



Centre for Cellular and Molecular Biology, Hyderabad, India

The worst luck in the world? The heart disease mutation carried by 60 million people

Heart disease is the number one killer in the world. It is estimated that the highest death rates in India are associated with problems of the heart and blood circulatory system in people aged 35–64 years. According to a conservative estimate, at least 30 million people suffer from heart diseases in India. By the year 2010, India is predicted to carry 60 per cent of the burden of world's heart diseases.

An international team of 25 researchers led by CCMB Scientists has provided a clue to why this should be so in their recent research, published in the prestigious scientific journal *Nature Genetics* from the United States of America.

There are many causes of heart attack, some genetic and others linked to our lifestyle, but all seemingly complex, hard to pin down, and not yet completely understood. About 20 genes that are implicated in cardiac disease have been identified so far. Of these, Myosin binding protein-C (MYBPC3) is one of the major genes involved in maintaining the structure of cardiac muscle, and regulates cardiac contraction. Mutations in this gene account for about 44% of the sudden cardiac arrest.

Scientists have analysed the DNA (genetic material) of 800 cardiac patients - who were reporting to cardiac Centres at Hyderabad, Madurai, Thirunalveli, Tiruvanandapuram, Kozhikode, Mumbai, Bhubaneswar, Delhi and Chandigarh - along with age and ethnically matched 699 normal individuals. They found that a 25 base pair deletion within the gene making the heart protein MYBPC was significantly more frequent in cardiac patients compared to the normal individuals. In addition, they found that if an individual had both copies of this gene defective (homozygous, containing the 25 base pair deletion), he or she may die at a very early age before reaching 5 years. They confirmed this by analysing post-mortem samples with a history of sudden cardiac arrest. But, if the individuals carry the mutation in only one copy of the gene (heterozygous), they can live without any symptoms of heart problems up to the age of 45; however, beyond 45 years they suffer from a range of effects, including sudden heart attack leading to death. Since the deletion leads to the formation of an abnormal protein, such individuals, therefore, have both abnormal as well as normal proteins. In young people this abnormal protein is degraded efficiently by cellular machinery called the proteasome and carriers thus remain healthy, but as they get older the protein degrading machinery becomes inefficient and leads to a build-up of abnormal protein eventually resulting in symptoms of cardiac problem and leading to sudden heart attack. In order to find out how widespread this mutation is in Indian populations, Scientists screened 6273 randomly selected individuals from 107 ethnic populations, including tribes, castes and sub-castes belonging to all religious groups (Hindu, Sikhs, Muslim, Christian etc.) living across India, and found that about 4% of the individuals studied had this genetic defect (25 base pair deletion in the gene MYBPC3).

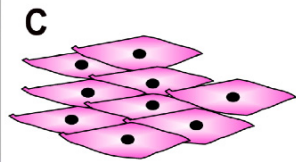
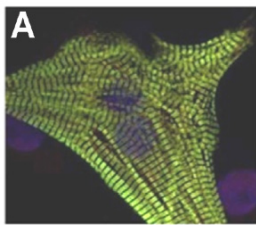
Scientists investigated whether this genetic abnormality is restricted to India or is widely distributed all over the world. They analysed the DNA of an additional 2085 individuals belonging to 70 populations from 26 countries. **They found that this genetic defect is present only in the people of the Indian subcontinent and nearby (India, Pakistan, Sri Lanka, Indonesia and Malaysia) but not in other countries.**

How can such a harmful mutation be so common?

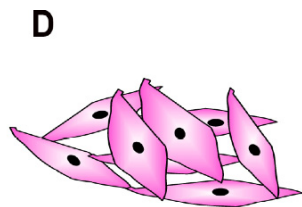
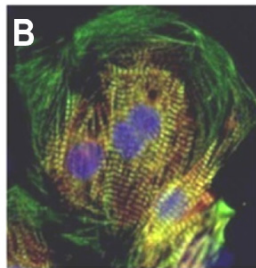
Scientists have estimated that it seems to have originated around 33,000 years ago in India, and spread to Pakistan, Sri Lanka, Malaysia and Indonesia. It has persisted in the population, because its effects usually develop only after people have had their children.

The lifetime risk of developing heart failure is roughly one in five for a person aged 40 years. Now that the defect has been identified, there is a new glimmer of hope. It could be detected very early during pregnancy. If parents choose, a foetus having two copies of the defective gene (homozygous) could be aborted after genetic counselling. Carriers of the defect could be identified at a young age by genetic screening and advised to adopt a healthier lifestyle. **Perhaps eventually new drugs could be developed to enhance the degradation of the abnormal protein and postpone the onset of symptoms. Cardiac stem cell transplant might in the future be used very effectively to expand the lifespan of the individuals who carry the deletion.** There is a market of 60 million people waiting for such therapy.

