

GENETICS, NOTEWORTHY

# A LONGE FUSE

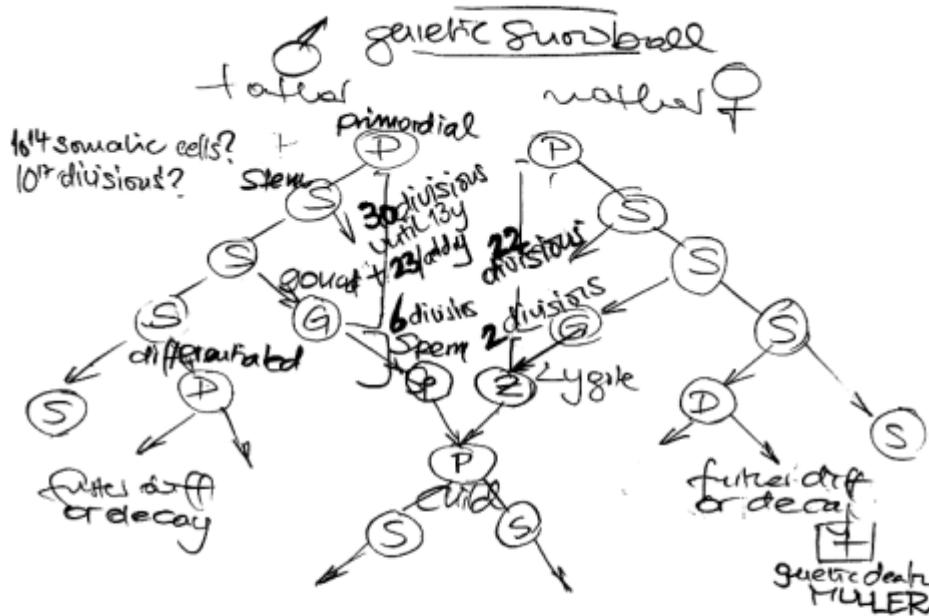
12.01.2007

Mutation accumulation in the human genome is a largely neglected research field. Most mutations have a very small effect (if any) and may be compensated by environmental improvements. I have already argued in that way in my [2003 Triple T](#) paper and will reiterate it soon in PLOS medicine (just found that James Crow [1997 in PNAS](#) and [2000 in nat gen rev](#) had the same opinion). In principle, the improvement of sanitation and better medical care is leading to a retention of mutations that would be otherwise subject of purifying selection.

Another important factor seems to be the increase of parental age in Western societies. A 20 year old man had about 150 chromosome replications while a 40 year old had about 610 replications. To count the number of your somatic mutations, you need to add all events of your lifetime plus the age of your father at birth minus 9 months ... Even with the high fidelity of polymerases, DNA replication remains an error prone process leading eventually to an increase of germline mutations (as may be seen with achondroplasia, Apert syndrome, neurofibromatosis and prostate cancer). With the increasing age of fathers we are now nearly doubling the absolute number of mutations every generation – and we keep them in the pool in contrast to previous centuries. Crow in PNAS 1997 even said

I do regard mutation accumulation as a problem. It is something like the population bomb, but it has a much longer fuse

CROW 1997/2000  
STRACHAN



mutations extrapolated for earlier gene data  
for 50 year old man

$$1.7 \times 10^{-8} \times 25000 \times 20 \times 23 \times 70$$

less estimate from textbooks may be even more  
 $1.7 \times 10^{-6}$

as there is 1 extra division per gene per year  
 $20 \text{ years in 50 years}$   
 $10^{-1000} \text{ mutations}$

rather higher numbers, may be corrected by selection and  
 development of incompatible mutations  
 at least we are largely mosaics (6) sufficient cases

