-Fos induction in wildtype and no induction in APP/PS1. These results clearly indicate that addition of an emotional valence (affect) to otherwise neutral experience led to a bias in neuronal mechanisms leading to altered memory recall in APP/PS1 at a very young age. To further verify whether affectively salient (emotive, motivational) attributes of learning are affected early on during AD pathogenesis, we performed FOP. In FOP we monitor the preference of mice towards novelty vs reward or diminished preference for either of the cues. We observed that APP/PS1 had a significantly enhanced preference for the reward than novelty. However, wildtype mice explored novelty and reward equally. FOP left similar pattern of neuronal activation in the CA3 region of the hippocampus as observed after cFC in APP/PS1. We further tried to understand the molecular mechanism underlying this dysfunction. Noradrenergic neurons form a neurotransmitter system in the brain when activated experts effects on different rain areas including amygdala and hippocampus during arousal, alertness etc. Given the role of NE (Noradrenergic) signalling in processing and consolidating salient stimuli which are highly arousing, we hypothesized that local NE signalling acting through β-adrenergic receptors could be compromised in the hippocampus in 2-month old APP/PS1. Targeted modulation of the β-Adrenergic receptor in CA3 was found to be sufficient to enhance the perseverance of memory in APP/PS1 in cFC, and thus alter the behavioural phenotype.

To further investigate whether long-range connectivity alterations might be causally related, we are currently performing retrograde neuroanatomical tracing experiments in the laboratory. Studies using animal models have also shown that the ventral hippocampal neurons project to the Basolateral Amygdala (BLA) and medial prefrontal cortex. There are ‘‘dual-projecting’’ neurons as well which regulates and coordinates the mPFC and BLA activity during fear memory recall, an imbalance in which might cause recall deficit. To our surprise, we observed enhanced neuronal activation as marked by c-Fos expression specifically in the BLA, paralleled by an increased induction of GAD67, a marker for inhibitory neurons in the central nuclei of amygdala in APP/PS1 but not in the wildtype upon cFC recall. In the naive control animals, both c-Fos and GAD67 maintained a baseline pattern of activation. This strongly suggests a state of imbalance of excitatory/inhibitory (E/I) neuronal network. The E/I status of the hippocampus-amygdala circuitry upon fear learning in APP/PS1 is currently under investigation using electrophysiological techniques..

A hypothetical model of the E/I imbalance in hippocampal - amygdala circuitry in APP/PS1 vs wildtype upon fear recall:



2. AWARDS/DISTINCTIONS

Dr. Bratati Kahali was awarded the Science and Engineering Research Board Early Career Fellow 2019 by Department of Science and Technology, Government of India. Ongoing project: Epistasis analysis of APOE in understanding the genetic architecture of Alzheimer's disease: A computational generic approach.

3. EVENTS

3.1 International Scientific Advisory Board – Meeting

The meeting of the International Advisory Board of CBR was held on 17th May 2019 at Boston. The Advisory Board Committee meeting was preceded with a meeting which was attended by the members of the Advisory Committee, representative of international funding agencies, Tata Trust and other influential faculty members. The meeting was a great success and the activities of CBR have been well appreciated. The funding agencies have shown interest in collaborating and funding the activities. It is proposed to keep up this momentum in the activities of CBR.

Prof. Anurag Kumar, Director, IISc and Mr. Kris Gopalakrishnan also attended the meeting.

3.2 Scientific Advisory Committee – Meeting

The Scientific Advisory Committee met on 3rd October 2018 and considered the new project proposals and reviewed the ongoing project and gave valuable suggestions.

3.4 CBR Lecture

The current focus of CBR is on neurodegenerative disorders involving researchers from the field of epidemiology, clinicians, genetics, MRI, computational bioinformatics and molecular biology. Many of the fields mentioned above are in their nascent state in the Indian research arena .Hence,CBR has made an effort to bring experts from these diverse fields and give lectures in Indian Institute of Science to create awareness about integrative research in the field of neurodegenerative, These lectures are well published and researchers from different background within IISc and neighboring institutions and attend these lectures series often called as the "CBR popular lectures series". During the year the following lectures have been arranged under this;

1. "Human Origin, Health and Disease: Genomic Perspectives" Dr. K Thangaraj is a Chief Scientist and Group Leader at the Centre for Cellular and Molecular Biology (CCMB), Hyderabad, held on 31st May 2018.

