Supplementary Figure 1

Association of paternal age of *de novo* mutation location with epigenetic variables.

Using a linear regression model, we tested the association of seven epigenetic variables (DNA replication timing, expression levels, recombination rates, and the H3K27ac, H3K4me1 and H3K4me3 histone modifications), while correcting for GC content, CpG status and sequence coverage. Here we plot the significance of the associations we found with the different epigenetic variables along with the significance threshold level after Bonferroni correction for the six tests we performed (gray dashed line).
Supplementary Figure 2

Separation of replication timing profiles between the offspring of younger and older fathers.

We separated our de novo mutation data in two groups based on paternal age. To select a threshold that maximizes the difference in the groups, we considered every integer age in our study as a possible threshold and applied a Kolmogorov-Smirnoff test to compare the distribution of replication timing of de novo mutations between the groups. This plot shows the $P$ values obtained for each of the 27 tests as well as the significance threshold after Bonferroni correction (gray dashed line).
Supplementary Figure 3

Paternal age effect on de novo mutation replication timing measured in six cell types.

The distribution of replication timing around de novo mutations in the offspring of younger fathers (orange curves; <28 years old), older fathers (blue curves; ≥28 years old) and simulations (gray areas; 200 simulation sets of 11,020 mutations) in 3 cell types from 4 cell lines41: embryonic stem cells (BG01 ESC, H7 ESC), induced pluripotent stem cells (iPS4) and neural precursor cells (BG01 NPC).
Supplementary Figure 4

Paternal and maternal age effect estimates on replication timing based on *de novo* mutations with known parental origin.

All effect estimates were computed using a linear regression model. The red line represents the effect estimate from the 630 maternal mutations. The black curve shows the effect estimate for 10,000 samplings of 630 paternal mutations out of the 1,991 available. The effect estimate is significantly larger for paternal mutations \((P = 0.0019)\) when considering the same number of mutations.
Supplementary Figure 5

Power to detect non-CpG mutation depletion in regulatory regions marked by DNase I–hypersensitive sites (DHSs).

The graph shows the power to detect non-CpG mutation depletion in regulatory regions marked by DNase I–hypersensitive sites (DHSs) using the 9,048 non-CpG observed de novo mutations in our data and 177,347 uniformly simulated mutations. The y axis illustrates the power for detecting an effect at the 0.05 significance level using a $\chi^2$ test for different effect sizes (here expressed as the relative depletion of mutations in DHSs when compared to other regions).
Supplementary Figure 6

Comparison of nucleotide context–specific mutation rates based on comparative genomics and observed de novo mutations.

Each point represents one of the 96 substitutions in a specific trinucleotide context. The black line shows the best fit ($r^2 = 0.993$). The rate of transition mutations is 2.15 times greater than the transversion rate (Ti/Tv ratio). The highest mutation rates are observed for cytosine bases in a CpG context.
Supplementary Figure 7

Mutational spectrum in transcribed regions.

