

Reporting Summary

Nature Portfolio wishes to improve the reproducibility of the work that we publish. This form provides structure for consistency and transparency in reporting. For further information on Nature Portfolio policies, see our [Editorial Policies](#) and the [Editorial Policy Checklist](#).

Statistics

For all statistical analyses, confirm that the following items are present in the figure legend, table legend, main text, or Methods section.

- |                                     |                                                                                                                                                                                                                                                                                                |
|-------------------------------------|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| n/a                                 | Confirmed                                                                                                                                                                                                                                                                                      |
| <input type="checkbox"/>            | <input checked="" type="checkbox"/> The exact sample size ( <i>n</i> ) for each experimental group/condition, given as a discrete number and unit of measurement                                                                                                                               |
| <input checked="" type="checkbox"/> | <input type="checkbox"/> A statement on whether measurements were taken from distinct samples or whether the same sample was measured repeatedly                                                                                                                                               |
| <input type="checkbox"/>            | <input checked="" type="checkbox"/> The statistical test(s) used AND whether they are one- or two-sided<br><i>Only common tests should be described solely by name; describe more complex techniques in the Methods section.</i>                                                               |
| <input type="checkbox"/>            | <input checked="" type="checkbox"/> A description of all covariates tested                                                                                                                                                                                                                     |
| <input type="checkbox"/>            | <input checked="" type="checkbox"/> A description of any assumptions or corrections, such as tests of normality and adjustment for multiple comparisons                                                                                                                                        |
| <input type="checkbox"/>            | <input checked="" type="checkbox"/> A full description of the statistical parameters including central tendency (e.g. means) or other basic estimates (e.g. regression coefficient) AND variation (e.g. standard deviation) or associated estimates of uncertainty (e.g. confidence intervals) |
| <input type="checkbox"/>            | <input checked="" type="checkbox"/> For null hypothesis testing, the test statistic (e.g. <i>F</i> , <i>t</i> , <i>r</i> ) with confidence intervals, effect sizes, degrees of freedom and <i>P</i> value noted<br><i>Give P values as exact values whenever suitable.</i>                     |
| <input checked="" type="checkbox"/> | <input type="checkbox"/> For Bayesian analysis, information on the choice of priors and Markov chain Monte Carlo settings                                                                                                                                                                      |
| <input checked="" type="checkbox"/> | <input type="checkbox"/> For hierarchical and complex designs, identification of the appropriate level for tests and full reporting of outcomes                                                                                                                                                |
| <input type="checkbox"/>            | <input checked="" type="checkbox"/> Estimates of effect sizes (e.g. Cohen's <i>d</i> , Pearson's <i>r</i> ), indicating how they were calculated                                                                                                                                               |

Our web collection on [statistics for biologists](#) contains articles on many of the points above.

Software and code

Policy information about [availability of computer code](#)

|                 |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                         |
|-----------------|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| Data collection | Individual-level ultrasound imaging data were previously collected by investigators in the PESA study using VPQ software v13 (Philips Healthcare) and CM2020 software (Philips Research Analysis). No other software was used for data collection.                                                                                                                                                                                                                                                                                                                                                                                                                                                                                      |
| Data analysis   | Statistical analyses were performed using RStudio (v2022.07.2+576) with R version 4.2.2. The code is publicly available and can be found at: <a href="https://github.com/Unidad-Bioinformatica-CNIC/CHIP-candidate_mutations">https://github.com/Unidad-Bioinformatica-CNIC/CHIP-candidate_mutations</a> . The source code from the R-packages used in this study are freely available online ( <a href="https://cran.r-project.org/">https://cran.r-project.org/</a> ). The association between variables of interest and mutant clone expansion were evaluated through mixed-effects models (R package lme4 v1.1.34). Statistical power analyses were performed using the G*power software (v3.1.9.7) and the R package pwrss v0.3.1. |

For manuscripts utilizing custom algorithms or software that are central to the research but not yet described in published literature, software must be made available to editors and reviewers. We strongly encourage code deposition in a community repository (e.g. GitHub). See the Nature Portfolio [guidelines for submitting code & software](#) for further information.

## Data

Policy information about [availability of data](#)

All manuscripts must include a [data availability statement](#). This statement should provide the following information, where applicable:

- Accession codes, unique identifiers, or web links for publicly available datasets
- A description of any restrictions on data availability
- For clinical datasets or third party data, please ensure that the statement adheres to our [policy](#)

Clonal hematopoiesis-related mutations identified through high-sensitivity genomic DNA sequencing are listed in Supplementary Table 2. Other data from PESA participants are not publicly available for privacy and legal reasons. Access to these data can be requested to the PESA Scientific Committee via the corresponding authors or by e-mailing pesa-h@cnic.es. Data access will require a research proposal and approval by the PESA Scientific Committee, which meets every other month to evaluate such requests. To gain access, data requestors will need to sign a data access agreement and a non-disclosure agreement. Human genome build GRCh38 (GCF\_000001405.40) is available at <https://gatk.broadinstitute.org/hc/en-us/articles/360035890811-Resource-bundle>. The present article includes all other data generated or analyzed during this study.

