

FOR more than 70 years and over four generations, a Pune-based family had been struggling with cancer, losing at least six members to it. The coincidence was heart-breaking, but they never thought it was more than just that—a coincidence. Till early 2011, when tests at the cancer unit of Mumbai's Tata Memorial Hospital showed that what the family had was hereditary cancer.

First the immediate relatives of the deceased were tested, then extended and then yet more distant kin, from the ages of five to 65, till the count worked out to 21 till June 2011. Eleven of the 21 tested carried a mutation of the gene 'RET oncogene' that was being passed down successive generations. All 11 of them were diagnosed with tumours. While none of them had cancer at that stage, nine of the 11 had their thyroid and parathyroid glands removed, while the adrenaline gland tumour was removed in one patient. The first diagnosed case succumbed to cancer before a surgery could be performed.

The Tata Memorial Hospital's genetic oncology wing has other such cases, of mutations being inherited, of families with a string of members dying of the same type of cancers, and of their relatives battling desperately against despair.

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It was in November 2010 that a 30-year-old from the Pune family first came to the Tata hospital with advanced Multiple Endocrine Neoplasia (MEN) syndrome, that causes cancers of thyroid, adrenaline and pituitary glands, as well as benign nodules on the lips, tongue and eyelids. Doctors told him he was beyond the stage of a surgical remedy. Though chemotherapy was started, he breathed his last in May 2011.

Struck by how young the victim was, the doctors sensed they might be looking at something different when his mother let slip during a conversation that his two paternal uncles as well as an aunt and a great grandfather had all died of "unknown reasons" in their late 20s or early 30s. The great grandfather had died in 1950, the uncle in 1962, and another uncle and aunt in 1982 and 1998, respectively.

Soon after the 30-year-old's death, the family was referred to the genetic oncology wing. His uncle, a professor of mathematics at Pune University, says, "His parents (my sister and her husband) were the first to be explained that there was possibility of a genetic mutation running in the family."

Tests soon corroborated what was then still just a theory. "Inheritance is associated with the virtues of wisdom, wealth or good looks," says the uncle. "But how do you deal with the inheritance of a disease? Especially when it is seen as instant death?"

Having established the hereditary nature of the illness, doctors began the exercise of convincing family members to get tested, with the help of "genetic counsellors". They started with the immediate family members of the deceased, who in turn contacted their extended family.

Many were reluctant at first, but the victim's parents persisted. "There were conference calls; they were very persuasive. It must have been terribly hard for them to do all this so soon after losing their own son, but I think they had decided that knowing was better than living in oblivion," the professor says.

Tests took place over six months from June 2011. The 11 of the 21 who tested positive for a mutated 'RET oncogene', who were between the ages of 14 and 56, all carried MEN's II tumours.

There are two kinds of genes associated with cancers—oncogenes and tumour suppressors. Oncogenes are genes that regulate the normal growth and division of a cell. If these genes mutate, they can cause widespread cell divisions, leading to cancer. Tumour suppressor genes, on the



NARENDRA VASKAR

# The inheritance of a disease

The first such data for India put together by Tata Memorial Hospital shows some cancers as hereditary, affecting families down generations, striking them young. **PRITHA CHATTERJEE** reports

other hand, contain codes to protect the body from cancer, or to prevent uncontrolled cell division. Sometimes, these genes get deactivated and end up causing cancers.

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From available medical records and family accounts, the doctors pieced together a family tree, or a pedigree of the disease in medical terms. Explains a family member, "My great grandfather passed this mutation on to three of his four children, who in turn passed it on to some of their children. We now have a map—something definitive."

Those who tested positive but did not have the cancer were put through another round of counselling before they agreed to excise the organs that could contract the disease. The surgeries were held between June and August 2012.

"Effectively, this cancer was prevented in 10 of our loved ones, and the other 10 who did not test positive now know that despite being genetically predisposed, they are not likely to get the disease. Not only did we find the key to this mystery, but after 70 years, we can finally control it," the professor says.

However, two arms of the family—a sister from the first generation, and one from the fourth generation—did not agree to the genetic test. Three people related to the former have now started to show symptoms of MEN's II tumours.