2. **"Insight into Mental Illness from New Technology—and the Road Ahead"** Prof Steven E Hyman Department of Stem Cell and Regenerative Biology, Harvard University; Director, Stanley Center for Psychiatric Research and Core Member, Broad Institute of MIT and Harvard. Held on 19th September 2018. **Sharwaree Gokhale's Second Memorial Lecture.**

3. "Cardiovascular Disease in Indians: From reductionist paradigms to a holistic Context is a cardiologist and epidemiologist by training". Dr. D. Prabhakaran Vice President (Research & Policy), Public Health Foundation of India, Executive Director of Centre for Chronic Disease Control, New Delhi, India. Held on 4th October 2018.

4. **"Human genome research in the context of P4 medicine-How rosy and notso rosy is the picture?"** Dr. Thelma K faculty member and Team leader of the Centre of excellence in Genome sciences and predictive medicine in the Department of Genetics at the University of Delhi south campus, New Delhi. Held on 15th November 2018.
5. **"Early life origins of diabetes in Indians"** by Prof. Yajnik, Director of the Diabetes Unit at the King Edward Memorial Hospital and Research Centre in Pune, India, on 18th January 2019.

3.4 Conference

The Alzheimer's Association International Conference (AAIC) satellite symposium was held at Ritz Carlton, Bangalore during 18-19 December 2018.More than 300 researchers from all over the world have participated and the conference was a great success. CBR was a co-sponsor of the Conference.

As a Pre-conference event of Alzheimer's Association Satellite Symposium, a Public program on Alzheimer's disease has also been held at NIMHANS on 17th December 2018. More than 100 participants of the TATA Study have participated in this event.

4. ACADEMIC COLLABORATION

4.1. Indian Institute of Science:

IISc has approved joint academic and research programmes as per the following;

- Up to two Ph. D students would be allowed to carry out collaborative research at CBR in areas aligned with the mandate and vision of CBR. But the students will be admitted to the Institute and be under the supervision of the Institute faculty. A faculty member from CBR would be the co-supervisor, similar to the ERP Program.
- The scholarship for the students would be provided by the CBR and students may be encouraged to stay outside the institute campus.
- CBR faculty may get involved in offering courses at IISc either individually or jointly with IISc faculty.

As per this two students have joined during the academic year 2018.

4.2 Affiliation of CBR to Manipal Academy of Higher Education:

In order to admit more students in the relevant field of research at CBR, it is necessary that CBR faculty should be able to take students independently, as it may be difficult to find a faculty in IISc who has interest in the research areas of CBR to function as research supervisor. Moreover a few clinicians have also shown in interest in joining research program at CBR and they may not be able to get admission directly to IISc.

In order to facilitate this CBR has approached MAHE for affiliation for the Ph.D programme. The application is under process.

5.PUBLICATIONS

Ahmad F, Das D, Kommaddi RP, Diwakar L, Gowaikar R, Rupanagudi KV, Bennett DA, **Ravindranath V**. Isoform-specific hyperactivation of calpain-2 occurs presymptomatically at the synapse in Alzheimer's disease mice and correlates with memory deficits in human subjects. Sci Rep. 2018 Sep 3;8(1):13119.

Kashyap G, Bapat D, Das D, Gowaikar RD, Amritkar RE, Rangarajan G, Ravindranath V and Ambika G: Synapse loss and progress of Alzheimer's disease – a network model. Sci Rep. 2019 Apr 25;9(1):6555. doi: 10.1038/s41598-019-43076-y.

Chauhan et. al., Genetic and lifestyle risk factors for MRI-defined brain infarcts in a population-based setting. Neurology (2018)

Protein-coding variants implicate novel genes related to lipid homeostasis contributing to body fat distribution (Accepted). Justice AE, …., ***Bratati Kahali,***…., North KE, Lindgren CM. **Nature Genetics** 2018**.**

Malik R, Chauhan G, Traylor M, Sargurupremraj M, Okada Y, Mishra A, et al. Multiancestry genome-wide association study of 520,000 subjects identifies 32 loci associated with stroke and stroke subtypes. Nat Genet. 2018; 50(4): 524- 37.

Chauhan G et. al., Genetic and lifestyle risk factors for MRI-defined brain infarcts in a population- based setting. ***Neurology 2019.***

Protein-coding variants implicate novel genes related to lipid homeostasis contributing to body fat distribution (Accepted). Justice AE, …., ***Bratati Kahali,***, North KE, Lindgren CM. **Nature Genetics** 2018 (Accepted)**.**

Mishra A, Chauhan G, Violleau MH, Vojinovic D, Jian X, Bis JC, et al. Association of variants in HTRA1 and NOTCH3 with MRI-defined extremes of cerebral small vessel disease in older subjects. Brain. 2019; 142(4): 1009-23

Larsson SC, Traylor M, Burgess S, Boncoraglio GB, Jern C, Michaelsson K, et al. Serum magnesium and calcium levels in relation to ischemic stroke: Mendelian randomization study. Neurology. 2019; 92(9): e944-e50. [Chauhan G is listed as a collaborator]

Protein-coding variants implicate novel genes related to lipid homeostasis contributing to body fat distribution. Justice AE, Karaderi T, Highland HM, Young KL, Graff M, Lu Y, …., ***Bratati Kahali,***…., North KE, Lindgren CM. **Nature Genetics** 51(3), 452-469, 2019**.**

6. BUILDING

A new building for CBR is under construction in the land identified for CBR at IISc Campus.

