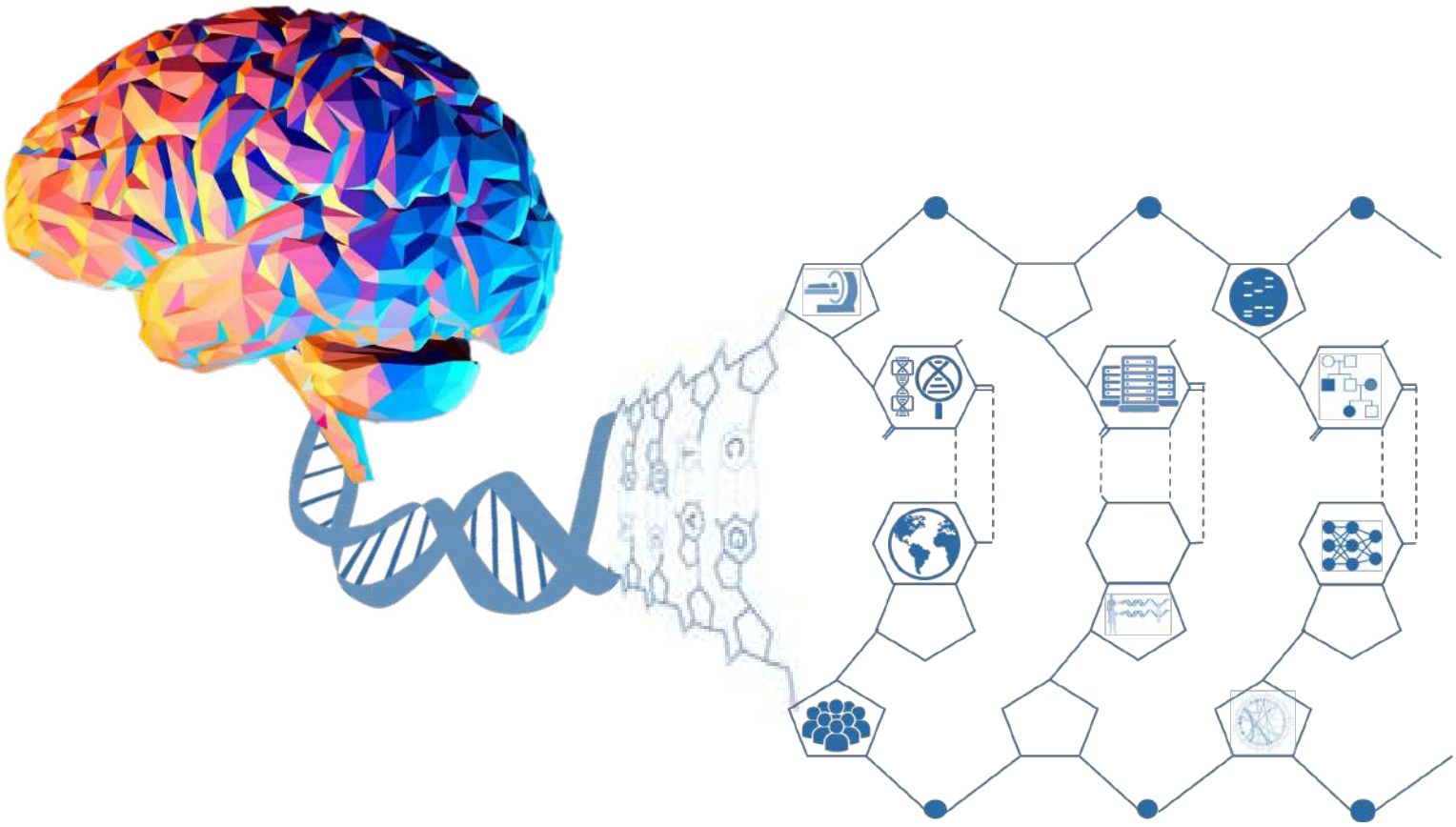
CBR Currents

Newsletter of the Centre for Brain Research, IISc

WAVE 3 MAY 2023



Harnessing the power of genomics to decipher brain aging

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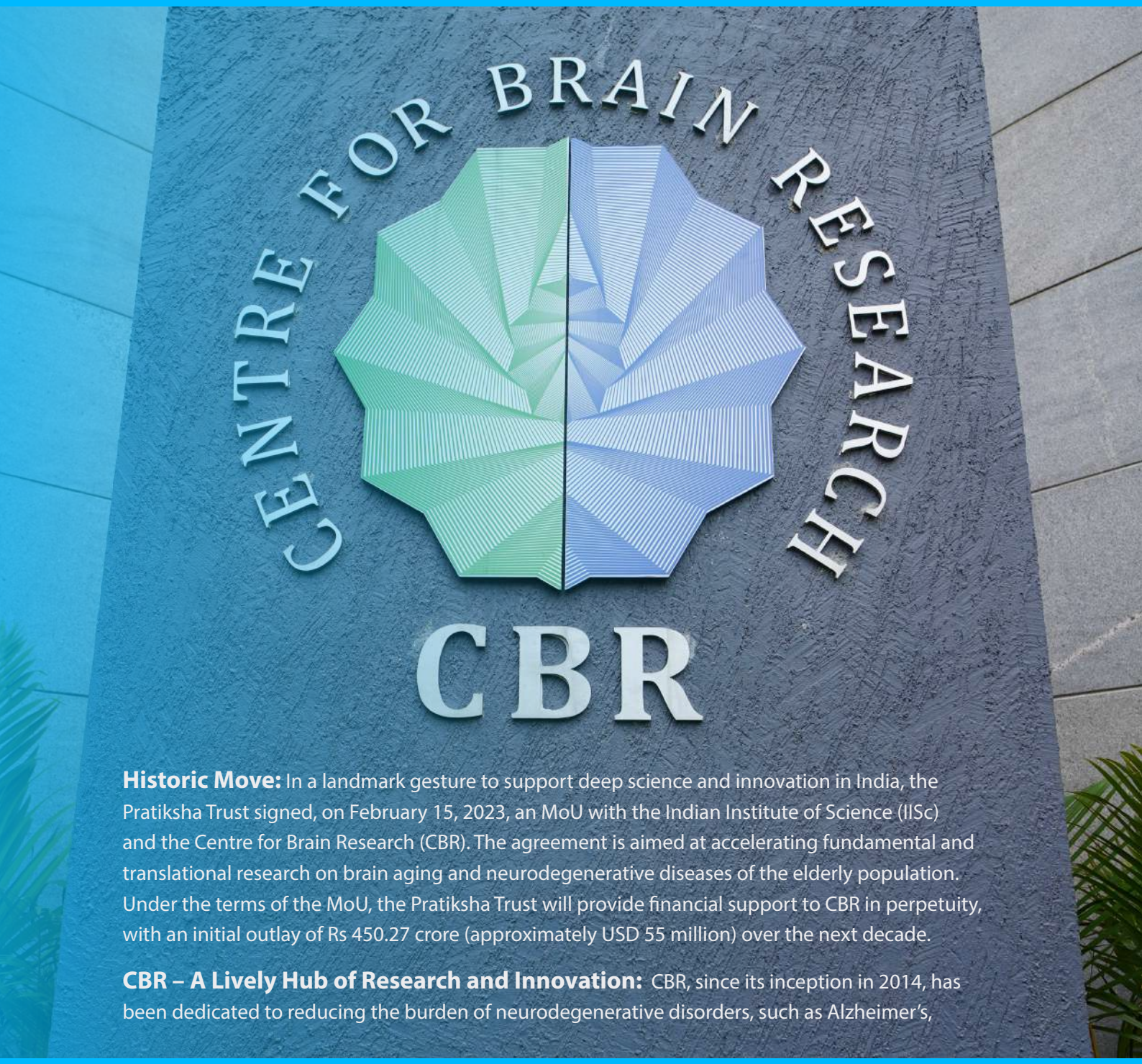
EDITORIAL