The proportion of de novo mutations of each substitution type in transcribed regions classified based on their corresponding strand (transcribed or non-transcribed). There is a strong asymmetry of mutations between the two strands, with significantly elevated A>G substitutions on the transcribed strand, consistent with the action of transcription-coupled nucleotide excision repair.
<table>
<thead>
<tr>
<th>Cell type</th>
<th>Cell line</th>
<th>Replicate</th>
<th>Linear regression</th>
<th>M-W younger vs older fathers</th>
<th>M-W younger fathers vs simulations</th>
<th>M-W older fathers vs simulations</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td>p</td>
<td>β</td>
<td>p</td>
<td>β</td>
</tr>
<tr>
<td>Lymphoblastoid cells</td>
<td>6 lines</td>
<td>-</td>
<td>0,0022</td>
<td>0,158</td>
<td>1,3E-04</td>
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<td></td>
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<td>1</td>
<td>0,0305</td>
<td>0,110</td>
<td>1,7E-03</td>
<td>-0,042</td>
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<tr>
<td></td>
<td>C0202</td>
<td>2</td>
<td>0,0285</td>
<td>0,111</td>
<td>9,9E-04</td>
<td>-0,050</td>
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<tr>
<td>Neural precursor cell</td>
<td>BG01</td>
<td>1</td>
<td>0,0265</td>
<td>0,108</td>
<td>1,5E-03</td>
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<tr>
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<td>BG01</td>
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<td>0,0257</td>
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<td>BG01</td>
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<td>7,7E-04</td>
<td>0,171</td>
<td>3,6E-04</td>
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<tr>
<td></td>
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<td></td>
<td>H7</td>
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<td>0,0036</td>
<td>0,146</td>
<td>3,2E-03</td>
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<tr>
<td></td>
<td>H9</td>
<td>-</td>
<td>0,0021</td>
<td>0,155</td>
<td>7,1E-04</td>
<td>-0,050</td>
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<tr>
<td>Induced pluripotent stem cell</td>
<td>iPS4</td>
<td>1</td>
<td>6,1E-04</td>
<td>0,172</td>
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<td>iPS4</td>
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<td>-0,045</td>
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</table>

**Supplementary Table 1. Paternal age effect on de novo mutation replication timing measured in 6 cell types**

The source of the replication timing data was Koren et al. for the 6 lymphoblastoid cell lines (1st row) and Ryba et al. for all other cell lines. The linear regression column contains p-values and estimates (β) for the parsimonious model described in Methods. The M-W test columns contain the p-values and estimated difference using a Mann-Whitney test between the distribution of mutation replication timing values of: offspring of younger (<28 years old) vs older (≥28 years old); offspring of younger fathers vs simulations; offspring of older fathers vs simulations. Significant p-values are highlighted in bold font.
**Supplementary Table 2. Predictive power of local substitution rates.**

Predictive power of primate substitution rates for local *de novo* mutation rates using the Poisson regression model described in the Supplementary Note. Only **S→W** and **W→W** substitutions have significant predictive power for local *de novo* mutation rates.

<table>
<thead>
<tr>
<th>Substitution</th>
<th>Predictive Power</th>
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</thead>
<tbody>
<tr>
<td>T→G</td>
<td>0.54</td>
</tr>
<tr>
<td>C→T</td>
<td>0.00696</td>
</tr>
<tr>
<td>G→C</td>
<td>0.0502</td>
</tr>
<tr>
<td>T→C</td>
<td>0.221</td>
</tr>
<tr>
<td>T→A</td>
<td>0.025</td>
</tr>
<tr>
<td>C→A</td>
<td>$6.06 \times 10^{-6}$</td>
</tr>
<tr>
<td>CpG→TpG</td>
<td>$1.98 \times 10^{-6}$</td>
</tr>
</tbody>
</table>
Supplementary Table 3. Dependency of local mutation rates on recombination rates

Summarizes the estimated dependency of local mutation rates on recombination rates. Only C→A and CpG→TpG exhibit a significant dependency.

