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The ICGC/TCGA Pan-Cancer Analysis of Whole Genomes Consortium[§]

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Data availability

The PCAWG-generated alignments, somatic variant calls, annotations and derived data sets are available for general research use for browsing and download at http://dcc.icgc.org/pcawg/ (Box 1; Supplementary Table 4). In accordance with the data access policies of the ICGC and TCGA projects, most molecular, clinical and specimen data are in an open tier which does not require access approval. To access potentially identifying information, such as germline alleles and underlying read data, researchers will need to apply to the TCGA Data Access Committee (DAC) *via* dbGaP (https://dbgap.ncbi.nlm.nih.gov/aa/wga.cgi?page=login) for access to the TCGA portion of the data set, and to the ICGC Data Access Compliance Office (DACO; http://icgc.org/daco) for the ICGC portion. In addition, to access somatic single nucleotide variants derived from TCGA donors, researchers will also need to obtain dbGaP authorisation.

Beyond the core sequence data and variant call-sets, the analyses in this paper used a number of datasets that were derived from the variant calls (Supplementary Table 4). The individual data sets are available at Synapse (https://www.synapse.org/), and are denoted with synXXXXX accession numbers; all these datasets are also mirrored at https://dcc.icgc.org, with full links, filenames, accession numbers and descriptions detailed in Supplementary Table 4. The datasets encompass: clinical data from each patient including demographics, tumour stage and vital status (syn10389158); harmonised tumour histopathology annotations using a standardised hierarchical ontology (syn1038916); inferred purity and ploidy values for each tumour sample (syn8272483); driver mutations for each patient from their cancer genome spanning all classes of variant, and coding versus non-coding drivers (syn11639581); mutational signatures inferred from PCAWG donors (syn11804065), including APOBEC mutagenesis (syn7437313); and transcriptional data from RNA-sequencing, including gene expression levels (syn5553985, syn5553991, syn8105922) and gene fusions (syn10003873, syn7221157).

Code availability

Computational pipelines for calling somatic mutations are available to the public at https://dockstore.org. A range of data visualisation and exploration tools are also available for PCAWG data (Box 1).

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Integration, phasing, and validation of germline variant callsets

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Abstract

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Validation, benchmarking and merging of somatic variant calls

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Data and code availability

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Pan-cancer burden of somatic mutations

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Panorama of driver mutations in human cancer

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PCAWG tumours with no apparent driver mutations

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Patterns and oncogenicity of kataegis and chromoplexy

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Timing clustered mutational processes during tumour evolution

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Germline genetic determinants of the somatic mutation landscape

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Replicative Immortality

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Ethical considerations of genomic cloud computing

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Box 1: Online resources for data access, visualisation, exploration and analysis

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Methods 1.1 Validation Process

L Jonathan Dursi[12,25], Christina K Yung[15], Matthew H Bailey[26,27], Gordon Saksena[3], Keiran M Raine[1], Ivo Buchhalter[28,29,30], Kortine Kleinheinz[28,30], Matthias Schlesner[28,31], Yu Fan[32], David Torrents[40,76], Matthias Bieg[139,140], Paul C Boutros[12,18,20,21], Ken Chen[141], Zechen Chong[142], Kristian Cibulskis[3], Oliver Drechsel[47,49], Roland Eils[28,30,143,144], Robert S Fulton[26,27,35], Josep Gelpi[40,145], Mark Gerstein[63,64,69], Santiago Gonzalez[7,8], Gad Getz[3,4,5,6], Ivo G Gut[49,74], Faraz Hach[146,147], Michael Heinold[28,30], Taobo Hu[148], Vincent Huang[12], Barbara Hutter[140,149,150], Hyung-Lae Kim[56], Natalie Jäger[28], Jongsun Jung[151], Sushant Kumar[63,64], Yogesh Kumar[148], Christopher Lalansingh[12], Ignaty Leshchiner[3], Ivica Letunic[62], Dimitri Livitz[3], Eric Z Ma[148], Yosef Maruvka[3,19,152], R Jay Mashl[27,57], Michael D McLellan[26,27,35], Ana Milovanovic[40], Morten Muhlig Nielsen[153], Brian O'Connor[15,37], Stephan Ossowski[47,48,49], Nagarajan Paramasivam[28,140], Jakob Skou Pedersen[153,154], Marc D Perry[14,15], Montserrat Puiggròs[40], Romina Royo[40], Esther Rheinbay[3,6,19], S Cenk Sahinalp[147,155,156],

Cancer is driven by genetic change, and the advent of massively parallel sequencing has enabled

Iman Sarrafi[147,156], Chip Stewart[3], Miranda D Stobbe[49,74], Grace Tiao[3], Jeremiah A Wala[3,6,157], Jiayin Wang[27,58,158], Wenyi Wang[32], Sebastian M Waszak[8], Joachim Weischenfeldt[8,99,100], Michael Wendl[27,159,160], Johannes Werner[28,161], Zhenggang Wu[148], Hong Xue[148], Sergei Yakneen[8], Takafumi N Yamaguchi[12], Kai Ye[58,59], Venkata Yellapantula[67,68], Junjun Zhang[15], David A Wheeler[33,34], Li Ding[26,27,35] and Jared T Simpson[12,36]

Methods 1.2 Processing of Validation Data

Christina K Yung[15], Brian D O'Connor[15,37], Sergei Yakneen[8], Junjun Zhang[15], Kyle Ellrott[38], Kortine Kleinheinz[28,30], Naoki Miyoshi[39], Keiran M Raine[1], Romina Royo[40], Gordon Saksena[3], Matthias Schlesner[28,31], Solomon I Shorser[12], Miguel Vazquez[40,41], Joachim Weischenfeldt[8,99,100], Denis Yuen[12], Adam P Butler[1], Brandi N Davis-Dusenbery[162], Roland Eils[28,30,143,144], Vincent Ferretti[15,86], Robert L Grossman[163], Olivier Harismendy[125], Youngwook Kim[164,165], Hidewaki Nakagawa[81], Steven J Newhouse[7], David Torrents[40,76] and Lincoln D Stein[12,13]

Methods 2. Whole Genome Sequencing Somatic Variant Calling

Junjun Zhang[15], Christina K Yung[15] and Solomon I Shorser[12]

Methods 2.1 Whole Genome Alignment

Keiran M Raine[1], Junjun Zhang[15] and Brian O'Connor[15,37]

Methods 2.2.1 DKFZ Pipeline

Kortine Kleinheinz[28,30], Tobias Rausch[8], Jan O Korbel[7,8], Ivo Buchhalter[28,29,30], Michael C Heinold[28,30], Barbara Hutter[140,149,150], Natalie Jäger[28], Nagarajan Paramasivam[28,140] and Matthias Schlesner[28,31]

Methods 2.2.2 EMBL Pipeline

Joachim Weischenfeldt[8,99,100], Tobias Rausch[8]

Methods 2.2.3 Sanger Pipeline

Keiran M Raine[1], Jonathan Hinton[1], David R Jones[1], Andrew Menzies[1] and Lucy Stebbings[1]

Methods 2.2.4 Broad Pipeline

Gordon Saksena[3], Dimitri Livitz[3], Esther Rheinbay[3,6,19], Julian M Hess[3,152], Ignaty Leshchiner[3], Chip Stewart[3], Grace Tiao[3], Jeremiah A Wala[3,6,157], Amaro Taylor-Weiner[90], Mara Rosenberg[3,19], Andrew J Dunford[3], Manaswi Gupta[3], Marcin Imielinski[166,167], Matthew Meyerson[3,6,157], Rameen Beroukhim[3,6,168] and Gad Getz[3,4,5,6]

Methods 2.2.5 MuSE Pipeline

Yu Fan[32] and Wenyi Wang[32]

Methods 2.3 Consensus Somatic SNV/Indel Annotation

Andrew Menzies[1], Matthias Schlesner[28,31], Jüri Reimand[12,18], Priyanka Dhingra[71,73] and Ekta Khurana[70,71,72,73]

Methods 2.4.1 Somatic SNV and indel Merging

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Methods 2.4.2 Somatic SV Merging

Joachim Weischenfeldt[8,99,100], Francesco Favero[169] and Yilong Li[1]

Methods 2.4.3 Somatic Copy Number Alteration Merging

Stefan Dentro[1,65,91], Jeff Wintersinger[170,171,172] and Ignaty Leshchiner[3]

Methods 2.5.3 Oxidative Artefact Filtration

Dimitri Livitz[3], Ignaty Leshchiner[3], Chip Stewart[3], Esther Rheinbay[3,6,19], Gordon Saksena[3] and Gad Getz[3,4,5,6]

Methods 2.5.4 Strand Bias Filtration

Matthias Bieg[139,140], Ivo Buchhalter[28,29,30], Johannes Werner[28,161] and Matthias Schlesner[28,31]

Methods 2.6 miniBAM generation

Jeremiah Wala[3,6,157], Gordon Saksena[3], Rameen Beroukhim[3,6,168] and Gad Getz[3,4,5,6]

Methods 3. Germline Variant Identification from WGS

Tobias Rausch[8], Grace Tiao[3], Sebastian M Waszak[8], Bernardo Rodriguez-Martin[42,43,44], Suyash Shringarpure[45], Dai-Ying Wu[46], Sergei Yakneen[8], German M Demidov[47,48,49], Olivier Delaneau[50,51,52], Shuto Hayashi[39], Seiya Imoto[39,39], Nina Habermann[8], Ayellet V Segre[3,53], Erik Garrison[1], Andy Cafferkey[7], Eva G Alvarez[42,43,44], Alicia L Bruzos[42,43,44], Jorge Zamora[1,42,43,44], José María Heredia-Genestar[54], Francesc Muyas[47,48,49], Oliver Drechsel[47,49], L Jonathan Dursi[12,25], Adrian Baez-Ortega[55], Hyung-Lae Kim[56], Matthew H Bailey[26,27], R Jay Mashl[27,57], Kai Ye[58,59], Ivo Buchhalter[28,29,30], Vasilisa Rudneva[8], Ji Wan Park[173], Eun Pyo Hong[173], Seong Gu Heo[173], Anthony DiBiase[60], Kuan-lin Huang[27,61], Ivica Letunic[62], Michael D McLellan[26,27,35], Steven J Newhouse[7], Matthias Schlesner[28,31], Tal Shmaya[46], Sushant Kumar[63,64], David C Wedge[1,65,66], Mark H Wright[45], Venkata D Yellapantula[67,68], Mark Gerstein[63,64,69], Ekta Khurana[70,71,72,73], Tomas Marques-

systematic documentation of this variation at whole genome scale[1–3]. We report the integrative

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Methods 4. RNA-Seq analysis

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Methods 5. Clustering of tumour genomes based on telomere maintenance-related features

David Haan[9], Lincoln D Stein[12,13] and Joshua M Stuart[9]

Methods 6. Clustered mutational processes in PCAWG

Jonas Demeulemeester[91,92], Maxime Tarabichi[1,91], Matthew W Fittall[91], Peter J Campbell[1,2], Jan O Korbel[7,8] and Peter Van Loo[91,92]

Methods 7. Tumours without detected driver mutations

Esther Rheinbay[3,6,19], Amaro Taylor-Weiner[90], Radhakrishnan Sabarinathan[87,88,89], Peter J Campbell[1,2] and Gad Getz[3,4,5,6]

Methods 8. Panorama of driver mutations in human cancer

Radhakrishnan Sabarinathan[87,88,89], Oriol Pich[87,89], Iñigo Martincorena[1], Carlota Rubio-Perez[87,89,203], Malene Juul[153], Jeremiah Wala[3,6,157], Steven Schumacher[3,204], Ofer Shapira[3,157], Nikos Sidiropoulos[100], Sebastian M Waszak[8], David Tamborero[87,89], Loris Mularoni[87,89], Esther Rheinbay[3,6,19], Henrik Hornshøj[153], Jordi Deu-Pons[89,205], Ferran Muiños[87,89], Johanna Bertl[153,206], Qianyun Guo[154], Chad J Creighton[200], Joachim Weischenfeldt[8,99,100], Jan O Korbel[7,8], Gad Getz[3,4,5,6], Peter J Campbell[1,2], Jakob Pedersen[153,154], Rameen Beroukhim[3,6,168] and Abel Gonzalez-Perez[87,89,207]

Notes 1. Pilot-63 benchmarking, variant consensus development and validation

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Notes 4. Production somatic variant calling on the PCAWG Compute Cloud

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Notes 5. PCAWG data portals

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analysis of >2,600 whole cancer genomes and their matching normal tissues across 38 tumour

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Novel somatic mutation calling methods

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types, by the ICGC/TCGA Pan-Cancer Analysis of Whole Genomes (PCAWG) consortium. We

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describe the generation of the PCAWG resource, facilitated by international data sharing using

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Providers of tumour sequencing data

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compute clouds. Cancer genomes contained 4-5 driver mutations on average when combining

Tumour Specific Providers – Australia (Ovarian cancer)
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Tumour Specific Providers – Australia (Pancreatic cancer)
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Tumour Specific Providers – Australia (Skin cancer)
Lauri A Aaltonen[111], Andreas Behren[435], Hazel Burke[436], Jonathan Cebon[435], Rebecca A Dagg[437], Ricardo De Paoli-Iseppi[438], Ken Dutton-Regester[340], Matthew A Field[439], Anna Fitzgerald[440], Sean M Grimmond[368], Peter Hersey[436], Oliver Holmes[340,341], Valerie Jakrot[436], Peter A Johansson[340], Hojabr Kakavand[438], Stephen H Kazakoff[340,341], Richard F Kefford[441], Loretta MS Lau[442], Conrad R Leonard[340,341], Georgina V Long[443], Felicity Newell[340,341], Katia Nones[340,341], Ann-Marie Patch[340,341], John V Pearson[340,341], Hilda A Pickett[442], Antonia L Pritchard[340], Gulietta M Pupo[444], Robyn PM Saw[443], Sarah-Jane Schramm[445], Mark Shackleton[271], Catherine A Shang[440], Ping Shang[443], Andrew J Spillane[443], Jonathan R Stretch[443], Varsha Tembe[445], John F Thompson[443], Ricardo E Vilain[446], Nick M Waddell[341], Nicola Waddell[340,341], James S Wilmott[443], Scott Wood[340,341], Qinying Xu[340,341], Jean Y Yang[447], Nicholas K Hayward[340,436], Graham J Mann[448,449] and Richard A Scolyer[413,443,446,450]