This will have a state of art Brain Research Laboratory and Clinical research facilities and the intention is to develop this project as a unique world class facility and one of its kind research facility. The built up area is 1,10,000 sq.ft in a configuration consisting of basement + ground + 5 stories totaling 7 stories. The facility shall cater to 100 professionals and have a minimum of LEED Gold rating. It is envisioned to position the brain and DNA bank in the basement. The ground floor of the facility will be used for research work related to human subjects including clinical, cognitive evaluation, EEG etc. It will also have a cafeteria, lounge for the volunteers who have agreed to participate in the Research and Administrative Office. Wet labs for genetics and basic biology, informatics, cognitive science and related research will be provided on the 1st, 3rd, 4th and 5th floors. The 2nd floor will have the services and an auditorium. It will be centrally air-conditioned building. The estimated cost of the building is around 45 Crores.

The building is funded by Pratiksha Trust.

The Contract has been awarded and Bhoomi Pooja was conducted on 13th August 2018.The work is progressing well, and it is expected to complete by April 20-20.

The Construction activities are monitored by a committee consisting of following;

Prof. H. P. Khincha	Chairman
Prof. Vijayalakshmi Ravindranath, Director, CBR	Member
Prof. A. Sridharan	Member
Prof. B.R. Srinivasamurthy	Member
Prof. B.K. Raghuprasad	Member
Prof. G. Rangarajan	Member
Prof. Y. Narahari,	Member
Mr. R. Mohan Das, Special Officer, CBR	Member

7. FINANCE

The total receipts for the year 2018-19 was Rs.1629.87 Lakhs and the payments for various activities of the Centre was Rs.894.79 Lakhs

The Details of Receipts and Payments for the Year 2018-19 are as follows

Sl.No.	Particulars	Receipts	Payments
1	Donations from Pratiksha Trust towards Activities Account	950.00	497.09
2	SPARC Project - Sun Pharma Advanced Research Company Ltd	12.02	1.17
3	Ramalingaswami Fellowship	7.48	18.91
4	Fixed Deposit Matured against LC	23.38	23.38
5	Donations from Pratiksha Trust towards Construction of New Building	500.00	254.65
6	Tender Application Fees	0.40	0.40
7	Security Deposit from Tenderers	136.60	99.19
	Total	**1629.87**	**894.79**

8.GOVERNANCE STRUCTURE & PEOPLE AT CBR

8.1 Society

Centre for Brain Research (CBR) is a registered society under the Karnataka Societies Act 1960. The Society has very eminent persons from the different fields, as its members. The current members of the Society are following

Dr. Palle Rama Rao
Chairman, Governing Council, IISc (Ex- Officio)

Prof. Anurag Kumar
Director
Indian Institute of Science (Ex- Officio)

Chief Secretary,
Govt of Karnataka (Ex- Officio)

Additional Chief Secretary
Govt of Karnataka (Ex- Officio)

Principal Secretary (Finance)
Govt of Karnataka (Ex- Officio)

Secretary to Govt of Karnataka
Dept of IT, BT & Science & Technology
Govt Secretariat (Ex- Officio)

Dr. Ramesh Babu
No.17 Nirvana, Trans Indus, Tataguni
Bangalore

Dr. Girija Ramesh Babu
No.17 Nirvana, Trans Indus, Tataguni
Bangalore

Dr. B N Gangadhar,Director
NIMHANS, Bangalore

Mr. Kris Gopalakrishnan
#855,13th Main,4th A Cross
III Block Koramangala
Bangalore

Smt. Sudha Gopalakrishnan
#855,13th Main,4th A Cross
III Block Koramangala
Bangalore

Dr. K Krishnaswamy Kasturirangan
Chairman, Governing Council
Raman Research Institute
Bangalore

Prof. H P Khincha
No.11,4th Main Road, Chamrajpet
Bangalore
Prof. Paturu Kondaiah
Dept of MRDG, IISc