<table>
<thead>
<tr>
<th></th>
<th>$p_{sr}$</th>
<th>$P(p_{sr} = 0)$</th>
<th>$f_s$</th>
</tr>
</thead>
<tbody>
<tr>
<td>G→A</td>
<td>-2.485 x 10^{-5}</td>
<td>0.23</td>
<td>1.034</td>
</tr>
<tr>
<td>T→A</td>
<td>2.597 x 10^{-6}</td>
<td>0.649</td>
<td>0.891</td>
</tr>
<tr>
<td>C→A</td>
<td>-9.857 x 10^{-5}</td>
<td>&lt; 2 x 10^{-16}</td>
<td>1.014</td>
</tr>
<tr>
<td>CpG→CpA/TpG</td>
<td>-0.00449</td>
<td>&lt; 2 x 10^{-16}</td>
<td>0.988</td>
</tr>
<tr>
<td>Log Likelihood</td>
<td>GoNL uniform</td>
<td>Primate $r_{ti}$</td>
<td>Corrected $\mu_{ti}$(%/%)*</td>
</tr>
<tr>
<td>----------------</td>
<td>--------------</td>
<td>-----------------</td>
<td>----------------------------</td>
</tr>
<tr>
<td>Recomb. rates</td>
<td>No</td>
<td>No</td>
<td>Male</td>
</tr>
<tr>
<td>$\log L_{G\rightarrow G}$</td>
<td>-1,591.0</td>
<td>-1,605.3</td>
<td>-1,584.6 (0.4% / 1.3%)</td>
</tr>
<tr>
<td>$\log L_{G\rightarrow A}$</td>
<td>-2,974.5</td>
<td>-2,961.7</td>
<td>-2,959.2 (0.5% / 0.1%)</td>
</tr>
<tr>
<td>$\log L_{G\rightarrow C}$</td>
<td>-1,735.6</td>
<td>-1,736.5</td>
<td>-1,728.3 (0.4% / 0.5%)</td>
</tr>
<tr>
<td>$\log L_{G\rightarrow T}$</td>
<td>-3,176.2</td>
<td>-3,183.5</td>
<td>-3,152.0 (0.8% / 1.0%)</td>
</tr>
<tr>
<td>$\log L_{A\rightarrow G}$</td>
<td>-1,439.8</td>
<td>-1,437.7</td>
<td>-1,434.5 (0.4% / 0.2%)</td>
</tr>
<tr>
<td>$\log L_{A\rightarrow C}$</td>
<td>-1,852.2</td>
<td>-1,836.7</td>
<td>-1,832.5 (1.1% / 0.2%)</td>
</tr>
<tr>
<td>$\log L_{A\rightarrow T}$</td>
<td>-2,696.2</td>
<td>-2,439.6</td>
<td>-2,435.8 (9.7% / 0.2%)</td>
</tr>
<tr>
<td>$\log L_{C\rightarrow G\rightarrow A/T}$</td>
<td>-2,696.2</td>
<td>-2,439.6</td>
<td>-2,435.0 (9.7% / 0.2%)</td>
</tr>
<tr>
<td>Total</td>
<td>-15,465.6</td>
<td>-15,201.0</td>
<td>-15,126.9 (2.2% / 0.5%)</td>
</tr>
</tbody>
</table>

* In parenthesis is the percent change of log likelihood of $\mu_{ti}$ compared to GoNL uniform model and uncorrected primate rate model $r_{ti}$.

Supplementary Table 4. Likelihood of the observed data under different mutation rate models

Likelihood of the observed de novo mutation data by substitution type based on (a) a uniform mutation rate model derived from the observed mutations, (b) the uncorrected primate rate matrix $r_{ti}$ and (c) the computed mutation rate matrix $\mu_{ti}$.
Supplementary Note

Mutation rate map

For each 1Mb window $i$, a substitution rate matrix was inferred using the context-dependent primate substitution model described in Duret et al. for seven types of substitutions, parameterized by $r_{t,i}$ with $t \in \{T \rightarrow G, G \rightarrow C, T \rightarrow C, T \rightarrow A, C \rightarrow A, C \rightarrow T, \text{CpG} \rightarrow \text{TpG}\}$ (to account for hyper-mutability of CpG sites).

First, we tested if the observed de novo mutation rates co-vary with primate substitution rates across the genome using the following Poisson regression model with log link function:

$$\log(n_{t,i}) = \beta_{r,t}r_{t,i} + \beta_{r,t,0} + \log(N_{t,i}) \quad \text{for } t \neq \text{CpG} \rightarrow \text{TpG}$$

$$= \beta_{r,t}(r_{t,i} + r_{C \rightarrow T,i}) + \beta_{r,t,0} + \log(N_{t,i}) \quad \text{for } t = \text{CpG} \rightarrow \text{TpG}$$

where $n_{t,i}$ is the observed count of de novo mutations of type $t$ in window $i$, $r_{t,i}$ is the substitution rate of type $t$ in window $i$, and $N_{t,i}$ is the number of sites at which de novo mutations of type $t$ can be detected with high confidence in window $i$. The offset term $\log(N_{t,i})$ was added since the number of called de novo mutations is dependent on detection power. The $C \rightarrow T$ mutation of CpG sites requires special treatment since it can be attributed to context-independent $C \rightarrow T$ substitution as well as hyper-mutability of CpG.

