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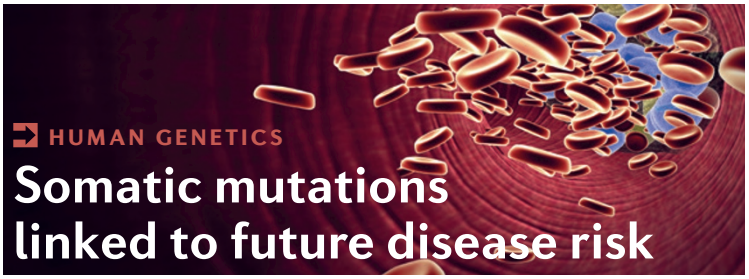

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> somatic mutations were associated with future development of cancer

Detecting somatic mutations that affect cancer driver genes in precancerous cells could inform early clinical interventions. Two exome sequencing studies have now identified the frequent age-dependent clonal expansion of somatic mutations in the human haematopoietic system that is associated with an increased risk of future haematopoietic malignancies and other illnesses.

In the largest studies of their type to date, Jaiswal *et al.* and Genovese *et al.* carried out whole-exome sequencing on blood samples from 17,182 and 12,380 people, respectively, who had no clinically apparent haematological pathologies. Somatically acquired driver mutations were identified by two complementary approaches. Jaiswal *et al.* focused on scanning known haematological malignancy driver genes for pathogenic mutations. By contrast, Genovese *et al.* looked broadly for somatic variants that were at sufficient allelic frequency in the blood (~10–20%) to suggest that they provided a proliferative advantage to haematopoietic cells to result in their clonal expansion, but that were still below the 50% frequency expected from a heterozygous germline variant.

Both teams found that the most frequent mutations were in three chromatin-related genes: DNA methyltransferase 3A (*DNMT3A*), TET methylcytosine dioxygenase 2 (*TET2*, which is involved in DNA demethylation) and the Polycomb group gene *ASXL1*, which maintains repressive chromatin. Interestingly, the mutation frequencies increased with age — mutations in any of these genes were found in ≤1% of people under 50 years of age, but in ≥10% of people aged more than 65 years.

Crucially, somatic mutations were associated with future development of cancer: where they were present, there was a >10-fold increased risk for subsequent haematological malignancies. Somatic variants also increased the risks of non-cancerous adverse events and death; for example, Jaiswal *et al.* identified an increased risk of coronary heart disease and stroke, albeit through unknown mechanisms.

Genovese *et al.* also sequenced cancer cells from three study participants who subsequently developed haematological malignancies. The cancer cells harboured the same mutations that were detected at the presymptomatic stage, as well as further acquired mutations. This finding is consistent with the mutant cells detected in healthy individuals being genuine premalignant cells that can progress to cancer through further mutagenesis.

Despite their findings, both teams caution against immediately adopting such mutational testing as a clinical screening tool in healthy individuals. The presence of mutations in a given individual has only limited predictive power, as conversion to haematological malignancy was rare regardless of mutation status (even for mutation carriers only ~1% progressed to malignancy per year). Moreover, there is currently a lack of a preventive therapy to slow the growth of any detected mutant clones.

As the mutations in these studies affect chromatin-related genes, it will be interesting to determine whether chromatin profiling techniques could enhance the predictive value of the mutation screening by assessing the extent to which the mutations in precancerous cells have resulted in aberrant chromatin states.

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ORIGINAL RESEARCH PAPERS Jaiswal, S. *et al.* Age-related clonal hematopoiesis associated with adverse outcomes. *N. Engl. J. Med.* http://dx.doi.org/10.1056/NEJMoa1408617 (2014) | Genovese, G. *et al.* Clonal hematopoiesis and blood-cancer risk inferred from blood DNA sequence. *N. Engl. J. Med.* http://dx.doi.org/10.1056/NEJMoa1409405 (2014)