CENTRE FOR BRAIN RESEARCH

An autonomous Centre of the Indian Institute of Science

ANNUAL REPORT

2020-2021

CONTENTS

CBR at a Glance

The Centre for Brain Research (CBR) was established in 2014, as an autonomous centre of IISc to carry out research on the ageing brain with a goal to identify risk and protective factors that contribute to healthy aging. An integrative approach is adopted at CBR encompassing genetic, imaging, molecular, functional and computational methods, while bringing together large groups with diverse expertise to address the complex challenges of understanding the functioning of the human brain in health and disease. We foster large-scale research programs and build capacity focused on inter disciplinary neuroscience research in India. We believe this will set 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 Mr. Kris Gopalakrishnan, co-founder of Infosys and Mrs. Sudha Gopalakrishnan. CBR is immensely thankful for their philanthropic support that enables the research.

Mandate and Vision

- Carrying out basic research to understand brain function in health and disease.
- Fostering 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

TATA Longitudinal Study of Aging (TLSA)

TLSA was designed with a goal to create a cohort of aging population and longitudinal follow up, in order to identify risk and protective factors responsible for cognitive decline and Alzheimer's disease. TLSA (projected n=1000) is a prospective, community-based cohort study of individuals more than 45 years of age, recruited from urban Bengaluru, in the state of Karnataka, India.

Awareness programs are conducted in the city to inform participants about the disease and the study, from where the participants are recruited. Participants who give consent undergo detailed clinical, neurocognitive, biochemical, genetic and neuroimaging (MRI) assessments, which is done in 1-2 visits. The first visit occurs at Indian Institute of Science where participants undergo detailed clinical and cognitive assessments. In the second visit they undergo neuroimaging which also occurs in the Indian Institute of Science. Blood is drawn at their residence for biochemical and genetic assessments.

Awareness activities and community engagement activities in TLSA before the pandemic

Recruitment for the study started in 2015 and so far 464 participants have consented for the study, and all of them have completed their baseline assessments. The study progress for the period 1st April 2020 to 31st March 2021 is given below.

1) COVID-19 crisis, suspension of the study and our crisis response

Recruitment was halted from March 2020 as COVID restrictions against public meetings rendered us unable to conduct awareness sessions. However, we engaged with our participants in the following useful ways.

a) Regular telephonic contact with participants

Accommodations were made in the project to navigate during the pandemic while still engaging the volunteers through the lockdown; in this regard, they were informed about suspending in-house assessments and routinely contacted through telephonic means to check-up on them. Around 400 participants were contacted in total. When necessary, the doctor in the team also offered telephonic health-related advice for the participants who sought help for their medical problems. Further, they were provided with virtual tours of museums to continue engagement.

b) Telephonic screening of depression and anxiety

As the COVID-19 pandemic combined with the prolonged lockdown and social isolation could result in depression, we decided to assess prevalence of depression and anxiety in our participants through brief telephonic assessments to assess the psychological impact of the COVID-19 pandemic in this vulnerable population. At the time of this survey we had recruited 464 participants and out of which 297 (64%) consented. Out of 297 participants 18 (6%) had depression and 5 (2%) had anxiety. These figures are lower when compared to SANSOG but higher than national level prevalence of 3.2% for this age group.

c) Safety-related SOP:

We continuously monitored the COVID-19 situation in Bangalore, while keeping ourselves updated with the official advisories and guidelines. We prepared a detailed SOP, describing all the safety precautions to be undertaken for the safety of the staff and participants, when restarting study recruitment and assessments.

2. Restarting the study with COVID-19 safety precautions

We started online clinical and cognitive assessments in September 2021 and following CBR Ethics Committee's approval of our SOPs for COVID-19-related safety precautions, we resumed in-person recruitment and assessments on 16th November 2020. Prior to restarting, all staff were screened for COVID-19 using RT-PCR swab testing and reports were confirmed to be negative; periodic RT-PCR testing of all staff was continued to ensure safety of the participants. All assessment staff were provided with personal protective equipment such as face-shields, masks and gloves. All staff had their temperatures screened and recorded before starting work every day. Hand-sanitizers were provided in the office and office premises was sanitized with disinfectants periodically.

Initially, we started the assessments with a minimum number of 1 participant per day. After a period of stabilizing the logistics and ensuring that assessments proceeded smoothly with the COVID-19 safety precautions in place, we gradually increased the

number of assessments. We then restarted blood investigations and subsequently MRI sessions.

3. Recruitment

During the period: 1st April 2020 – 31st March 2021 we have recruited 15 new participants and 180 follow up assessments. We could not conduct awareness activities as most apartment complexes and old age homes are hesitant due to COVID 19.

4. Assessments – baseline & follow-up

15 baseline assessments and 180 follow-up assessments were completed (total of 479 baseline assessments and 564 follow-up assessments since start of the study).

5. Brain MRI

A specific SOP was drafted and approved by the CBR Ethics Committee for safety procedures to be followed for recruiting and performing MRI scans at the JN Tata Memorial MRI Centre at IISc. 53 brain MRI scans were performed after restarting the study, till 31st March 2021 (total of 541 scans since start of the study).

6. Future directions

We aim to ramp recruitment of new volunteers and continue follow up sessions. We also plan to start Optical Coherence Tomography (OCT) to all consented participants.

Table: TLSA study progress (1st April 2020 – 31st March 2021)

Title	Overall					April 2020 to March 2021				
Participants consented	479					15				
Baseline assessments	479					15				
Follow up assessments	F1	F2	F3	F4		F1	F2	F3	F4	
	324	168	64	8		45	84	44	7	
Brain MRI	BL	F1	F2	F3	F4	BL	F1	F2	F3	F4
	281	168	63	24	5	0	21	18	10	4
Sample collection completed	BL	F1	F2	F3	F4	BL	F1	F2	F3	F4
	375	262	131	51	5	18	43	74	32	5
Feedback/consultation sessions completed	All participants are given feedback immediately after the assessments					All participants are given feedback immediately after the assessments				
Awareness programs	50					0				
Community engagement (brain health talk + sports events)	2					0				

Srinivaspura Aging, Neuro Senescence and Cognition (SANSCOG) study

SANSCOG study is a first of its kind, large, prospective cohort study that is being conducted in the rural Indian population (projected n=10,000), from the villages of Srinivaspura taluk in Kolar district of Karnataka. This study aims to understand the risk and protective risk factors for dementia and related disorders. It follows an interdisciplinary, multimodal approach including detailed clinical, neurocognitive, biochemical, genetic and neuroimaging assessments, with long-term follow-up.

Prior to recruitment of participants, we liaise with the local public health officials and work closely with the grassroot level leaders and community health workers, to build better connections with the community and to create awareness about our study. Recruited participants undergo detailed assessments that are done following a three-visit protocol. The first visit happens at the participant's home, during which socio-demographic data and written consent to participate in the study is obtained. The second visit is at the project site office in Srinivaspura or in a mobile unit, where detailed clinical and neurocognitive assessments are done. Biochemical and genetic tests are done through periodic blood collection camps at the villages due to logistic reasons. The third visit involves neuroimaging, where a subset of the cohort undergoes brain MRI at the Indian Institute of Science (IISc) or National Institute of Mental Health and Neurosciences (NIMHANS) in Bangalore.

Recruitment for the study started in January 2018. The pilot phase of the study (n=1,000) was completed in March 2019. The main phase of the study is currently ongoing, and the follow-up assessments have also commenced from February 2020. The study progress for the period **1st April 2020 to 31st March 2021** is given below.

1) COVID-19 crisis, suspension of the study and our crisis response

Due to first wave of the COVID-19 pandemic in India and the associated lockdowns, study recruitment and assessments had to be suspended from 13th March 2020. However, we engaged with our participants in the following useful ways.

a) Regular telephonic contact with participants

Throughout the lockdown period we maintained regular telephonic contact with our participants, to enquire about their well-being and to reassure them. A total of 1890 SANSCOG cohort participants were contacted. When necessary, the doctors in the clinical team also offered telephonic health-related advice for the participants who sought help for their medical problems.

b) DiNC's service to participants:

In view of poor awareness in rural areas regarding the COVID-19 pandemic and safety precautions, we collaborated with the Digital Nerve Centre (DiNC) – a digital health service initiative by the Tata Group, operating in Kolar district, to offer their telephonic counselling services to our study participants. All consenting participants received telephonic counselling from the DiNC team regarding awareness about disease and safety precautions to be adopted. Our participants were appreciative that our team was concerned about their welfare during this difficult time and reported benefitting from DiNC's service.

c) Telephonic screening of depression and anxiety:

As the COVID-19 pandemic, combined with the prolonged lockdown and adverse financial impact was likely to have resulted in increased levels of psychological distress, we decided to assess the prevalence of depression and anxiety in our participants through brief telephonic assessments, namely the Geriatric Depression Scale (GDS-7) and Generalized Anxiety Disorder (GAD-7) questionnaire, respectively. Further, as our participants have already had depression assessments done before the COVID-19 crisis (as part of their regular clinical assessments), comparing their pre-COVID and post-COVID depression scores could provide valuable information on the psychological impact of the COVID-19 pandemic in this vulnerable population. A total of 744 subjects completed the depression and anxiety assessments. Out of these participants, 212 (28.4%) scored above the threshold score for depressive disorder on GDS-7, whereas 41 (5.5%) scored above the threshold score for anxiety disorder on GAD-7. Among the 697 subjects who had pre-COVID GDS scores, the proportion of subjects having pre-COVID versus post-COVID depression was compared. We found that 212 (28.98%) had depression after the COVID-19 pandemic as compared to 54 (7.74%) who had depression before COVID-19.

d) Safety-related SOP

We continuously monitored the COVID-19 situation in Kolar district, while keeping ourselves updated with the official advisories and guidelines. We prepared a detailed SOP, describing all the safety precautions to be undertaken for the safety of the staff and participants, when restarting study recruitment and assessments.

