Rate of de novo mutations and the importance of father's age to disease risk.

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Journal Club

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At 500,000 years, the dating of this skull of *Homo heidelbergensis* clashed with previous DNA dates for Neanderthal origins.

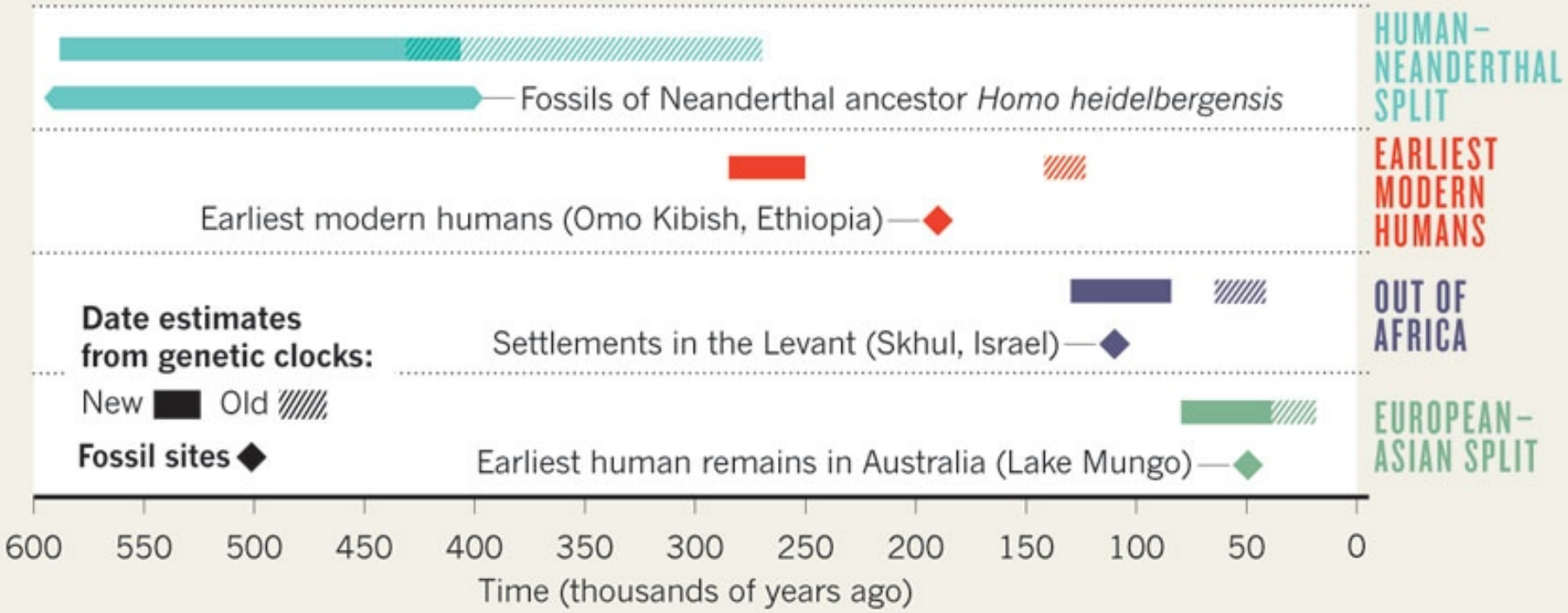
ANTHROPOLOGY

Studies slow the human DNA clock

Nature News “Studies slow the human DNA clock” by Ewen Callaway 18 September 2012

BETTER AGREEMENT OVER THE HUMAN STORY

Dates estimated from DNA evidence conflicted with those from fossil sites that document key events in prehistory, but dates gained using a slower DNA clock are resolving some conflicts.



Kong, A. et al. Mutation rate $1.2*10^{-8}$

“Rate of de novo mutations and the importance of father’s age to disease risk”

Nature 488, 471–475 (2012)

Sun, J. X. et al. Mutation rate $1.82*10^{-8}$

“A direct characterization of human mutation based on microsatellites”

Nature Genet. http://dx.doi.org/10.1038/ng.2398 (2012).