Tumour Specific Providers – Canada (Pancreatic cancer)
John Bartlett[451,452], Prashant Bavi[453], Ivan Borozan[12], Dianne E Chadwick[454], Michelle Chan-Seng-Yue[453], Sean Cleary[453,455], Ashton A Connor[455,456], Karolina Czajka[241], Robert E Denroche[453], Neesha C Dhani[457], Jenna Eagles[241], Vincent Ferretti[15,86], Steven Gallinger[453,455,456], Robert C Grant[453,456], David Hedley[457], Michael A Hollingsworth[458], Gun Ho Jang[453], Jeremy Johns[241], Sangeetha Kalimuthu[453], Sheng-Ben Liang[459], Ilinca Lungu[453,460], Xuemei Luo[12], Faridah Mbabaali[241], Treasa A McPherson[456], Jessica K Miller[241], Malcolm J Moore[457], Faiyaz Notta[453,461], Danielle Pasternack[241], Gloria M Petersen[462], Michael H A Roehrl[18,453,463,464,465], Michelle Sam[241], Iris Selander[456], Stefano Serra[411], Sagedeh Shahabi[459], Morgan L Taschuk[15], Sarah P Thayer[458], Lee E Timms[241], Gavin W Wilson[12,453], Julie M Wilson[453], Bradly G Wouters[466], Thomas J Hudson[240,241], John D McPherson[241,453,467] and Lincoln D Stein[12,13]

Tumour Specific Providers – Canada (Prostate cancer)
Timothy A Beck[15,468], Vinayak Bhandari[12], Colin C Collins[147], Shadrielle MG Espiritu[12], Neil E Fleshner[469], Natalie S Fox[12], Michael Fraser[12], Syed Haider[12], Lawrence E Heisler[470], Vincent Huang[12], Emilie Lalonde[12], Julie Livingstone[12], John D McPherson[241,453,467], Alice Meng[471], Veronica Y Sabelnykova[12], Adriana Salcedo[12], Yu-Jia Shiah[12], Theodorus Van der Kwast[472], Takafumi N Yamaguchi[12], Paul C Boutros[12,18,20,21] and Robert G Bristow[18,473,474,475,476]

Tumour Specific Providers – China (Gastric cancer)
Shuai Ding[477], Daiming Fan[478], Yong Hou[180,181], Yi Huang[158,257], Lin Li[180], Siliang Li[180,181], Dongbing Liu[180,181], Xingmin Liu[180,181], Yongzhan Nie[478,479], Hong Su[180,181], Jian Wang[180], Kui Wu[180,181], Xiao Xiao[158], Rui Xing[222,480], Shanlin Yang[477], Yingyan Yu[481], Xiuqing Zhang[180], Yong Zhou[180], Shida Zhu[180,181], Youyong Lu[221,222,223] and Huanming Yang[180]

Tumour Specific Providers – EU: France (Renal cancer)
Rosamonde E Banks[482], Guillaume Bourque[483,484], Alvis Brazma[7], Paul Brennan[485], Louis Letourneau[486], Yasser Riazalhosseini[484], Ghislaine Scelo[485], Naveen Vasudev[487], Juris Viksna[488], Mark Lathrop[484] and Jörg Tost[489]

Tumour Specific Providers – EU: United Kingdom (Breast cancer)
Sung-Min Ahn[490], Ludmil B Alexandrov[1,101], Samuel Aparicio[491], Laurent Arnould[492], MR Aure[493], Shriram G Bhosle[1], E Birney[7], Ake Borg[494], S Boyault[495], AB Brinkman[496], JE Brock[497], A Broeks[498], Adam P Butler[1], AL Børresen-Dale[493], C Caldas[499,500], Peter J Campbell[1,2], Suet-Feung Chin[499,500], Helen Davies[1,351,352], C Desmedt[501,502], L Dirix[503], S Dronov[1], Anna Ehinger[504], JE Eyfjord[505], A Fatima[204], JA Foekens[506], PA Futreal[507], Øystein Garred[508,509], Moritz Gerstung[7,8], Dilip D Giri[510], D Glodzik[1], Dorthe Grabau[511], Holmfridur Hilmarsdottir[505], GK Hooijer[512], Jocelyne Jacquemier[513], SJ Jang[514], Jon G Jonasson[505], Jos Jonkers[515], HY Kim[513], Tari A King[516,517], Stian Knappskog[1,518,518], G Kong[513], S Krishnamurthy[519], SR

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coding and non-coding genomic elements, but ~5% of cases had no drivers identified, suggesting

Lakhani[520], Anita Langerød[493], Denis Larsimont[521], HJ Lee[514], JY Lee[522], Ming Ta Michael Lee[507], Yilong Li[1], Ole Christian Lingjærde[523], Gaetan MacGrogan[524], JWM Martens[506], Sancha Martin[1,362], Iñigo Martincorena[1], Andrew Menzies[1], Sandro Morganella[1], Ville Mustonen[347,348,349], Serena Nik-Zainal[1,351,352,353], Sarah O'Meara[1], I Pauporté[214], Sarah Pinder[525], X Pivot[526], Elena Provenzano[527], CA Purdie[528], Keiran M Raine[1], M Ramakrishna[1], K Ramakrishnan[1], Jorge Reis-Filho[510], AL Richardson[204], M Ringnér[494], Javier Bartolomé Rodriguez[40], FG Rodríguez-González[261], G Romieu[529], Roberto Salgado[411], Torill Sauer[523], R Shepherd[1], AM Sieuwerts[506], PT Simpson[520], M Smid[506], C Sotiriou[234], PN Span[530], Lucy Stebbings[1], Ólafur Andri Stefánsson[531], Alasdair Stenhouse[532], HG Stunnenberg[181,533], Fred Sweep[534], BK Tan[535], Jon W Teague[1], Gilles Thomas[536], AM Thompson[532], S Tommasi[537], I Treilleux[538,539], Andrew Tutt[204], NT Ueno[387], S Van Laere[503], Peter Van Loo[91,92], GG Van den Eynden[503], P Vermeulen[503], Alain Viari[419], A Vincent-Salomon[533], David C Wedge[1,65,66], Bernice Huimin Wong[540], Lucy Yates[1], X Zou[1], CHM van Deurzen[541], MJ van de Vijver[411], L van't Veer[542] and Michael Rudolf Stratton[1]

Tumour Specific Providers – Germany (Malignant lymphoma)

Ole Ammerpohl[543,544], Sietse Aukema[545,546], Anke K Bergmann[547], Stephan H Bernhart[311,312,315], Hans Binder[311,312], Arndt Borkhardt[548], Christoph Borst[549], Benedikt Brors[127,150,323], Birgit Burkhardt[550], Alexander Claviez[551], Roland Eils[28,30,143,144], Maria Elisabeth Goebler[552], Andrea Haake[543], Siegfried Haas[549], Martin Hansmann[553], Jessica I Hoell[548], Steve Hoffmann[311,312,314,315], Michael Hummel[554], Daniel Hübschmann[30,120,143,242,243], Dennis Karsch[555], Wolfram Klapper[545], Kortine Kleinheinz[28,30], Michael Kneba[555], Jan O Korbel[7,8], Helene Kretzmer[312,315], Markus Kreuz[556], Dieter Kube[557], Ralf Küppers[558], Chris Lawerenz[144], Dido Lenze[554], Peter Lichter[149,399], Markus Loeffler[556], Cristina López[80,543], Luisa Mantovani-Löffler[559], Peter Möller[560], German Ott[561], Bernhard Radlwimmer[399], Julia Richter[543,545], Marius Rohde[562], Philip C Rosenstiel[563], Andreas Rosenwald[564], Markus B Schilhabel[563], Matthias Schlesner[28,31], Stefan Schreiber[565], Peter F Stadler[311,312,315], Peter Staib[566], Stephan Stilgenbauer[567], Stephanie Sungalee[8], Monika Szczepanowski[545], Umut H Toprak[30,568], Lorenz HP Trümper[557], Rabea Wagener[80,543], Thorsten Zenz[150] and Reiner Siebert[79,80]

Tumour Specific Providers – Germany (Paediatric Brain cancer)

Ivo Buchhalter[28,29,30], Juergen Eils[143,144], Roland Eils[28,30,143,144], Volker Hovestadt[399], Barbara Hutter[140,149,150], David TW Jones[331,332], Natalie Jäger[28], Christof von Kalle[120], Marcel Kool[246,331], Jan O Korbel[7,8], Andrey Korshunov[246], Pablo Landgraf[569,570], Chris Lawerenz[144], Hans Lehrach[571], Paul A Northcott[572], Stefan M Pfister[246,331,573], Bernhard Radlwimmer[399], Guido Reifenberger[570], Matthias Schlesner[28,31], Hans-Jörg Warnatz[571], Joachim Weischenfeldt[8,99,100], Stephan Wolf[574], Marie-Laure Yaspo[571], Marc Zapatka[399] and Peter Lichter[149,399]

Tumour Specific Providers – Germany (Prostate cancer)

Yassen Assenov[575], Benedikt Brors[127,150,323], Juergen Eils[143,144], Roland Eils[28,30,143,144], Lars Feuerbach[127], Clarissa Gerhauser[320], Jan O Korbel[7,8], Chris Lawerenz[144], Hans Lehrach[571], Sarah Minner[576], Christoph Plass[320], Thorsten Schlomm[99,577], Nikos Sidiropoulos[100], Ronald Simon[578], Hans-Jörg Warnatz[571], Dieter Weichenhan[320], Joachim Weischenfeldt[8,99,100], Marie-Laure Yaspo[571], Guido Sauter[578] and Holger Sültmann[150,579]

Tumour Specific Providers – India (Oral cancer)

Nidhan K Biswas[580], Luca Landoni[415], Arindam Maitra[580], Partha P Majumder[580] and Rajiv Sarin[581]

Tumour Specific Providers – Italy (Pancreatic cancer)

Davide Antonello[415], Stefano Barbi[423], Claudio Bassi[415], Samantha Bersani[418], Giada Bonizzato[419], Cinzia Cantù[419], Ivana Cataldo[418,419], Sara Cingarlini[229], Vincenzo Corbo[419,423], Maria Vittoria Davi[424], Angelo P Dei Tos[582], Matteo Fassan[583], Sonia Grimaldi[419], Luca Landoni[415], Rita T Lawlor[419], Claudio Luchini[418], Andrea Mafficini[419], Giuseppe Malleo[415], Giovanni Marchegiani[415], Michele Milella[229], Marco Miotto[415], Salvatore Paiella[415], Antonio Pea[415], Paolo Pederzoli[415], Borislav C Rusev[419], Andrea Ruzzenente[415], Roberto Salvia[415], Maria Scardoni[418], Elisabetta Sereni[415], Michele Simbolo[423], Nicola Sperandio[419], Giampaolo Tortora[229,230], Caterina Vicentini[419] and Aldo Scarpa[419]

Tumour Specific Providers – Japan (Biliary tract cancer)

Yasuhito Arai[226], Natsuko Hama[226], Nobuyoshi Hiraoka[584], Fumie Hosoda[226,226], Mamoru Kato[361], Hiromi Nakamura[226], Hidenori Ojima[585], Takuji Okusaka[586], Yasushi Totoki[226], Tomoko Urushidate[227] and Tatsuhiro Shibata[226,227]

Tumour Specific Providers – Japan (Gastric cancer)

Yasuhito Arai[226], Masashi Fukayama[587], Natsuko Hama[226], Fumie Hosoda[226,226], Shumpei Ishikawa[588], Hitoshi Katai[589], Mamoru Kato[361], Hiroto Katoh[588], Daisuke Komura[588], Genta Nagae[310,318], Hiromi Nakamura[226], Hirofumi Rokutan[361], Mihoko Saito-Adachi[361], Akihiro Suzuki[310,590], Hirokazu Taniguchi[591], Kenji Tatsuno[310], Yasushi Totoki[226], Tetsuo Ushiku[587], Shinichi Yachida[226,592], Shogo Yamamoto[310], Hiroyuki Aburatani[310] and Tatsuhiro Shibata[226,227]

Tumour Specific Providers – Japan (Liver cancer)

Hiroyuki Aburatani[310], Hiroshi Aikata[593], Koji Arihiro[593], Shun-ichi Ariizumi[594], Keith A Boroevich[81,233], Kazuaki Chayama[593], Akihiro Fujimoto[81], Masashi Fujita[81], Mayuko Furuta[81], Kunihito Gotoh[595], Natsuko Hama[226], Takanori Hasegawa[39], Shinya Hayami[596], Shuto Hayashi[39], Satoshi Hirano[597], Seiya Imoto[39,39], Mamoru Kato[361], Yoshiiku Kawakami[593], Kazuhiro Maejima[81], Satoru Miyano[39], Genta Nagae[310,318], Hiromi Nakamura[226], Toru Nakamura[597], Kaoru Nakano[81], Hideki Ohdan[593], Aya Sasaki-Oku[81], Yuichi Shiraishi[39], Hiroko Tanaka[39], Yasushi Totoki[226], Tatsuhiko Tsunoda[233,294,295,296], Masaki Ueno[596], Rui Yamaguchi[39], Masakazu Yamamoto[594], Hiroki Yamaue[596], Hidewaki Nakagawa[81] and Tatsuhiro Shibata[226,227]