2. Restarting the study with COVID-19 safety precautions

Following CBR Ethics Committee's approval of our SOPs for COVID-19-related safety precautions, we resumed recruitment and assessments on 5th October 2020. Prior to restarting, all field staff and assessment staff were screened for COVID-19 using RT-PCR swab testing and reports were confirmed to be negative; periodic RT-PCR testing of all staff was continued to ensure safety of the participants). All assessment staff were provided with personal protective equipment, such as face-shields, masks and gloves. All staff had their temperatures screened and recorded before starting work every day. Hand-sanitizers were provided in the office, mobile unit and for the field staff. Every participant was

provided with a mask when coming for assessments and its usage was ensured. The project office premises as well as the mobile unit was sanitized with disinfectants periodically.

Initially, we started the assessments with a minimum number of 2 participants per day. To avoid participant travel and make it more convenient, the mobile unit was deployed at Srinivaspura, and the assessments were carried out in the participants villages itself. After a period of stabilizing the logistics and ensuring that assessments proceeded smoothly with the COVID-19 safety precautions in place, we gradually increased the number of assessments. We restarted assessments at the SANSCOG project office also, from 24th November 2020. We then gradually increased the number of assessments to 8 per day, with mobile unit and office assessments running parallelly). The backlog of blood camps and feedback camps that had been stalled due to the lockdown were also cleared. All camps (awareness camps, blood camps, feedback camps) were conducted with restricted numbers, social distancing, temperature screening for participants as well as providing masks for all participants and staff.

Post-COVID awareness / blood collection camps and assessments with safety precautions

3. Recruitment

During the period: 1st April 2020 – 31st March 2021, 15 villages were surveyed and 495 new participants from 9 villages were recruited (total of 35 village surveys and 2621 recruitments from 34 villages since start of the study).

4. Camps

A total of 16 awareness camps (both general awareness camps and MRI awareness camps) were conducted. In addition, 33 blood collection camps and 24 feedback / consultation camps were conducted during the abovementioned period (total of 47 awareness camps, 78 blood collection camps and 64 feedback / consultation camps since start of the study)

5. Assessments – baseline & follow-up

384 baseline assessments and 114 follow-up assessments were completed (total of 2214 baseline assessments and 126 follow-up assessments since start of the study).

6. Brain MRI

A specific SOP was drafted and approved by the CBR Ethics Committee for safety procedures to be followed for recruiting and performing MRI scans at the JN Tata Memorial MRI Centre at IISc. Further to this MRI scans were restarted for the SANSCOG study participants. 16 brain MRI scans were performed after restarting the study, till 31st March 2021 (total of 116 scans since start of the study.

7. Future directions

We plan to further ramp up the recruitment and assessments in the study, while following appropriate COVID-related safety protocols, to ensure safety of our staff and participants. We also plan to continue data analysis of the baseline data from various domains (clinical, cognitive, biochemical, genetic and MRI data).

Table: SANSCOG study progress (1st April 2020 – 31st March 2021)

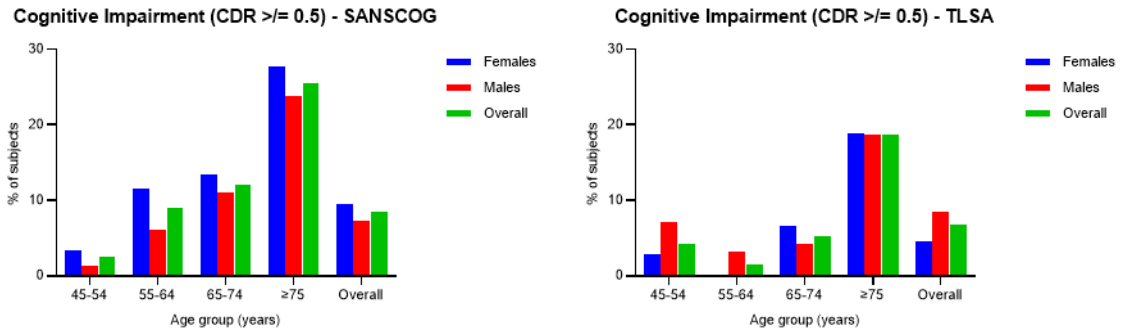
Title	1st April 2020 – 31st March 2021	Overall
Participants consented	**495**	2621
Villages recruited from	9	34
Baseline assessments	384	2214
Follow up assessments	**114**	126
Brain MRI	16	116
Interim telephonic + home visit contact	0	1208
Based on interim contact, participants interested in follow up	0	1117
Blood sample collection camps	33	78
Sample collection completed	469	2252
Feedback/consultation sessions completed	24	64

Village surveys	15	35
Awareness programs	16	47
Community engagement activities	0	4

Selected preliminary results from TLSA and SANSCOG.

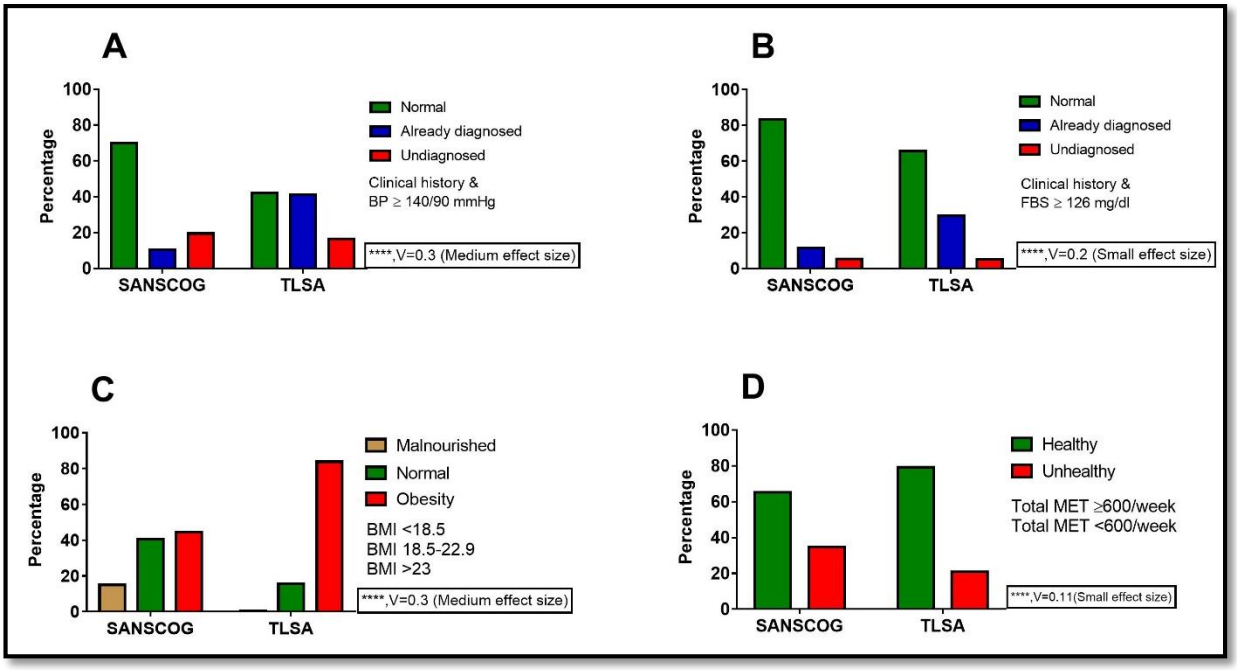
A comparative analysis of the baseline clinical data of TLSA and SANSCOG study cohorts revealed that there was no significant difference in the overall prevalence of cognitive impairment (CDR >/= 0.5) between rural (8.4%) and urban (6.7%) cohorts. However, on age-stratification, there was higher prevalence of cognitive impairment in rural compared to urban subjects in the age group of 55-64 years (rural 9% vs. urban 1.5%, p=0.003) and 65-74 years (rural – 12.1% vs. urban 5.3%, p=0.015). Females in the age groups of 55-64 years and >/= 75 years in the rural cohort had a significantly higher prevalence of cognitive impairment as compared to females of the same age groups in the urban cohort (Figure 1).

Figure 1: Comparison of prevalence of cognitive impairment (age- and gender-stratified) between rural (SANSCOG) and urban (TLSA) cohorts.



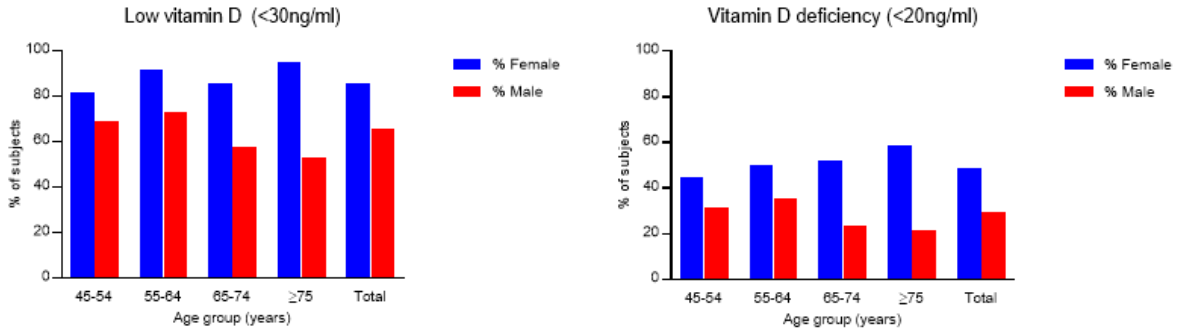
Interestingly, the prevalence of vascular risk factors for dementia, such as hypertension, diabetes mellitus, obesity and physical inactivity were higher in urban cohort when compared to the rural cohort (Figure 2). However, the proportion individuals with of undiagnosed hypertension and diabetes mellitus was far more in rural cohort than the urban cohort.

