Your manuscript has been checked for clarity and against journal policies and formatting style. The issues listed below must be addressed; failure to do so will cause delays in acceptance.

For further information, please see our [formatting instructions](https://www.nature.com/documents/ncomms-formatting-instructions.pdf).

Please highlight all changes in the manuscript text file, either using the track changes feature in Microsoft Word or coloured highlighting in LaTeX.

Please include your response to these requests in the space provided and return this checklist with your final submission.

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| EDITORIAL REQUESTS: | AUTHOR RESPONSE: |

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|  | EDITORIAL REQUESTS: | AUTHOR RESPONSE: |
| **1.** | **Data presentation:** Please ensure that data presented in a plot, chart or other visual representation format shows data distribution clearly (e.g. dot plots, box-and-whisker plots). When using bar charts, please overlay the corresponding data points (as dot plots) whenever possible and always for n ≤ 10. (Please see the following editorial for the rationale behind this request and an example <https://www.nature.com/articles/s41551-017-0079>). | |
| **2.** | **Statistics:** Wherever statistics have been derived (e.g. error bars, box plots, statistical significance) the legend needs to provide and define the n number (i.e. the sample size used to derive statistics) as a precise value (not a range), using the wording “n=X biologically independent samples/animals/cells/independent experiments/n= X cells examined over Y independent experiments” etc. as applicable. | |
| **Legends requiring revision:**   1. Please note that this information is missing in the legends of figures 2b, 4e, 5a-d (lower panel), supplementary figure 1c, 8b, 8d, 8f, 8h, 10b. 2. Please provide a precise value of ‘n’ in the legends of figures 1b; 2a-d; 3a-d; 6 (bar plots). | The requested changes have been made. |
| **3.** | Please note that statistics such as error bars significance and p values cannot be derived from n<3 and must be removed from all such cases. | |
| We strongly discourage deriving statistics from technical replicates, unless there is a clear scientific justification for why providing this information is important. Conflating technical and biological variability, e.g., by pooling technically replicates samples across independent experiments is strongly discouraged. (For examples of expected description of statistics in figure legends, please see the following <https://www.nature.com/articles/s41467-019-11636-5> or <https://www.nature.com/articles/s41467-019-11510-4>). | |
| All error bars need to be defined in the legends (e.g. SD, SEM) together with a measure of centre (e.g. mean, median). For example, the legends should state something along the lines of “Data are presented as mean values +/- SEM” as appropriate.  All box plots need to be defined in the legends in terms of minima, maxima, centre, bounds of box and whiskers and percentile. | |
| **Legends requiring revision:**   1. Please note that the box plots need to be defined in terms of centre in the legend of figures 4e, 5a-d (lower panel); supplementary figures 1b; 2a-d; 3a-d. 2. Please note that the box plots need to be defined in terms of minima, maxima, centre, bounds of box and whiskers and percentile in the legend of figure 1c. | For all figures with box plots, we include the following to explain their features: “For the box-plots, the box demarcations represent the 25th, 50th, and 75th percentiles and the whiskers extend from the box to the largest and smallest data points at most 1.5 times the inter-quartile range away from the median.” |
| **4.** | The figure legends must indicate the statistical test used. Where appropriate, please indicate in the figure legends whether the statistical tests were one-sided or two-sided and whether adjustments were made for multiple comparisons.  For null hypothesis testing, please indicate the test statistic (e.g. F, t, r) with confidence intervals, effect sizes, degrees of freedom and P values noted.  Please provide the test results (e.g. P values) as exact values whenever possible and with confidence intervals noted. | |
| **Legends requiring revision:**   1. Please note that the exact p value should be provided, when possible, in the legends of figures 2b, 4e, supplementary figure 2a-d, 3a-d, 10b 2. Please note that for the figure 4e and supplementary figure 10b, \*\*\*p-values and statistical tests are indicated in the legends. However, comparison for the same, "\*\*\*" has not been represented in the figures. Please rectify this in the figures or legends as applicable. Also, if appropriate, please provide exact p-values. | Stars representing p-values in all figures have been replaced with the precise p-values. |
| **5.** | **Reproducibility:** Please state in the legends how many times each experiment was repeated independently with similar results. This is needed for all experiments, but is particularly important wherever results from representative experiments (such as micrographs) are shown. If space in the legends is limiting, this information can be included in a section titled “Statistics and Reproducibility” in the methods section. | |
| **6.** | **Data availability:** This journal strongly supports public availability of data and custom code associated with the paper in a persistent repository where they can be freely and enduringly accessed or as a supplementary data file when no appropriate repository is available. If data and code can only be shared on request, please explain why in your data Availability Statement, and also in the correspondence with your editor. For more information, please refer to <https://www.nature.com/nature-research/editorial-policies/reporting-standards#availability-of-data> | |
| Please ensure that datasets deposited in public repositories are now publicly accessible, and that accession codes or DOI are provided in the "Data Availability" section. As long as these datasets are not public, we cannot proceed with the acceptance of your paper. For data that have been obtained from publicly available sources, please provide a URL and the specific data product name in the data availability statement. Data with a DOI should be further cited in the methods reference section. | The appropriate links and DOI numbers have been added to the “Data Availability” section and all data is publicly available. |