Prof. N Balakrishnan,
Dept of SERC, IISc

Shri. Dinesh Krishnaswamy
No.467,19th Main,36th Cross
4th T Block, Jayanagar
Bangalore

Dr. Satyajit Mayor
Director
NCBS Bangalore

Smt. Sudha Murthy
No.575, Amoghavarsha,21st Main,35th Cross,
4th T Block, Jayanagar
Bangalore

Prof. Y Narahari
Dept of Computer Science and Automation,IISc

Prof. Govindarajan Padmanabhan
Emeritus Professor
Dept of Biochemistry
IISc

Shri. S V Ranganath
No.25,8th Cross,2nd Block, Jayanagar
Bangalore

Prof. M R S Rao
JNCASR, Bangalore

Prof. Govindan Rangarajan
Dept of Mathematics, IISc

Prof. Vijayalakshmi Ravindranath
Director, CBR

Shri S D Shibulal
No.383,42nd Cross,9th Main,5th Block, Jayanagar,
Bangalore

Dr. M S Valiathan
National Research Professor
Manipal University, Madhav Nagar
Manipal

Shri. M N R Venkatachaliah
Former Chief Justice of India

Prof. Umesh Varshney
Dept of Microbiology and Cell Biology, IISc

Prof. D N Rao
Dept of Biochemistry, IISc

8.2 Governing Board

The affairs of the CBR are administrated, directed and controlled, by the Governing Board. The Governing Board of the Society shall consist of the following Members;

i) Chairman, who shall be ex-officio Director, IISc
ii) Four Members of the Society as may be nominated by Pratiksha Trust.
iii) Five Members of the Society as may be nominated by the Council of IISc
iv) Member Secretary shall be the Director of Centre for Brain Research

The current composition of the Governing Board is as follows;

Prof. Anurag Kumar, Chairman
Director
IISc (Ex Officio)

Shri. Kris Gopalakrishnan
#855,13th Main,4th A Cross
III Block Koramangala
Bangalore

Mrs. Sudha Gopalakrishnan
#855,13th Main,4th A Cross
III Block Koramangala
Bangalore

Prof. H.P. Khincha
No.11,4th Main Road, Chamrajpet
Bangalore

Shri. Dinesh Krishnaswamy
No.467,19th Main,36th Cross
4th T Block, Jayanagar
Bangalore

Shri. S D Shibulal
No.383,42nd Cross,9th Main,5th Block, Jayanagar,
Bangalore

Prof. Y. Narahari
Dept of Computer Science and Automation, IISc

Prof. G Rangarajan
Dept of Mathematics, IISc

Prof. D N Rao
Dept of Biochemistry, IISc

Prof. Umesh Varshney
Dept of Microbiology and Cell Biology, IISc

Prof. Vijayalakshmi Ravindranath
Director, CBR (Member Secretary)

8.3 Finance Committee

CBR has a Finance Committee which meets every three months to review the financial positions of the Centre and make recommendations to the Governing Board from time to time. Finance Committee consists of the following;

Prof. Anurag Kumar, Chairman
Director
IISc (Ex Officio)

Prof. Vijayalakshmi Ravindranath
Director, CBR

Prof. Jayanth M Modak
Deputy Director, IISc

Prof. G Rangarajan
Dept Of Mathematics, IISc

Mr. K C Ganesh
Pratiksha Trust

Mr. R Mohan Das
Secretary, Special Officer, CBR

8.4 Ethics Committee

An Ethics Committee has been constituted by the Governing Board, as mandated by the National Ethical Guidelines for Biomedical and Health Research involving human participants, Indian Council of Medical Research (ICMR) Govt. of India.

Dr. B. A. Chandramouli, Chairman
Neurosurgeon
Aster Hospital
Bangalore

Dr. Kiran Khanapure
M S Ramaiah hospital, New BEL Rd,
M S Ramaiah Nagar, Mathikere,
Bengaluru- 560054

Mr. Arvind Moorchung
King & Partridge advocates,
48, Lavelle Rd,
Bengaluru- 560001

Mr. Alaganandan Balaraman
CGN Global,
562/640, 2nd floor, above Kalyani Motors,
Bannerghatta Main Rd,
Bilekahalli, Bengaluru- 560076

Prof. Anitha Kurup
National Institute of Advanced Studies,
Indian Institute of Science campus,
C V Raman Avenue
Bengaluru- 560012.