Figure 2: Comparison of proportion of (A) hypertension, (B) diabetes mellitus, (C) obesity and (D) physical inactivity between rural (SANSCOG) and urban (TLSA) cohorts.



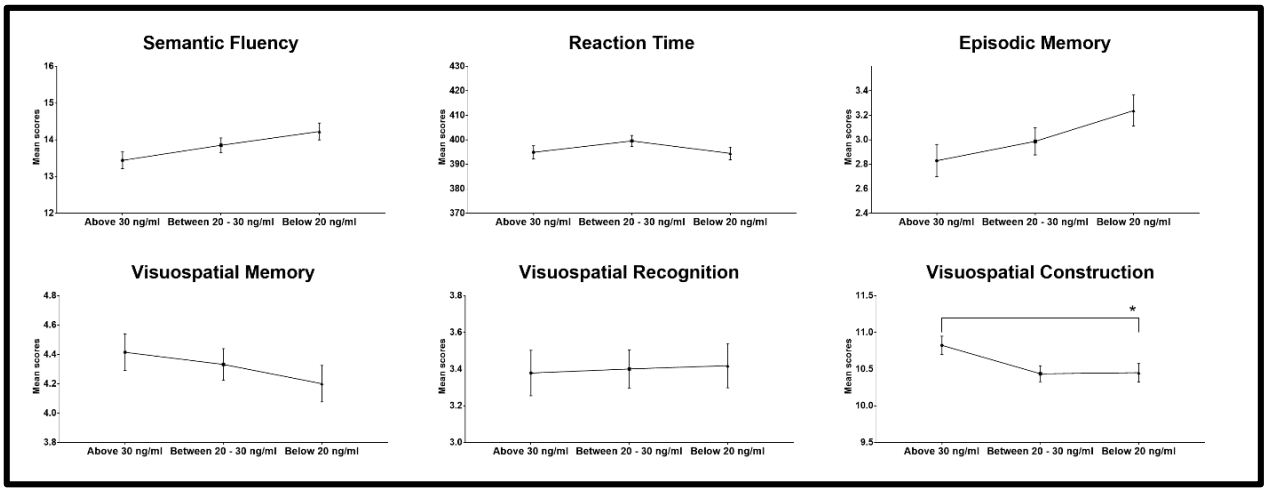
We also found that the rural cohort had a high burden of inadequate vitamin D. The overall prevalence of low vitamin D (< 30 ng/ml) and vitamin D deficiency (< 20 ng/ml) were 75.7% and 39.1%, respectively (Figure 3). We observed that females had significantly higher prevalence of low vitamin D (85.5% vs. 64.7; $p < 0.001$) as well as vitamin D deficiency (47.8% vs. 29.2%; $p < 0.001$). In comparison to the rural cohort, the urban cohort had a much higher prevalence (61.5%).

Figure 3: Percentages of the study population having a) Low Vitamin D (< 30ng/ml) and Vitamin D deficiency (< 20ng/ml), stratified according to age and gender.



We further evaluated the effect of vitamin D on cognitive performance in the rural cohort and found that only the *visuospatial construction* domain was affected by Vit D levels and that all other domains were not affected (Figure 4).

Figure 4: Cognitive performance among SANSCOG cohort in Vit D normal group, Vit D insufficient group and Vit D deficient group



The GenomeIndia Project

CBR co-ordinates the national GenomeIndia project which is aimed at cataloguing the common and low frequency genetic variations in Indians by Whole Genome Sequencing (WGS) of 10,000 representative individuals in the first phase. There are 20 national institutes across the country who form the working consortium.

Genetic variations in individuals predispose them to certain diseases, as well as cause inherited disorders, determine their response to drugs, and help track migration and evolutionary patterns of population groups. Indian population, with more than a billion individuals is extremely diverse with the presence of more than 4500 ethnic groups spread across the length and breadth of the country. A majority of these groups follow endogamy, and these factors have contributed to the genetic diversity of the current day Indian population. Thus, the Indian population harbors distinct variations and often, many disease-causing mutations are amplified within some of these groups. Therefore, findings from population-based or disease-based human genetics research from other populations of the world cannot be extrapolated to Indians.

GenomeIndia project aims to construct an exhaustive catalogue of genetic variations for our diverse population, by identifying the genetic variations (common, low frequency, rare, single nucleotide polymorphisms or SNPs, and structural variations) present in Indians through whole genome sequencing of representative population groups across the country. The variations data will be made available through a web portal. The successful completion of its goals will ultimately aid in a better understanding of the disease susceptibilities in the Indian population based on an individual's genetic makeup. This reference catalogue of genetic variations will help in identifying the causal variations for monogenic disorders in our population. Currently, India also does not have a country-specific genome wide genotyping array, and the results from GenomeIndia will facilitate designing such array(s) that will make large scale comprehensive genetic studies affordable in our country.

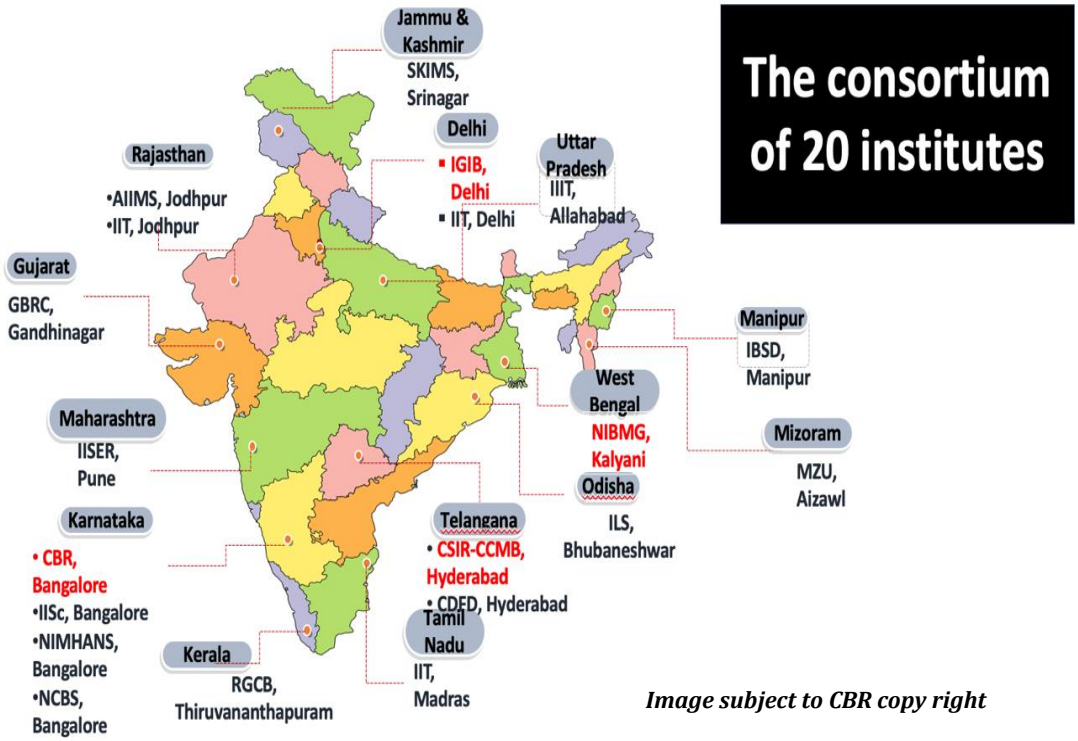
Specific aims for the project are:

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.



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The project has been sanctioned by Department of Biotechnology, Government of India in January 2020. The total funding is for INR 237.74 crores. As part of this project, CBR has helped conduct several workshops in the partner institutions between January-March 2020 for population identification, community outreach and best practices for sample collection. Most importantly, one workshop was taught by instructors from BROAD institute of MIT and Harvard who are part of the GATK and Terra developing team, the program suite used worldwide by various researchers for this purpose.

At CBR, 905 individuals have been contacted for probable participation in the study. 765 individuals from varied population groups have consented and been recruited into the study. Sample collection and phenotyping has been done for these 905 individuals. In total, 6177 individuals have been recruited into the project by all the sample collecting institutes. CBR has installed the data collection app for the participating sample collecting institutes that would aid in having background information of study subjects as well as store and transfer anthropometric, biochemical data for all subjects enrolled in the project from across 13 sample collecting institutes in the country.

Genomewide genotyping (GWAS) on Precision Medicine Research Array (PMRA Affymetrix) upon the high throughput GeneTitan scanner has been performed for the 1160 samples at CBR. Whole genome sequencing upon next generation sequencing platform (Illumina Novaseq 6000 for WGS) has been done for 819 samples at CBR, and 132 WGS done by three other institutes. CBR also has approved biobanking facility where biological samples, example, blood, plasma, serum and DNA will be stored in a cryo-preserved protected manner as per global standards.

CBR houses a scalable storage system of 2 Petabytes for data storage and high-performance computing infrastructure of 170 Teraflops capacity; both are currently being doubled in capacity, that supports data analysis and storage of the massive amounts of multimodal data generated by human studies spearheaded by CBR.

4 standard Corriell cell lines were obtained from the NIST Genome in a Bottle consortium. The cells were passaged, and the extracted DNA was shared with the 3 other sequencing centres. We, at CBR, also sequenced the 4 samples of standard DNA, and the variant calling concordance for SNPs and InDels was $>$ 94% between our results and benchmarked NA12878 cell line dataset. The coverage for all these four cell line samples were $>$37X. Concordance check of these results with those from other sequencing centres is currently underway.

CBR has analyzed data from 819 WGS. Call rate is in the range of 96 to 99%, and mean genotype quality for most samples is $>$70. The average transition-transversion ratio is 1.8 across autosomes and sex chromosomes. About 40 million genetic variations were identified from 650 individuals, and 34.5 million of them are single nucleotide polymorphisms (SNPs), and 5.4 million are short insertions and deletions (InDels). Among the SNPs and InDels that are present in both Indians as well as other populations, about 1.76 million variations differ in prevalence among Indians and others by at least 15% frequency of the alternate allele. 8.4 million SNPs are unique to the Indian population, 565,000 are novel InDels. Majority of the novel variations uncovered in Indian population are of low frequency (1-5% frequency) or rare ($<$1%).