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Delhi-based Payel Bhattacharya wishes she had the power of such knowledge. When she was three, the



NARENDRA VASKAR

(Top) Patients outside a research lab of Tata Memorial Hospital in Mumbai; Dr Rajiv Sarin, head of the hospital's genetics cancer department

first symptoms of what was eventually diagnosed as a rare hereditary illness—Von Hippel-Lindau syndrome—first started surfacing. She carries a mutation of the VHL gene that causes the gene that's meant to suppress tumours to result in tumours in several organs, including the brain and spine, kidneys, liver, eyes, ears and genital tract. The tumours could be malignant or benign.

Now 33, Payel has undergone nine surgeries for tumours all over her body, including one open-brain procedure and a liver transplant. Latest scans show two more tumours in her brain. She has also been diagnosed with multi-drug-resistant tuberculosis.

"My doctors have advised radiotherapy for the new tumours, but I don't have the money. I have been making online appeals," she says. An appeal made to the PMO for funds was turned down.

Dr Aditya Gupta, a senior neuro-

surgeon at Medanta Medicity and a former faculty member at AIIMS, who operated on Payel's brain tumours, says, "The genetic mutation causes new tumours to surface every few years and they are tough to manage because they have very rich blood supply. Unless they are removed, they can cause internal bleeding in retinal tumours or the ones in the brain."

Though Payel gave her DNA samples for testing at AIIMS for a special research project, under which genetic tests were being performed for free, the project fell through and her diagnosis could never be confirmed genetically. With her father's death in 2010, that door closed.

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According to Dr Rajiv Sarin, head of the genetics cancer department at Mumbai's Tata Memorial Hospital, "Cancers from these mutations have certain characteristics that distinguish them from non-hereditary can-

cers. They spurt at very young ages—patients may be in their early 20s or 30s. It also makes patients prone to developing other cancers, at other sites, once the primary tumour is treated. Often paired organs like both breasts or kidneys get affected."

In India, there is still no organised study on genetic cancers. Studies in Caucasian populations show 2-5 per cent of all cancers are hereditary. If you extrapolate from this data, says Dr Sarin, of the one million new cancer cases occurring in India annually, 50,000 Indians may be suffering from familial cancers, requiring specialised genetic counselling and treatment.

The first round of counselling involves mapping the disease over successive generations. Immediate members of the family who share the patient's gene pool then are urged to take the genetic test. For those who are confirmed to be mutation carriers, regular screening is advised, as well as advanced tumour marker testing in blood, to detect cancer at an early stage.

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The largest cancer hospital in Asia, Tata Memorial Hospital has been providing free genetic tests to families suspected to have hereditary cancer since 2007 under a joint project with the Indian Council of Medical Research. The programme has identified over 1,700 Indian families nationwide with hereditary cancers.

With the programme completing its first leg, the hospital is expected to soon start documenting their findings in peer-reviewed journals, on different mutations within sub-groups of the Indian populations, their interpretation and psychological and social impact of the disease on families.

Listing the problems, Dr Sarin says, "Often medical records of deceased members, especially those who died two-three generations earlier, are not maintained. Patients can at best tell us that they remember a grandfather or a parent dying of symptoms which we may deduce to be of the same or similar cancers as in the index cases."

The lack of enough data has another aspect. "We know there is some mutation, but we cannot accurately say whether it is harmful or not," Dr Sarin says.

Still, the hospital has identified communities like the Konknanastha Brahmins who could be predisposed to genetic cancer. Soon tests will be performed in community temples of this group.



Payel (right) has had 9 surgeries, is suspected to have inherited illness

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In many cases, genetic tests confirm hereditary mutations long after the patient has been cured. Does the knowledge inhibit leading a normal life?

Ask this 31-year-old. Her mother passed away from ovarian cancer years ago. In 2004, at the age of 22, she was detected with breast cancer. "During this period, my maternal uncle's daughter was also diagnosed with breast cancer and died soon after," she says. It took a year of chemotherapy, radiotherapy and surgery for her to be declared cured of cancer.