Tumour Specific Providers – Singapore (Biliary tract cancer)

Su Pin Choo[598], Ioana Cutcutache[196,346], Narong Khuntikeo[415,599], John R McPherson[196,346], Choon Kiat Ong[600], Chawalit Pairojkul[411], Irinel Popescu[601], Steven G Rozen[196,197,346], Patrick Tan[190,195,196,197] and Bin Tean Teh[195,196,197,198,199]

Tumour Specific Providers – South Korea (Blood cancer)

Keun Soo Ahn[602], Hyung-Lae Kim[56], Youngil Koh[336,337] and Sung-Soo Yoon[337]

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that cancer driver discovery is not yet complete. Chromothripsis is frequently an early event in

Tumour Specific Providers – Spain (Chronic Lymphocytic Leukaemia)
Marta Aymerich[603], Josep Ll Gelpi[40,145], Ivo G Gut[49,74], Marta Gut[49,74], Armando Lopez-Guillermo[604], Carlos López-Otín[605], Xose S Puente[605], Romina Royo[40], David Torrents[40,76] and Elias Campo[606,607]
Tumour Specific Providers – United Kingdom (Bone cancer)
Fernanda Amary[608], Daniel Baumhoer[609], Sam Behjati[1], Bodil Bjerkehagen[609,610], PA Futreal[507], Ola Myklebost[518], Nischalan Pillay[611], Patrick Tarpey[612], Roberto Tirabosco[613], Olga Zaikova[614], Peter J Campbell[1,2] and Adrienne M Flanagan[615]
Tumour Specific Providers – United Kingdom (Chronic myeloid disorders)
Jacqueline Boultwood[616], David T Bowen[1], Adam P Butler[1], Mario Cazzola[617], Carlo Gambacorti-Passerini[270], Anthony R Green[329], Eva Hellstrom-Lindberg[618], Luca Malcovati[617], Sancha Martin[1,362], Jyoti Nangalia[619], Elli Papaemmanuil[1], Paresh Vyas[340,620] and Peter J Campbell[1,2]
Tumour Specific Providers – United Kingdom (Oesophageal cancer)
Yeng Ang[621], Hugh Barr[622], Duncan Beardsmore[623], Matthew Eldridge[328], James Gossage[624], Nicola Grehan[352], George B Hanna[625], Stephen J Hayes[626,627], Ted R Hupp[628], David Khoo[629], Jesper Lagergren[618,630], Laurence B Lovat[189], Shona MacRae[137], Maria O'Donovan[352], J Robert O'Neill[631], Simon L Parsons[632], Shaun R Preston[633], Sonia Puig[634], Tom Roques[635], Grant Sanders[24], Sharmila Sothi[636], Simon Tavaré[328], Olga Tucker[637], Richard Turkington[638], Timothy J Underwood[639], Ian Welch[640] and Rebecca C Fitzgerald[352]
Tumour Specific Providers – United Kingdom (Prostate cancer)
Daniel M Berney[641], Johann S De Bono[396], G Steven Bova[126], Daniel S Brewer[394,395], Adam P Butler[1], Declan Cahill[642], Niedzica Camacho[396], Nening M Dennis[642], Tim Dudderidge[642,643], Sandra E Edwards[396], Cyril Fisher[642], Christopher S Foster[644,645], Mohammed Ghori[1], Pelvender Gill[620], Vincent J Gnanapragasam[379,646], Gunes Gundem[278], Freddie C Hamdy[647], Steve Hawkins[328], Steven Hazell[642], William Howat[379], William B Isaacs[648], Katalin Karaszi[620], Jonathan D Kay[189], Vincent Khoo[642], Zsofia Kote-Jarai[396], Barbara Kremeyer[1], Pardeep Kumar[642], Adam Lambert[620], Daniel A Leongamornlert[1,396], Naomi Livni[642], Yong-Jie Lu[641,649], Hayley J Luxton[189], Andy G Lynch[328,329,339], Luke Marsden[620], Charlie E Massie[328], Lucy Matthews[396], Erik Mayer[642,650], Ultan McDermott[1], Sue Merson[396], Thomas J Mitchell[1,329,379], David E Neal[328,379], Anthony Ng[651], David Nicol[642], Christopher Ogden[642], Edward W Rowe[642], Nimish C Shah[379], Jon W Teague[1], Sarah Thomas[642], Alan Thompson[642], Peter Van Loo[91,92], Clare Verrill[620,652], Tapio Visakorpi[126], Anne Y Warren[379,653], David C Wedge[1,65,66], Hayley C Whitaker[189], Jorge Zamora[1,42,43,44], Hongwei Zhang[649], Nicholas van As[642], Colin S Cooper[395,396,397] and Rosalind A Eeles[396,642]
Tumour Specific Providers – United States (TCGA)
Adam Abeshouse[278], Nishant Agrawal[163], Rehan Akbani[352,654], Hikmat Al-Ahmadie[278], Monique Albert[452], Kenneth Aldape[400,655], Adrian Ally[656], Yeng Ang[621], Elizabeth L Appelbaum[27,189], Joshua Armenia[657], Sylvia Asa[632,658], J Todd Auman[659], Matthew H Bailey[26,27], Miruna Balasundaram[656], Saianand Balu[24], Jill Barnholtz-Sloan[660,661], Hugh Barr[622], John Bartlett[451,452], Oliver F Bathe[662,663], Stephen B Baylin[123,643], Duncan Beardsmore[623], Christopher Benz[664], Andrew Berchuck[665], Benjamin P Berman[313,321,322], Rameen Beroukhim[3,6,168], Mario Berrios[666], Darell Bigner[667], Michael Birrer[19], Tom Bodenheimer[24], Lori Boice[634], Moiz S Bootwalla[666], Marcus Bosenberg[668], Reanne Bowlby[656], Jeffrey Boyd[669], Russell R Broaddus[400], Malcolm Brock[670], Denise Brooks[656], Susan Bullman[3,168], Samantha J Caesar-Johnson[231], Thomas E Carey[671], Rebecca Carlsen[656], Robert Cerfolio[672], Vishal S Chandan[673], Hsiao-Wei Chen[621,657], Andrew D Cherniack[3,3,157,168], Jeremy Chien[674], Juok Cho[3], Eric Chuah[656], Carrie Cibulskis[3], Kristian Cibulskis[3], Leslie Cope[675], Matthew G Cordes[27,635], Kyle Covington[34], Erin Curley[676], Bogdan Czerniak[400,629], Ludmila Danilova[675], Ian J Davis[677], Timothy Defreitas[3], John A Demchok[231], Noreen Dhalla[656], Rajiv Dhir[678], Li Ding[26,27,35], HarshaVardhan Doddapaneni[34], Adel El-Naggar[400,629], Ina Felau[231], Martin L Ferguson[679], Gaetano Finocchiaro[680], Kwun M Fong[681], Scott Frazer[3], William Friedman[682], Catrina C Fronick[27,635], Lucinda A Fulton[27], Robert S Fulton[26,27,35], Stacey B Gabriel[3], Jianjiong Gao[657], Nils Gehlenborg[3,683], Jeffrey E Gershenwald[684,685], Gad Getz[3,4,5,6], Ronald Ghossein[510], Nasra H Giama[686], Richard A Gibbs[34], Carmen Gomez[687], James Gossage[624], Ramaswamy Govindan[26], Nicola Grehan[352], George B Hanna[625], D Neil Hayes[24,688,689], Stephen J Hayes[626,627], Apurva M Hegde[137,138], David I Heiman[3], Zachary Heins[278], Austin J Hepperla[24], Katherine A Hoadley[23,24], Andrea Holbrook[666], Robert A Holt[656], Alan P Hoyle[24], Ralph H Hruban[675,675], Jianhong Hu[34], Mei Huang[634], David Huntsman[690], Ted R Hupp[628], Jason Huse[278], Christine A Iacobuzio-Donahue[510], Michael Ittmann[691,692], Joy C Jayaseelan[34], Stuart R Jefferys[24], Corbin D Jones[693], Steven JM Jones[694], Hartmut Juhl[695], Koo Jeong Kang[696], Beth Karlan[697], Katayoon Kasaian[694], Electron Kebebew[698,699], David Khoo[629], Hark Kyun Kim[700], Jaegil Kim[3], Tari A King[516,517], Viktoriya Korchina[34], Ritika Kundra[621,657], Jesper Lagergren[618,630], Phillip H Lai[666], Peter W Laird[316], Eric Lander[3], Michael S Lawrence[3,19,233], Alexander J Lazar[22], Xuan Le[701], Darlene Lee[656], Douglas A Levine[278,702], Lora Lewis[34], Tim Ley[703], Haiyan Irene Li[656], Pei Lin[3], W M Linehan[704], Eric Minwei Liu[71,73,278], Fei Fei Liu[380], Laurence B Lovat[189], Yiling Lu[138], Lisa Lype[705], Yussanne Ma[656], Shona MacRae[137], Dennis T Maglinte[666,706], Elaine R Mardis[27,669,707], Jeffrey Marks[415,708], Marco A Marra[656], Thomas J Matthew[37], Michael Mayo[656], Karen McCune[709], Michael D McLellan[26,27,35], Samuel R Meier[3], Shaowu Meng[24], Matthew Meyerson[3,6,157], Piotr A Mieczkowski[23], Tom Mikkelsen[710], Christopher A Miller[27], Gordon B Mills[711], Richard A Moore[656], Carl Morrison[411,712], Lisle E Mose[24], Catherine D Moser[686], Andrew J Mungall[656], Karen Mungall[656], David Mutch[713], Donna M Muzny[714], Jerome Myers[715], Yulia Newton[37], Michael S Noble[3], Peter O'Donnell[716], Brian Patrick O'Neill[717], Angelica Ochoa[278], Akinyemi I Ojesina[191,192,193], Joong-Won Park[718], Joel S Parker[719], Simon L Parsons[632], Harvey Pass[720], Alessandro Pastore[112], Chandra Sekhar Pedamallu[3,6,168], Nathan A Pennell[721], Charles M Perou[722], Gloria M Petersen[462], Nicholas Petrelli[723], Olga Potapova[724], Shaun R Preston[633], Sonia Puig[634], Janet S Rader[725], Suresh Ramalingam[726], W Kimryn Rathmell[727], Victor Reuter[510], Sheila M Reynolds[705], Matthew Ringel[728], Jeffrey Roach[729], Lewis R Roberts[686], A Gordon Robertson[656], Tom Roques[635], Mark A Rubin[274,287,288,289,290], Sara Sadeghi[656], Gordon Saksena[3],

tumour evolution: in acral melanoma, for example, these clustered events precede most somatic

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point mutations and affect several cancer genes simultaneously. Cancers with abnormal telomere

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maintenance often originate in tissues with low replicative activity, with several different

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mechanisms of escaping critical telomere attrition. Common and rare germline variants affect

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patterns of somatic mutation, including point mutations, structural variants and somatic

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retrotransposition. PCAWG found few non-coding mutations that drive cancer beyond those in the

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TERT promoter[4]; identified new signatures of mutational processes causing base substitutions,

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genes and promoter activity[8,9]; and evaluated a range of more specialised features of cancer

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genomes[8,10–18].

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Cancer is the second most frequent cause of death worldwide, killing more than 8 million

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is a catch-all term used to denote a set of diseases characterised by autonomous expansion