Pratiksha Trust's Acceleration for CBR



Historic Move: In a landmark gesture to support deep science and innovation in India, the Pratiksha Trust signed, on February 15, 2023, an MoU with the Indian Institute of Science (IISc) and the Centre for Brain Research (CBR). The agreement is aimed at accelerating fundamental and translational research on brain aging and neurodegenerative diseases of the elderly population. Under the terms of the MoU, the Pratiksha Trust will provide financial support to CBR in perpetuity, with an initial outlay of Rs 450.27 crore (approximately USD 55 million) over the next decade.

CBR – A Lively Hub of Research and Innovation: CBR, since its inception in 2014, has been dedicated to reducing the burden of neurodegenerative disorders, such as Alzheimer's,

Parkinson's, and Vascular Dementia, among the elderly population. CBR is emerging as a vibrant hub of talented and dedicated researchers in molecular and cellular biology, neuroscience, clinical research, computational genomics, and data science. The Centre currently has 10 Principal Investigators, supported by more than 20 Research Scientists, Post-Doctoral Fellows, and Medical Officers, and 22 PhD students. CBR is engaged intensely in two unique longitudinal studies, spanning 15 to 20 years, to track the aging brain in individuals older than 45 years of age. One study is being conducted in a rural cohort in Srinivaspura Taluk of Kolar District, Karnataka, with 10,000 volunteers, while the other is being conducted in an urban cohort in and around Bengaluru, with 1,000 volunteers. These cohort studies are providing a wealth of data, and preliminary analysis of the data collected so far is revealing important insights with implications for understanding the risk factors and protective factors for neurodegeneration. Additionally, CBR is leading 'GenomeIndia', a large-scale, nationwide initiative involving a consortium of 20 research institutions. This initiative aims to discover India-specific genetic basis for diseases through whole genome sequencing of 10,000 samples collected from across the country. With more than 30 publications in high-impact journals, including *Nature Reviews Neurology, Journal of Neuroscience, and Alzheimer's & Dementia*, CBR has caught the attention of the global research community and is now attracting notable funding from external agencies.

An Exciting Future Ahead: The generous support of the Pratiksha Trust through the MoU will significantly scale up research and innovation activities at the Centre. This funding will help identify new early biomarkers and molecular targets for novel drugs, investigate the efficacy of evidence-based interventions (lifestyle-based as well as therapeutic), and enable the Centre to proactively explore and achieve bench-to-bedside translation of the outcomes from the interdisciplinary research.

We, at CBR, gratefully acknowledge the sustained support of Mr Kris Gopalakrishnan and Mrs Sudha Gopalakrishnan, whose contributions have helped pursue transformational research in mission mode. This will help reduce the burden of neurodegenerative diseases and improve the quality of life for the elderly population. Their continued support has also set an exemplary benchmark that shows the way for philanthropic support for biomedical research in India. With determination and fortitude, CBR will make a single-minded effort to tackle the scientifically challenging problems ahead and dedicate itself to the service of the nation. CBR will strive to achieve global excellence and aspire to be among the top three such centres in the world in the coming decade.

We thank our readers for warmly receiving the earlier editions of *CBR Currents* and believe *Wave 3* would meet with comparable reception and support. In this issue, we feature spotlights on a few computational genomics research projects being carried out at the Centre and the associated infrastructure that renders this research possible. Overviews of a couple of other key initiatives and accounts of numerous exciting events that filled the past couple of months are also presented. We hope you enjoy browsing through this issue and would greatly appreciate your comments and suggestions; please write to director.cbr@iisc.ac.in.

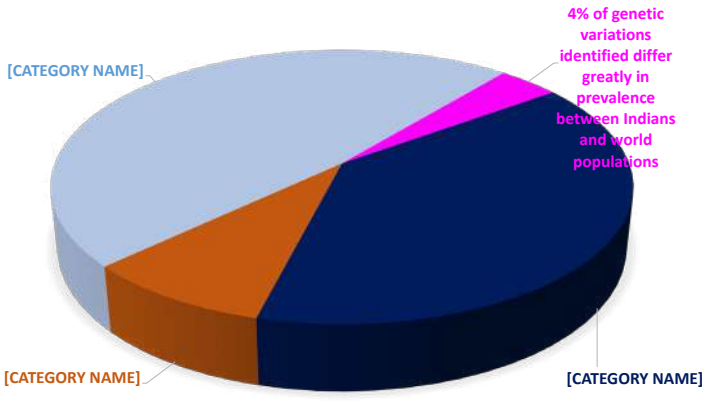
Y. Narahari, Director

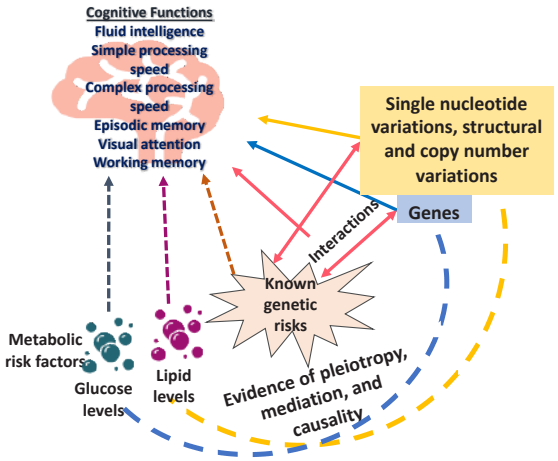
Unleashing the Potential of Computational Genomics for Aging Brain Research

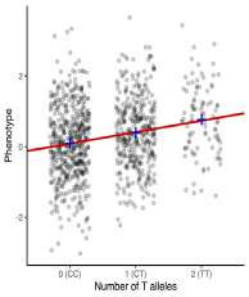
CBR pursues active research in the field of human genetics and genomics focusing on addressing questions pertaining to our genetic susceptibilities to complex diseases. For this purpose, its young researchers get trained in and employ state-of-the-art approaches to study and analyze human genetics and bioinformatics data, particularly in the Indian population, with special emphasis on whole genome and whole exome sequencing data analyses in families and population-based cohort studies, using sophisticated statistical methodology and the use of high-performance computing resources.