About 56% and 34% of all the variations are respectively intergenic and intronic. Out of the exonic variants, ~53% are nonsynonymous, and ~38% are synonymous changes. About 5% of the insertions and deletions are present in exonic region, which points to enormous consequences in terms of protein coding variations affecting phenotypic changes on our population.

Faculty Research:

Dr. Bratati Kahali

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

Polygenic and complex human diseases 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. General obesity measured by body mass index (BMI) and central obesity often co-occur with or predispose individuals to other complex human disease like, type 2 diabetes (T2D), cardiovascular disease, non-alcoholic fatty liver disease (NAFLD) and Alzheimer's dementia (AD). There is considerable overlap of genetic loci for these metabolic and neurodegenerative conditions, thus suggesting their shared genetic underpinnings and partly shared biological pathways. However, epidemiological studies cannot provide much information on causality of adiposity to the related metabolic and neurodegenerative conditions. Large scale comprehensive genetic analyses for such complex disorders are lacking in India.

The aim of this project is to investigate the genetic basis of the causal relationship of adiposity (general obesity and central obesity) to T2D, NAFLD, AD using Mendelian Randomization (MR).

For the genetic analysis to progress in Indian samples, currently a pipeline is being developed for accurate and efficient genotype imputation for Indian samples. The genotype data of >500 Indian samples from Affymetrix scanner and PMRA arrays have been analyzed. Haplotype merging of international cosmopolitan reference datasets as well as publicly available South Asian datasets with Indian WGS data has been done to create an intermediate and accurate imputation panel. In this experiment, a modified imputation reference panel was built by merging 1000 Genomes data along with Indian samples joint calling data at CBR, IISc. Increased accuracy of imputation is observed for Indian GWAS samples using this merged panel, although not significantly more. However, it is important to note that this is an evolving exercise and the merged panel with more data from Indian WGS is capable of showing reliable results regarding marked increase in imputation accuracy. Additionally, genome wide association studies are being conducted for phenotypes BMI and T2D for array wide data for these Indian samples, which will form the basic summary stats for the MR work downstream.

Project title: Epistasis analysis of ApoE in understanding the genetic architecture of Alzheimer's disease: A computational genetics approach

Funding: SERB Early Career Research Award
Project personnel: Sheldon D'Silva

Large scale meta-analysis of genome wide association studies (GWAS) and family-based studies have implicated several genomic loci to be strongly associated with Alzheimer's disease (AD). This includes apolipoprotein E (*ApoE*), the biggest genetic risk factor for AD. The derived combinations of *ApoE* genetic polymorphisms rs7412, rs429358 give rise to the ε2, ε3, ε4 isoforms of *ApoE*, the last one being of greatest risk when present in homozygous form in an individual. However, the genetic loci fail to account for substantial phenotypic variation for Alzheimer's disease. In addition to rare alleles driving the major genetic component of the disease, one of the causes for this unexplained variance, commonly known as the missing heritability for complex diseases, can be attributed to gene-gene or gene by environment interactions.

In this project, the aim is to decipher how epistasis defines the genetic architecture of AD by investigating pairwise SNP interactions implicated in AD.

Different regression based, machine learning based, information theory based, multidimensionality reduction based, and Bayesian theory- based approaches for gene-gene interactions have been tested with publicly available datasets. The actual implementation of these programs required interventions and modifications in source code. Additionally, in house programs are currently being developed to scale currently available programs for higher order epistatic interactions for >5000 single nucleotide variations, while adjusting for covariates and the same is to be implemented in continuous as well as binary phenotypes.

Ultimately, a machine learning algorithm that reduces the combinations of genotypes between 2 or more loci as an array of high risk 1 and low risk 0 values using the case/control ratio for each combination have been finalized as the best choice. The models are trained on 9 parts of the parsed genotype matrix and tested on the final 10^{th} part. This is where they are evaluated for their predictive accuracy and confidence score. This program has crucial features – the ability to input the phenotype of interest as quantitative values, parsing the heterozygous configurations in the genotype matrix, model-free: provides for better detection when mode of inheritance is unknown, nonparametric: number of interaction terms does not grow exponentially with increase in variables, the ability to compute orders of interaction beyond 2, provides for covariate adjustment which increases the accuracy for risk assessment.

To overcome computational limitation, runtime scripts were developed that enable the search space to be reduced. This was achieved by recursively chunking the genotype matrix and eliminating the SNP least probable to interact, resulting in a pruning of 10 SNPs per recursion. By employing the developed runtime optimizations, significant reduction in the execution time for the large dataset to approximately 5 hours for up to 5^{th} order interaction was achieved, which was earlier entirely unable to process in existing computation configurations. This protocol will be further deployed to parse larger datasets in order to define the epistasis that governs interactions with ApoE for AD.

Dr. Smitha Karunakaran

Project Title: Role of Locus Coeruleus in maintaining cognitive function in normal and pathological ageing, such as dementia

Funding: CBR core fund

Project personnel: Abhijit Shankaran

PhD student: Srushti Kushwaha

Studies in our laboratory are focused on understanding the functional importance of hippocampal projecting neurons/systems specially locus coeruleus, and how they transform hippocampal network activity and modulate behaviour in APP/PS1 mouse model of Alzheimer's disease (AD). Recent findings from our laboratory demonstrated that, 2-month-old APP/PS1 mice upon hippocampus dependent 'contextual' fear conditioning (cFC) displayed an intact short-term memory, and an impaired long-term memory. We further demonstrated that the persistence of long-term memories was critically dependent on the beta-adrenergic signaling time window that spanned between 0 - +2.5h post learning (Karunakaran, 2021). Currently we are probing for the molecular mechanisms underlying these deficits and how administration of beta-adrenergic agonist reverses this deficit. We first determined the protein expression levels of dopamine beta hydroxylase (DBH) and tyrosine hydroxylase (TH) using immunoblotting. Hippocampus was dissected out from the Wild Type (WT) and APP/PS1 mice at 2h and 24h upon fear learning. To monitor the baseline levels, we also dissected out the hippocampus from cage control animals. Upon cFC, we found that DBH levels in the APP/PS1 mice were almost similar to that of WT at 2h, but their levels were not sustained as in WT mice at 24h. This finding supports intact short-term memory at 2h in both the WT and APP/PS1 mice, and the inability of APP/PS1 hippocampus to sustain the levels of DBH and the strength of the memory long term at 24h. Since dopamine serves as the substrate for norepinephrine (NE) synthesis we probed for the levels TH in this sample set. There was a surge in the levels of TH at 2h upon cFC in the WT and levels went back to baseline at 24h. Interestingly, in the APP/PS1 mice we noticed that the baseline levels were altered or was significantly lesser

compared to their WT counterpart reflecting a paucity of substrate for NE synthesis. Moreover, the basal levels of TH did not alter at 2 and 24h upon cFC.

We further probed for the total GAD67 levels, the inhibitory neuron marker upon cFC in the hippocampus. Inhibitory neurons determine the temporal precision of pyramidal cell firing, regulation of firing rates. GAD67 was elevated at 2h upon cFC in both WT and APP/PS1, however the levels were not sustained like WT at 24h. This result resonates with the DBH levels upon cFC. This deficit may be due to almost negligible dopamine or dysfunctional noradrenergic signaling in the hippocampus of 2-month-old APP/PS1 mice. The impact of noradrenergic signaling on inhibitory neurons in the hippocampus during behavioural learning is not well studied though they express alpha- and beta-adrenergic receptors. Other than the inhibitory neurons, the non-neuronal cell type whose function is heavily dependent upon noradrenergic signaling are the astrocytes. The persistence of noradrenergic signaling is pertinent for astrocytic plasticity and neural network activity to promote long term fear memory consolidation (PMID: 27402767, PMID: 25622143). This led us to probe for the levels of the astrocytic marker glial fibrillary acidic protein (GFAP) in the hippocampus. Interestingly, the total GFAP levels were very low at baseline in 2-month-old APP/PS1 hippocampus, which did not change significantly upon cFC. In the WT mice we saw a decrease in GFAP expression upon cFC, which is in agreement with previous reports indicating that altered astrocytic plasticity is necessary to induce learning which leads to decreased levels of GFAP upon cFC (PMID: 27460927; PMID: 32846133; PMID: 29230165). Considering the astrocytic heterogeneity, we still not know which type of astrocytes are dysfunctional in 2-month-old APP/PS1 mice.

Our findings put together broadly indicate how imbalance in the major monoamine neurotransmitter systems can have an impact on astrocytic and GABAergic driven operations during fear memory consolidation in the hippocampus at 2 months of age in APP/PS1 mice.

Dr. Vivek Tiwari

Project Title: Magnetic Resonance Imaging (MRI) investigations of Structural changes and small vessel pathologies with aging in TLSA and SANSCOG cohorts.

Funding: CBR core fund

Group members: Darshit Thakar, Susmita Chakraborty

Vascular and structural changes are an unavoidable risk associated with aging. Aging is a major risk for dementia. Therefore, my main research focus is to understand structural, vascular, and biochemical changes in the brain during normal and pathological aging. We

are employing comprehensive magnetic resonance imaging (MRI) investigations in a subset of participants from the urban cohort, Tata Longitudinal Study on Aging (TLSA) and the rural cohort, Srinivaspura Aging, Neuro Senescence and COGnition (SANSCOG) using 3-Tesla MRI scanner. We are performing brain MRI measurements in TLSA and SANSCOG subjects at the baseline and periodic follow-ups, close to the clinical and cognitive visits.