Samples

- Sequencing project in Iceland
- 78 trios, 219 individuals, 30X coverage
- 44 offspring autism spectrum disorder
- 21 offspring shizophrenic

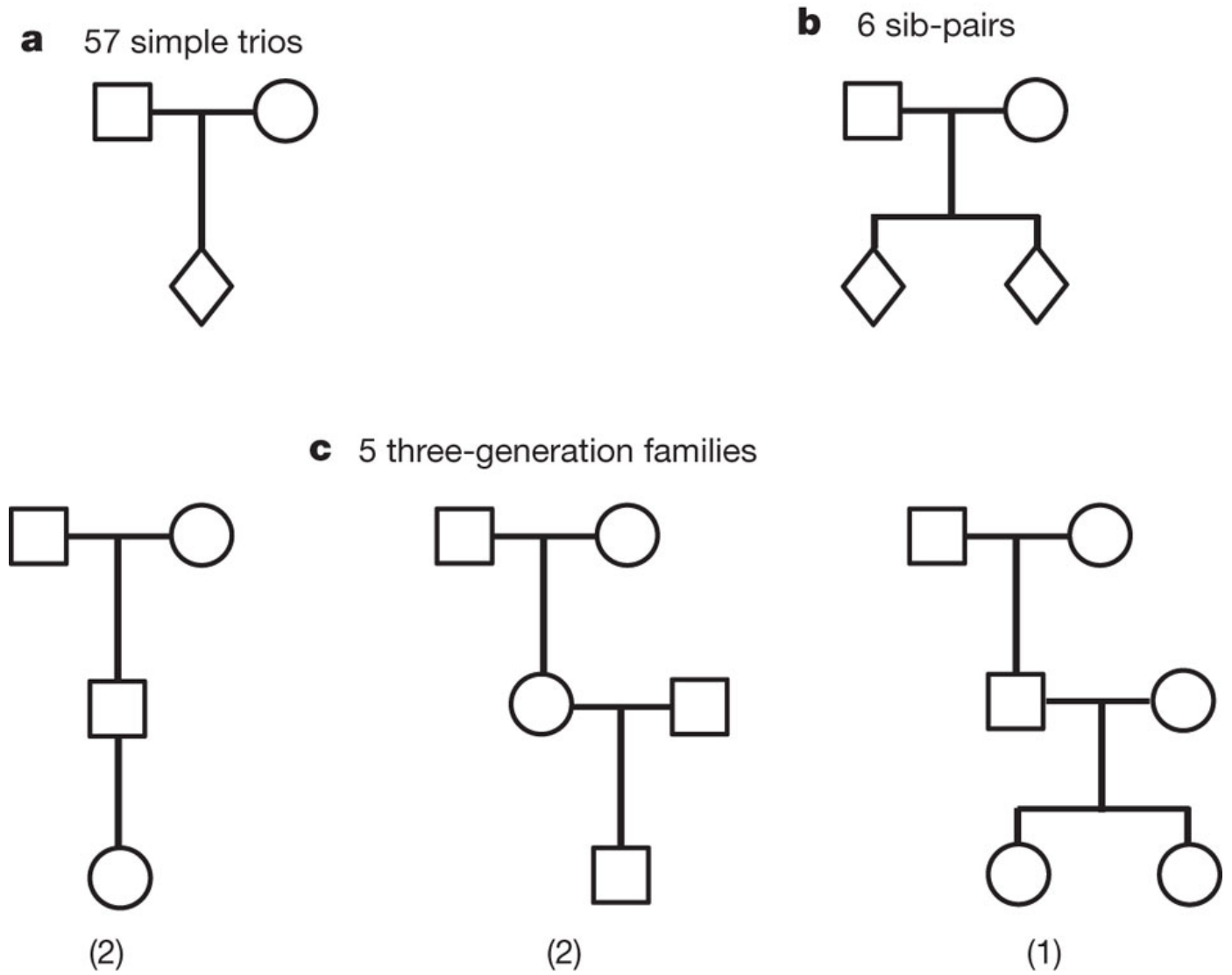
- Additional 1859 as population samples (all at least 10x, 469 more than 30x)

Number of de novo mutation

- After filtering 6221 candidate de novo mutation
- After extra filtering 4933 de novo mutation (average 63.2 per trio)

- GATK software
- Validated randomly 111 mutation (11 primer design failure, 6 no results, 93 confirmed)

A summary of the family types.



a, Fifty-seven simple trios. b, Six sib-pairs accounting for 12 trios. c, Five three-generation families accounting for nine trios.