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Competing interests

The following authors declare that they have competing interests: **Hikmat Al-Ahmadie** (H. A. is consultant to AstraZeneca and Bristol-Myers-Squibb); **Samuel Aparicio** (Founder and shareholder of Contextual Genomics Inc.); **Pratiti Bandopadhayay** (P.B. receives grant funding from Novartis from an unrelated project.); **Rameen Beroukhim** (R.B. owns equity in Ampressa Therapeutics); **Andrew Biankin** (Grant funding from Celgene, AstraZeneca; Consultancies/Advisory boards: AstraZeneca, Celgene, Elstar Therapeutics, Clovis Oncology, Roche.); **E Birney** (Consultant to Oxford Nanopore, Dovetail and GSK); **Marcus Bosenberg** (Eli Lilly and Company); **Atul Butte** (A.B. is a co-founder and consultant to Personalis, NuMedii; consultant to Samsung, Geisinger Health, Mango Tree Corporation, Regenstrief Institute, and in the recent past 10x Genomics and Helix; shareholder in Personalis; minor shareholder in Apple, Twitter, Facebook, Google, Microsoft, Sarepta, 10x Genomics, Amazon, Biogen, CVS, Illumina, Snap, and Sutro; and has received honoraria and travel reimbursement for invited talks from Genentech, Roche, Pfizer, Optum, AbbVie, and many academic institutions and health systems.); **C Caldas** (C.C. has served on the Scientific Advisory Board of Illumina.); **Lorraine Chantrill** (L.C. acted on an advisory board for AMGEN Australia in the last 2 years.); **Andrew D Cherniack** (A.D.C. receives research funding from Bayer AG.); **Helen Davies** (Helen Davies is an inventor on a number of patent filings encompassing the use of mutational signatures); **Francisco De La Vega** (Employment at Annai Systems Inc. during part of the project.); **Ronny Drapkin** (R.D. serves on the SAB of Repare Therapeutics and Siamab Therapeutics.); **Rosalind Eeles** (GU-ASCO meeting in San Francisco – Jan 2016 – Honorarium as speaker $500. 2. RMH FR meeting – Nov 2017 – support from Janssen, honorarium as speaker £1100 (Title: Genetics and Prostate Cancer). 3. University of Chicago invited talk May 2018 – Honorarium as speaker $1000. 4. EUR 200 educational honorarium paid by Bayer & Ipsen to attend GU Connect “Treatment sequencing for mCRPC patients within the changing landscape of mHSPC” at a venue at ESMO, Barcelona, 28 September 2019.); **Paul Flicek** (Member of the Scientific Advisory Boards of Fabric Genomics, Inc., and Eagle Genomics, Ltd.); **Gad Getz** (G.G. receives research funds from IBM and Pharmacyclics and is an inventor on patent applications related to MuTect, ABSOLUTE, MutSig, MSMuTect, MSMutSig and POLYSOLVER); **Ronald Ghossein** (veracyte, inc); **D Glodzik** (D.G. is an inventor on a number of patent filings encompassing the use of mutational signatures.); **Eoghan Harrington** (Eoghan Harrington is a full-time employee of Oxford Nanopore Technologies Inc. and is a stock option holder); **Yann Joly** (Responsible for the Data Access Compliance Office (DACO) of ICGC 2009-2018.); **Sissel Juul** (SJ is a full-time employee of Oxford Nanopore Technologies Inc. and is a stock option holder); **Vincent Khoo** (VK has received personal fees and non-financial support from Accuray, Astellas, Bayer, Boston Scientific, and Janssen.); **Stian Knappskog** (co-PI on clinical trial receiving research funding from AstraZeneca and Pfizer); **Ignaty Leshchiner** (Consulting-PACT Pharma); **Yong-Jie Lu** (CA16672 and R50CA221675); **Carlos López-Otín** (CLO has ownership interest (including stock, patents, etc.) from DREAMgenics); **Matthew Meyerson** (Scientific advisory board chair of, and consultant for, OrigiMed. Research funding from Bayer and Ono Pharma. Patent royalties from LabCorp.); **Serena Nik-Zainal** (S. N.-Z. is an inventor on a number of patent filings encompassing the use of mutational signatures.); **Nathan Pennell** (N.P. has done consulting work with Merck, Astrazeneca, Eli Lilly, and BMS.); **Xose Puente** (XSP has ownership interest (including stock, patents, etc.) from DREAMgenics); **Benjamin Raphael** (BJR is a consultant at and has ownership interest (including stock, patents, etc.) in Medley Genomics.); **Jorge Reis-Filho** (Consultant of Goldman Sachs and REPARE Therapeutics; member of the scientific advisory board of Volition RX and Paige.AI; ad hoc member of the scientific advisory board of Ventana Medical Systems, Roche Tissue Diagnostics, InVicro, Roche, Genentech and Novartis); **Lewis Roberts** (LRR has received grant support from ARIAD Pharmaceuticals, Bayer, BTG International, Exact Sciences, Gilead Sciences, Glycotest, Inc., RedHill Biopharma, Inc., Target PharmaSolutions, and Wako Diagnostics; he has provided advisory services to Bayer, Exact Sciences, Gilead Sciences, GRAIL, Inc., QED Therapeutics and TAVEC Pharmaceuticals Inc.); **Richard Scolyer** (Richard A. Scolyer reports receiving fees for professional services from Merck Sharp & Dohme, GlaxoSmithKline Australia, Bristol-Myers

and spread of a somatic clone. To achieve this behaviour, the cancer clone must co-opt multiple cellular pathways that enable it to disregard the normal constraints on cell growth, to modify the local microenvironment favouring its own proliferation, to invade through tissue barriers, to spread to other organs, and to evade immune surveillance[21]. No single cellular programme directs these behaviours. Rather, there is a large pool of potential pathogenic abnormalities from which individual cancers draw their own combinations: the commonalities of macroscopic features across tumours belie a vastly heterogeneous landscape of cellular abnormalities.

This heterogeneity arises from the stochastic nature of Darwinian evolution. The preconditions for Darwinian evolution are three: characteristics must vary within a population; this variation must be heritable from parent to offspring; and there must be competition for survival within the population. In the context of somatic cells, heritable variation arises from mutations acquired stochastically throughout life, notwithstanding additional contributions from germline and epigenetic variation. A subset of these mutations alter cellular phenotype, and a small subset of those variants confer an advantage on clones in their competition to escape the tight physiological controls wired into somatic cells. Mutations providing selective advantage to the clone are termed ‘driver' mutations, as opposed to selectively neutral ‘passenger' mutations.

Initial studies using massively parallel sequencing demonstrated the feasibility of identifying every somatic point mutation, copy number change, and structural variant in a given cancer[1–3]. In 2008, recognising the opportunity this advance in technology provided, the global cancer genomics community established the International Cancer Genome Consortium (ICGC) with the goal of systematically documenting the somatic mutations driving common tumour types[22].

Pan-Cancer Analysis of Whole Genomes

The maturing of whole genome sequencing studies from individual ICGC and TCGA working groups presented the opportunity to undertake a meta-analysis of genomic features across tumour types. To achieve this, the Pan-Cancer Analysis of Whole Genomes (PCAWG) consortium was established. A Technical Working Group implemented informatics analyses, aggregating the raw sequencing data from working groups studying individual tumour types, aligning to the human genome, and delivering a set of high-quality somatic mutation calls for downstream analysis (Extended Figure 1). Given the recent meta-

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analysis of exome data from the TCGA Pan-Cancer Atlas[23–25], scientific working groups concentrated their efforts on analyses best informed by whole genome sequencing data.

We collected genome data from 2,834 donors (Extended Table 1), of which 176 were excluded after quality assurance. A further 75 had minor issues that could impact some analyses (grey-listed donors), and 2,583 had data of optimal quality (white-listed donors; Supplementary Table 1). Across the 2,658 white- and grey-listed donors, whole genome sequencing data were available from 2,605 primary tumours and 173 metastases or local recurrences. Mean read coverage was 39x for normal samples, while tumours had a bimodal coverage distribution with modes at 38x and 60x (Supplementary Figure 1). RNA-sequencing data was available for 1,222 donors. The final cohort comprised 1,469 males (55%) and 1,189 females (45%), with a mean age of 56 years (range, 1-90 years) across 38 tumour types (Extended Table 1; Supplementary Table 1).

In order to identify somatic mutations, we analysed all 6,835 samples using a uniform set of algorithms for alignment, variant calling and quality control (Extended Figure 1; Supplementary Figure 2; Supplementary Methods S2). We deployed three established pipelines to call somatic single nucleotide variations (SNVs), small insertions and deletions (indels), copy number alterations (CNAs), and structural variants (SVs). Somatic retrotransposition events, mitochondrial DNA mutations and telomere lengths were also called by bespoke algorithms. RNA-Sequencing data were uniformly processed to call transcriptomic alterations. Germline variants identified via three separate pipelines included single nucleotide polymorphisms (SNPs), indels, structural variants and mobile element insertions (Supplementary Table 2).

The requirement to uniformly realign and call variants on ~5,800 whole genomes presented significant computational challenges, and raised ethical issues due to the use of data from different jurisdictions (Box 1). We used cloud computing[26,27] to distribute alignment and variant calling across 13 data centres in three continents (Supplementary Table 3). Core pipelines were packaged into Docker containers[28] as reproducible, stand-alone packages, which we have made available for download. Data repositories for raw and derived datasets, together with portals for data visualisation and exploration have also been created (Box 1; Supplementary Table 4).

Benchmarking of genetic variant calls

To benchmark mutation calling, we ran the three core pipelines, together with 10 additional pipelines, on 63 representative tumour/normal genome pairs (Supplementary Note 1). For 50 of these cases, we performed validation by hybridisation of tumour and matched normal DNA to a custom bait-set with deep sequencing[29]. The three core somatic variant-calling pipelines had individual estimates of sensitivity of 80-90% to detect a true somatic SNV called by any of the 13 pipelines; with >95% of SNV calls made by each of the core pipelines being genuine somatic variants (Figure 1A). For indels, a more challenging class of variants to identify with short-read sequencing, the three core algorithms had individual sensitivity estimates in the range 40-50%, with precision 70-95% (Figure 1B). For individual

SV callers, we estimated precision to be in the range 80-95% for samples in the pilot-63 dataset.

Next, we defined a strategy to merge results from the three pipelines into one final call-set to be used for downstream scientific analyses (Methods, Supplementary Note 2). Sensitivity and precision of consensus somatic variant calls were 95% ($CI_{90\%}$=88-98%) and 95% ($CI_{90\%}$=71-99%) respectively for SNVs (Extended Figure 2). For somatic indels, sensitivity and precision were 60% (34-72%) and 91% (73-96%) respectively (Extended Figure 2). Regarding somatic SVs, we estimate the sensitivity of merged calls to be 90% for true calls generated by any one caller; precision was estimated as 97.5%. The improvement in calling accuracy from combining different callers was most noticeable in variants having low variant allele fractions, which likely originate in tumour subclones (Figure 1C-D). Germline variant calls, phased using a haplotype-reference panel, displayed a precision >99% and sensitivity of 92%-98% (Supplementary Note 2).

Analysis of PCAWG data

The uniformly generated, high quality set of variant calls across >2,500 donors provided the springboard for a series of scientific working groups to explore the biology of cancer. A comprehensive suite of companion papers detailing the analyses and discoveries across these thematic areas is co-published with this paper (Extended Table 3).

Pan-cancer burden of somatic mutations

Across the 2,583 white-listed PCAWG donors, we called 43,778,859 somatic SNVs; 410,123 somatic multi-nucleotide variants; 2,418,247 somatic indels; 288,416 somatic structural variants; 19,166 somatic retrotransposition events; and 8,185 *de novo* mitochondrial DNA mutations (Supplementary Table 1). There was considerable heterogeneity in the burden of somatic mutations across patients and tumour types, with a broad correlation in mutation burden among different classes of somatic variation (Extended Figure 3). Analysed at a per-patient level, this correlation held, even when considering tumours with similar purity and ploidy (Supplementary Figure 3). Why such correlation should apply on a pan-cancer basis is unclear. It is likely that age plays some role, as we observe a correlation of most classes of somatic mutation with age at diagnosis (~190 SNVs/year, p=0.02; ~22 indels/year, $p=5x10^{-5}$; 1.5 SVs/year, $p<2x10^{-16}$; linear regression with likelihood ratio tests; Supplementary Figure 4). Other factors are also likely to contribute to the correlations among classes of somatic mutation, since there is evidence that some DNA repair defects can cause multiple types of somatic mutation[30], and a single carcinogen can cause a range of DNA lesions[31].

Panorama of driver mutations in cancer

We extracted the subset of somatic mutations in PCAWG tumours that have high confidence to be driver events, based on current knowledge. One challenge to pinpointing the specific driver mutations in an individual tumour is that not all point mutations in recurrently mutated cancer genes are drivers[32]. For genomic elements significantly mutated in the

PCAWG, we developed a '*rank-and-cut*' approach to identify the likely drivers (Supplementary Methods 8.1). This works by *ranking* the observed mutations in a given genomic element based on recurrence, estimated functional consequence, and expected pattern of drivers in that element. We then estimate the excess burden of somatic mutations in that genomic element above that expected for the background mutation rate, and *cut* the ranked mutations at this level. Mutations in that element with the highest driver ranking will then be assigned as likely drivers; those below the threshold will probably have arisen through chance, and be assigned as likely passengers. Improvements to features employed to rank the mutations and the methods used to measure them will contribute to further maturation of the rank-and-cut approach.

We also needed to account for the fact that some *bona fide* cancer genomic elements were not rediscovered in PCAWG data because of low statistical power. We therefore added previously known cancer genes to the discovery set, creating a 'Compendium of Mutational Driver Elements' (Supplementary Methods 8.2). Then, using stringent rules to nominate driver point mutations affecting these genomic elements on the basis of prior knowledge[33], we separated likely driver from passenger point mutations. To cover all classes of variant, we also created a compendium of known driver SVs, using analogous rules to identify which somatic CNAs and SVs most likely act as drivers in each tumour. For likely pathogenic germline variants, we identified all truncating germline point mutations and SVs affecting high-penetrance germline cancer genes.

This analysis defined a set of mutations that we could confidently assert, based on current knowledge, drove tumorigenesis in the >2,500 tumours of PCAWG. We found that 91% of tumours had at least one identified driver mutation, with an average of 4.6 drivers per tumour identified, showing extensive variation across cancer types (Figure 2A). For coding point mutations, the average was 2.6 drivers per tumour, similar to numbers estimated in known cancer genes in TCGA tumours using similar approaches[32].

To address the frequency of non-coding driver point mutations, we combined promoters and enhancers that are known targets of non-coding drivers[34–37] with those newly discovered on PCAWG data, reported in a companion paper[4]. Using this approach, only 13% (785/5913) of driver point mutations were non-coding in PCAWG. Nonetheless, 25% of PCAWG tumours bear at least one putative non-coding driver point mutation, with one third (237/785) affecting the *TERT* promoter (9% of PCAWG tumours). Overall, then, non-coding driver point mutations are less frequent than coding drivers. With the exception of the *TERT* promoter, individual enhancers and promoters are only infrequent targets of driver mutations[4].

Across tumour types, SVs and point mutations make different relative contribution to tumorigenesis. Driver SVs are more prevalent in breast adenocarcinomas (6.4±3.7 SVs vs. 2.2±1.3 point mutations on average±SD; $p<10^{-16}$, Mann-Whitney U test) and ovary adenocarcinomas (5.8±2.6 SVs vs. 1.9±1.0 point mutations; $p<10^{-16}$), while driver point mutations make a larger contribution in colorectal adenocarcinomas (2.4±1.4 SVs vs. 7.4±7.0 point mutations; $p=4x10^{-10}$) and mature B-cell lymphomas (2.2±1.3 SVs vs. 6±3.8

point mutations; $p<10^{-16}$), as shown previously[38]. Across tumour types, there are differences in which classes of mutation affect a given genomic element (Figure 2B).

We confirmed that many driver mutations affecting tumour suppressor genes are two-hit inactivation events (Figure 2C). For example, of the 954 tumours in the cohort with driver mutations in *TP53*, 736 (77%) had both alleles mutated, 96% of which (707/736) combined a somatic point mutation affecting one allele with somatic deletion of the other allele. Overall, 17% of patients harboured rare germline protein-truncating variants (PTVs) in cancer predisposition genes[39], DNA damage response genes[40] and somatic driver genes. Biallelic inactivation due to somatic alteration on top of a germline PTV was observed in 4.5% of patients overall, with 81% of these affecting known cancer predisposition genes (such as *BRCA1, BRCA2* and *ATM*).