We have analyzed the T1-weighted and FLAIR MRI data from TLSA (N=284) and SANSCOG (N=91) cohorts to measure neuroanatomic volumes and micro vessel pathologies. Segmentation of T1-weighted brain MR images from TLSA and SANSCOG cohorts shows significant loss in gray matter volume and white matter volume with aging. This structural loss is concurrently observed with increase in ventricles in both the cohorts. We have observed significantly faster loss in gray matter volume and increase in ventricular volume in the rural cohort compared to the urban cohort (Fig 1 A-B). Left and right hippocampus volume also showed significant ($p<0.001$) negative association with age in both the cohorts (Fig 1C-D) and the rate of hippocampus volume reduction with age was not significantly different between TLSA and SANSCOG cohorts.

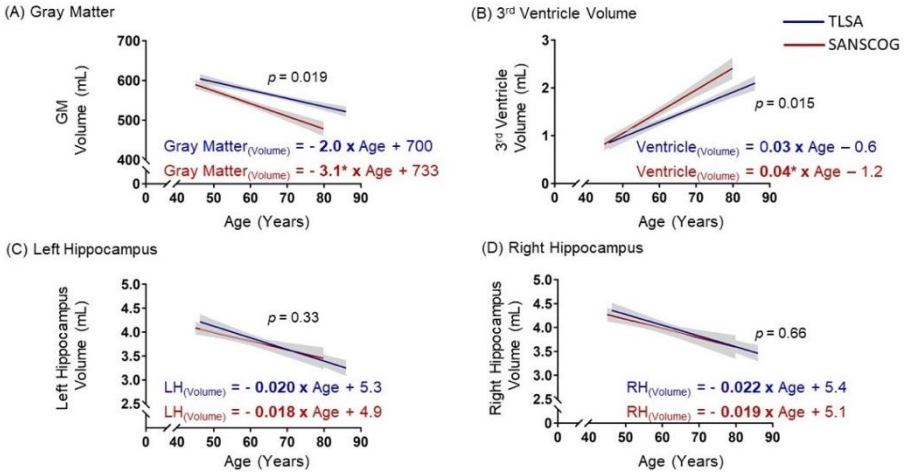

Figure 1 Association of brain structure volume with aging. Volumes were obtained from M segmentation.

In addition to structural changes in the TLSA and SANSCOG cohort, we also quantified small vessel pathology, seen as white matter hyperintensity (WMH) on brain MRI, at baseline and one year follow up. In our attempt to understand the longitudinal alterations we evaluated changes in WMH, and anatomic volumes were evaluated for 128-subjects who had MRI measurement at both baseline visit (V0) and first visit (V1) in the ongoing TLSA study. WMH and anatomic volume changes for one year follow up were calculated as (Delta= Volume at V1 – Volume at V0).

Quantification of change in WMH (Delta WMH) in the TLSA-subjects at V1 and V0 reveals that 65% of the subjects showed progression in WMH volume while another 35% did not show WMH-progression (Fig.2A). This indicates that there is a subset of cohorts that show progression in WMH volume (0.5 – 7.9 ml), while another subset of subjects does not exhibit WMH change.

Moreover, brain segmentation analysis showed that the subset of the cohort that showed progression in WMH volume had significantly larger decline in gray matter and increase in CSF volume at the follow up visit (V1): a characteristic typical of pathological aging.

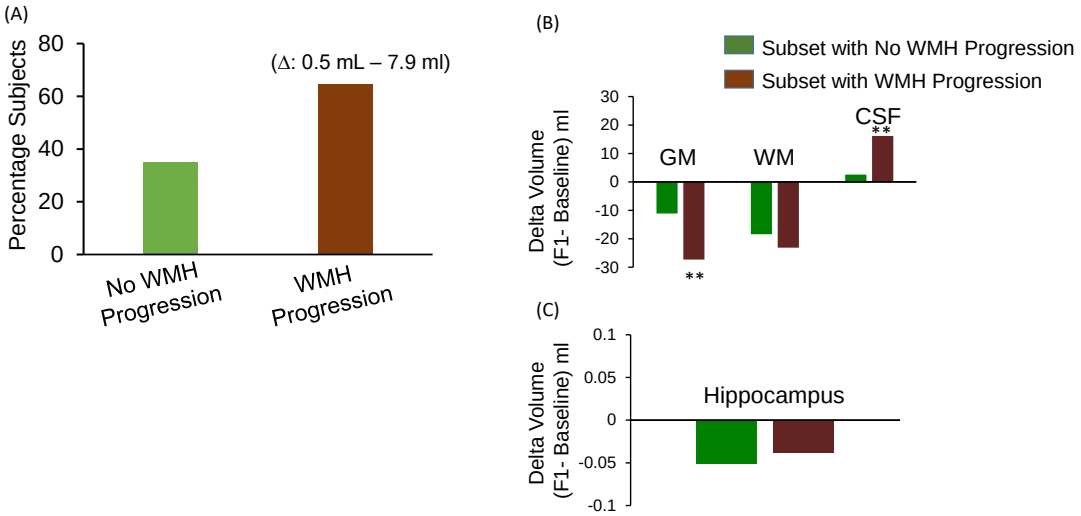

Figure 2 Changes in the brain structure volume at follow up visit stratified across the subs of cohorts that showed progression in WMH volume compared to the subset th did not had changes in WMH volume.

With these preliminary findings, we may argue that extent of gray matter loss with aging may be accelerated with concurrent progression in WMH burden. We are further extending these MRI measurements across large number of subjects in both TLSA and SANSCOG cohorts. We are also deducing the effect of aging on microstructural integrities such as strength of white fiber connections and its association with WMH progression and gray matter loss.

In addition to the measurements in the TLSA and SANSCOG cohort, we are performing a comprehensive multimodal multivariate study using brain MRI and neuropsychological data from National Alzheimer's Coordinating Center (NACC) and Alzheimer's Dementia Neuroimaging Initiative (ADNI). This provides us an opportunity to investigate the trajectory of normal and pathological in other population of the world, and sets a platform to compare and evaluate the aging trajectory of TLSA and SANSCOG cohorts.

Dr. SN Suresh

Project title: Investigating regulation of mitochondrial-mediated late endosome fission: Implications in Alzheimer's disease

Efficient functioning of mitochondria fosters metabolism that plays a central role in maintaining cellular homeostasis. Depending on cellular needs and context, the fission-fusion of mitochondrial tubules occur (PMID: 32017944). Interestingly, mitochondria can interact with organelles such as endoplasmic reticulum (ER), lysosomes *via* MCS (PMID: 30006038). ER is found at a fission site while segregating mitochondrial DNA (PMID: 27418514). On the other hand, LAMP1 positive vesicles regulate mitochondrial fission that is modulated by Rab7 GTP hydrolysis (PMID: 31231042). On the contrary, the precise role of mitochondria in regulating dynamics of Rab7 compartments is not known yet. Endocytic pathways encompass the formation of unique membrane compartments that internalize the plethora of molecules from plasma membrane (PMID: 30383243). Early as well as late endosomes undergo fusion and fission to sort and deliver cargo to its destination such as lysosomes, recycling back to plasma membrane or trans-Golgi network (TGN) (PMID: 19317650). Our previous results suggested that mitochondria regulated Rab7 compartment fission for the efficient sorting and targeting. However, the molecular machineries and its associated mechanisms are not known yet. We will employ cutting-edge live cell microscopic techniques; CRISPR/Cas9 mediated genetic manipulation, biochemical, molecular and cell biological methods to address these intriguing questions.

Project update:

To understand the role of mitochondria and Rab7 compartment contact sites in HEK293 cells, endogenous locus of CoxIV and Rab7 is tagged with BFP and RFP respectively using CRISPR/Cas9 (designated as double knock-in line, HEK293^{DKI}). We observed that mitochondria and Rab7 compartments form stable MCS. Next, using super-resolution imaging, we identified that the role of close apposition of mitochondria is to regulate fission of Rab7 compartments. "Rab7 compartment fission" can be defined as the appearance of a) constriction site, b) partition (on Rab7 compartment) and c) pinching-off new Rab7 compartment (termed as daughter bud) from mother bud. We intend to assess the

localization of PI4KB during mitochondria and Rab7 compartment interaction. Notably, we identified PI4KB as an important player that regulates mitochondrial mediated Rab7 compartment fission. Around 75 percent of Rab7 compartments are positive for PI4KB that are associated with mitochondria. As reported earlier, we noted significant localization of PI4KB on mitochondria as well (PMID: 32193326). However, PI4KB is predominantly localized on Rab7 compartments as well as its contact sites with mitochondria. These observations indicate that PI4KB is localized on dividing Rab7 compartments that are associated with mitochondria. PI4KB is reported to be associated with lysosomes as well as Golgi (PMID: 23258225). We aim to assess either Golgi or lysosomal pools of PI4KB is regulating Rab7 compartment fission. GFP-PI4KB is enriched at Rab7 compartment constriction sites that is also positive for mitochondria and then extend towards Rab7 compartments as revealed from video analyses of ~153 fission events. Post-fission, Rab7 compartments as well as mitochondria are positive for GFP-PI4KB. Notably, GFP-PI4KB is significantly co-localized with TGN46 mcherry (Golgi marker). These results indicate that Golgi associated pools of GFP-PI4KB is primarily involved in Rab7 compartment division. Biochemical characterization indicated that helical domain of PI4KB is essential for its interaction with Rab7 compartment. PI4KB-Rab7 interaction could bring about the following molecular events during fission, a) contribution of PI4P to regulate Rab7 compartment dynamics, b) recruitment of effectors such as retromer and WASH complex on budding Rab7 compartments.