Much of these efforts are spearheaded by the group of Prof. Bratati Kahali. The overarching goal of this laboratory is to develop and evaluate biological hypotheses for answering how human genetic variation can affect metabolic and neurodegenerative conditions – for example, (a) why humans have different genetic susceptibility to these complex diseases, and (b) find single nucleotide and structural variants that associate with the disease of interest, (c) unravel the physiological pathways relevant to the disease being studied, (d) investigate if metabolic risk factors such as abdominal adiposity, type 2 diabetes, and dyslipidemia can cause cognitive impairment and neurodegeneration at the genetic level; and if these metabolic risks share genetic basis with neurodegenerative disorders, (e) how interactions among multiple genetic loci could contribute to shaping complex phenotypes and (f) how evolution has shaped these genomic characteristics. The group also integrates methylation, RNA expression, and other -omics data for developing more powerful genomics-based predictors for such diseases.

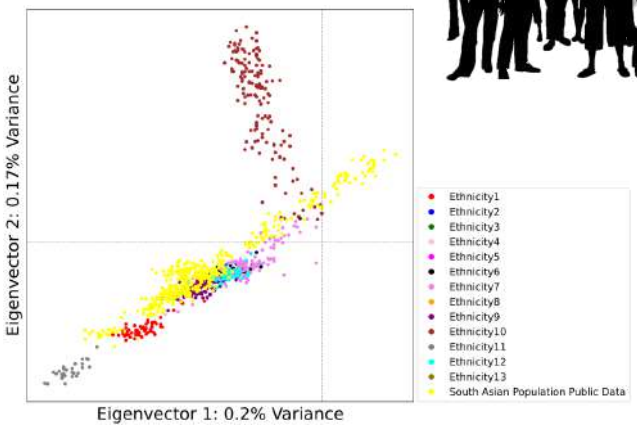
The lab leads CBR's efforts to coordinate the GenomeIndia project wherein one of the main aims is to construct an exhaustive catalogue of genetic variations for our diverse population, by identifying the genetic variations, comprising of, common, low frequency, rare, single nucleotide variations or SNVs, and structural variations, present in Indians through whole genome sequencing (WGS) of representative population groups across the country. These variations data will be made available through a web portal. This is crucial because genetic variations are known to predispose individuals to complex polygenic multifactorial diseases, cause rare inherited disorders, determine individuals' responses to drugs, and help track migration and evolutionary patterns of population groups. The 1.3 billion strong Indian population is extremely diverse with the presence of more than 4500 prominent ethnic groups. Several of these groups follow unique socio-cultural







GenomeINDIA



Genome-Wide association analysis

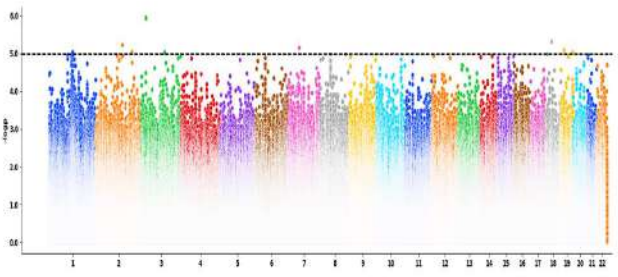


Image credit: Ms. Shreya Chakraborty, Ms. Krithika Subramanian, and others, Prof. Bratati Kahali's lab

practices, like endogamy, and multiple other factors have contributed to the Indian population harboring distinct variations and often many disease-causing mutations to be amplified within some of these groups. Therefore, large-scale sequencing-based variant identification from the Indian population is required to further human genetics research and understand disease susceptibilities in our population. This will help to identify the genetic variations in our population that result in the manifestation of complex diseases such as diabetes, cardiovascular diseases, obesity, and neurodegeneration, among others. The comprehensive list of genetic variations obtained from healthy individuals will serve as a filter for non-causal mutations and help perform genetic studies on monogenic disorders. 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. The results from GenomeIndia will be greatly helpful in predicting the risk of complex diseases and help inform healthcare policies for the nation.

CBR is also involved in population-scale whole genome sequencing data analysis in the Indian population for uncovering the genetic architecture of cognitive changes associated with aging. Cognitive functioning is heritable, with metabolic risk factors known to accelerate age-associated cognitive decline. Identifying genetic underpinnings of cognition is thus crucial. Rare variations (many of which could be novel in the Indian population), copy number variations, structural variations and their susceptibilities towards complex diseases, including dementia, can only be detected through WGS that comprehensively captures genotypes of all ~ 3.2 billion basepairs in the human genome. Therefore, our WGS data analysis will help to identify these genetic variations, and hence discern the genetic architecture of human cognitive changes in healthy aging as well as neurodegeneration, which has been hitherto unexplored in the field of genomics and computational biology for Indians.

The CBR-SANSCOG and CBR-TLSA cohorts comprise mostly cognitively healthy individuals, and some are diagnosed as mild cognitive impaired (MCI) and very few are affected with dementia during the assessments. The genomic characterization of these individuals that are cognitively healthy or MCI at a comparatively older age without developing diseases suggests that healthy aging is a distinct phenotype and that their genetic studies may help us understand the protective genetic factors for cognitive decline and dementia. Moreover, as the individuals are followed every year for a long term and some of them develop dementia, the genomic variations available from these projects' analyses will empower us to decipher the genetic underpinnings of individuals who are predisposed to be affected with cognitive

10,000 Indian genomes to be sequenced by year-end

We have sequenced close to 7,000 genomes and 3,000 of these are already available for public access, says Secretary, Department of Biotechnology

April 07, 2023 08:33 pm | Updated 08:33 pm IST – NEW DELHI

JACOB KOSHY

COMMENTS SHARE READ LATER

Creating a database of Indian genomes means that researchers anywhere can learn about genetic variants that are unique to India's population groups and use that to customise drugs and therapies. | Photo Credit: Bloomberg

https://www.thehindu.com/news/national/10000-indian-genomes-to-be-sequenced-by-year-end/article66710592.ece

> The Genome India Project, a Centre-backed initiative to sequence 10,000 Indian human genomes and create a database, is about two-thirds through. We have sequenced close to 7,000 genomes and 3,000 of these are already available for public access by researchers. We expect the 10,000 genomes to be completely sequenced by the end of the year.
>
> – Dr. Rajesh Gokhale, Secretary, DBT

impairment and should be monitored closely, thus improving the overall healthcare conditions.