PCAWG tumours with no apparent drivers

Although >90% PCAWG cases had identified drivers, we found none in 181 tumours (Extended Figure 4A). Reasons for missing drivers have not yet been systematically evaluated in a pan-cancer cohort, and could arise from either technical or biological causes.

Technical explanations could include poor quality samples; inadequate sequencing; or failures in the bioinformatic algorithms deployed. Assessing the quality of samples, four of the 181 ‘missed-driver’ cases had >5% tumour DNA contamination in their matched normal (Figure 3A). Using an algorithm designed to correct for this contamination[41], we identified previously missed mutations in genes relevant to the respective cancer types. Similarly, if the fraction of tumour cells in the cancer sample is low through stromal contamination, detection of driver mutations can be impaired. Most missed-driver tumours had an average power to detect mutations close to 100%, but a few had power in the 70-90% range (Figure 3B; Extended Figure 4B). Even in adequately sequenced genomes, lack of read depth at specific driver loci can impair mutation detection. For example, only ~50% of PCAWG tumours had sufficient coverage to call a mutation (≥90% power) at the two *TERT* promoter hotspots, likely because of the region’s high GC-content causing biased coverage (Figure 3C). In fact, six Liver-HCC and two Biliary-AdenoCa tumours among the 181 missed-driver cases actually did carry *TERT* mutations upon deep targeted sequencing[42].

Finally, technical reasons for missing driver mutations include failures in the bioinformatic algorithms. This affected 35 myeloproliferative neoplasms in PCAWG, where the $JAK2^{V617F}$ driver mutation should have been called. Our somatic variant-calling algorithms rely on ‘panels of normals’, typically from blood samples, to remove recurrent sequencing artefacts. Since 2-5% healthy individuals carry occult haematopoietic clones[43], recurrent driver mutations in these clones can enter panels of normals.

Turning to biological causes, tumours may be driven by mutations in cancer genes not yet discovered in that tumour type. Using driver discovery algorithms on missed-driver tumours, no individual genes reached significance for point mutations. However, we identified a recurrent CNA spanning *SETD2* in medulloblastomas lacking known drivers (Figure 3D), indicating that restricting hypothesis-testing to missed-driver cases can improve power if

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undiscovered genes are enriched in such tumours. Inactivation of *SETD2* in medulloblastoma significantly decreased gene expression (p=0.002; Extended Figure 4C). Interestingly, *SETD2* mutations occurred exclusively in medulloblastoma group 4 tumours ($p<1x10^{-4}$). Group 4 medulloblastomas are known for frequent mutations in other chromatin-modifying genes[44], and our results suggest that *SETD2* loss-of-function is an additional driver affecting chromatin regulators in this subgroup.

Two tumour types had a surprisingly high fraction of patients without identified driver mutations: chromophobe renal cell carcinoma (44%; 19/43) and pancreatic neuroendocrine cancers (22%; 18/81) (Extended Data Figure 4A). A striking feature of the missed-driver cases in both tumour types was a remarkably consistent profile of chromosomal aneuploidy, patterns that have been reported previously[45,46] (Figure 3E). The absence of other identified driver mutations in these patients raises the intriguing hypothesis that certain combinations of whole chromosome gains and losses may be sufficient to initiate a cancer in the absence of more targeted driver events such as point mutations, fusion genes of focal CNAs.

Even after accounting for technical issues and novel drivers, 5.3% of PCAWG tumours still had no identifiable driver events. In a research setting, where we are interested in drawing conclusions about populations of patients, the consequences of technical issues affecting occasional samples will be mitigated by sample size. In a clinical setting, where we are interested in the driver mutations in a specific patient, these issues become substantially more important. Careful and critical appraisal of the whole pipeline, including sample acquisition, genome sequencing, mapping, variant calling, and driver annotation, as done here, should be required for laboratories offering clinical sequencing of cancer genomes.

Patterns of clustered mutations and SVs

Some mutational processes generate multiple mutations in a single catastrophic event, typically clustered in genomic space, leading to substantial reconfiguration of the genome. Three such processes have been described: (i) chromoplexy, in which repair of co-occurring dsDNA breaks, typically on different chromosomes, results in shuffled chains of rearrangements[47,48] (example in Extended Figure 5A); (ii) kataegis, a focal hypermutation process leading to locally clustered nucleotide substitutions, biased towards a single DNA strand[49–51] (Extended Figure 5B); and (iii) chromothripsis, in which tens to hundreds of DNA breakages occur simultaneously, clustered on one or a few chromosomes, with near-random stitching together of the resulting fragments[52–55] (Extended Figure 5C). We characterised the PCAWG genomes for these three processes (Figure 4).

Chromoplexy events and reciprocal translocations were identified in 467 (17.8%) samples (Figure 4A,C). Chromoplexy was prominent in prostate adenocarcinoma and lymphoid malignancies, as described previously[47,48], and, unexpectedly, thyroid adenocarcinoma. Different genomic loci were recurrently rearranged by chromoplexy across the three tumour types, mediated by positive selection for particular fusion genes or enhancer-hijacking events. Of 13 fusion genes or enhancer hijacking events in 48 thyroid adenocarcinomas, at least 4 (31%) were caused by chromoplexy, with a further 4 (31%) part of complexes containing chromoplexy footprints (Extended Figure 5A). These generated fusion genes

involving *RET* (2 cases) and *NTRK3* (1 case)[56], and juxtaposition of the oncogene *IGF2BP3* with regulatory elements from highly expressed genes (5 cases).

Kataegis events were seen in 60.5% of all cancers, with particularly high abundance in lung squamous cell carcinoma, bladder cancer, acral melanoma and sarcomas (Figure 4A,B). Typically, kataegis comprises C>N mutations in TpC context, likely due to APOBEC activity[49–51], although a T>N at TpT or CpT process attributed to error-prone polymerases has recently been described[57]. The APOBEC signature accounted for 81.7% of kataegis events and correlated positively with *APOBEC3B* expression levels, somatic SV burden and age at diagnosis (Supplementary Figure 5). 5.7% of kataegis events involved the T>N error-prone polymerase signature and 2.3% of events, most notably in sarcomas, showed cytidine deamination in an alternative GpC or CpC context.

Kataegis events were frequently associated with somatic SV breakpoints (Figure 4A, Supplementary Figure 6A), as previously described[50,51]. Deletions and complex rearrangements were most strongly associated with kataegis, while tandem duplications and other simple SV classes were only infrequently associated (Supplementary Figure 6B). The C[T>N]T-type kataegis was enriched near deletions, specifically those in the 10-25kbp range (Supplementary Figure 6C).

Samples with extreme kataegis burden (>30 foci) comprise four types of focal hypermutation (Extended Figure 6): (i) off-target somatic hypermutation and C[T>N]T foci in B-cell non-Hodgkin lymphoma and oesophageal adenocarcinomas, respectively; (ii) APOBEC kataegis associated with complex rearrangements, notably in sarcoma and melanoma; (iii) rearrangement-independent APOBEC kataegis on the lagging strand and in early-replicating regions, mainly in bladder and head and neck cancer; (iv) a mix of the previous two types. Kataegis only occasionally led to driver mutations (Supplementary Table 5).

We identified *chromothripsis* in 587 samples (22.3%), most frequently amongst sarcoma, glioblastoma, lung squamous cell carcinoma, melanoma, and breast adenocarcinoma[58]. Chromothripsis increased with whole genome duplications in most cancer types (Extended Figure 7A), as previously shown in medulloblastoma[59]. The most recurrently associated driver was *TP53*[52] (pan-cancer odds ratio=3.22; pan-cancer $p=8.3x10^{-35}$; $q<0.05$ in breast lobular (OR=13), colorectal (OR=25), prostate (OR=2.6) and hepatocellular cancers (OR=3.9); Fisher-Boschloo tests). In two cancer types (osteosarcoma and B-cell lymphoma), females showed higher incidence of chromothripsis than males (Extended Figure 7B). In prostate cancer, we observed a higher incidence of chromothripsis in patients with late-onset than early-onset disease[60] (Extended Figure 7C).

Chromothripsis regions coincided with 3.6% of all identified drivers in PCAWG and ~7% of copy number drivers (Figure 4D). These proportions are considerably enriched compared to expectation if selection were not acting on these events (Extended Figure 7D). The majority of coinciding driver events were amplifications (58%), followed by homozygous deletions (34%), and SVs within genes or promoter regions (8%). We frequently observed ≥2-fold increased or decreased expression of amplified or deleted drivers, respectively, when these

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loci were part of a chromothripsis event, compared to samples without chromothripsis (Extended Figure 7E).

Chromothripsis manifested in diverse patterns and frequencies across tumour types, which we categorised based on five characteristics (Figure 4A). In liposarcoma for example, chromothripsis events often involved multiple chromosomes, with universal *MDM2* amplification[61] and co-amplification of *TERT* in 4 of 19 cases (Figure 4D). In contrast, in glioblastoma, the events tended to affect a smaller region on a single chromosome, distant from the telomere, resulting in focal *EGFR* and *MDM2* amplification, and *CDKN2A* loss. Acral melanomas frequently exhibited *CCND1* amplification, and lung squamous cell carcinomas *SOX2* amplifications. In both cases, these drivers were more frequently altered by chromothripsis compared to other drivers in the same cancer type, and to other cancer types for the same driver (Figure 4D, Extended Figure 7F). Finally, in chromophobe renal cell carcinoma, chromothripsis nearly always affected chromosome 5 (Supplementary Figure 7): these samples had breakpoints immediately adjacent to *TERT*, increasing *TERT* expression 80-fold on average over samples without rearrangements (p=0.0004; Mann-Whitney U test).

Timing clustered mutations in evolution

An unanswered question for clustered mutational processes is whether they occur early or late in cancer evolution. To address this, we used molecular clocks to define broad epochs in each tumour's life history[49,62]. One transition point is between clonal and subclonal mutations: clonal mutations occurred before, and subclonal mutations after, emergence of the most recent common ancestor. In regions with copy number gains, molecular time can be further divided according to whether mutations preceded the copy number gain (and were themselves duplicated) or occurred after the gain (and therefore present on only one chromosomal copy)[63].

Chromothripsis tended to have greater relative odds of being clonal than subclonal, suggesting it occurs early in cancer evolution, especially in liposarcomas, prostate adenocarcinoma and squamous cell lung cancer, among others (Figure 5A). As previously reported, chromothripsis was especially common in melanomas[64]. We identified 89 separate chromothripsis events affecting 66 melanomas (61%), with 47/89 events affecting genes known to be recurrently altered in melanoma[65] (Supplementary Table 6). Involvement of a region on chromosome 11 that includes the cell-cycle regulator *CCND1* occurred in 21 cases (10/86 cutaneous, 11/21 acral or mucosal melanomas), typically combining chromothripsis with amplification (19/21 cases; Extended Figure 8). Co-involvement of other cancer genes in the same chromothripsis event was also frequent, including *TERT* (5 cases), *CDKN2A* (3 cases), *TP53* (2 cases) and *MYC* (2 cases) (Figure 5B). In these co-amplifications, a chromothripsis event involving multiple chromosomes initiated the process, creating a derivative chromosome in which hundreds of fragments were stitched together in near-random order (Figure 5B). This derivative then rearranged further, leading to massive co-amplification of the multiple target oncogenes together with regions located nearby on the derivative chromosome.

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In these cases of amplified chromothripsis, we can use the inferred number of copies bearing each SNV to time the amplification process. SNVs present on the chromosome before amplification will themselves be amplified, and therefore reported in a high fraction of sequence reads (Figure 5B; Extended Figure 8). In contrast, late SNVs that occur after the amplification has concluded, will be present on only one chromosome copy out of many, and thus have low variant allele fraction. Regions of *CCND1* amplification had few, sometimes zero, mutations at high variant allele fraction in acral melanomas, contrasting with later *CCND1* amplifications in cutaneous melanomas (Figure 5B; Extended Figure 9A,B). Thus, both chromothripsis and the subsequent amplification generally occurred very early during the evolution of acral melanoma. By comparison, in lung squamous cell carcinomas, similar patterns of chromothripsis followed by *SOX2* amplification are characterised by many amplified SNVs, suggesting a later event in the evolution of these cancers (Extended Figure 9C).

Interestingly, in cancer types where mutational load was sufficiently high, we could detect a larger than expected number of SNVs on an intermediate number of DNA copies, suggesting that they appeared during the amplification process (Supplementary Figure 8).