### EDITORIAL REQUESTS:

#### POLICIES AND CHECKLISTS

An updated editorial policy checklist must be completed and uploaded as a related manuscript file with the revised manuscript. All points on the policy checklist must be addressed; if needed, please revise your manuscript in response to these points. Please note that this form is a dynamic 'smart pdf' and must therefore be downloaded and completed in Adobe Reader, instead of opening it in a web browser.

<https://www.nature.com/authors/policies/Policy.pdf>

The requested changes have been implemented and an updated Editorial Policy Checklist has been included in the resubmission.

Please find attached a reporting summary that includes comments on how to revise it in line with our policies and requests the addition of further information in the text. An updated reporting summary must be completed and uploaded as a supplementary information file with the revised manuscript. This checklist is published alongside your manuscript online. Please note that this form is a dynamic 'smart pdf' and must therefore be downloaded and completed in Adobe Reader, instead of opening it in a web browser.

<https://www.nature.com/authors/policies/ReportingSummary.pdf>

The requested changes have been implemented and an updated Reporting Summary has been included in the resubmission.

Please also find below a list of comments requesting additional information in the figure legends, text, and methods section to comply with our reporting policies.

#### TITLE PAGE (page 2 of our formatting instructions)

To adhere to journal style, I suggest the following revision to the title. If you would like to suggest an alternative title, please ensure that it does not exceed 15 words and does not contain punctuation.

“Oncogenic *KRAS* mutations are allele and tissue-specific”

I would prefer the following title: “The origins and genetic interactions of *KRAS* mutations are allele- and tissue-specific”. This puts the focus on the genetic interactions of the *KRAS* mutations, not just the *KRAS* mutations themselves.

The abstract should briefly discuss the background and context of the work, followed by the major results and conclusions of the paper. The discussion of the current work should begin with "Here we report" or an equivalent phrase and should be written in the present tense. Please ensure your abstract conforms to this structure.

When discussing the current work in the abstract, please use the present tense.

The abstract uses the phrase “Here, were analyze…” to lead into the discussion of the current work. The discussion of the current work in the abstract is now in the present tense.

#### MAIN TEXT (pages 1 to 3 of our formatting instructions)

The following sections must be present in the manuscript and must begin with a heading: Abstract, Introduction, Results, and optional Discussion and Methods. We also allow a combined Results and Discussion section. All other main text section headings should be removed or renamed.

Abstract and Introduction headings have been added and the Acknowledgements, Author contributions, and Competing interests headings have been changed to subheadings.

#### LANGUAGE AND STYLE (page 6 of our formatting instructions)

Please do not use italics, bold font, underlining or speech marks unless required for technical terms (in both the main text and the display items).

All unnecessary use of italics and bold text have been removed in both the main text and display items.

Please use italics for gene names, and roman font for protein names. This applies to both the main text and display items.

All genes have been italicized in both the main text and display items.

Please make sure that mathematical terms throughout your manuscript and Supplementary Information (including in figures, figure axes, and legends) conform strictly to the following guidelines. Equations must be supplied in editable format, and not as images. Scalar variables (e.g. x, V, χ) must be typeset in italic, whereas multi-letter variables and functions (e.g. log) must be formatted in roman. Vectors (such as the wavevector k or the magnetic field vector B) must be typeset in bold without italics.