While investigating the genetic architecture of cognition in a large-scale single-variant and gene-based association analyses conducted for six neurocognitive phenotypes across six cognition domains in whole-exome sequencing data from >150,000 individuals in a European ancestry cohort, CBR has identified 20 genetic variants that interact with APOE, a significant genetic risk factor for cognitive decline, controlling for lipid and glycemic risks, towards influencing cognition, while controlling for APOE isoform-carrier status and metabolic risk factors. Eighteen of these are novel and implicated in genes that function in biological pathways relevant to oxidative stress, synaptic plasticity and connectivity, and neuroinflammation. Some of these variants exhibit pleiotropic effects on metabolic traits. Further, they exhibit features of mediating effect of metabolic traits on cognition. We have also detected novel pairwise interactions between four of these loci and APOE isoform-defining variants that were not known earlier. The findings also suggest, for the first time, that APOC1 and LRP1 have plausible roles along shared pathways of amyloid beta (Aβ) and lipid and/or glucose metabolism in affecting complex processing speed and visual attention.

In the Indian population too, we are detecting genetic variants relevant to neurodegeneration and having implications for fine-mapping in genome-wide association studies through whole genome-sequencing derived genotypes. Therefore, reliable identification (through genomic analyses) of individuals at risk of development of dementia and the possibility of doing comparative studies in Indian and other ancestry individuals even before the development of clinical features provide a unique opportunity to initiate disease-modifying interventions which can alter the course of the illness and delay the onset of dementia.

On the cover - Harnessing the power of genomics to decipher brain aging:

Human complex traits and diseases such as type 2 diabetes, dyslipidemia, and neurodegenerative disorders are caused with contribution from multiple genetic loci and their interaction with environmental factors. CBR conducts cutting-edge genomic analyses to understand the genetic architecture of cognition and cognitive decline at the population level. CBR is also working towards developing novel tools for such large-scale genetic analyses in the Indian population in the GenomeIndia project.

(Cover image credit: *Ms. Jani Siddhi Pushkarbhai, Prof. Bratati Kahali's lab*)

Understanding the progression of young- and late-onset PD

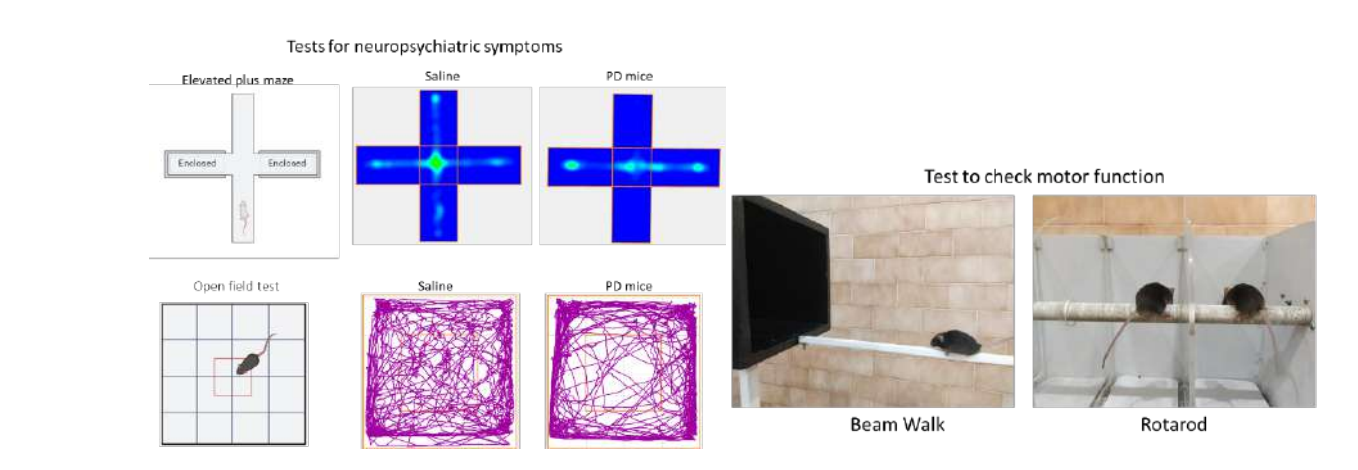
As a Centre whose primary goal is to minimise the burden of neurodegenerative diseases of the elderly population, CBR invests in studying Parkinson's disease (PD), the second most common neurodegenerative disorder typically characterized by uncontrolled movements and impaired posture, balance, and coordination. PD has a prolonged course with slow and gradual progression. It is caused by the degeneration of nerve cells in a part of the brain called substantia nigra, and the loss of the ability to produce a vital neurotransmitter called dopamine. PD typically manifests around the age of 60 and is more prevalent in men than women, with a 50% higher risk.

The 'Young and late-onset Parkinson's disease (YLOPD)' project, spearheaded by CBR, is a longitudinal study funded by the SKAN Research Trust, a public charitable trust set up by the Soota and Karedan families to promote research focused on the treatment of geriatric and neurological diseases. CBR's partnership with SKAN, focusing on research in PD, began in 2021 as a collaborative undertaking between the CBR and the National Institute of Mental Health and Neurosciences (NIMHANS), Bengaluru.

CBR researchers with Mr. Ashok Soota, Chairman/Managing Trustee, SKAN Research Trust

Clinical research studies over the years have shown that people who develop young-onset PD (YOPD) tend to live longer with disease burden compared to late-onset PD (LOPD). The quality-of-life impairment, and hence the potential treatment options, are different in these two scenarios. Growing evidence highlights the importance of better understanding YOPD and LOPD and their impact on a person's quality of life. However, the multifactorial causation, neuroanatomical features, and genetic architecture of YOPD and LOPD are not fully understood.