Germline effects on somatic mutations

We integrated the set of 88 million germline genetic variant calls with somatic mutations in PCAWG, to study germline determinants of somatic mutation rates and patterns. First, we performed a genome-wide association study (GWAS) of somatic mutational processes with common germline variants (minor allele frequency (MAF) >5%) in individuals with inferred European ancestry. An independent GWAS was performed in East Asian individuals from Asian cancer genome projects. We focused on two prevalent endogenous mutational processes: spontaneous deamination of 5methyl-C at CpG dinucleotides[66] (signature 1) and activity of the APOBEC3 family of cytidine deaminases[67] (signatures 2 and 13). No locus reached genome-wide significance ($p<5x10^{-8}$) for signature 1 (Extended Figure 10A,B). However, a locus at 22q13.1 predicted APOBEC3B-like mutagenesis at the pan-cancer level[68] (Figure 6A). The strongest signal at 22q13.1 was driven by rs12628403, and the minor (non-reference) allele was protective against APOBEC3B-like mutagenesis (β=-0.43, $p=5.6x10^{-9}$, MAF=8.2%, n=1,201 donors; Extended Figure 10C). This variant tags a common ~30kb germline SV that deletes the *APOBEC3B* coding sequence and fuses the *APOBEC3B* 3'-UTR with the coding sequence of *APOBEC3A*. The deletion is known to increase breast cancer risk and APOBEC mutagenesis in breast cancer genomes[69,70]. Here, we found that rs12628403 reduces APOBEC3B-like mutagenesis specifically in cancer types with low levels of APOBEC mutagenesis (β_{low}=-0.50, $p_{low}=1x10^{-8}$; β_{high}=+0.17, p_{high}=0.2), and increases APOBEC3A-like mutagenesis in cancer types with high levels of APOBEC mutagenesis (β_{high}=+0.44, $p_{high}=8x10^{-4}$; β_{low}=-0.21, p_{low}=0.02). Moreover, we identified a second, novel locus at 22q13.1 that associated with APOBEC3B-like mutagenesis across cancer types (rs2142833, β=+0.23, $p=1.3x10^{-8}$). We independently validated the association between both loci and APOBEC3B-like mutagenesis using East Asian individuals from Asian cancer genome projects ($\beta_{rs12628403}$=+0.57, $p_{rs12628403}=4.2x10^{-12}$; $\beta_{rs2142833}$=+0.58, $p_{rs2142833}=8x10^{-15}$; Extended Figure 10D). Of note, in a conditional analysis that accounted for rs12628403, rs2142833 and rs12628403

are inherited independently in Europeans (r^2<0.1), while rs2142833 remained significantly associated with APOBEC3B-like mutagenesis in Europeans (β_{EUR}=+0.17, p_{EUR}=3x10^{-5}) and East Asians (β_{ASN}=+0.25, p_{ASN}=2x10^{-3}) (Extended Figure 10E,F). Analysis of donor-matched expression data further suggests that rs2142833 is a *cis*-eQTL for *APOBEC3B* at the pan-cancer level (β=+0.19, p=2x10^{-6}; Extended Figure 10G-H), consistent with *cis*-eQTL studies in normal cells[71,72].

Second, we performed a rare variant association study (RVAS) (MAF<0.5%) to investigate the relationship between germline protein-truncating variants (PTVs) and somatic DNA rearrangements in individuals with European ancestry (Extended Figure 11A-C). Germline *BRCA2* and *BRCA1* PTVs associated with an increased burden of small (<10kb) somatic SV deletions (p=1x10^{-8}) and tandem duplications (p=6x10^{-13}), respectively, corroborating recent studies in breast and ovarian cancer[30,73]. In PCAWG data, this pattern extends to other tumour types as well, including adenocarcinomas of the prostate and pancreas[6], typically in the setting of biallelic inactivation. In addition, tumours with high levels of small SV tandem duplications frequently exhibited a novel and distinct class of SVs termed 'cycles of templated insertions'[6]. These complex SV events consist of DNA templates that are copied from across the genome, joined into one contiguous sequence, and inserted into a single derivative chromosome. We found a significant association between germline *BRCA1* PTVs and templated insertions at the pan-cancer level (p=4x10^{-15}; Extended Figure 11D,E). Whole genome long-read sequencing data generated for a *BRCA1*-deficient PCAWG prostate tumour verified the small tandem duplication and templated insertion SV phenotypes (Figure 6B). Virtually all (20/21) of *BRCA1*-associated tumours with a templated insertion SV phenotype displayed combined germline and somatic hits in the gene. Together, these data suggest that biallelic inactivation of *BRCA1* is a driver of the templated insertion SV phenotype.

Third, rare variant association analysis revealed that patients with germline *MBD4* PTVs exhibited increased rates of somatic C>T mutation rates at CpG dinucleotides (P<2.5x10^{-6}; Figure 6C; Extended Figure 11F,G). Analysis of previously published TCGA WES samples (n=8,134) replicated the association between germline *MBD4* PTVs and increased somatic CpG mutagenesis at the pan-cancer level (P=7.1x10^{-4}; Extended Figure 11H). Moreover, gene expression profiling revealed a significant but modest correlation between *MBD4* expression and somatic CpG mutation rates between and within PCAWG tumour types (Extended Figure 11I-K). *MBD4* encodes a DNA repair gene that removes thymidines from T:G mismatches within methylated CpG sites[74], a suggestive functionality for CpG mutational signatures in cancer.

Fourth, we assessed LINE-1 (L1) elements that mediate somatic retrotransposition events[75–77]. We identified 114 germline source L1 elements capable of active somatic retrotransposition, including 70 that represent insertions with respect to the human reference genome (Figure 6D, Supplementary Table 7), and 53 that were tagged by SNPs in strong linkage disequilibrium (Supplementary Table 7). Only 16 germline L1 elements accounted for 67% (2,440/3,669) of all L1-mediated transductions[10] detected in the PCAWG dataset (Extended Figure 12A). These 16 hot-L1 elements followed two broad patterns of somatic activity (8 of each), which we term Strombolian and Plinian in analogy to patterns of

volcanic activity. Strombolian L1s are frequently active in cancer, but mediate only small to modest eruptions of somatic L1 activity in cancer samples (Extended Figure 12B). In contrast, Plinian L1s are more rarely seen, but display aggressive somatic activity. Whereas Strombolian elements are typically relatively common (MAF>2%) and sometimes even fixed in the human population, all Plinian elements were infrequent (MAF≤2%) in PCAWG donors (Extended Figure 12C; p=0.001; Mann-Whitney U test). This dichotomous pattern of activity and allele frequency may reflect differences in age and selective pressures, with Plinian elements potentially inserted into the human germline more recently. PCAWG donors bear on average between 50-60 L1 source elements and 5-7 elements with hot activity (Extended Figure 12D), but only 38% (1075/2814) of PCAWG donors carry ≥1 Plinian element. Some L1 germline source loci caused somatic loss of tumour suppressor genes (Extended Figure 12E). Many are restricted to individual continental population ancestries (Extended Figure 12F-J).

Replicative immortality

One of the hallmarks of cancer is its ability to evade cellular senescence[21]. Normal somatic cells typically have finite cell division potential, with telomere attrition one mechanism to limit numbers of mitoses[78]. Cancers enlist multiple strategies to achieve replicative immortality. Over-expression of the telomerase gene, *TERT*, which maintains telomere lengths, is especially prevalent. This can be achieved via point mutations in the promoter that lead to *de novo* transcription factor binding[34,37]; hitching *TERT* to highly active regulatory elements elsewhere in the genome[46,79]; insertions of viral enhancers upstream of the gene[80,81]; and increased dosage through chromosomal amplification, as we have seen in melanoma (Figure 5B). In addition, there is an ‘alternative lengthening of telomeres’ (ALT) pathway, in which telomeres are lengthened through homologous recombination, mediated by loss-of-function mutations in the *ATRX* and *DAXX* genes[82].

As reported in a companion paper, 16% of tumours in the PCAWG dataset exhibited somatic mutations in at least one of *ATRX*, *DAXX* and *TERT*[83]. *TERT* alterations were detected in 270 samples, whereas 128 tumours had alterations in *ATRX* or *DAXX*, of which 71 were protein-truncating. In the companion paper, which focused on describing patterns of ALT and *TERT*-mediated telomere maintenance[83], twelve features of telomeric sequence were measured on the PCAWG cohort. These included counts of nine variants of the core hexameric sequence, the number of ectopic telomere-like insertions within the genome, the number of genomic breakpoints, and telomere length as a ratio between tumour and normal. Here we used the twelve features to overview telomere integrity across all tumours in the PCAWG dataset.

Based on these twelve features, tumour samples formed four distinct sub-clusters (Figure 7A, Extended Figure 13A), suggesting that telomere maintenance mechanisms are more diverse than the well-established *TERT*/ALT dichotomy. Clusters C1 (47 tumours) and C2 (42 tumours) were enriched for traits of the ALT pathway, having longer telomeres, more genomic breakpoints, more ectopic telomere insertions, and variant telomere sequence motifs (Supplementary Figure 9). C1 and C2 were distinguished from one another by the latter having striking elevation in the number of TTCGGG and TGAGGG variant motifs

among the telomeric hexamers. Thyroid adenocarcinomas were strikingly enriched among C3 samples (26/33 C3 samples; $p<10^{-16}$); the C1 cluster (ALT subtype 1) was common among sarcomas; and both pancreatic endocrine neoplasms and low-grade gliomas had a high proportion of samples in the C2 cluster (ALT subtype 2) (Figure 7B). Interestingly, some of the thyroid adenocarcinomas and pancreatic neuroendocrine tumours that cluster together (Cluster C3) had matched normals that also cluster together (Normal cluster N3, Extended Figure 13A), and which share common properties. For example, the GTAGGG repeat was overrepresented among samples in this group (Supplementary Figure 10).

Somatic driver mutations were also unevenly distributed across the four clusters (Figure 7C). C1 tumours were enriched for *RB1* mutations or structural variants ($p=3x10^{-5}$), as well as frequent structural variants affecting *ATRX* ($p=6x10^{-14}$), but not *DAXX*. *RB1* and *ATRX* mutations were largely mutually exclusive (Extended Figure 13B). In contrast, C2 tumours were enriched for somatic point mutations in *ATRX* and *DAXX* ($p=6x10^{-5}$), but not *RB1.* The enrichment of *RB1* mutations in C1 remained significant when only leiomyosarcomas and osteosarcomas were considered, confirming that this enrichment is not merely a consequence of the different distribution of tumour types across clusters. C3 samples had frequent *TERT* promoter mutations (30%; $p=2x10^{-6}$).

The predominance of *RB1* mutations in C1 was striking. Nearly a third of the samples in C1 contained an *RB1* alteration, evenly distributed across truncating SNVs, SVs and shallow deletions (Extended Figure 13C). Previous work has shown that *RB1* mutations are associated with long telomeres in the absence of *TERT* mutations and *ATRX* inactivation[84], and mouse models have revealed that knock-out of Rb-family proteins causes elongated telomeres[85]. The association with the C1 cluster here suggests that *RB1* mutations can represent another route to activating the ALT pathway, with subtly different properties of telomeric sequence compared to inactivating *DAXX*, which fall almost exclusively in cluster C2.

Tumour types with the highest rates of abnormal telomere maintenance mechanisms often originate in tissues that have low endogenous replicative activity (Figure 7D). In support of this, we found an inverse correlation between previously estimated rates of stem cell division across tissues[86] and the frequency of telomere maintenance abnormalities (p=0.01, Poisson regression; Extended Figure 13D). This suggests that restriction of telomere maintenance is a critical tumour suppression mechanism, particularly in tissues with low steady-state cellular proliferation, in which a clone must overcome this constraint to achieve replicative immortality.

Conclusions and future perspectives

The resource reported in this paper and its companion papers has yielded insights into the nature and timing of the many mutational processes that shape large and small-scale somatic variation in the cancer genome; the patterns of selection acting on these variations; the widespread impact of somatic variants on transcription; the complementary roles of coding and non-coding genome, for both germline and somatic mutations; the ubiquity of intratumoral heterogeneity; and the distinctive evolutionary trajectory of each cancer type.

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Many of these insights can only be obtained from an integrated analysis of all classes of somatic mutation on a whole genome scale, and would not be accessible with, for example, targeted exome sequencing.

The promise of precision medicine is to match patients to targeted therapies using genomics. A major barrier to its evidence-based implementation is the daunting heterogeneity of cancer chronicled in these pages, from tumour type to tumour type, from patient to patient, from clone to clone and from cell to cell. Building meaningful clinical predictors from genomic data can be achieved, but will require knowledge banks comprising tens of thousands of patients with comprehensive clinical characterisation[87]. Since these sample sizes will be too large for any single funding agency, pharmaceutical company or health system, international collaboration and data sharing will be required. The next phase of ICGC, ICGC-ARGO (https://icgc-argo.org/), will bring the cancer genomics community together with healthcare providers, pharma, data science and clinical trials groups to build comprehensive knowledge banks of clinical outcome and treatment data from patients with a wide variety of cancers, matched with detailed molecular profiling.

Extending the story begun by TCGA, ICGC and other cancer genomics projects, PCAWG has brought us closer to a comprehensive narrative of the causal biological changes that drive cancer phenotypes. We must now translate this knowledge into sustainable, meaningful clinical impacts.

Methods

Samples

We compiled an inventory of matched tumour/normal whole cancer genomes in the ICGC Data Coordinating Centre. Most samples came from treatment-naïve, primary cancers, but there were a small number of donors with multiple samples of primary, metastatic and/or recurrent tumours. Our inclusion criteria were: (i) matched tumour and normal specimen pair; (ii) a minimal set of clinical fields; and (iii) characterisation of tumour and normal whole genomes using Illumina HiSeq paired-end sequencing reads.

We collected genome data from 2,834 donors, representing all ICGC and TCGA donors that met these criteria at the time of the final data freeze in autumn 2014 (Extended Table 1). After quality assurance (Supplementary Methods S2.5), data from 176 donors were excluded as unusable, 75 had minor issues that could impact some analyses (grey-listed donors), and 2,583 had data of optimal quality (white-listed donors; Supplementary Table 1). Across the 2,658 white- and grey-listed donors, there were whole genome sequences from 2,605 primary tumours and 173 metastases or local recurrences. Matching normal samples were obtained from blood (2,064 donors), tissue adjacent to the primary (87 donors), or distant sites (507 donors). Whole genome sequencing data were available on tumour and normal DNA for the entire cohort. The mean read coverage was 39x for normal samples, while tumours had a bimodal coverage distribution with modes at 38x and 60x (Supplementary Figure 1). The majority of specimens (65.3%) were sequenced using 101 bp paired-end reads. An additional 28% were sequenced with 100 bp paired-end reads. Of the remaining specimens, 4.7% were sequenced with read lengths longer than 101 bp, and 1.9% with read

lengths shorter than 100 bp. The distribution of read lengths by tumour cohort is shown in Supplementary Figure 11. Median read length for WGS paired end reads was 101 bp (mean=106.2, SD=16.7; min-max=50-151). RNA-sequencing data was collected and re-analysed centrally for 1,222 donors, including 1,178 primary tumours, 67 metastases or local recurrences, and 153 matched normal tissue samples adjacent to the primary tumour.