Prof. Arun Kumar
Department of Molecular Reproduction, Development and Genetics (MRDG),
Biological Sciences Building,
Indian Institute of Science campus,
C V Raman Avenue, Bengaluru- 560012

Prof. Sundar Sarukkai
National Institute of Advanced Studies,
Indian Institute of Science campus,
C V Raman Avenue
Bengaluru- 560012

8.5 International Scientific Advisory Board

An International Advisory Board consisting of International as well as national experts shall be constituted by the Governing Board. The Board meets biannually.

International Advisory Board consisting of the following;

Prof. Steven E Hyman, Chairman

Prof. John Morris, Washington Uni

Prof. Maria Corrillo, CSO, AA

Prof. Stanley Fahn, Columbia

Prof. Sudha Seshadri, San Antonie

Prof. Crla Shatz,Stanford

Prof. Mary Ganguly, Pittsburg

Prof. Srinath Reddy, PHFI, New Delhi

Prof. B N Gangadhar, NIMHANS, Bangalore

Prof. Vijayalakshmi Ravindranath, Director, CBR

8.6 Scientific Advisory Committee

The Scientific Advisory Committee (SAC) for the Centre for Brain Research monitors and provides guidelines on the scientific activities of the Centre. The members of the SAC are as follows;

Prof. Srinath Reddy, Chairman
PHFI, Delhi

Dr. Ramesh Hariharan
Strand Life Sciences, Bangalore

Prof. Gangadhar BN
Director NIMHANS, Bangalore

Prof. Arun Kumar
MRDG-IISc, Bangalore

Prof. Partha Majumdar
NBMG, West Bengal

Prof. Anurag Agarwal
IGIB, New Delhi

Prof. Vijayalakshmi Ravindranath
Director CBR

8.7 People at CBR

8.7.1 Academic Staff

Director

Prof. Vijayalakshmi Ravindranath

Assistant Professor

Dr. Ganesh Chauhan

Dr. Bratati Kahali

Dr. Smitha Karunakaran

Inspire Faculty Fellow

Dr. Suresh S N

Visiting Faculty

Prof. Sivakumar P T
Dept of Psychiatry
NIMHANS, Bangalore

Prof. Ganesan Venkatasubramanian
Dept of Psychiatry
NIMHANS, Bangalore

Prof Girish N Rao
Dept of Epidemiology
NIMHANS, Bangalore

Prof. Naren P Rao
Dept of Psychiatry
NIMHANS, Bangalore

Prof. Gaiti Hasan
Senior Professor. (Retd) SERB Distinguish Fellow
NCBS, TIFR, Bangalore

Adjunct Faculty

Prof. Y Narahari
Dept of Computer Science and Automation, IISc

Prof.Govindan Rangarajan
Dept of Mathematics,IISc

Prof. H P Khincha
Prof. (Retd)
Dept of Electrical Engg, IISc

Dr. Sridharan Devarajan
Centre for Neuroscience
Bangalore

8.7.2 Scientific:

Scientific Officer

Dr. Khader Valli Rupanagudi

8.7.3 Technical:

Technical Assistant

Mr. Karthik S

Mr. Sangeethkumar Saminathan

Lab Assistant

Mr. Mohana C

8.7.4 Administrative:

Special Officer

Mr. R Mohan Das

Executive Assistant

Ms. Aruna Poojary

Ms. Sudha Srikanth

8.7.5 Other Staff

Post-Doctoral Fellows

Dr. Devendra Meena

Dr. K S Harsha

Dr. Abhiram P N

Dr. Ammu Lukose

Dr. Manasi Oza

Dr. Vishwas Yadawad

Dr. Santi Natarajan

Dr. Aneelraj Devar

Dr. Praveen S R

Dr. Shashank kumar Maurya

Project Engineer

Mr. Sudarshan Rao

Ph. D Students

Ms. Soumi Chaudhury

Ms. Diksha Chaudhuri

Psychologist/Psychiatrist

Ms. Anu K N

Mr. Rahul K V

Ms. Mino Susan Joseph

Project Associate

Mr. Shrihari A

Mr. Abhishek Panda

Project Assistant

Ms. Shreya Jha

Ms. Krithika Subramanian

Ms. Ruby Gupta

Ms. Anupriya S

Ms. Diji Kuriakose

Field Staff:

Mr. Ramesh K – Office Manager

Mr. Rajesh M D – Field Data Supervisor

Mr. Harikrishna G – Field Data Collector

Mr. Yashwanthkumar K - Field Data Collector

Ms. Gayathri P S - Nurse

Mr. Shashikumar - Field Data Collector

Mr. Vinod Raja T - Field Data Collector

Mr. Shivaraj S - Field Data Collector

Mr. Gangaraja V - Field Data Collector

Ms. Priyanka R - Field Data Collector

Ms. Gamana T - Field Data Collector