The YLOPD study, funded by the SKAN Research Trust, aims to recruit 1000 patients with young and late-onset PD and follow them up periodically to study the natural history of disease progression. It involves



Schematics and images from behavioural experiments on mice models of PD

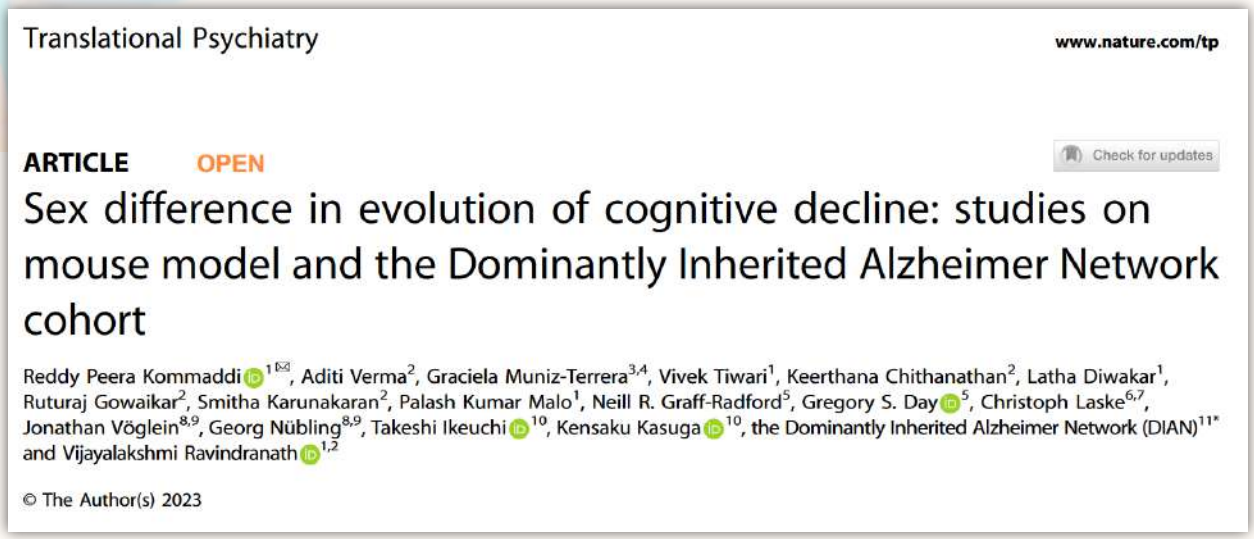
comprehensive multimodal evaluation of clinical, electrophysiological, and cognitive functions, brain and retinal imaging (performed at NIMHANS), genome-wide association and whole genome sequencing, blood-based inflammatory and protein biomarkers, and studies on heavy metal and pesticide exposure with emphasis on differential involvement in YOPD and LOPD (carried out at CBR).

Recent studies indicate that clinical and pathological features of PD are much more than motor symptoms and include neuropsychiatric symptoms, cognitive impairment, and dementia which need to be factored in for PD treatment. There is also a significant degree of interindividual variability in the clinical presentation and rate of disease progression. The YLOPD study is, therefore, focused on linking the insights from clinical literature to an understanding of the molecular underpinnings of the emergence of such behavioural symptoms, especially non-motor symptoms (NMS), and motor symptoms (MS) of PD; this is attempted to be achieved through suitable mouse models. As these mice replicate clinical manifestations and disease progression, they help in strengthening our understanding of the pathological mechanisms that drive PD.

To investigate non-motor symptoms, mice are subjected to a series of behavioural tests such as the elevated plus maze, open field test, and forced swim test. These tests allow us to assess anxiety- and depressive-like behaviours. Tests such as the rotarod test, tail swing test, and beam walk test aid in the assessment of motor coordination and balance in the mice. Data from these experiments, together with those from histopathology analyses and complementary studies, would lead to a comprehensive view of the potential mechanisms of disease progression.

It is hoped that this 'bench-to-bedside' study will shed light on many unanswered questions on PD which can be effectively used to support the implementation of effective interventions and modification of existing treatment protocols.

Publication Spotlight



Translational Psychiatry www.nature.com/tp

ARTICLE OPEN Check for updates

Sex difference in evolution of cognitive decline: studies on mouse model and the Dominantly Inherited Alzheimer Network cohort

Reddy Peera Kommaddi[1✉], Aditi Verma[2], Graciela Muniz-Terrera[3,4], Vivek Tiwari[1], Keerthana Chithanathan[2], Latha Diwakar[1], Ruturaj Gowaikar[2], Smitha Karunakaran[2], Palash Kumar Malo[1], Neill R. Graff-Radford[5], Gregory S. Day[5], Christoph Laske[6,7], Jonathan Vöglein[8,9], Georg Nübling[8,9], Takeshi Ikeuchi[10], Kensaku Kasuga[10], the Dominantly Inherited Alzheimer Network (DIAN)[11*] and Vijayalakshmi Ravindranath[1,2]

The number of women living with Alzheimer's disease (AD) is greater than men, which has been attributed to longer lifespan in women. Women are well protected from neurodegenerative diseases than men prior to menopause; however, when the female sex hormone levels drop abruptly during menopause, the clinical outcomes worsen. Sex hormones serve a critical role in sex-specific brain differences. Although estrogen is a neuroprotective hormone, the molecular mechanisms underlying estrogen's function, social behavioral deficits, and the higher prevalence of AD pathogenesis in women are not fully understood.

Among the molecular mechanisms, the Akt/mTOR signaling pathway plays a crucial role in neurotransmission and synaptic plasticity. Akt/mTOR dysregulation has been observed in AD post-mortem subjects. However, it has not yet been determined how Akt/mTOR signaling pathways regulate activity-dependent new protein synthesis at synapses. Led by Dr Reddy Kommaddi, a study at CBR has attempted to gain a better understanding of the molecular mechanisms

underlying the pathogenesis and progression of AD using a mouse model. We have also analyzed the longitudinal clinical data from the Dominantly Inherited Alzheimer Network (DIAN) study (in which participants carry one of the familial mutations in the APP, PSEN1, or PSEN2 genes) to understand how the mouse model findings translate to humans.

In AD mouse model, a remarkable sex difference in disease progression was observed, with male animals showing early behavioral impairment

that worsens over time, whereas female mice did not exhibit impairments until eight months of age. It is hypothesized that in male mice, where the deficits begin early, the brain would produce compensatory responses. Until menopause, estrogen is neuroprotective and can counteract the pathogenic effects of β-amyloid accumulation. However, there is a substantial difference in disease progression when estrogen levels decrease.

We have also discovered that the age- and sex-dependent dysregulation of Akt/mTOR signaling in AD mice may contribute to behavioral deficits. Therefore, an increase in Akt/mTOR signaling at the synapse may be essential for synaptic plasticity throughout the life span, especially in post-estropausal females.