Demographically, the cohort included 1,469 males (55%) and 1,189 females (45%), with a mean age of 56 years (range, 1-90 years) (Supplementary Table 1). Using population ancestry-differentiated single nucleotide polymorphisms (SNPs), the ancestry distribution was heavily weighted towards donors of European descent (77% of total) followed by East Asians (16%), as expected for large contributions from European, North American and Australian projects (Supplementary Table 1).

We consolidated histopathology descriptions of the tumour samples, using the ICD-0-3 tumour site controlled vocabulary[93]. Overall, the PCAWG data set comprises 38 distinct tumour types (Extended Table 1; Supplementary Table 1). While the most common tumour types are included in the dataset, their distribution does not match the relative population incidences, largely due to differences among contributing ICGC/TCGA groups in numbers sequenced.

Uniform processing and somatic variant calling

In order to generate a consistent set of somatic mutation calls that could be used for cross-tumour analyses, we analysed all 6,835 samples using a uniform set of algorithms for alignment, variant calling, and quality control (Extended Figure 1; Supplementary Figure 2; Supplementary Table 3; Supplementary Methods S2). We used the BWA-MEM algorithm[94] to align each tumour and normal sample to human reference build hs37d5 (as used in the 1000 Genomes Project[95]). Somatic mutations were identified in the aligned data using three established pipelines, run independently on each tumour/normal pair. Each of the three pipelines, labelled “Sanger”[96–99], “EMBL/DKFZ”[100,101] and “Broad”[102–105] after the computational biology groups that created or assembled them, consisted of multiple software packages for calling somatic single nucleotide variations (SNVs), small insertions and deletions (indels), copy number alterations (CNAs), and somatic structural variants (SVs; with intrachromosomal SVs defined as those >100bp). Two additional variant callers[106,107] were included to further improve accuracy across a broad range of clonal and subclonal mutations. We tested different merging strategies using validation data, choosing the optimal method for each variant type to generate a final consensus set of mutation calls (Supplementary Methods S2.4).

Somatic retrotransposition events, including *Alu* and LINE/L1 insertions[75], L1-mediated transductions[76] and pseudogene formation[108], were called using a dedicated pipeline[76]. We removed these retrotransposition events from the somatic SV call-set. Mitochondrial DNA mutations were called using a published algorithm[109]. RNA-Sequencing data were uniformly processed to quantify normalised gene-level expression, splicing variation and allele-specific expression, and to identify fusion transcripts, alternative promoter usage and sites of RNA editing[110].

Integration, phasing, and validation of germline variant call-sets

Calls of common (≥1% frequency in PCAWG) and rare (<1%) germline variants including single nucleotide polymorphisms (SNPs), indels, structural variants and mobile element insertions were generated using a population-scale genetic polymorphism detection approach[95,111]. The uniform germline data processing workflow comprised variant identification using six different variant callers[100,112,113], and orchestrated via the Butler workflow system[114].

We performed call-set benchmarking, merging, variant genotyping and statistical haplotype-block phasing[95] (Supplementary Methods S3.4). Using this strategy, we identified 80.1 million germline SNPs, 5.9 million germline indels, 1.8 million multi-allelic short (<50bp-sized) germline variants, as well as germline SVs ≥50bp in size including 29,492 biallelic deletions and 27,254 mobile element insertions (MEIs) (Supplementary Table 2). We statistically phased this germline variant set utilising 1000 Genomes Project[95] haplotypes as a reference panel, yielding an N50 phased block length of 265 kb based on haploid chromosomes from donor-matched tumour genomes. Precision estimates for germline SNVs and indels were >99% for the phased merged call-set, and sensitivity estimates ranged from 92% to 98%.

Core alignment and variant calling by cloud computing

The requirement to uniformly realign and call variants on nearly 5,800 whole genomes (tumour plus normal) presented significant computational challenges, and raised ethical issues due to the use of data from different jurisdictions (Box 1). To process the data, we adopted a cloud-computing architecture[26] in which the alignment and variant calling was spread across 13 data centres in three continents, representing a mixture of commercial, infrastructure-as-a-service, academic cloud compute, and traditional academic high-performance computer clusters (Supplementary Table 3). Altogether, the effort used 10 million CPU core-hours.

To generate reproducible variant-calling across the 13 data centres, we built the core pipelines into Docker containers[28], in which the workflow description, required code and all associated dependencies were packaged together in stand-alone packages. These heavily tested, extensively validated workflows are available for download (Box 1).

Validation, benchmarking and merging of somatic variant calls

In order to evaluate the performance of each of the mutation-calling pipelines and determine an integration strategy, we performed a large-scale deep sequencing validation experiment (Supplementary Notes 1). We selected a pilot set of 63 representative tumour/normal pairs, on which we ran the three core pipelines, together with a set of 10 additional somatic variant-calling pipelines contributed by members of the SNV Calling Working Group. Sufficient DNA remained for 50 of the 63 cases for validation, which was performed by hybridisation of tumour and matched normal DNA to a custom RNA bait-set, followed by deep sequencing, as described previously[29]. Although performed using the same sequencing chemistry as the original whole genome sequencing, the considerably greater depth achieved in the validation experiment enabled accurate assessment of sensitivity and precision of

variant calls. Variant calls in repeat-masked regions were not tested due to the challenge of designing reliable validation probes in these areas.

The three core pipelines had individual estimates of sensitivity of 80-90% to detect a true somatic SNV called by any of the 13 pipelines; with >95% of SNV calls made by each of the core pipelines being genuine somatic variants (Figure 1A). For indels, a more challenging class of variants to identify in short read sequencing data, the three core algorithms had individual sensitivity estimates in the range 40-50%, with precision 70-95% (Figure 1B). Validation of SV calls is inherently more difficult because methods based on PCR or hybridisation to RNA baits often fails to isolate DNA spanning the breakpoint. To assess accuracy of SV calls, we therefore used the property that an SV must either generate a copy number change or be balanced, whereas artefactual calls will not respect this property. For individual SV callers, we estimated precision to be in the range 80-95% for samples in the pilot-63 dataset.

Next, we examined multiple methods for merging calls made by several algorithms into a single definitive call-set to be used for downstream analysis. The final consensus calls for SNVs were based on a simple approach that required two or more methods to agree on a call. For indels, because methods were less concordant, we used stacked logistic regression[115,116] to integrate the calls. The merged SV set includes all calls made by two or more of the four primary SV callers[100,104,117,118]. Consensus CNA calls were obtained by joining the outputs of six individual CNA callers with SV consensus breakpoints to obtain base-pair resolution CNAs (Supplementary Methods 2.4.3). Consensus purity and ploidy were derived, and a multi-tier system was developed for consensus copy number calls (Supplementary Methods 2.4.3, and described in detail elsewhere[63]).

Overall, the sensitivity and precision of the consensus somatic variant calls were 95% ($CI_{90\%}$: 88-98%) and 95% ($CI_{90\%}$: 71-99%) respectively for SNVs (Extended Figure 2). For somatic indels, sensitivity and precision were 60% (34-72%) and 91% (73-96%) respectively. Regarding SVs, we estimate the sensitivity of the merging algorithm to be 90% for true calls generated by any one caller; precision was estimated as 97.5%. That is, 97.5% of SVs in the merged SV call-set have an associated copy number change or balanced partner rearrangement. The improvement in calling accuracy from combining different callers was most noticeable in variants having low variant allele fractions, which are likely to originate in subclonal populations of the tumour (Figure 1C-D). There remains much work to be done in improving indel callers; we still lack sensitivity for calling even fully clonal complex indels from short-read sequencing data.

Extended Data

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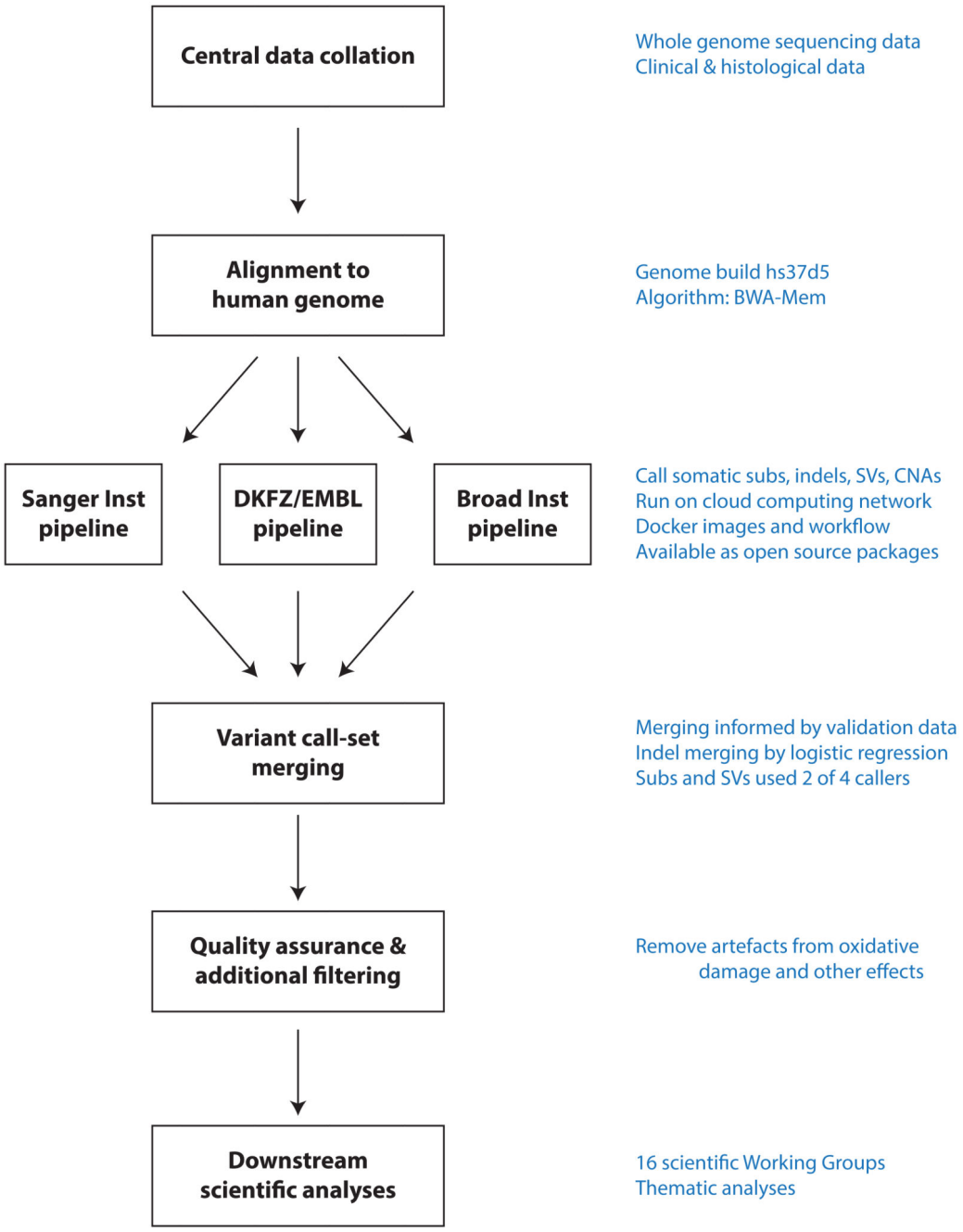

Extended Figure 1. Flow-chart showing key steps in the analysis of PCAWG genomes.

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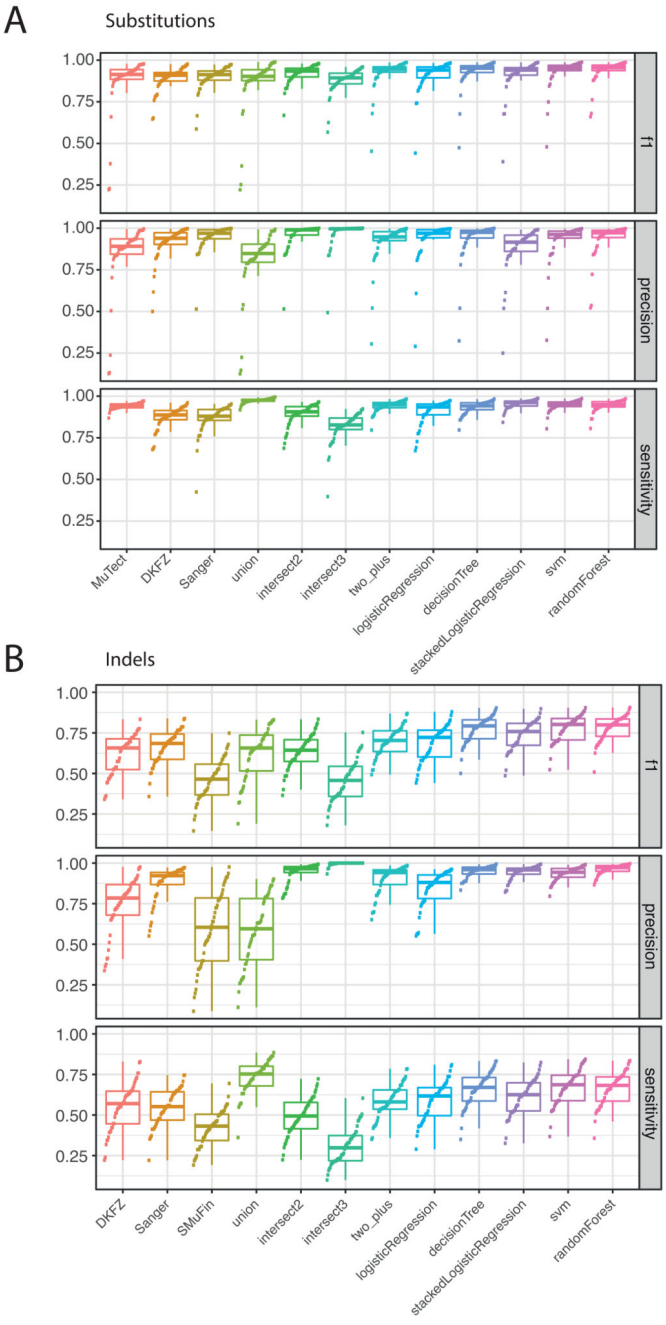

Extended Figure 2. Distribution of accuracy estimates across algorithms and samples from validation data.

