Supplementary Materials: Global Autozygosity is Associated with Cancer Risk, Mutational Signature and Prognosis

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Figure S1. Scatter plot for \( \text{HR}_{\text{NonRef}} \) vs \( \text{HR}_{\text{Minor}} \). Three clear clusters based on race can be observed. This suggests that HR is strongly associated with race.

Figure S2. Comparison of \( \text{HR}_{\text{NonRef}} \) and ROH between sex across all three races tested. This is equivalent to Figure 3 from the main text without but removed data from sex chromosomes X and Y. The sex difference observed in Figure 3 were mostly gone.
Figure S3. ROC curves based on the cancer risk analysis in Table 1.

Table S1. Cancer types encompassed in The Cancer Genome Atlas.

| Cancer Abbreviation | Cancer Full Name                  | Sample Size |
|---------------------|-----------------------------------|-------------|
| BRCA                | Breast Invasive Carcinoma         | 883         |
| COAD                | Colon Adenocarcinoma              | 264         |
| HNSC                | Head and Neck Squamous Cell Carcinoma | 476   |
| LIHC                | Liver Hepatocellular Carcinoma    | 299         |
| LUAD                | Lung Adenocarcinoma               | 340         |
| LUSC                | Lung Squamous Cell Carcinoma      | 250         |
| OV                  | Ovarian Serous Cystadenocarcinoma | 410         |
| PAAD                | Pancreatic Adenocarcinoma         | 143         |
| PRAD                | Prostate Adenocarcinoma           | 134         |
| READ                | Rectum Adenocarcinoma             | 84          |
| SKCM                | Skin Cutaneous Melanoma           | 455         |
| STAD                | Stomach Adenocarcinoma            | 319         |

Table S2. COSMIC mutational signatures (v3).

| Signature | Etiology |
|-----------|----------|
| SBS1      | An endogenous mutational process initiated by spontaneous or enzymatic deamination of 5-methylcytosine to thymine which generates G:T mismatches in double stranded DNA. Failure to detect and remove these mismatches prior to DNA replication results in fixation of the T substitution for C. |
| SBS2      | Attributed to activity of the AID/APOBEC family of cytidine deaminases on the basis of similarities in the sequence context of cytosine mutations caused by APOBEC enzymes in experimental systems. APOBEC3A is probably responsible for most mutations in human cancer, although APOBEC3B may also contribute (these differ in the sequence context two bases 5’ to the mutated cytosine, see 1,536 mutation classification signature extraction). SBS2 mutations may be generated directly by DNA replication across uracil or by error prone polymerases replicating across abasic sites generated by base excision repair removal of uracil. |
| SBS3      | Defective homologous recombination-based DNA damage repair which manifests predominantly as small indels and genome rearrangements due to abnormal double strand break repair but also in the form of this base substitution signature. |
| SBS4      | Associated with tobacco smoking. Its profile is similar to the mutational spectrum observed in experimental systems exposed to tobacco carcinogens such as benz[a]pyrene. SBS4 is, therefore, likely due to direct DNA damage by tobacco smoke mutagens. |
| SBS5      | Unknown |

SBS5 mutational burden is increased in bladder cancer samples with ERCC2 mutations and in many cancer types due to tobacco smoking.
SBS6 is associated with defective DNA mismatch repair and is found in microsatellite unstable tumours.

SBS7a
SBS7a/SBS7b/SBS7c/SBS7d are found in cancers of the skin from sun exposed areas and are thus likely to be due to exposure to ultraviolet light. SBS7a may possibly be the consequence of just one of the two major known UV photoproducts, cyclobutane pyrimidine dimers or 6-4 photoproducts. However, there is currently no evidence for this hypothesis and it is unclear which of these photoproducts may be responsible for SBS7a.

SBS7b
SBS7a/SBS7b/SBS7c/SBS7d are found in cancers of the skin from sun exposed areas and are likely to be due to exposure to ultraviolet light. SBS7b may possibly be the consequence of just one of the two major known UV photoproducts, cyclobutane pyrimidine dimers or 6-4 photoproducts. However, there is no evidence for this hypothesis and it is unclear which of these photoproducts may be responsible for SBS7b.