To evaluate the translational potential to performance in humans with AD, we examined the sex-specific difference in the rate of cognitive decline in the DIAN cohort. We found that the rate of change in performance in cognitive tests (Weschler's logical memory) in mutation carriers showed different trends when the performance was assessed in women versus men as function of age, where men exhibited more rapid cognitive decline than women. Our studies indicate a potential difference in the trajectory of cognitive decline between men and women, especially when the onset of the disease occurs earlier in life before the age of 50 years.

These findings, recently published in Translational Psychiatry, suggest that premenopausal women are protected from memory deficits, that hormone replacement therapy may be beneficial, and that the cost-benefit ratio must be reevaluated in light of the increasing global burden of AD and the disproportionate impact on women.

Please read the full story at https://www.nature.com/articles/s41398-023-02411-8

We conclude that sufficient estrogen levels provide protection in both human and mouse models. Even in the presence of AD mutations, it protects and delays the onset of the disease. A deeper understanding of the signaling pathways is required to identify creative approaches for reducing the adverse effects of hormone replacement therapy.

CSR funding adds impetus to CBR's pursuit

CBR researchers with Ms. Padma Reddy and colleagues from the Software AG team

Software AG India is a prominent arm of Software AG, a multinational enterprise software company headquartered in Darmstadt, Germany. It specialises in digital integration & API management, IoT & analytics, and business transformation technologies. As part of its Corporate Social Responsibility (CSR) initiative, Software AG India has extended generous support to CBR to bolster the latter's mission to minimise the burden of dementia in the elderly population.

The endowment from Software AG India will enable the establishment of a state-of-the-art laboratory to investigate the role of the cardiac autonomic nervous system (ANS) functions in brain aging and dementia risk. The CBR-SANSLab (Software AG Autonomic Nervous System Laboratory) will conduct advanced scientific research and explore the potential of cardiac ANS dysfunction as an early biomarker for dementia and related disorders. It will provide for key assessments such as cardiac autonomic reflex tests, heart rate variability analysis (HRV) ECG, heart rate response to deep breathing, heart rate response to standing or tilt, etc. In essence, the lab's deliverables will perfectly complement the efforts under CBR's

ongoing longitudinal cohort studies of aging.

It is being increasingly felt that public communication of science is important to enhance the impact of research, to generate awareness of contemporary science issues and health challenges, to motivate the next generation of scientists, and to help the public take independent and informed decisions in matters that require scientific knowledge. In this view, two Science-Society partnership initiatives have been envisioned under the aegis of the Software AG Community Outreach Program for Elderly (SCOPE).

(1) Project VIKAS (Visual Infographics, Knowledge, Awareness and workSheets) – Understanding dementia

(2) Project YAAD (Youth and Alzheimer's Dementia) – Empowering the 'future caregivers'

Research work at the CBR-SANSLab and outreach efforts through the SCOPE program will serve to address CBR's multipronged mandate of better understanding the aging brain, preserving cognitive functions in aging, and mitigating the risk and burden of aging-related, neurodegenerative disorders.

"We are happy to support the CBR team's research in this field," says Ms Padma Reddy, COO R&D Operations & Shared Services, Software AG India. "We really hope with such research & awareness sessions we can reduce the occurrence of dementia in the future", she adds.

CBR gratefully acknowledges the immense faith, inspiring vision, and exemplary generosity of Software AG India and looks forward to their constant support and engagement.

Events @ CBR

Since the last *Wave* of *CBR Currents*, it has been an extraordinarily busy and exciting time at the Centre. This section captures highlights of some of the most significant events

Reinforced enthusiasm for aging brain research and innovation

As noted in the Editorial, on 15th February 2023, Pratiksha Trust (co-founded by Mr Kris Gopalakrishnan and Mrs Sudha Gopalakrishnan) kindly signed an MoU with CBR and IISc to continue its acclaimed patronage for fundamental and translational research on brain aging and aging-related brain disorders. Through this MoU, the Pratiksha Trust has generously affirmed its support to CBR in perpetuity, with an initial outlay to the tune of INR 450.27 crore (approximately USD 55 million) over the next 10 years, for research, innovation, and translation. This agreement is viewed as a landmark development in philanthropic support for deep science in India and has further strengthened the Centre's resolve in its mission to reduce the pain, agony, and burden of an important part of our society: the elderly population.

More information on the memorandum is available at https://iisc.ac.in/events/pratiksha-trust-signs-mou-with-iisc-neurodegenerative-disease/

Sharwaree Gokhale Memorial Lecture

A brilliant IAS Officer from the 1974 batch, Ms. Sharwaree Gokhale became the first

woman Collector of Mumbai City and retired as Additional Chief Secretary (Environment) after 36 years of distinguished administrative service. In an admirable gesture of payback and service to society, she bequeathed her sprawling apartment in Mumbai to CBR to promote research in neuroscience. She passed away in January 2016; CBR instituted a lecture series in her memory. The fourth lecture in the series was delivered on 15th February 2023 by Dr. Avindra Nath, Clinical Director, National Institute of Neurological Disorders and Stroke, National Institutes of Health, Bethesda, Maryland, USA.

Dr. Nath is a physician–scientist who specialises in neuro-immunology and neurovirology. His research is aimed at studying pathophysiology and developing treatments for neurological infections. The lecture, attended by faculty and students of multiple departments of IISc, focused on Dr. Nath's research on the role of endogenous retroviruses in brain development and neurodegeneration. Mr. Kris Gopalakrishnan, Chair, Governing Council, IISc, and Prof. G. Rangarajan, Director, IISc participated as the guests of honour.

If you would like to read about Dr. Nath's professional journey and research interests, please visit https://irp.nih.gov/pi/avindra-nath.

Orientation workshop for PhD students

At the core of the CBR ecosystem are its PhD students whose creativity and hard work steer its research projects and other endeavours. With a rapidly expanding student community at CBR, the need for an academic orientation session was strongly felt. On 24th February 2023, CBR organised a half-day workshop to reiterate the goals of the doctoral program and expectations from the students. Prof. Y. Narahari, Director, provided pointers on how to aim for and work towards a world-class PhD at CBR. Prof. Umesh Varshney, Dean, Faculty of Science, IISc, and CBR Research Coordinator, kindly shared his wisdom through tips on how to enjoy research while staying productive. In addition to these motivational talks, the coursework and other academic details of the CBR PhD program were discussed for the benefit of the students. Admission processes for the next batch of enthusiastic students are currently underway; watch this space for updates.