Table 1 | *De novo* mutations observed with parental origin assigned

			Number of *de novo* mutations in proband		
	Father's age (yr)	Mother's age (yr)	Paternal chromosome	Maternal chromosome	Combined
Trio 1	21.8	19.3	39	9	48
Trio 2	22.7	19.8	43	10	53
Trio 3	25.0	22.1	51	11	62
Trio 4	36.2	32.2	53	26	79
Trio 5	40.0	39.1	91	15	106
Mean	29.1	26.5	55.4	14.2	69.6
s.d.	8.4	8.8	20.7	7.0	23.5
Variance	70.2	77.0	428.8	48.7	555.3

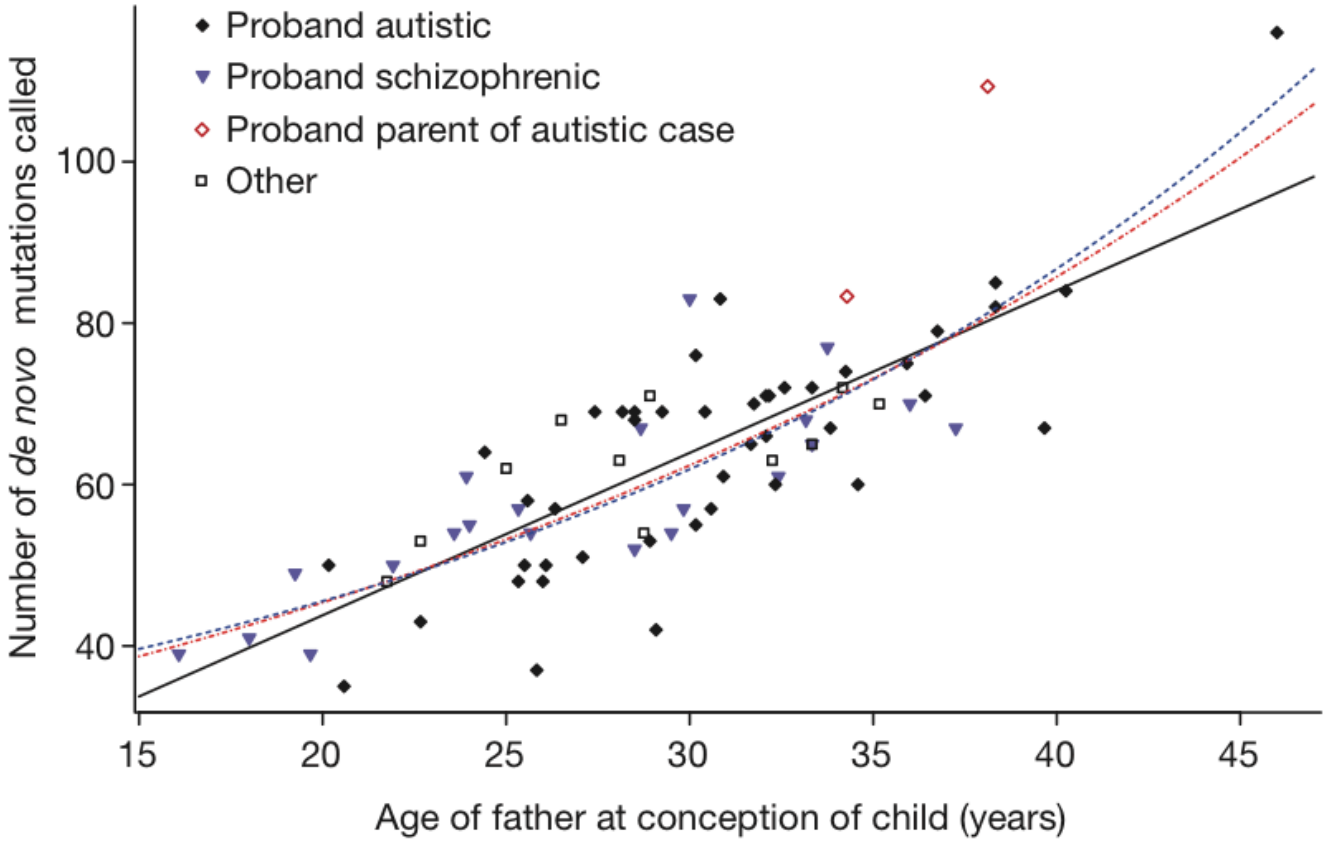


Figure 2 | Father's age and number of *de novo* mutations. The number of *de novo* mutations called is plotted against father's age at conception of child for the 78 trios. The solid black line denotes the linear fit. The dashed red curve is based on an exponential model fitted to the combined mutation counts. The dashed blue curve corresponds to a model in which maternal mutations are assumed to have a constant rate of 14.2 and paternal mutations are assumed to increase exponentially with father's age.