SBS7c
SBS7a/SBS7b/SBS7c/SBS7d are found in cancers of the skin from sun exposed areas and are likely to be due to exposure to ultraviolet light. SBS7c is possibly the consequence of translesion DNA synthesis by enzymes with propensity to insert T, rather than A, opposite ultraviolet induced thymidine and cytidine photodimers. The preponderance of T>A rather than T>C mutations may reflect the heavier burden of thymidine compared to cytidine dimers induced by UV light.

SBS7d
SBS7a/SBS7b/SBS7c/SBS7d are found in cancers of the skin from sun exposed areas and are likely to be due to exposure to ultraviolet light. SBS7d is possibly the consequence of translesion DNA synthesis by error-prone polymerases with greater propensity to insert G, rather than A, opposite UV light induced thymidine and cytidine photodimers.

SBS8
Unknown

SBS9
May be due in part to mutations induced during replication by polymerase eta as part of somatic hypermutation in lymphoid cells.

SBS10a
Polymerase epsilon exonuclease domain mutations.

SBS10b
Polymerase epsilon exonuclease domain mutations.

SBS11
SBS11 exhibits a mutational pattern resembling that of alkylating agents. Patient histories indicate an association between previous treatment with the alkylating agent temozolomide and SBS11 mutations.

SBS12
Unknown

SBS13
Attributed to activity of the AID/APOBEC family of cytidine deaminases on the basis of similarities in the sequence context of cytosine mutations caused by APOBEC enzymes in experimental systems. APOBEC3A is probably responsible for most mutations in human cancer, although APOBEC3B may also contribute (these differ in the sequence context two bases 5' to the mutated cytosine, see 1536 mutation classification signature extraction). SBS13 mutations are likely generated by error prone polymerases (such as REV1) replicating across abasic sites generated by base excision repair removal of uracil.

SBS14
Concurrent polymerase epsilon mutation and defective DNA mismatch repair.

SBS15
Defective DNA mismatch repair.

SBS16
Unknown

SBS17a
Unknown

SBS17b
Unknown

SBS18
Possibly damage by reactive oxygen species.

SBS19
Unknown

SBS20
Concurrent POLQ1 mutations and defective DNA mismatch repair.

SBS21
DNA mismatch repair deficiency.

SBS22
Aristolochic acid exposure. Found in cancer samples with known exposures to aristolochic acid and the pattern of mutations exhibited by the signature is consistent with that observed in experimental systems of aristolochic acid exposure.

SBS23
Unknown

SBS24
Aflatoxin exposure. SBS24 has been found in cancer samples with known exposures to aflatoxin and the pattern of mutations exhibited by the signature is consistent with that observed in experimental systems exposed to aflatoxin.

SBS25
Unknown
However, some Hodgkin’s cell line samples in which the signature has been found were from patients exposed to chemotherapy and it is possible that SBS25 is due to chemotherapy treatment.

SBS26
Defective DNA mismatch repair.

SBS28
Unknown

SBS29
SBS29 has been found in cancer samples from individuals with a tobacco chewing habit.

SBS30
SBS30 is due to deficiency in base excision repair due to inactivating mutations in NTHL1.

SBS31
Prior chemotherapy treatment with platinum drugs.

SBS32
Prior treatment with azathioprine to induce immunosuppression. Associated mutation classes and signatures

SBS33
N/A

SBS34
Unknown

SBS35
Prior chemotherapy treatment with platinum drugs.

SBS36
Defective base excision repair, including DNA damage due to reactive oxygen species, due to biallelic germline or somatic MUTYH mutations.

SBS37
Unknown
| SBS38 | Unknown          | Found only in ultraviolet light associated melanomas suggesting potential indirect damage from UV-light. |
|------|-----------------|-----------------------------------------------------------------------------------------------------|
| SBS39| Unknown         |                                                                                                     |
| SBS40| Unknown         |                                                                                                     |
| SBS41| Unknown         |                                                                                                     |
| SBS42| Occupational exposure to haloalkanes.                                                                 |
| SBS44| Defective DNA mismatch repair.                                                                         |
| SBS84| Activity of activation-induced cytidine deaminase (AID).                                                 |
| SBS85| Indirect effects of activation-induced cytidine deaminase (AID) induced somatic mutagenesis in lymphoid cells. |

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