We have double checked all mathematical terms in the main text and display items. In Fig. 2, we now use a “χ” symbol typeset in italics.

#### METHODS AND DATA (page 3 of our formatting instructions)

Sufficient details of the experiments must be provided in the Methods section such that they could be reproduced without reference to published papers. Use of the term 'as described previously' is not encouraged.

Read through all of the Methods sections and fill them out with all details. I think this is specifically referring to the mutational signature portion.

All manuscripts must include a Data Availability statement as a separate section after the Methods section but before the References. For acceptable examples, see:

<https://www.nature.com/documents/nr-data-availability-statements-data-citations.pdf>

The Data Availability statement should include:

* Accession codes with hyperlinks for deposited data
* Other unique identifiers (such as DOIs and hyperlinks for any other datasets)
* At a minimum, a statement confirming that all relevant data are available from the authors
* If applicable, a statement regarding data available with restrictions

If a dataset has a Digital Object Identifier (DOI) as its unique identifier, we strongly encourage including this in the Reference list and citing the dataset in the Data Availability Statement

**Please note that the data must be released publicly by the time you resubmit your final manuscript; we will not be able to accept your manuscript if the data are not publicly available.**

In particular, please add a data availability statement along the following lines. ‘The XX data are available in the YY database under accession code ZZ [Add hyperlink here].’ Please add a sentence along these lines for each data set that you accessed. Please describe the type of data e.g WGS, WES. Please add a final clause to the data availability statement along the lines of ‘The remaining data are available within the Article, Supplementary Information or available from the authors upon request.’

Nature Research policies (<https://go.nature.com/data-availability-AIP>) strongly encourage deposition of research data in public repositories. In some cases this is mandatory, and you may have been previously advised if that was the case. If you need help depositing and curating your research data (including raw and processed data, text, video, audio and images) you should consider:

* Contacting Springer Nature’s Research Data Helpdesk (<https://go.nature.com/helpdesk-AIP>) for advice
* Finding a suitable data repository (<https://go.nature.com/RD-policies-AIP>) for your data
* Uploading your data to Springer Nature’s Research Data Support service (<https://go.nature.com/RDS-AIP>)

Research Data Support is an optional Springer Nature service. There are fees (<https://go.nature.com/RDS-pricing-AIP>) for using this service, however, if you receive funding from the Wellcome Trust or are affiliated to a Wellcome Centre you can use Research Data Support at no cost. See <https://go.nature.com/wellcome-RDS-AIP> for more information.

If you choose to use Research Data Support, please do not submit your revised manuscript until you have been supplied with the DOI for your data by the Research Data Support team. Please also ensure that you update your Data Availability statement with this DOI and the information provided by the team.

Please provide a unique identifier for the data (for example a DOI or a permanent URL) in the data availability statement, if possible. If the repository does not provide identifiers, we encourage authors to supply the search terms that will return the data. For data that have been obtained from publicly available sources, please provide a URL and the specific data product name in the data availability statement. Data with a DOI should be included in the reference list and cited where relevant.

Alternatively, include the data in the Supplementary Information. For datasets for which mandatory deposition is not required and the data can only be shared on request, please explain why in your Data Availability Statement and in your response here.

Please refer to our data policies here: <http://www.nature.com/authors/policies/availability.html>

We have expanded our “Data Availability” section to detail the availability and location of all the data sources used in this study. All data sets are already publicly available. Links have been provided.

We strongly encourage authors to deposit all code or script associated with the paper in a persistent repository where they can be freely and enduringly accessed. For all studies developing new software or using custom code that is deemed central to the conclusions, a statement must be included, under the heading ‘Code Availability,’ indicating whether and how the code can be accessed, including any restrictions to access. If the code can only be shared on request, please explain why in your Code Availability Statement and in your response here.

We notice that you have deposited your code in a Github repository, which we fully support. We strongly encourage you to make your code citable by obtaining a DOI for the Github repository. This can be done by linking the repository to Zenodo, following the instructions here: <https://guides.github.com/activities/citable-code/>.Please cite the Github repository in your manuscript text or Code Availability statement and in your reference list: authors, title (this paper), repository name, DOI identifier, year.