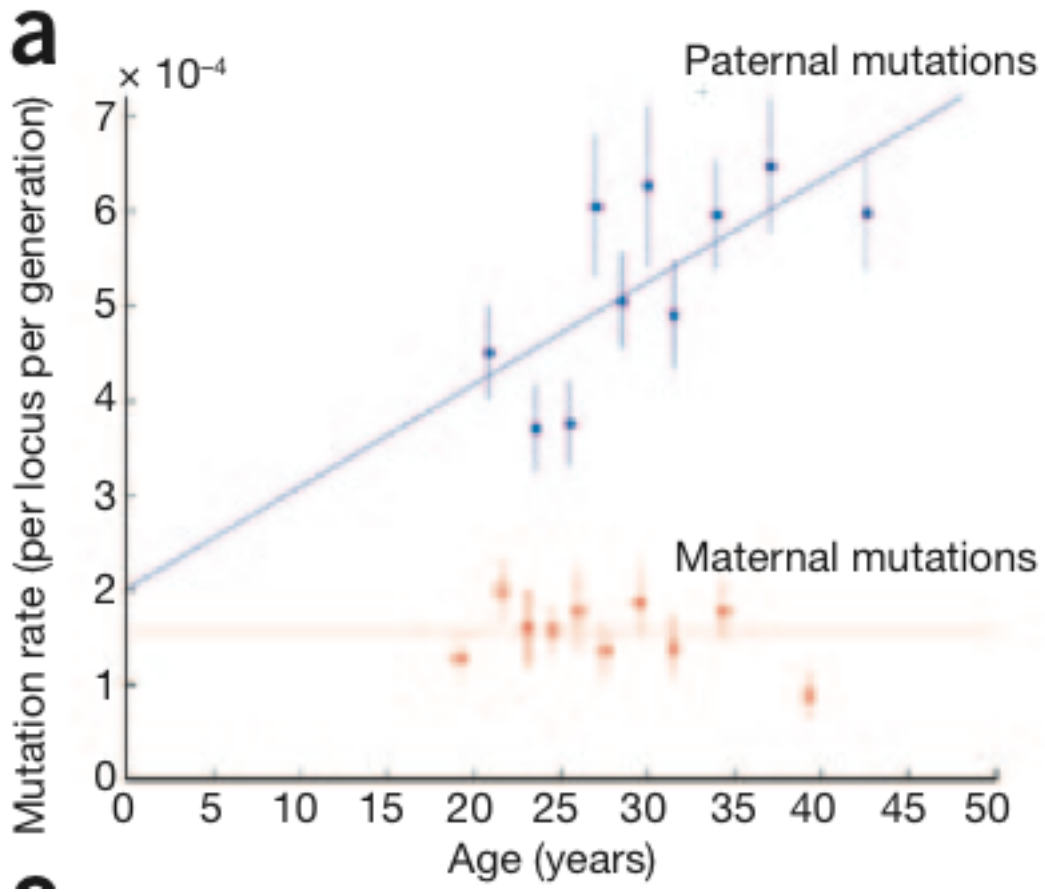


Figure 2 Characteristics of the microsatellite mutation process. (a) Paternal (blue) and maternal (red) mutation rates. The x axis shows the parental age at childbirth. Data points are grouped into ten bins (vertical bars show one standard error). The paternal rate shows a positive correlation with age (logistic regression of raw data: P = 9.3 × 10-5; slope = 1.1 × 10-5 mutations per year), with an estimated doubling of the rate from age 20 to 58. The maternal rate shows no evidence of increasing with age (P = 0.47).
Sun, J. X. et al. Nature Genet. 2012

Table 2 | Germline mutation rates at CpG and non-CpG sites

Type of mutation	*n*	Rate per base per generation
Transition at non-CpG	2,489	6.18×10^{-9}
Transition at CpG	855	1.12×10^{-7}
Transversion at non-CpG	1,516	3.76×10^{-9}
Transversion at CpG	73	9.59×10^{-9}
All	4,933	1.20×10^{-8}

Mutation rates are per generation per base. For non-CpG sites, the effective number of bases examined is taken as 2.583 billion, whereas for CpG sites the number is 48.8 million. These numbers take into account the variation of local coverage in sequencing (Supplementary Information).

Table 3 | Strong-to-weak and weak-to-strong mutation rates

Mutation type	S→W (*n*) rate	W→S (*n*) rate	S→W rate/W→S rate
Transition	(2,025) 1.21×10^{-8}	(1,319) 5.42×10^{-9}	2.24
Transversion	(446) 2.67×10^{-9}	(358) 1.47×10^{-9}	1.82
All	(2,471) 1.48×10^{-8}	(1,677) 6.89×10^{-9}	2.15

n denotes observed mutation counts, and mutation rates are calculated per generation per base. For strong (S; G:C) to weak (W; A:T), the effective number of sites examined is taken as 1.071 billion, and for weak to strong the number is 1.56 billion.