What are the downstream molecular events occur after recruitment of PI4KB on Rab7 compartments? Towards this, we hypothesize that PI4KB localization could play an important role during cargo sorting. We then assessed if CI-M6PR cargo sorting is defective in cells lacking PI4KB. For this, we generated a stable HEK293 cell line that is depleted with PI4KB using CRISPR/Cas9. Interestingly, we noted significant CI-M6PR cargo sorting defect in PI4KB KO. Since CI-M6PR cargo sorting is defective, we asked if retromer localization changes in PI4KB KO. Immunofluorescence revealed the significant localization of VPS35 (Vacuolar protein sorting ortholog 35), SNX2 (Sorting nexin 2) and SNX6 (Sorting nexin 6) on Rab7 compartments in control cells. However, in PI4KBKO, we

noted that significantly more Rab7 compartments are not positive for VPS35, SNX6 and SNX2 (manuscript under revision).

To summarize, we demonstrate, 1) the novel role of mitochondria in regulating fission of Rab7 compartments, 2) the role of PI4KB that are localized in Rab7 compartments in regulating cargo sorting and delivery. Currently, we are performing the quantitative proteomics of PI4KB KO cells to identify the changes in levels and distribution of cargo molecules.

2. AWARDS/DISTINCTIONS

- **Prof Vijayalakshmi Ravindranath** was awarded the **Prof. M.G.K. Menon Memorial Award** for the year 2020 by the National Academy of Sciences (NASI).
- **Prof Vijayalakshmi Ravindranath** was awarded the **Lifetime Achievement Award** for the year 2021 by the Delhi Neurological Association (DNA).
- **Dr Bratati Kahali** was awarded **"National Supercomputing Mission 2020-2021"**- Department of Science and Technology (DST) and Ministry of Electronics and Information Technology (MeITy) Government of India funding for project titled "Population scale whole genome sequencing data analysis in Indians: Implications for uncovering the genetic architecture of cognitive changes associated with aging" in March 2021.
- **Dr SN Suresh** was awarded the **INSA young scientist award**, **NASI young scientist platinum jubilee award,** and the **DBT- Innovative Young Biotechnologist award**, all for the year 2020.

3. LECTURES / TALKS / PRESENTATIONS

- **Prof Vijayalakshmi Ravindranath** gave a **plenary talk** titled, **"The Two Indias"** at the **Alzheimer's Association International Conference** in July 2020.
- **Prof Vijayalakshmi Ravindranath** presented a **scientific talk** titled, **"Aging and dementia: mechanisms to interventions"** at the **Indo-US Scientific Meeting** in December 2020.
- **Prof Vijayalakshmi Ravindranath** participated in **World Dementia Council - Round Table on LMICs** as **panel discussant** on March 13, 2021.

- **Prof Vijayalakshmi Ravindranath** participated in **Dementia Research Blueprint meeting** on May 19, 2020.
- **Dr Smitha Karunakaran** presented a poster titled "Early β-adrenergic receptor dependent time window for long term memory persistence in APPswe/PS1dE9 mouse model of Alzheimer's disease" at the **Alzheimer's Association International Conference - Neuroscience Next,** which was held on November 9-10th, 2020.
- **Dr Smitha Karunakaran** presented a poster titled "Early β adrenoceptor dependent time window for fear memory persistence in APPswe/PS1dE9 mice" at **The Neurodegenerative Diseases: Biology & Therapeutics 2020 | Cold Spring Harbor Meeting,** held on December 2 – 4th, 2020.
- **Kommaddi RP**, Diwakar L, Gowaikar RG, Karunakaran S, and Ravindranath V. Impairment in recall after contextual fear conditioning and activity dependent protein translation in ovariectomized Alzheimer's disease mouse model. Poster presented at the **Alzheimer's Association International Conference-2020,** July 27-31, 2020.
- **Kommaddi RP**, Verma A, Chandran M, Jaleel A, and Ravindranath V. Synaptosomal actin interactome analysis in an Alzheimer's disease mouse model. Poster presented at the **Alzheimer's Association International Conference-2020,** July 27-31, 2020.
- **Diwakar L**, Chithanathan K, Tomar DS, Gowaikar R and Ravindranath V. Single bilateral injection of endothelin -1 leads to temporary deficits in memory and synaptic dysfunction. Poster presented at the **Alzheimer's Association International Conference-2020,** July 27-31, 2020.
- **Diwakar L**, Maurya SK, and Ravindranath V. Recurrent vascular insult leads to memory impairment and synaptic dysfunction detected as F actin loss. Poster presented at the **Alzheimer's Association International Conference-2020,** July 27-31, 2020.
- **Jonas Sundarakumar**, Ganesh Chauhan, Girish N Rao, Palanimuthu T Sivakumar Naren P Rao, Vijayalakshmi Ravindranath & SANSCOG and TLSA Study Teams. Srinivaspura Aging, Neuro Senescence and COGnition (SANSCOG) study and Tata Longitudinal Study on Aging (TLSA): Study Protocols. Poster presented at the **Alzheimer's Association International Conference-2020,** July 27-31, 2020.
- **Jonas Sundarakumar**, Palanimuthu T Sivakumar, Naren P Rao, Vijayalakshmi Ravindranath & SANSCOG and TLSA Study Teams. Comparison of obesity, diabetes, hypertension and depression in two parallel, aging study cohorts from rural and urban India – SANSCOG study and TLSA. Poster presented at the **Alzheimer's Association International Conference-2020,** July 27-31, 2020.
- **Jonas Sundarakumar**, Smitha Karunakaran, Sumathi ME, Kalyani Raju, Palanimuthu T Sivakumar, Naren P Rao, Vijayalakshmi Ravindranath & SANSCOG and TLSA Study Teams. Comparison of fasting blood sugar, HbA1c, vitamin B12, homocysteine and vitamin D in two parallel, aging study cohorts from rural and urban India – SANSCOG study and TLSA. Poster presented at the **Alzheimer's Association International Conference-2020,** July 27-31, 2020.

- **Bratati Kahali**, Siddharth Dutt, Naren P Rao, Vijayalakshmi Ravindranath, team members of TLSA and SANSCOG. Impact of age, gender, and education on the performance of Addenbrooke's Cognitive Examination (ACE- III) in urban and rural Indians. **Alzheimer's Association International Conference**, July 27-31, 2020.
- **Kiran Chaudhary**, Girish N Rao, Palanimuthu T Sivakumar, Jonas Sundarakumar, Naren Rao, Vijayalakshmi Ravindranath. Approaches to overcome recruitment challenges in a rural setting in India: Strategies adopted in Srinivasapur Aging, Neuro Senescence and COGnition (SANSCOG) study. Poster presented at the **Alzheimer's Association International Conference-2020,** July 27-31, 2020.
- **Tiwari V**, Kallur K, Rao NP, Sivakumar PT, Balakrishnan A, Ravindranath V and SANSCOG and TLSA Investigators. MRI investigations of white matter hyperintensity and structural abnormalities of brain in urban and rural cohorts of India. Poster presented at the **Alzheimer's Association International Conference-2020,** July 27-31, 2020.

4. EVENTS

4.1 International Scientific Advisory Board – Meeting

The International Scientific Advisory Board meeting was held online this year owing to the COVID-19 pandemic. The meeting was held on 16th July, 2020. 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.

4.2 Scientific Advisory Committee – Meeting

The Scientific Advisory Committee meeting was held online on 8th December 2020. The committee reviewed the on-going projects and gave valuable suggestions. New projects proposals were also considered during these meetings.

5. ACADEMIC COLLABORATION

5.1. 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.

5.2 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 approached MAHE for affiliation for the Ph.D programme. The application was approved, and four students have enrolled in this programme during the year 2019-20, and 6 more have enrolled in the year 2020-21.

6. PUBLICATIONS

- **Karunakaran S**. Unraveling Early Signs of Navigational Impairment in APPswe/PS1dE9 Mice Using Morris Water Maze. **Front Neurosci.** Dec **2020**; 14: 568200. PMCID: PMC7770143
- **Karunakaran S**. Early β adrenoceptor dependent time window for fear memory persistence in APPswe/PS1dE9 mice. **Sci Rep.** Jan **2021**, 11:870. PMID: 33441593
- **SNSuresh** et al., Pharmacological tools to modulate autophagy in neurodegenerative diseases. Journal of molecular biology. 2020 Apr 3;432(8):2822-2842.
- Tharun, **SNSuresh** et al., Soluble 4R0N Tau Abrogates Endocytic Vesicular Dynamics. **Frontiers ageing neuroscience**. 2020 Nov 5;12:537712.
- Allele Specific Variation at ApoE Increases Non-alcoholic Fatty Liver Disease and Obesity but Decreases Risk of Alzheimer's Disease and Myocardial Infarction. Palmer N*, **Kahali Bratati***, Kuppa A*…Speliotes EK. **Human Molecular Genetics.** Accepted March 2021.
- Common noncoding variant at PPP1R3B promotes liver glycogen storage and metabolic syndrome, but protect against myocardial infarction. **Bratati Kahali***, Yue Chen*, Mary F Feitosa*, Lawrence F Bielak*, Jeffrey R O'Connell*, ….. Elizabeth K Speliotes. Journal of **Clinical Endocrinology and Metabolism.** 2021 Jan;106(2):372-387.
- Implementation of human whole genome sequencing data analysis: A containerized framework for sustained and enhanced throughput. **Abhishek Panda, Krithika Subramanian and Bratati Kahali***. Manuscript under review.