## Research involving human participants, their data, or biological material

Policy information about studies with [human participants or human data](#). See also policy information about [sex, gender \(identity/presentation\), and sexual orientation](#) and [race, ethnicity and racism](#).

|                                                                    |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                       |
|--------------------------------------------------------------------|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| Reporting on sex and gender                                        | Sex was determined based on self-reporting, and validated based on sequencing data. 36% of the study population were women. Sex was considered in statistical analyses, as indicated in figure legends and main text.                                                                                                                                                                                                                                                                                                                                                                                                                                 |
| Reporting on race, ethnicity, or other socially relevant groupings | All participants in the cohort are Caucasian individuals of middle age, residing in the same geographical region, and possessing similar demographic characteristics.                                                                                                                                                                                                                                                                                                                                                                                                                                                                                 |
| Population characteristics                                         | Progression of Early Subclinical Atherosclerosis (PESA) is an observational, longitudinal and prospective cohort study of 4184 asymptomatic employees of the Santander Bank in Madrid who were 40 to 55 years old at the time of recruitment, between June 2010 and February 2014. Individuals with prior cardiovascular disease or any condition reducing life expectancy or affecting study adherence were not included. In the current study, the study population included 3,692 participants with available blood DNA samples, multimodal vascular imaging data at multiple timepoints and written informed consent for DNA sequencing analyses. |
| Recruitment                                                        | PESA study recruitment was based on volunteer participation, as described in <a href="https://doi.org/10.1016/j.ahj.2013.08.024">https://doi.org/10.1016/j.ahj.2013.08.024</a>                                                                                                                                                                                                                                                                                                                                                                                                                                                                        |
| Ethics oversight                                                   | The study protocol was approved by the Instituto de Salud Carlos III Ethics Committee (CEI PI_52/2019), and all eligible participants provided written informed consent.                                                                                                                                                                                                                                                                                                                                                                                                                                                                              |

Note that full information on the approval of the study protocol must also be provided in the manuscript.

## Field-specific reporting

Please select the one below that is the best fit for your research. If you are not sure, read the appropriate sections before making your selection.

☒ Life sciences ☐ Behavioural & social sciences ☐ Ecological, evolutionary & environmental sciences

For a reference copy of the document with all sections, see [nature.com/documents/nr-reporting-summary-flat.pdf](https://www.nature.com/documents/nr-reporting-summary-flat.pdf)

## Life sciences study design

All studies must disclose on these points even when the disclosure is negative.

|                 |                                                                                                                                                                                                                                                                                                                                                                                                                                                           |
|-----------------|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| Sample size     | No a priori sample size calculation was performed. The analyses within this work included all participants in the PESA cohort with available blood DNA samples, multimodal vascular imaging data at multiple timepoints and written informed consent for DNA sequencing analyses.                                                                                                                                                                         |
| Data exclusions | No exclusions                                                                                                                                                                                                                                                                                                                                                                                                                                             |
| Replication     | Not applicable to the current study, which is based on the integration of DNA sequencing data and multimodal non-invasive imaging data (including 3DVUS) collected at multiple timepoints in a population of apparently healthy individuals. No other comparable cohorts are currently available for replication.                                                                                                                                         |
| Randomization   | Not applicable to the analyses of the relationship between baseline CH and atherosclerosis burden. All PESA participants with available blood DNA samples, multimodal vascular imaging data at multiple time-points and written informed consent for DNA sequencing analyses were included in this part of the study. PESA participants included in the analysis of mutant clone expansion were selected randomly among CH mutation carriers at baseline. |
| Blinding        | To prevent potential biases, the analysis of imaging data, the sequencing of DNA samples, the bioinformatic processing of sequencing data,                                                                                                                                                                                                                                                                                                                |

the curation of somatic variants to identify CH driver mutations and the statistical analysis of associations were conducted independently by different investigators who were blind to other data.

# Reporting for specific materials, systems and methods

We require information from authors about some types of materials, experimental systems and methods used in many studies. Here, indicate whether each material, system or method listed is relevant to your study. If you are not sure if a list item applies to your research, read the appropriate section before selecting a response.

## Materials & experimental systems

| n/a                                 | Involved in the study                                  |
|-------------------------------------|--------------------------------------------------------|
| <input checked="" type="checkbox"/> | <input type="checkbox"/> Antibodies                    |
| <input checked="" type="checkbox"/> | <input type="checkbox"/> Eukaryotic cell lines         |
| <input checked="" type="checkbox"/> | <input type="checkbox"/> Palaeontology and archaeology |
| <input checked="" type="checkbox"/> | <input type="checkbox"/> Animals and other organisms   |
| <input checked="" type="checkbox"/> | <input type="checkbox"/> Clinical data                 |
| <input checked="" type="checkbox"/> | <input type="checkbox"/> Dual use research of concern  |
| <input checked="" type="checkbox"/> | <input type="checkbox"/> Plants                        |

## Methods

| n/a                                 | Involved in the study                           |
|-------------------------------------|-------------------------------------------------|
| <input checked="" type="checkbox"/> | <input type="checkbox"/> ChIP-seq               |
| <input checked="" type="checkbox"/> | <input type="checkbox"/> Flow cytometry         |
| <input checked="" type="checkbox"/> | <input type="checkbox"/> MRI-based neuroimaging |