To know more about the PhD program and the courses taught at CBR, please visit https://www.cbr.iisc.ac.in/academics/phd-programme-2/

Interaction with the G20 Finance Minsters' Delegation

CBR had the privilege of contributing to the Deep Tech Showcase to the G20 Finance Ministers' delegation that visited IISc on 25th February 2023 as part of the G20 summit. The event was coordinated by the Centre for Nano Science and Engineering, IISc, and was aimed at facilitating the 72-member delegation's engagement with scientists, tech-innovators, and entrepreneurs pursuing affordable and scalable solutions to significant challenges being faced by G20 member countries. Headed by Ms. Nirmala Sitharaman, Union Minister of Finance and Corporate Affairs, and accompanied by Dr. Kris Gopalakrishnan and Prof. G. Rangarajan, the delegation gained an overview of the vision of CBR and the goals of its flagship research projects.

IISc Director's visit to CBR-SANSCOG Study Centre

CBR Governing Board's Chair Prof. G. Rangarajan (Director, IISc), and Member Prof. Usha VijayRaghavan (Dean, Biological Sciences Division, IISc) kindly visited the CBR-SANSCOG study site in Srinivaspura on 28th February 2023. Accompanied by the Director, faculty members, and scientific officers of CBR, Prof. Rangarajan and Prof. VijayRaghavan were provided with a tour of the field office and updates on the logistics and progress of the study. They also interacted with the scientific officers, clinicians, nurses, and field data collectors who form an integral part of the CBR-SANSCOG study team. They offered valuable suggestions for improving the facilities at the field office and further streamlining its operations.

CBR Showcase at the IISc Open Day

The IISc Open Day is an annual event during which students, science enthusiasts, and the general public have an opportunity to go around the Institute campus and get a flavour of the exciting science and technology initiatives of various departments and centres. This much-awaited and extremely popular event happened on 04th March 2023 and turned out to be a warmly memorable occasion for CBR. For the first time at its new building, CBR organised and hosted a showcase of its research activities and engagement initiatives. This included informative poster presentations on the flagship projects and faculty-centric projects, demonstrations, quiz contests on neuroscience for school and college students, a display of the human brain, a kid's corner, mock clinical and cognitive assessment sessions for elderly visitors, and an interactive session with participants of CBR-TLSA. Over 3,500 members of the public visited CBR and gained an appreciation for its research and innovation efforts. Dressed uniformly in a striking blue, the CBR workforce came together with zeal and relentless energy to inform the public about the Centre's

service to society and to learn from the interactions.

For an overview of the IISc Open Day 2023, please see https://openday.iisc.ac.in/index.php

CBR Genomics Hackathon

On 24th March 2023, CBR conducted its first Genomics Hackathon as a part of its flagship project GenomeIndia. Aimed at spreading awareness of the tools and methods used in human genomics, and at getting students to appreciate the complexities and exciting challenges that genetic data analysis provides, this was a competition where 6 teams of students from institutes across the country were invited to computationally solve a

problem in genomics in 11 hours. The teams implemented statistical/ML methods on a human genomic dataset to attempt to answer questions about disease risk and underlying genetic structure in human populations in this dataset. Dr. Yogesh Simmhan (Department of Computational and Data Sciences, IISc) and Dr. Sridhar Sivasubbu (Institute of Genomics and Integrative Biology, New Delhi) kindly contributed as judges and guests of honour. The winning teams (from IISc, Savitribai Phule Pune University, and Pondicherry University) received attractive cash prizes.

Exploring resonance with Sudha Gopalakrishnan Brain Centre

Sudha Gopalakrishnan Brain Centre (SGBC), located on the IIT Madras campus and supported by Mr Kris Gopalakrishnan and Mrs Sudha Gopalakrishnan, spearheads a

multidisciplinary mission-mode project to map the human brain at the cellular and connectivity levels, with a focus on high-resolution brain imaging. CBR Director and Faculty Members were kindly hosted by SGBC on 26th April 2023. This visit enabled close interactions between the CBR and SGBC teams and provided a platform to explore focused scientific and technical partnerships.

For details of SGBC's mandate, please visit https://www.iitm.ac.in/happenings/press-releases-and-coverages/iit-madras-launches-sudha-gopalakrishnan-brain-centre-power

Neurophysiology training for the CBR workforce

As a training and capacity-building initiative, CBR organised a workshop on neurophysiology for the benefit of its students, scientific officers, and research staff from 2nd to 4th May 2023. The workshop included theoretical lectures and practical sessions handled by internal and external experts. The primary objective of the workshop was to familiarize the CBR fraternity with the state-of-the-art clinical instruments (such as those for electroneuromyography, transcranial magnetic stimulation, transcranial electrical stimulation, and electrocardiography) procured in the recent past and their potential applications for research projects.

Potential partnership with CeNSE

Keen to expand their interface with medical/biological research, and therefore, to collaborate with CBR, the Centre for Nano Science and Engineering (CeNSE), IISc hosted an interactive session for the faculty members on 8th May 2023. The event provided an opportunity for CBR and CeNSE faculty members to know more about each other's research interests and technical expertise. It has set the stage to effectively identify and pursue specific strands of research collaboration and cross-learning.

Reaching out to Bengaluru hospitals

With an urge to expand CBR's interface with the clinical/hospital ecosystem in Bengaluru, CBR organised a half-day event on 12th May 2023. This outreach event titled 'CBR initiative for Collaborative Research in Aging Brain' was attended by more than 30 reputed neurologists, neurosurgeons, neuro-physicians, and medical directors from leading hospitals such as NIMHANS, St. Johns, Apollo, Narayana Hospitals, M.S. Ramaiah Hospital, People Tree Maarga Hospital, and Shri Atal Bihari Vajpayee

Medical College. Prof. Narahari (Director, CBR) introduced CBR's vision and initiatives and Prof. Navakanta Bhat (Dean, Division of Interdisciplinary Sciences, IISc) gave a presentation on the IISc Medical Sciences Program. CBR faculty members presented an overview of research and innovation activities and opportunities for collaboration. This was followed by a guided tour of CBR facilities. The attendees expressed overwhelming interest in exploring avenues for collaboration with CBR.

Distinguished Visitors to CBR

Over the past few months, CBR has been pleased to host several distinguished visitors and invitees, who are well-wishers and potential partners in our research endeavours.