- Congruent outcomes from multiple approaches of epistasis analysis for human body mass index associated loci implicate neuronal, adipose biology and immunological pathways. **Sheldon D'Silva and Bratati Kahali***. Manuscript under review.
- Machine learning-based cognitive impairment classification with optimal combination of neuropsychological tests. Gupta A, **Kahali B***. **Alzheimers Dement** (N Y). 2020 Jul 19;6(1):e12049.
- Sai Manohar Thota, Kimberly Chan, Sai Sanwid Pradhan, Bhavana Nagabushana, Priyanka GB, Sunil H V, **Vivek Tiwari**, Krishna Murthy Vinnakote, Sanjaya Viswamitra, Madhav Thambisetty, Dileep Kumar, Vivek Tiwari*, Joshy EV, Venketesh Sivaramakrishnan*. Multimodal Imaging And Visual Evoked Potentials Reveal Key Structural And Functional Features That Distinguish Symptomatic From Pre-symptomatic Huntington's Disease Brain. **Neurology India** (2021) (in Press).
- Pegah Askari, Ivan E. Dimitrov, Sandeep K. Ganji, **Vivek Tiwari**, Michael Levy, Toral R. Patel, Edward Pan, Bruce E. Mickey, Craig R. Malloy, Elizabeth A. Maher, Changho Choi. Spectral fitting strategy to overcome the spectral overlap between 2- hydroxyglutarate and lipid resonances at 2.25 ppm. **Magnetic Resonance in Medicine** (2021). https://doi.org/10.1002/mrm.28829.
- **Verma A, Ravindranath V.** Cav1.3 L-Type Calcium Channels Increase the Vulnerability of Substantia Nigra Dopaminergic Neurons in MPTP Mouse Model of Parkinson's Disease. **Front Aging Neurosci.** 2020; 11:382. doi: 10.3389/fnagi.2019.00382.
- **Verma A, Ray A, Bapat D, Diwakar L, Kommaddi RP, Schneider B, Hirsch EC, Ravindranath V.** Glutaredoxin 1 Downregulation in the Substantia Nigra Leads to Dopaminergic Degeneration in Mice. **Movement Disorder,** 2021. https://doi.org/10.1002/mds.28190**.**
- Kivipelto M et al, **World-Wide FINGERS Network**. A global approach to risk reduction and prevention of dementia**. Alzheimer's and Dementia,** 2021. https://doi.org/10.1002/alz.12123.
- **Diwakar L**, Gowaikar R, Chithanathan K, Gnanabharathi B, Tomar DS and **Ravindranath V**: Endothelin-1 mediated vasoconstriction leads to memory impairment and synaptic dysfunction. **Scientific Reports** (2021) 11:4868 https://doi.org/10.1038/s41598-021-84258-xwww.nature.com/scientificreports.
- Gabriel A de Erausquin, Heather Snyder, María Carrillo, Akram A Hosseini, Traolach S Brugha, Sudha Seshadri, **CNS SARS-CoV-2 Consortium.** The chronic neuropsychiatric sequelae of COVID-19: The need for a prospective study of viral impact on brain functioning. **Alzheimers Dement** 2021 Jun;17(6):1056-1065. doi: 10.1002/alz.12255. Epub 2021 Jan 5.
- **Vijayalakshmi Ravindranath*** **and Jonas S Sundarakumar.** Changing demography and the challenge of Dementia in India. **Nature Reviews: Neurology** (Manuscript accepted).
- **The SANSCOG Study Team.** Srinivaspura Aging, Neuro Senescence and COGnition (SANSCOG) study: Study Protocol**. Alzheimer's and Dementia group of journals** (Manuscript submitted).
- **Ammu Lukose, Rahul KV, Mino Susan Joseph, Palanimuthu T Sivakumar, Girish N Rao, Bangalore N Gangadhar, Karen Ritchie, Aditi Balakrishnan, Vijayalakshmi Ravindranath*** **and Naren P Rao*** Cross-cultural adaption of the Computerized Assessment of Information Processing battery (COGNITO) for an Indian longitudinal study on rural elderly. **Alzheimer's and Dementia group of journals** (Manuscript submitted).

- **Abhishek M L, Jonas S Sundarakumar, Shafeeq K Shahul Hameed, SANSCOG & TLSA Study Teams and Vijayalakshmi Ravindranath***. Comparison of Risk Factors for Dementia among Rural and Urban Elderly Adults: Data from two cohort studies in India. **Alzheimer's and Dementia group of journals** (Manuscript submitted).
- **Jonas S Sundarakumar, Shafeeq K Shahul Hameed, Abhishek M L, SANSCOG & TLSA Study Teams and Vijayalakshmi Ravindranath*.** Prevalence of neuropsychiatric conditions and cognitive impairment in two parallel, aging study cohorts from rural and urban India. **Alzheimer's and Dementia group of journals** (Manuscript submitted).
- **Jonas S Sundarakumar, Shafeeq K Shahul Hameed, Babu Dilip, Shylashree Deepak, Vinay Kumar BR and Vijayalakshmi Ravindranath***. Approaches to engage an aging, rural cohort in southern India during the COVID-19 crisis and the psychological impact of COVID-19 in this cohort. **Alzheimer's and Dementia group of journals** (Manuscript submitted).
- **Tiwari V, Viswamitra S, SANSCOG & TLSA Study Teams and Ravindranath V***. Structural and Microvascular pathologies with aging: In vivo MRI findings from TLSA and SANSCOG cohorts of India. **Alzheimer's and Dementia group of journals** (Manuscript submitted).
- **Bratati Kahali, Aditi Balakrishnan, Sneha Dhanavanthri Muralidhara, Graciela Muniz Terrera, Karen Ritchie, SANSCOG study team and Vijayalakshmi Ravindranath***. COGNITO (Computerized assessment of adult information processing): Normative data for rural Indian population from SANSCOG study. **Alzheimer's and Dementia group of journals** (Manuscript submitted).
- **Bratati Kahali, Aditi Balakrishnan, Sneha Dhanavanthri Muralidhara, Graciela Muniz Terrera, TLSA study team and Vijayalakshmi Ravindranath***. Normative data for the Addenbrooke's Cognitive Examination (ACE-III) for urban Indian population from TLSA study. **Alzheimer's and Dementia group of journals** (Manuscript submitted).
- **Jonas S Sundarakumar, Shafeeq K Shahul Hameed and Vijayalakshmi Ravindranath**. Burden of vitamin D, vitamin B12 and folic acid deficiencies in an aging, rural Indian community. **Frontiers in Public Health** (Manuscript submitted).

7. 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. 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 almost complete. We expect to relocate to the new building as soon as the electricity connection is established.

The Construction activities are monitored by a committee consisting of following members.

- 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

8. FINANCE

The total receipts for the year 2020-21 was Rs. 7706.75 Lakhs and the payments for various activities of the Centre was Rs. 5693.03 Lakhs
The details of Receipts and Payments for the year 2020-2021 are as follows.

Sl.No.	Particulars	Receipts (In Lakhs)	Payments (In Lakhs)
1	Donations from Pratiksha Trust towards Activities Account	1000.00	1029.04
2	Other Receipts	394.31	0.15
3	Donations from Pratiksha Trust towards Construction of new building	3400.00	2797.28
4	Funds from External Agencies	2912.44	1866.56
Total		7706.75	5693.03

Funds Received from External Agencies during 2020-21					
Description	Funding Agency	Total Amount Sanctioned (In Lakhs)	Funds Received during 2020-21		
			Existing Projects (In Lakhs)	New Projects (In Lakhs)	Total Funds Received (In Lakhs)
DBT GenomeIndia Project - Prof Vijayalakshmi Ravindranath	Department of Biotechnology	5,652.00	1,768.50	-	1,768.50
DST Inspire Program - Dr Suresh S N	Department of Science & Technology	112.4	22.24	-	22.24
Ramalingaswami Fellowship - Dr Bratati Kahali	Department of Biotechnology	32.5	5	-	5
SERB Project - Dr Bratati Kahali	Science & Engineering Research Board	37.44	3.5	-	3.5
SPM Fellowship - Contingency Grant	Council of Scientific & Industrial Research	3.2	0.7	-	0.7
SERB Project - Dr Bratati Kahali	Science & Engineering Research Board	56.79	-	21.73	21.73
Tata Project - Prof Vijayalakshmi Ravindranath	JTTO	1,090.77	-	1,090.77	1,090.77
Total		6,985.10	1,799.94	1,112.50	2,912.44

Funds sanctioned from Fidelity Bermuda Foundation (In Lakhs)				251.25	251.25

9. GOVERNANCE STRUCTURE & PEOPLE AT CBR

9.1 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 the following.

Prof. G Rangarajan, Director, IISc (Ex Officio) : Chairperson
Dr. P Rama Rao, Governing Council, IISc, (Ex Officio) : Member
Chief Secretary to Government of Karnataka (Ex Officio) : Member
Additional Chief Secretary to Government of Karnataka (Ex Officio) : Member
Principal Secretary (Finance) Government of Karnataka (Ex Officio) : Member

Secretary, Dept. of IT & BT, Government of Karnataka (Ex Officio)	: Member
Prof. Vijayalakshmi Ravindranath, Director, CBR	: Member
Shri. Kris Gopalakrishnan, Co-Founder, Infosys	: Member
Mrs. Sudha Gopalakrishnan	: Member
Shri. Dinesh Krishnaswamy	: Member
Shri. S D Shibulal	: Member
Prof. Y Narahari, Dean, Electrical Electronics and Computer Sciences Division, IISc	: Member
Prof. Navakanta Bhat, Dean Interdisciplinary Sciences Division, IISc	: Member
Prof. D N Rao, Dept of Biochemistry	: Member
Prof. Usha Vijayraghavan, Dean, Biological Sciences Division, IISc	: Member
Prof. H P Khincha, Dept of Electrical Engg. (Retd), IISc	: Member
Dr. Ramesh Babu	: Member
Dr. Girija Ramesh Babu	: Member
Prof. Anurag Kumar, Dept of Electrical Engg., IISc	: Member
Prof. N. Balakrishnan, Dept of SERC, IISc	: Member
Dr. P. Satish Chandra	: Member
Dr. K. Kasturirangan Chairman, Governing Council, IISc, Raman Research Institute, Bangalore	: Member
Prof. P. Kondaiah, Dept of MRDG, IISc	: Member
Prof. S. Mayor, Director, NCBS, Bangalore	: Member
Mrs. Sudha Murthy	: Member
Dr. U. B. Muthane	: Member
Prof. G. Padmanabhan Emeritus Professor, Dept of Biochemistry, IISc	: Member
Mr. S. V. Ranganath	: Member
Prof. M. R. S. Rao, JNCASR, Bangalore	: Member
Dr. M. S. Valiathan	: Member
Justice M. N. R. Venkatachaliah	: Member