A reference to the source data file should be added in the ‘Data Availability’ section, using the text “Source data are provided with this paper.”

We have created a DOI for the GitHub repository and have included it in the Code Availability statement.

#### DISPLAY ITEMS (pages 4 and 5 of our formatting instructions)

The use or adaptation of previously published images is strongly discouraged. If this is unavoidable, please request the necessary rights documentation to re-use such material from the relevant copyright holders and return this to us when you submit your revised manuscript. Please check whether your manuscript or Supplementary Information contain third-party images, such as figures from the literature, stock photos, clip art or commercial satellite and map data.

Any abbreviations, symbols or colours present in your figures must be defined in the associated legends.

Please do not use symbols in your legend, instead write out the symbols in words (blue circles, red dashed line, etc.).

All colour scales must be defined and intensity levels must be provided in either the figure or its associated legend.

We have replaced symbols with text descriptions in the legends of Fig. 2 and Supplementary Fig. 3.

#### SUPPLEMENTARY INFORMATION (page 5 of our formatting instructions)

We do not edit Supplementary Information files; they will be uploaded with the published article as they are submitted with the final version of your manuscript. Any tracked changes should be removed from the file and the file should be provided as a PDF file. Supplementary Figures do not need to be provided separately.

Please supply legends for each Supplementary Movie/Audio/Data file in your response here (not in the Supplementary Information file). Please label each files as Supplementary Movie/Audio/Data 1, etc.

We have double-checked the Supplementary Figures and ensured the validity of the figure legends. We do not have any Supplementary Movies or Audio files. We do not have any legends for the study’s Supplementary Data.

Please ensure that a Source Data file is included with your resubmission. Within the Source Data file, the relevant raw data from each figure or table (in the main manuscript and in the Supplementary Information) should be represented by a single sheet in an Excel document, or a single .txt file or other file type in a zipped folder. Uncropped blots and gel images should be pasted in and labelled with the relevant panel and identifying information such as the antibody used. An example of the Source Data file is available demonstrating the correct format:

<https://www.nature.com/documents/ncomms-example-source-data.xlsx>

The file should be labelled 'Source Data', with the title and a brief description included in your response here, and should be mentioned in all relevant figure legends using the template text below:

""Source data are provided as a Source Data file."""

In particular, please provide a source data file that contains the data behind your most important box plots and analyses e.g at least all of those in the main text.

I need to make this. Think REALLY hard about the desired format and way of doing this.

Please rename the tables in your xls file as Supplementary Data 1 etc rather than Table.

The tables have been renamed to Supplementary Data 1, etc.

While we don’t have a strict reference limit >80 is somewhat excessive, please do your best to reduce the number of references.

We have reduced the number of citations from 113 to X.

#### PUBLICATION

Your paper will be accompanied by a two-sentence Editor's summary, of between 250-300 characters including spaces, when it is published online. I have drafted the summary below. If you would like to make changes to this, please provide me with a suitably edited version.

The KRas gene is mutated at several hotspot residues. Here, the authors examine the frequencies of the different Kras mutations across multiple cancer types and discover that the Kras mutations are found in both an allele and tissue specific manner.

We would like to adjust the focus of the summary from the *KRAS* mutations themselves to their allele-specific and tissue-specific genetic interactions. Below is an edited version that we prefer though are amenable to your suggestions:

“The *KRAS* gene is mutated at several hotspot residues, resulting in similar, yet distinct, functional impacts on the KRas protein. Here, the authors examine the genetic interactions of the different *KRAS* mutations across multiple cancer types and discover that *KRAS* mutations have allele and tissue-specific comutation and dependency interactions.”

As part of our efforts to communicate our content to a wider audience, we endeavour to highlight papers published in Nature Communications on the journal’s Twitter account (https://twitter.com/NatureComms). If you would like us to mention authors, institutions or lab groups in these tweets, please provide the relevant twitter handles.

Below are the Twitter handles that we would like to associate with the publication:

Haigis lab: @KevinHaigisLab

Park lab: @peter\_j\_park

(May I put mine or is that hacky?)