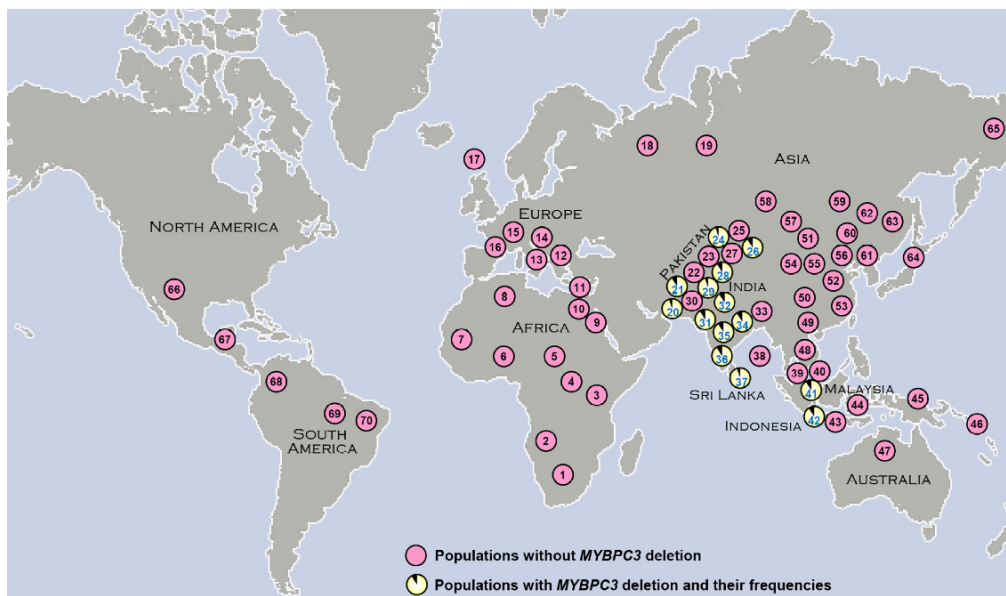
Eventually, with suitable therapy, such individuals may fully recover from the disease and live a long and normal life. For us this is most exciting and is a matter of great happiness that we have discovered something which is going to help mankind, particularly people in India, Pakistan, Sri Lanka, Malaysia and Indonesia. The estimated number of people at risk from heart disease due to this mutation is about 60 million, i.e. 1% of the world population.



A – Muscle fibres in heart cells under normal condition showing striated pattern due to systematic arrangement of cells (Schematic structure shown in C)



B – Muscle cells in the heart having mutation showing disrupted pattern (Schematic structure shown in D)



Global distribution of deletion of 25 base pairs of the heart protein gene MYBPC3 in indigenous populations.

Notes to Editors

Publication Details

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Selected Websites

<http://www.dawn.com/2008/04/25/int12.htm>

The Centre for Cellular and Molecular Biology (CCMB), Hyderabad, India, is one of the constituent national laboratories of the Council of Scientific and Industrial Research [CSIR](#), the premier multidisciplinary Research & Development organisation of the Government of India. It was set up as a semi-autonomous Centre in 1977 in Hyderabad, the capital city of Andhra Pradesh, became a full-fledged national laboratory during 1981-82, and was dedicated to the nation on 26 November, 1987 by the then Prime Minister of India late Shri Rajiv Gandhi. The ongoing research programmes at the CCMB are in three major categories - high quality basic research in the frontier areas of modern biology, research relevant to societal needs, and application-oriented research towards commercialisation. These include the areas of biomedicine & diagnostics, evolution & development, gene regulation in prokaryotes and eukaryotes, host-parasite interactions, membrane biology, protein structure, bioinformatics, functional genomics, theoretical biology, etc. CCMB has also taken lead in the dissemination of modern biological information through popularisation of science, science education in schools, and has been a meeting point for art and science.

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Madurai Kamaraj University, Madurai, India, established in 1966, has 18 Schools comprising 73 Departments. The Directorate of Distance Education of the University has a student strength of about 130,000. The University has 109 affiliated Colleges (9 Autonomous) including other approved institutions and 7 evening colleges. There are centres which promote research potential of teachers. Extension activities are carried out through Department of Youth Welfare, NSS, SC/ST cell and Adult Education programmes.

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The Wellcome Trust Sanger Institute, Hinxton, Cambs. CB10 1SA, UK, receives the majority of its funding from the Wellcome Trust, was founded in 1992. The Institute is responsible for the completion of the sequence of approximately one-third of the human genome as well as genomes of model organisms and more than 90 pathogen genomes. In October 2006, new funding was awarded by the Wellcome Trust to exploit the wealth of genome data now available to answer important questions about health and disease.

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