9.2 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. G Rangarajan, Director, IISc (Ex Officio)	: Chairperson
Shri. Kris Gopalakrishnan, Co-Founder Infosys	: Member

Shri. Dinesh Krishnaswamy	: Member
Shri. S D Shibulal	: Member
Mrs. Sudha Gopalakrishnan	: Member
Prof. Y Narahari, Dean, Electrical Electronics and Computer Sciences Division, IISc	: Member
Prof. Navakanta Bhat, Dean, Interdisciplinary Sciences Division, IISc	: Member
Prof. Usha Vijayraghavan, Dean, Biological Sciences Division, IISc	: Member
Prof. H P Khincha, Dept of Electrical Engg, (Retd) IISc	: Member
Prof. D N Rao, Dept Of Biochemistry, IISc	: Member
Prof. Vijayalakshmi Ravindranath, Director, CBR	: Member- Secretary

9.3 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. G Rangarajan	: Chairperson
Prof. Vijayalakshmi Ravindranath	: Member
Mr. K C Ganesh	: Member
Prof. P S Anilkumar	: Member
Prof. Navakanta Bhat	: Member
Mr. R Mohan Das	: Secretary

9.4 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. Chandramouli, B.A, Aster RV Hospital, Bangalore	: Chairperson
Prof. D N Rao, Dept of Biochemistry, IISc	: Member
Prof. K N Balaji, Dept of MCBL, IISc	: Member
Dr. Kiran Khanapure, Vikram Hospital, Bangalore	: Member
Dr. Girish Baburao Kulkarni, NIMHANS Bangalore	: Member
Adv. Arvind Moorchung, Sr Consultant	: Member
Prof. Anitha Kurup, NIAS Bangalore	: Member

Mr. Alagu Balaraman	: Member
Dr. Jonas Sundarakumar, CBR	: Member
Dr. Vivek Tiwari, Assistant Professor, CBR	: Member

9.5 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 consists of the following members:

Prof. Steven E Hyman, Director, Stanley Centre for Psychiatric Research at Broad Institute of Harvard and MIT	: Chairperson
Prof. John Morris, Washington Univ	: Member
Prof. Maria Corrillo, CSO, AA	: Member
Prof. Stanley Fahn, Columbia	: Member
Prof. Vijayalakshmi Ravindranath, Director, CBR	: Member
Prof. Sudha Seshadri, San Antonie	: Member
Prof. Carla Shatz, Stanford	: Member
Prof. Mary Ganguly, Pittsburg	: Member
Prof. Srinath Reddy, PHFI, New Delhi	: Member
Prof. B N Gangadhar, NIMHANS, Bangalore	: Member
Prof. Bart D Strooper, Director of UK Dementia Research Institute	: Member
Prof. Stacie Weninger, President of FBRI, USA	: Member
Prof. Vasant Honavar, Penn State University, USA	: Member

9.6 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 are as follows:

Prof. Srinath Reddy (PHFI, New Delhi)	: Chairman
Prof. Ramesh Hariharan (CEO, Strand Genomics, Bangalore)	: Member
Prof. Ravindra M Pandey (AIIMS, New Delhi)	: Member
Prof. Anurag Agrawal (IGIB, New Delhi)	: Member
Prof. K. Thangaraj, Director, CDFD	: Member
Prof. Vidita Vaidya (TIFR, Mumbai)	: Member
Prof. Vijayalakshmi Ravindranath (Director, CBR)	: Member

9.7 Constitution of Internal Committee against Sexual Harassment

Dr. Bratati Kahali, Assistant Professor, CBR	: Chair
Dr. Khader Valli Rupanagudi, Scientific Officer, CBR	: Member
Dr. Latha Diwakar, Senior Scientific Officer, CBR	: Member
Ms. Rashmi Misra Founder and Chairperson, Vidya, (NGO for integrated Development for youths and adults)	: Member

9.8 Institutional Biosafety Committee

Prof. Vijayalakshmi Ravindranath, Director, CBR	: Chair
Prof. Anita Mahadevan, NIMHANS, Bangalore	: DBT Nominee
Dr. Jonas S Sundarakumar, Scientific Officer, CBR	: Biosafety Officer
Dr. Ravi Manjithaya, JNCASR , Bangalore	: Outside Expert
Dr Ravi Muddshetty, Associate Professor, CBR	: Member
Dr Bratati Kahali, Assistant Professor, CBR	: Member
Dr Suresh S N, Inspire Faculty, CBR	: Member
Dr Khader Valli Rupanagudi, Scientific officer, CBR	: Member
Dr Smitha Karunakaran, Assistant Professor, CBR	: Secretary

9.9 People at CBR

9.9.1

Academic Staff

Prof Vijayalakshmi Ravindranath	: Director
Prof Ravi S Muddashetty	: Associate Professor
Dr Bratati Kahali	: Assistant Professor Grade I
Dr Smitha Karunakaran	: Assistant Professor Grade I
Dr Vivek Tiwari	: Assistant Professor Grade I
Dr Rahul Kumar	: Assistant Professor
Dr Suresh S N	: Inspire Faculty

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,IISc

Prof. Arun Kumar
Dept of Molecular Reproduction,
Development and Genetics (MRDG), IISc

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

Dr. Sanjaya Viswamitra
Dept. of Radiology
Sri Sathya Sai Institute of Higher Medical Sciences, Whitefield, Bangalore

9.9.2 Scientific:

Dr Kommaddi Reddy Peera	: Senior Scientific Officer
Dr Latha Diwakar	: Senior Scientific Officer
Dr Jonas S Sundarakumar	: Scientific Officer Grade I
Dr Khader Valli Rupanagudi	: Scientific Officer Grade II
Dr Shobha Anilkumar	: Scientific Officer Grade II
Dr Shafeeq K Shahul Hameed	: Scientific Officer Grade II

Technical Assistant

Mr Mohammed Hanif Kaba Mujawar	: Senior Technical Assistant
Mr Karthik S	: Technical Assistant
Mr Sangeethkumar Saminathan	: Technical Assistant
Ms Divya S	: Technical Assistant

Research

Dr Karru Venkata Ravi Teja	: Clinical Research Associate
Dr Ragasudha Botta	: Clinical Research Associate

Dr Abhishek M L	: Research Psychiatrist
Dr Naveen Gowda	: Post-doctoral Fellow
Dr Rajesh Kumar Gazara	: Post-doctoral Fellow
Ms Bharti Nawalpuri	: Senior Research Fellow
Dr Sandeep Kumar	: Research Associate
Ms Rajitha Narayanasamy	: Junior Research Intern
Ms Manasvi Vukku	: Junior Research Intern
Ms Rachana Navaneetha	: Junior Research Intern
Ms Santhoshi Kashyap	: Junior Research Intern
Ms Sneha Sadanand Palekar	: Junior Research Intern
Ms Varsha H J	: Junior Research Intern

Laboratory

Mr Prashant Deor	: Lab Technician
Ms Rehab Hussain	: Junior Technician
Ms Rupanagudi Sunitha	: Junior Technician
Mr Manjunatha	: Lab Assistant
Mr Mohana C	: Lab Assistant
Mr Rajesh G	: Lab Assistant
Ms Pavithra D P	: Lab Assistant
Mr. Goutham V	: Optometrist

9.9.3 Administrative:

Mr R Mohan Das	: Special Officer
Mr Manivannan P	: Finance Officer
Ms Aruna Poojary	: Executive Assistant
Ms Sudha Rani P	: Executive Assistant
Ms Sudha Srikanth	: Executive Assistant
Mr Ravi Kumar K L	: Administrative Assistant
Ms Chaithra B L	: Administrative Assistant
Ms Roopa R	: Administrative Assistant

9.9.4 Other Staff

Project Engineer
Mr. Sudarshan Rao

Medical Officer
Dr. Babu Dilip
Dr Vinay Kumar BR

Project Manager
Dr. Prathima Arvind

Sr. Project Associate
Mr Vinayak Hosawad

Data Analyst
Mr. Anand Kumar E
Mr. Naveenan S
Ms. Ankita Khan
Ms. Swetaleena Satpathy

Project Assistant
Ms Anupriya S
Ms Medha Sharma
Ms Pavani R
Ms Varsha Giridhar
Mr Darshit Thakar

Field Staff:

Mr Ramesh K	: Office Manager
Mr Naresh G	: Psychologist
Mr Rajakumar K M	: Psychologist
Ms Savitha B P	: Psychologist
Mr Rajesh M D	: Filed Supervisor
Mr Gangaraja V	: Field Data Collector
Mr Hari Kumar	: Field Data Collector
Mr Harikrishna G	: Field Data Collector
Mr Ravi K V	: Field Data Collector
Mr Shashikumar	: Field Data Collector
Mr Shivaraj S	: Field Data Collector
Mr Sreedhara N	: Field Data Collector
Mr Yashwanthkumar K	: Field Data Collector
Ms Priyanka R	: Field Data Collector
Ms Chaithra N	: Nurse
Ms Gayathri P S	: Nurse

Ms Nethravathi	: Nurse
Ms Pavithra K V	: Nurse
Ms Shyalashree Deepak	: Nurse
Ms Sujatha S N	: Nurse
Ms Sunitha H S	: Nurse
Ms Swathishree A N	: Nurse

PhD Students:

Mr Akhilesh Shailendra Khamkar
Ms Bindushree K R
Ms Haseena P A
Ms Krithika S
Ms Ramya M
Ms Richa Ashok Kakkar
Ms Shreya Chakraborty
Ms Srishti Kushwaha
Ms Susmita Chakraborty