MedicalXpress

Leukemia-associated mutations almost inevitable as we age

February 26 2015

It is almost inevitable that we will develop genetic mutations associated with leukaemia as we age, according to research published today in *Cell Reports*. Based on a study of 4219 people without any evidence of blood cancer, scientists estimate that up to 20 per cent of people aged 50-60 and more than 70 per cent of people over 90 have blood cells with the same gene changes as found in leukaemia.

Scientists investigating the earliest stages of cancer development used an exquisitely sensitive sequencing method capable of detecting DNA mutations present in as few as 1.6 per cent of blood cells, to analyse 15 locations in the genome, which are known to be altered in leukaemia. By comparing their findings with other research conducted with a lower degree of sensitivity over whole exomes, the scientists were able to conclude that the incidence of pre-leukaemic cells in the general population is much higher than previously thought and increases dramatically with age.

"Leukaemia results from the gradual accumulation of DNA mutations in blood stem cells, in a process that can take decades," explains Dr Thomas McKerrell, joint first author from the Wellcome Trust Sanger Institute. "Over time, the probability of these cells acquiring mutations rises. What surprised us was that we found these mutations in such a large proportion of elderly people. This study helps us understand how aging can lead to leukaemia, even though the great majority of people will not live long enough to accumulate all the mutations required to develop the disease."

The pre-leukaemic mutations studied appear to give a growth advantage to the cells carrying them and this starts a process in which cells with these mutations dominate blood making. As they increase in number, the likelihood that one or more of them will acquire more mutations becomes greater, something that could eventually lead to leukaemia and leukaemia-like disorders. Interestingly, the study found that mutations affecting two particular genes, SF3B1 and SRSF2, appeared exclusively in people aged 70, suggesting that these mutations only give a growth benefit later in life, when there is less competition. This finding explains why myelodysplastic syndromes, a group of leukaemia-like conditions associated with these genes, appear almost exclusively in the elderly.

None of the 4219 people studied were found to have a mutation in NPM1, the most common acute leukaemia gene mutated in up to 40 per cent of cases. This unexpected result suggests that mutations in NPM1 behave as gatekeepers for this cancer; once a mutation in this gene occurs in a cell with particular previously accumulated pre-leukaemic mutations, the disease progresses rapidly to become leukaemia.

"The significance of mutations in this gene is astonishingly clear from these results: it simply doesn't exist where there is no leukaemia," says Dr Naomi Park, joint first author from the Sanger Institute. "When it is mutated in the appropriate cell, the floodgates open and leukemia is then very likely to develop. This fits with studies we've conducted in the past in which we found that the gene primes blood stem cells for leukaemic transformation."

Leukaemia serves as a useful model for research into the origins of cancer because blood samples are much easier to obtain than tissue samples. Each cancer begins with a single mutation in just one cell; this research allows scientists to look at how these first mutated cells accumulate to form cancer.

"Ultra-deep sequencing has allowed us to see the very beginnings of cancer," says Dr George Vassiliou, senior author from the Sanger Institute and Cambridge University Hospitals NHS Trust. "These mutations will be harmless for the majority of people but for a few unlucky carriers they will take the body on a journey towards leukaemia. We are now beginning to understand the major landmarks on that journey."

More information: *Cell Reports*. DOI: 10.1016/j.celrep.2015.02.005

Provided by Wellcome Trust Sanger Institute