The primate substitution rates in the above Poisson regression model only had significant predictive power for local de novo mutation rates for $S \rightarrow W$ and $W \rightarrow W$ substitutions (Supplementary Table 2). For this reason, we only estimated local mutation rates based on the primate substitution rate for substitutions in $t_{SW} = \{T \rightarrow A, C \rightarrow A, C \rightarrow T, \text{CpG} \rightarrow \text{TpG}\}$. For the rest of substitutions ($t \in \{T \rightarrow G, T \rightarrow C, G \rightarrow C\}$), we used the genome-wide averaged mutation rates $r_t'$ estimated from our observed mutations:

$$r_t' = \frac{\sum_i n_{t,i}}{\sum_i N_{t,i}} \cdot \frac{1}{c}$$

$$c = \frac{\sum_i \sum_{t \in t_{SW}} n_{t,i}}{\sum_i \sum_{t \in t_{SW}} r_{t,i}N_{t,i} + \sum_i r_{C \rightarrow T,i}N_{\text{CpG} \rightarrow \text{TpG},i}}$$

where $c$ is a scaling factor to convert between de novo mutation rates and instantaneous substitution rates.

Second, we corrected for the biases due to local recombination rates. The observed local de novo mutation rates were not significantly correlated with recombination rates when considering each type of substitutions separately (Bonferroni-corrected p-value > 0.05). However, local substitution rates $r_{t,i}$ depend significantly on local sex-averaged recombination rates $\rho_i$ for $t = C \rightarrow A$ and $\text{CpG} \rightarrow \text{TpG}$ (Supplementary Table 3). To eliminate the dependency on recombination rate, we fit the following linear regression model:

$$r_{t,i} = \beta_{p,t} \rho_i + \beta_{0,t}$$

and residualized $r_{t,i}$ by subtracting the $\rho_i$-dependent term.

The final formula we used to compute the mutation rates for each 1Mb window $i$ is then:

$$\mu_{t,i} = (r_{t,i} - \beta_{p,t} \rho_i) \cdot f_t \quad \text{for } t \in \{C \rightarrow A, \text{CpG} \rightarrow \text{TpG}\}$$
\( \mu_{t,i} = r_{t,i} \cdot f_t \) for \( t \in \{ \text{T} \rightarrow \text{A}, \text{C} \rightarrow \text{T} \} \)
\( \mu_{t,i} = r'_{t,i} \) for \( t \in \{ \text{T} \rightarrow \text{G}, \text{T} \rightarrow \text{C}, \text{G} \rightarrow \text{C} \} \)

where \( f_t \) is a global scaling factor for substitution of type \( t \) to match the observed frequencies of different types of de novo mutations (Supplementary Table 4). In particular, \( \text{A} \rightarrow \text{T} \) mutation is over-represented in primate substitutions by 12% compared to our de novo data. For each \( t \) in \( t_{SW}, f_t \) is defined to satisfy the following conditions:

\[
\sum_i \mu_{t,i} N_{t,i} = \frac{1}{c} \sum_i n_{t,i} \quad \text{for} \quad t \in \{ \text{T} \rightarrow \text{A}, \text{C} \rightarrow \text{T}, \text{C} \rightarrow \text{A} \}
\]

\[
\sum_i (\mu_{t,i} + \mu_{C \rightarrow T,i}) N_{t,i} = \frac{1}{c} \sum_i n_{t,i} \quad \text{for} \quad t = \text{CpG} \rightarrow \text{TpG}
\]

Finally, the mutation rate \( \mu \) was scaled so that the overall mutation rate across the autosome is \( 1.2 \times 10^{-8} \) per nucleotide per generation.