Supplementary Table 2. Breakdown by gene context

Gene Content	Count of Mutations
Non_synonymous coding	60
Stop_gained	2
Synonymous coding	11
UTR_3_prime	16
Upstream	175
Downstream	267
Intergenic	2589
Intron	1808
Transcript*	5

NRXN1 gene (stop-gain mutation)

CUL3 gene (stop-gain mutation)

EPHB2 gene (splice site mutation)

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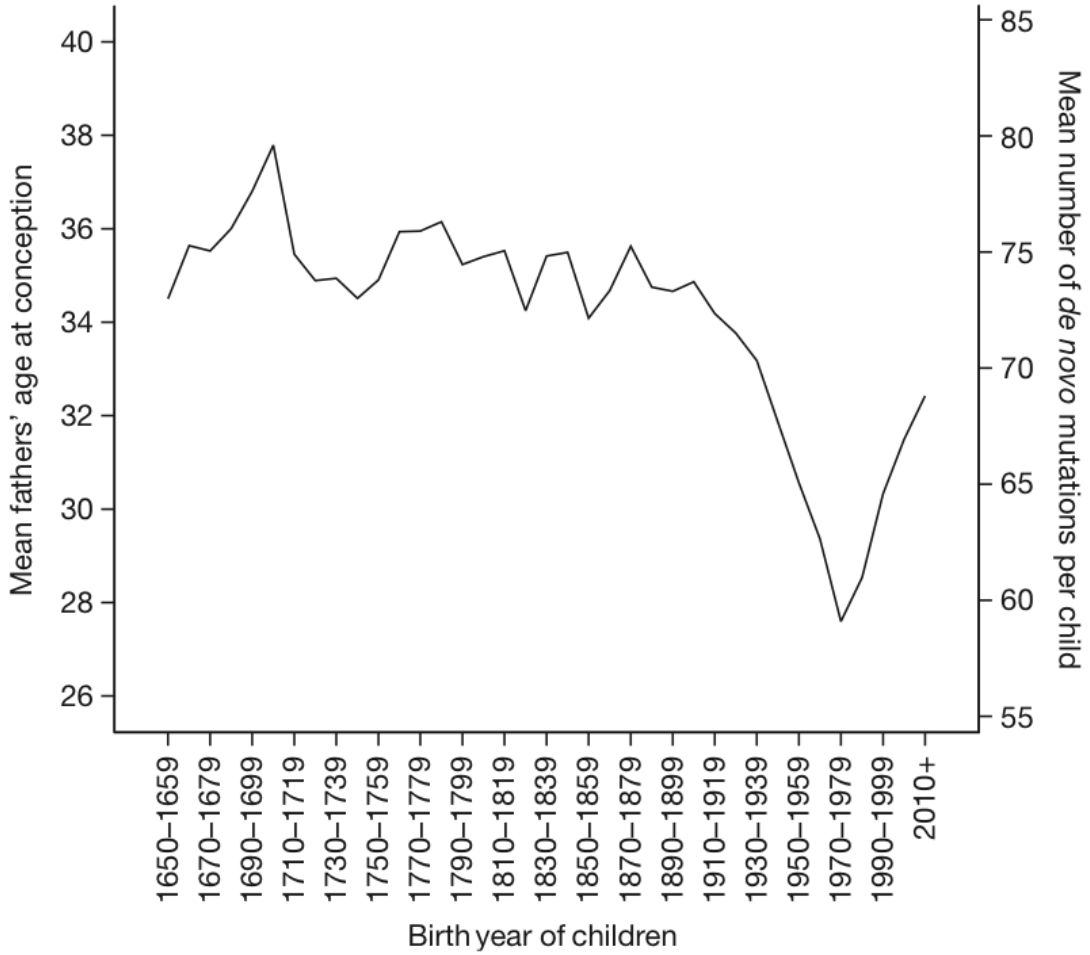

Demographics of Iceland and de novo mutations. The deCODE Genetics genealogy database was used to assess fathers' age at conception for all available 752,343 father–child pairs, in which the child's birth year was >=1650. The mean age of fathers at conception (left vertical axis) is plotted by birth year of child, grouped into ten-year intervals. On the basis of the linear model fitted for the relationship between father's age and the number of de novo mutations, the same plot, using the right vertical axis, shows the mean number of expected mutations for each ten-year interval.

Conclusion

- Women higher recombination rate
- Men transmit higher number of mutation
- Estimations: two extra mutation per year, doubling every 16.5 years

Reference

Kong, A. et al.

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THANK YOU