## Addendum 20 Nov 2013

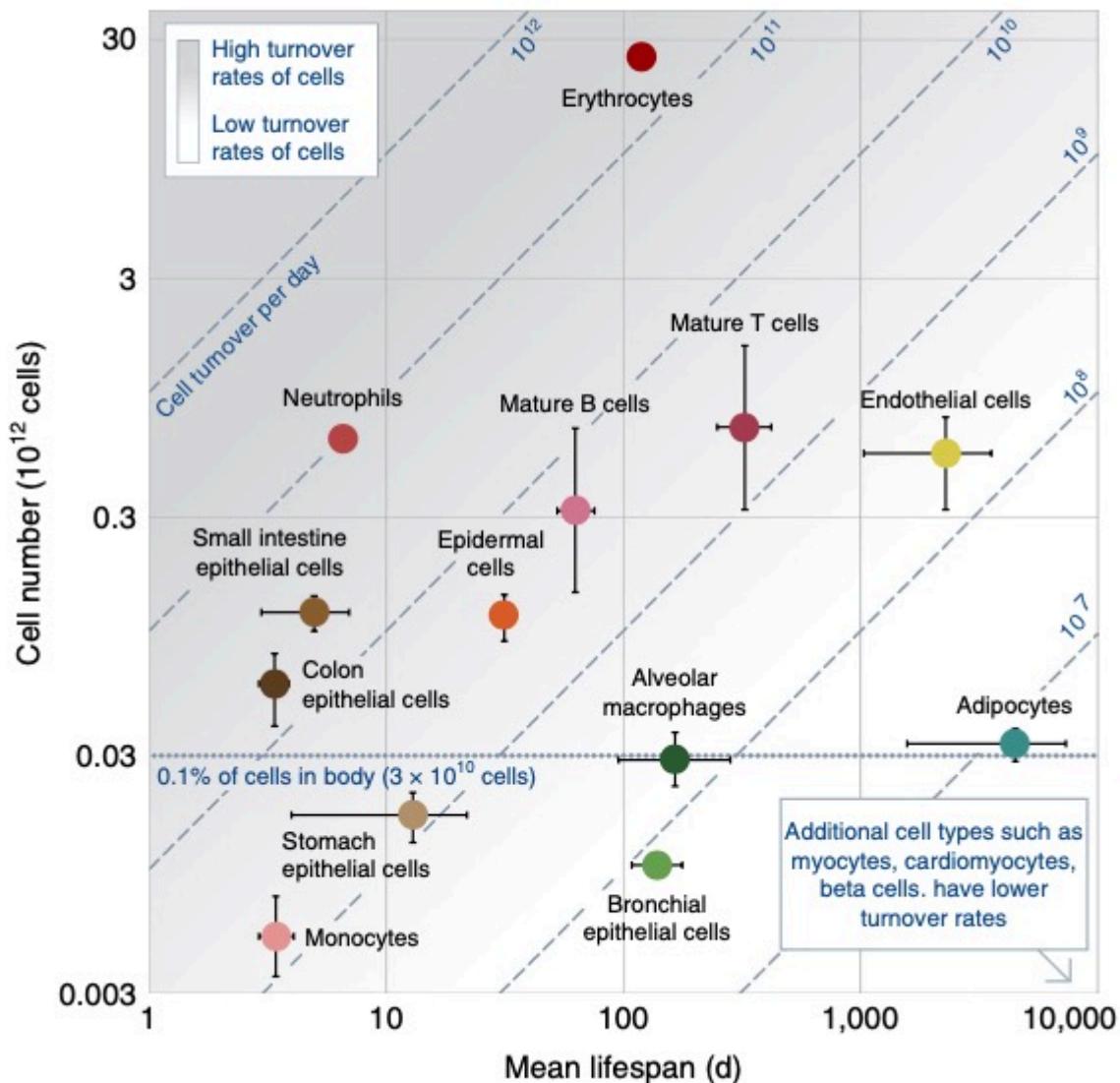
In another post, I detailed the [3,93 figure](#) derived from cancer tissues. The best human estimate at the moment is in this [Cell paper](#) that shows a rate between  $2.0$  and  $3.8 \times 10^{-8}$  cells. Sperm sequencing may not represent a good model as there are too many degenerate cells.

## Addendum 1 Jan 2021

Here is a new [nature medicine paper](#) on cell turnover.

What I do not understand - shouldn't we have a much higher leukemia rate in the population? [Leukemia is only on the 11th place](#).

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Addendum 29 Apr 2021

Another [Nature study](#) shows

Differentiated cells in blood and colon displayed remarkably similar mutation loads and signatures to their corresponding stem cells, despite mature blood cells having undergone considerably more divisions. We then characterized the mutational landscape of post-mitotic neurons and polyclonal smooth muscle, confirming that neurons accumulate somatic mutations at a constant rate throughout life without cell division, with similar rates to mitotically active tissues ...

this could be the answer to my previous question

These mutations may result from the interplay between endogenous DNA damage and repair that occurs in cells at all times. The similar mutation burden and signatures in granulocytes and haematopoietic stem cells, despite a different divisional load, could also be consistent with a time-dependent rather than a division-dependent accumulation of somatic mutations during haematopoiesis

although it will need independent corroboration before making any conclusion that damage repair is more important than replication.