To evaluate the fit of the estimated mutation rates to observed de novo mutations, we examined the likelihood \( L_t \) of the observed data given mutation rates, assuming homogenous Poisson process for each type of mutation \( t \) within each window \( i \):

\[
L_t(data|\mu_{t,i}) = \prod_i \text{Poisson} \left( n_{t,i} \bigg| \lambda = \frac{1}{c} \mu_{t,i} N_{t,i} \right) \quad \text{for} \quad t \neq \text{CpG} \rightarrow \text{TpG}
\]

\[
= \prod_i \text{Poisson} \left( n_{t,i} \bigg| \lambda = \frac{1}{c} (\mu_{t,i} + \mu_{C \rightarrow T,i}) N_{t,i} \right) \quad \text{for} \quad t = \text{CpG} \rightarrow \text{TpG}
\]

\[
c' = \frac{\sum_i \sum_t \mu_{t,i} N_{t,i} + \sum_i \mu_{C \rightarrow T,i} N_{CpG \rightarrow Tpg,i}}{c}
\]

The likelihood of the observed data under different models is summarized in Supplementary Table 4.

We estimated functional mutation rates in protein-coding region for autosomal protein-coding transcripts (downloaded from Ensembl4 v74). Excluding 24,508 transcripts (3,808 genes) outside our analysis windows for bias correction, we computed bias-corrected mutations rates for a total of 54,310 transcripts (15,462 genes). For maximum coverage of genes, however, we provide two additional functional mutation rates based on uncorrected local primate substitution rates \( r_{t,i} \) and the uniform genome-wide averaged mutation rates \( r'_t \) derived from our observed data.

For each transcript, the local mutation rate was determined by the 1Mb genomic window that overlapped the coordinate of midpoint between transcription start and end sites. Based on this rate, all possible nonsense, missense, synonymous and 4-fold degenerate synonymous mutations were examined with respect to the reference genome, and their mutation rates were aggregated over the entire transcript.

While we assumed the equal rate of \( \mu_{A \rightarrow C,i} \) and complementary \( \mu_{T \rightarrow C,i} \) in non-coding region, we adjusted for their strand bias in protein-coding region as follows:

\[
\mu_{A \rightarrow C,i}^{tx} = \frac{N_{A}^{tx} + N_{T}^{tx}}{N_{A}^{tx} + N_{T}^{tx}} \frac{Y_{sb}}{1 + Y_{sb}} \mu_{T \rightarrow C,i}^{nc}
\]

\[
\mu_{T \rightarrow C,i}^{tx} = \frac{N_{A}^{tx} + N_{T}^{tx}}{N_{A}^{tx} + N_{T}^{tx}} \frac{1}{1 + Y_{sb}} \mu_{T \rightarrow C,i}^{nc}
\]
\[
\gamma_{sb} = \frac{n_{A\rightarrow G}^T}{n_{T\rightarrow C}^A}
\]

where \( \mu_{A\rightarrow G,i}^{T\rightarrow C} \) is the local mutation rate of A:T\(\rightarrow\)G:C in non-coding region, \( \mu_{T\rightarrow C,i}^{A\rightarrow G} \) and \( \mu_{A\rightarrow G,i}^{T\rightarrow C} \) are the local mutation rates of T\(\rightarrow\)C and A\(\rightarrow\)G in protein-coding with respect to the transcribed strand, \( N_A^{T\rightarrow C} \) and \( N_A^{X} \) are the total numbers of protein-coding A and T bases in transcribed strand across the autosomes, and \( n_{T\rightarrow C}^A \) and \( n_{X}^{A\rightarrow G} \) are the genome-wide counts of observed T\(\rightarrow\)C and A\(\rightarrow\)G de novo mutations with respect to the transcribed strand in our dataset. \( \gamma_{sb} \) was estimated to be 1.389 and \( N_A^{T\rightarrow C}/(N_A^{T\rightarrow C} + N_A^{X}) \) to be 0.543 in our data.

The Genome of the Netherlands consortium

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Supplementary References