She was referred to the genetic oncology wing after her treatment was completed. "Back then, the relief of being cured of cancer was such that we did not dwell too much on this," she explains.

Life went on. She started working as a Marathi TV journalist, and marriage with her long-time boyfriend was on the anvil. Then, in 2005, a telephone call from the hospital almost brought everything to a standstill. She had tested positive for the BRCA 1 gene mutation that made the body susceptible to breast and ovarian cancers. "It was a big jolt, since in my mind, I was cured of cancer," she says.

Now, more than six years have passed. Her sister does not have the mutation, but her maternal uncle has tested positive. She is still trying to convince other relatives from her mother's side to take the test.

Most importantly, she is in a good job and is married to the man she loves. Her husband underwent genetic counselling with her doctors before they got married. "We know that when we have children, they will have a 50 per cent chance of inheriting this genetic mutation, but that helps us be prepared. Besides, it's only a 50 per cent chance," she adds.

She has to go in for follow-up every few months, but it is now a part of life, she says. "I need to make sure we catch the cancer early, if at all it happens."

## Living with cancer, and laughing with it

A Nagpur doctor talks about the cancer-causing gene that killed seven of their relatives

VIVEK DESHPANDE

LOOKING at the computer printout of her family tree, 65-year-old Dr Nirmala Vaze points to her 40-year-old daughter Sampada Peshve. "In all, seven of our 10 affected kin have died of cancer. Only the two of us are alive," she says. As the two laugh out loudly, Vaze corrects herself: "No, no, actually three (pointing to a third

name in the paper)."

A gynaecologist and obstetrician, Vaze finds nothing extraordinary in the fact that she can laugh about the disease or how it has affected their family. "We have always been absolutely open about it. There is nothing like social stigma here," she says. "When we were called by the Tata Memorial Hospital for gene testing, 35 of our kin got tested."



Dr Nirmala Vaze, daughter Peshve have had two bouts of cancer each

The tests showed two men of the family carried the gene, apart from Vaze and Peshve, having inherited it from the maternal side of Vaze's family, the Bhaves. The seven Bhave family members to have died of the disease so far have all been women. They died between 1972-2011, two

of them after dual episodes of cancer.

The mother and daughter have a sub-type of the cancer-causing BRCA gene, called Ashkenazi, generally associated with Jews of East Europe. "Konkanastha Brahmins are now known to be more susceptible to hereditary cancer caused by BRCA genes," Vaze notes.

She and Peshve have both survived two bouts of breast cancer each. Vaze first had the cancer in 1988 and then after a long gap in 2005. Each time, she underwent two-year-long treatments comprising surgery, chemo and radio therapies, while handling work at her Nagpur hospital.

Peshve was first diagnosed with breast cancer just a month after her marriage in 1999, and later in 2008.

About convincing her family members to get screened for the

BRCA-1 and BRCA-2 gene mutations associated with breast cancer, Vaze says the task was tough with her elder sisters. "People are so scared that even the power of knowledge that you are predisposed to it does not help," she admits.

Her son Amol, 38, has tested negative for cancer. Vaze says it is for the doctors to find out why the disease was fatal only for women members of the family.

Peshve adopted a girl rather than going in for a biological child who would carry the risk of inheriting cancer. Gargi, her daughter, is now four.

The first victim in Vaze's maternal family was her maternal uncle Padmakar Bhave's daughter Rupini in 1972, who had ovarian cancer. Two years ago, Rupini's granddaughter succumbed to the disease at the age of 20. Rupini's

sister Saroj and one of Saroj's daughters, Manju, also died of cancer. Vaze's sister Kishori Deshpande died of ovarian cancer in 1984 at the age of 41. Saroj's other daughter Varsha is among the three women of the Bhave family to have escaped death.

Vaze has used her own experience to help others, through counselling and newspaper articles. Her awareness campaigns have come to be supported by agencies such as the Obstetrics and Gynaecological Society, National Association for Reproductive and Child Health of India (of which she is the national vice-president) and Indian Menopause Society.

"Many people now come to me saying they have fought cancer successfully due to me," she says. "I myself started looking at life more positively after the two cancers."