The list includes:

Mr. Natarajan Chandrasekaran,
Chairman, Tata Sons

Mr. S. Ramadorai,
Former CEO, Tata Consultancy Services

Mr. Anand Mahindra,
Chairman, Mahindra Group

Prof. Vinod Menon, Cognitive and Systems Neuroscience Laboratory, Stanford University

Prof. L.S. Shashidhara, Director, National Centre for Biological Sciences

Infrastructure @ CBR

CBR's state-of-the-art infrastructure, which enables advanced research on the aging brain and related disorders, has been made possible with generous core funding from the Pratiksha Trust and support from other organisations (governmental and private) like DBT, DST, Tata Trusts, SKAN Research Trust, India Alliance, and Fidelity Foundation. Through this section of CBR Currents, we hope to inform our readers of the sophisticated research facilities available at the Centre.

Next Generation Sequencing Facility

The nucleotides A, C, G, and T form the genetic code for all life forms on earth. Next-generation sequencing

(NGS) is the process of sequencing DNA or RNA by producing billions of short stretches of nucleotide sequences ("reads") in a massively parallel manner in a short span of time. NGS is also known as deep sequencing and massively parallel sequencing. NGS has reduced the cost per genome significantly, making genomic data more affordable and accessible to individual researchers. By studying the sequence information generated from NGS and comparing them across multiple individuals, it is now possible to identify complex genetic differences that may cause disease and use the findings to advance diagnosis and treatment. The Illumina sequencing systems utilise sequencing by synthesis (SBS) technology and support both single-read and paired-end libraries.

CBR is home to two Illumina next-generation sequencers: MiSeq and NovaSeq 6000, along with the liquid handling system Beckman i5 for automatic rapid library preparation and high-throughput sequencing. This highly advanced setup helps the researchers in CBR and other institutes to apply the benefits of large-scale whole genome sequencing, exome sequencing, and transcriptomics in their research thus enabling world-class discoveries. This NGS infrastructure is integral to the progress of the flagship projects CBR-SANSCOG, CBR-TLSA, and GenomeIndia where breakthrough findings from genome sequencing provide insights into disease specificities of the Indian population.

MiSeq Sequencing System

The MiSeq sequencer is a benchtop sequencer. The Illumina MiSeq system uses SBS technology to sequence DNA fragments. It works on Illumina's 4-channel chemistry and uses non-patterned flow cells. The MiSeq is suitable for small-scale projects such as amplicon or small genome sequencing. Using the latest version of reagents (v3), MiSeq can generate 25 M sequencing reads and 15 Gb of data. This instrument is the only Illumina sequencer capable of generating longest 600bp paired-end reads. Cluster generation, sequencing, and analysis can all be performed on the MiSeq.

Applications: MiSeq sequencer has a broad range of applications like small genome sequencing, miRNA and small RNA sequencing, ChIP-Seq, 16S metagenomic sequencing, targeted gene sequencing, and metagenomics.

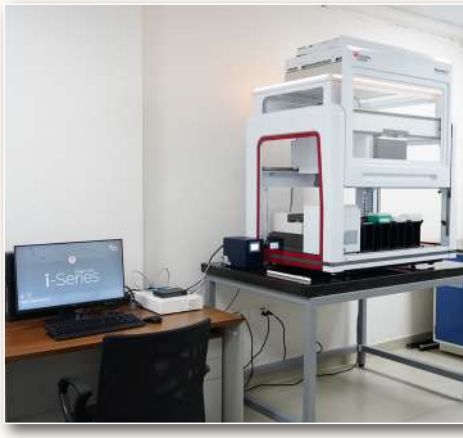
NovaSeq 6000 system

The NovaSeq 6000 is an ultra-high throughput NGS system, providing users with the throughput, speed, and flexibility to complete projects quicker and more economically than ever before. The instrument utilises Illumina's 2-channel sequencing by synthesis chemistry (v1.5), which requires only two images per cycle, and patterned flow cell technology to enable increasing sequence throughput and reduced imaging and data processing time. The NovaSeq 6000 System generates from 80 Gb/800 M reads to 3 Tb/10 B reads of data in single flow cell mode. In dual flow cell mode, output can be up to 6 Tb and 20 B reads in less than two days. The NovaSeq 6000 system enables sequencing of 48 human genomes in ~2 days with comprehensive coverage.

There are four flow cell options to allow a more flexible experiment design according to throughput needs. The NovaSeq 6000 offers two library loading workflows; the standard workflow allows pooled libraries to load into the entire flow cell, while the XP workflow enables the loading of individual flow cell lanes with different library types, thereby expanding flow cell flexibility. Illumina NovaSeq 6000 provides high-quality sequencing data.

Applications: Whole-genome sequencing, whole exome sequencing, transcriptome sequencing, targeted gene sequencing, methylation sequencing, metagenomics, and single-cell RNA-seq.

The Biomek i5 Automated Workstation



The Biomek i5 Automated Workstation is Beckman Coulter's latest addition to its liquid handling portfolio. The Biomek i5 automated liquid handler with enclosure is ideal for medium- to high-throughput workflows. It features an enclosed versatile workspace, LED light that illuminates the workspace, and a multichannel head (96) with a gripper. Its enclosed workspace has 25 deck positions, multicolour status bar, and onboard camera that facilitates remote service. The Biomek i5 has a multichannel head with gripper for 0.5 µL-300 µL pipetting volume ranges, enabling liquid level sensing and 25 deck positions, facilitating simple system operations for medium- to high-throughput workflows.

Applications: Pipetting, dilution, dispensing, PCR and sequencing reaction clean-up, cell-based assays, high content screening, high throughput screening, ELISA, siRNA screening, RNAi screening, phenotypic screening, 3D cell culture, sample prep for mass spectrometry, and library preparation for NGS.

GeneTitan™ Multi-Channel Instrument

The GeneTitan™ Multi-Channel (MC) Instrument for gene expression and genome-wide genotyping seamlessly integrates hybridization, washing, and imaging in a single bench-top machine to provide automated array processing. The imaging device in GeneTitan MC Instrument uses an exter high-intensity xenon lamp and dual excitation and emission filters to captu images from array plates. It supports gene expression studies on 16, 24, an 96 format and genotyping studies on 24, 96, and 384 format array plates. T instrument provides the highest throughput and laboratory productivity b minimising user intervention and allowing unattended, overnight processing of large numbers of samples in parallel.

Applications: Genome-wide association studies by identifying both single nucleotide variations and short insertions and deletions, marker-assisted selection, quantitative trait loci analyses, parentage, and traceability, genomic selection programs, replication studies, candidate-gene association, and targeted genotyping for animal genomics.

Editor: Madhankumar Anandhakrishnan

CONTACT

CBR Office
Centre for Brain Research
Indian Institute of Science Campus
CV Raman Avenue
Bangalore 560012. India.

Tel: +91 80 2293 3588
Fax: +91 80 2360 7766
Email : office.cbr@iisc.ac.in

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LinkedIn