(A) F_1 accuracy, precision and sensitivity estimates for somatic SNVs across the core algorithms and different approaches to merging the call sets. The box plots demarcate the interquartile range and median of estimates across the n=50 samples in the validation dataset. **(B)** F_1 accuracy, precision and sensitivity estimates for somatic indels (n=50 samples). SVM, support vector machine; union, calls made by all variant callers; intersect2,

calls made by any combination of two variant callers; intersect3, calls made by any three variant callers.

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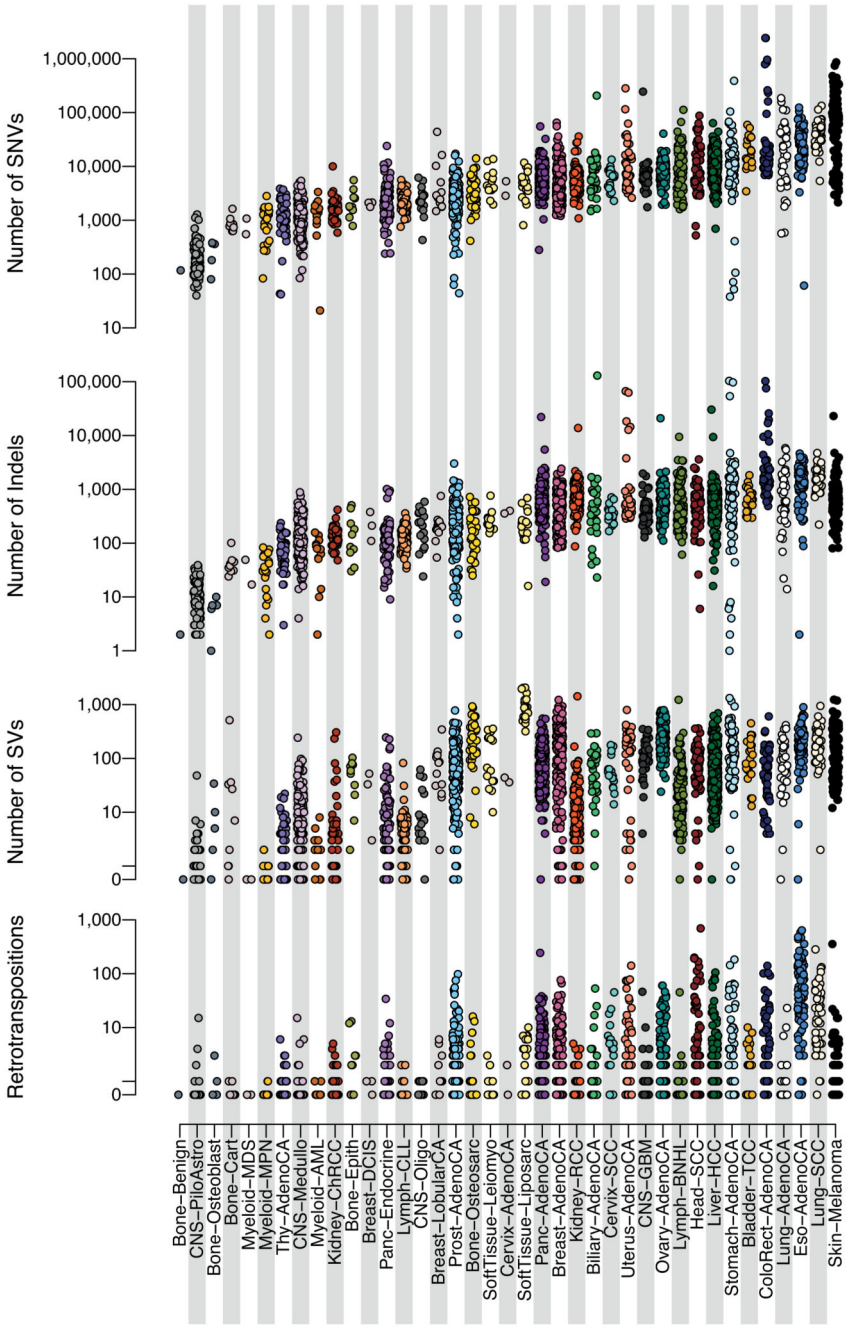
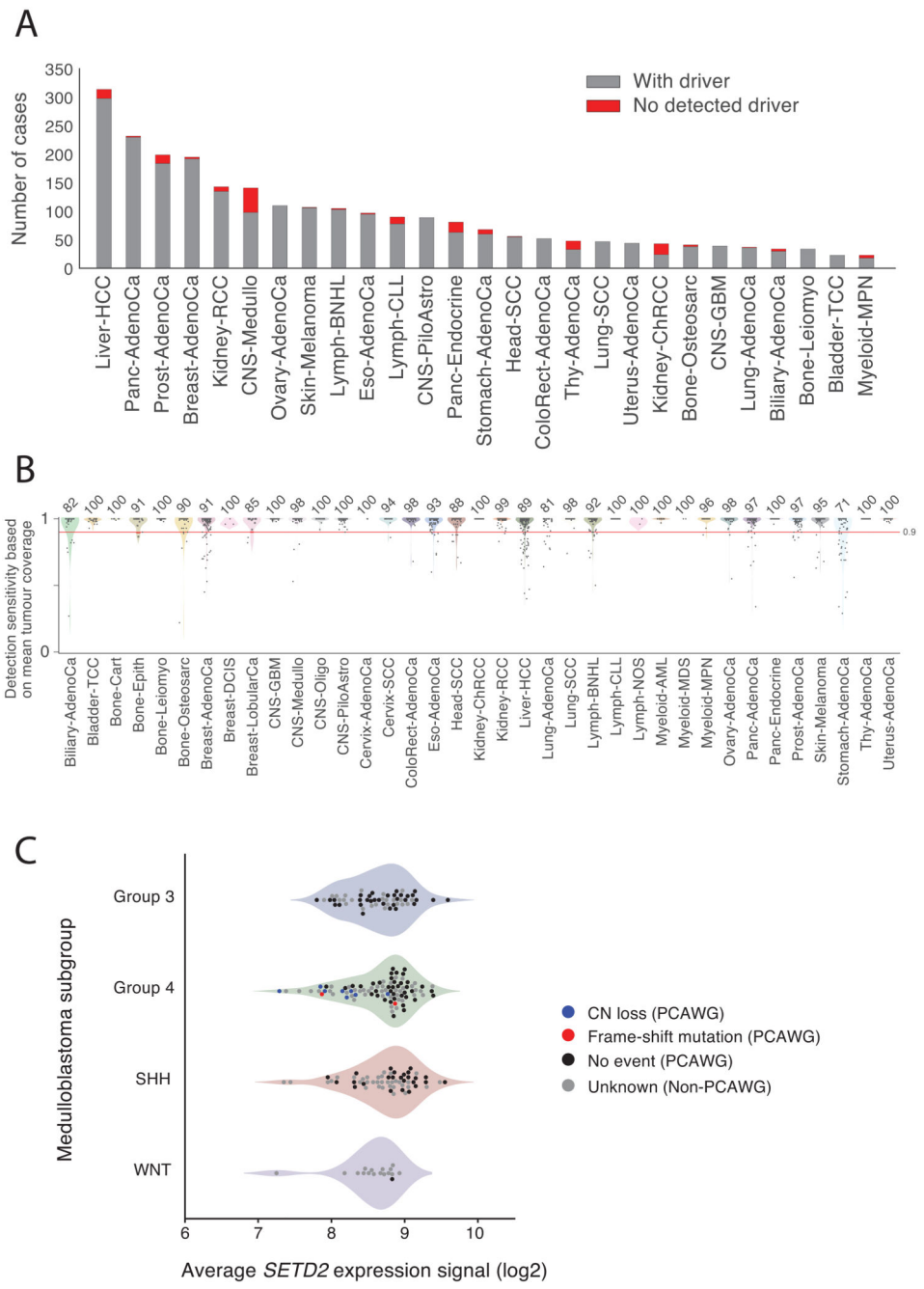


Extended Figure 3. Distribution of numbers of somatic mutations of different classes across tumour types.

The y axis is on a log scale. Plotted are the 2,583 donors with the highest quality metrics (white-listed donors). SNVs, single nucleotide variants (substitutions); Indels, insertions or deletions <100 base pairs in size; SVs, structural variants; Retrotranspositions, counts of somatic retrotransposon insertions, transductions and somatic pseudogene insertions combined.



Extended Figure 4. Patients with no detected driver mutations in PCAWG.

(A) Number (red) of patients without detected driver mutations distributed across the different tumour types studied. **(B)** Estimated sensitivity for detecting somatic point mutations genome-wide across tumour types (total sample size: n=2,583 patients). Each point represents the estimate for a single patient, layered on violin plots representing the estimated density distribution of sensitivity values for that tumour type (width proportional to density). **(C)** *SETD2* expression levels across different medulloblastoma subtypes. Points represent individual patients, coloured by whether the gene exhibited focal copy number

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loss, truncating point mutation, or was wild-type. The coloured areas are violin plots representing the estimated density distribution of expression values for that medulloblastoma subtype (width proportional to density).

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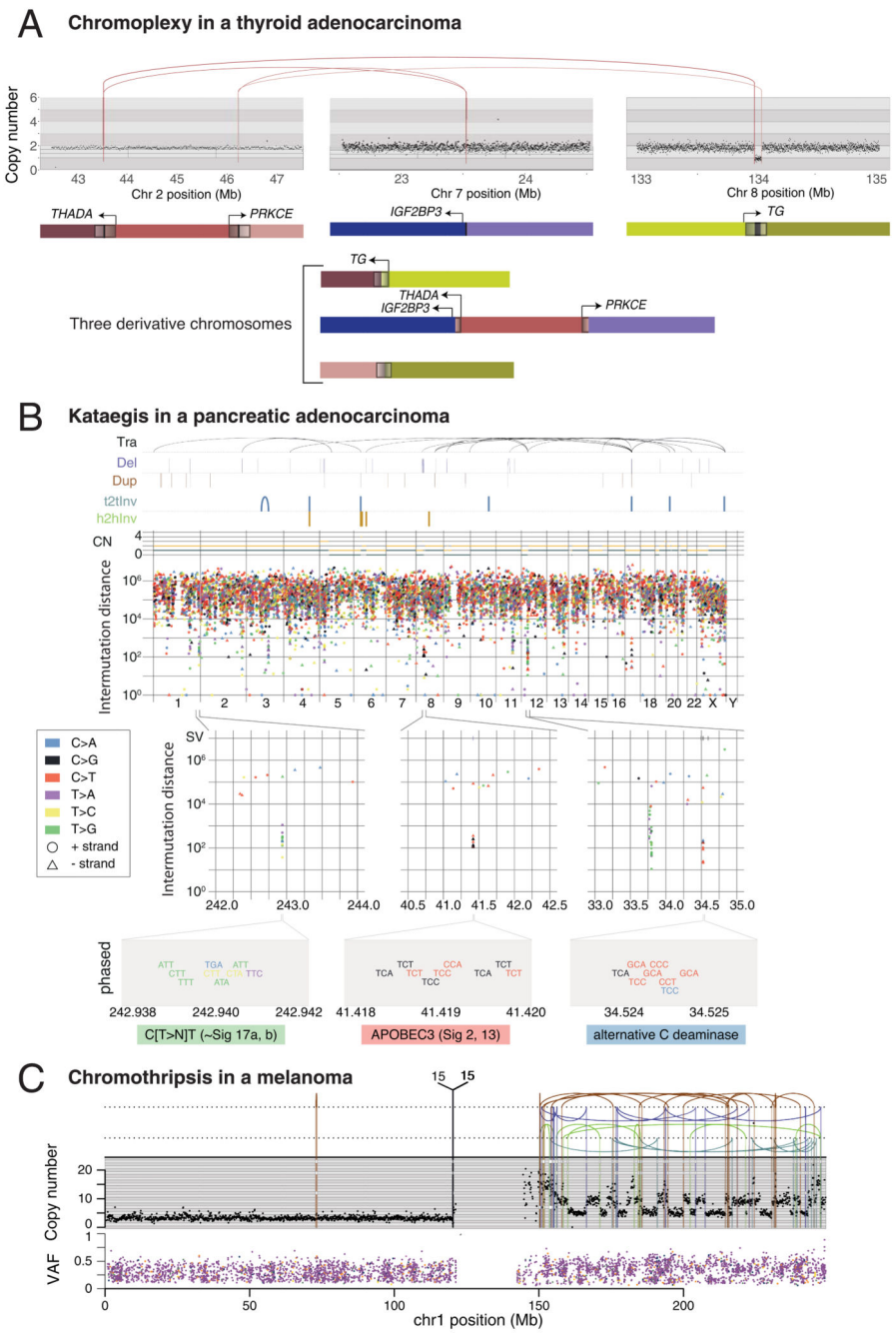

Extended Figure 5. Examples of clustered mutational processes.

(A) Chromoplexy example in a thyroid adenocarcinoma. Genes at the breakpoints are schematically depicted in their normal genomic context and again in the reconstructed derivative chromosomes below. **(B)** Distinct kataegis signatures in the genome of a pancreatic adenocarcinoma sample. SVs and their classification are shown above the main rainfall plot (Tra, translocation; Del, deletion; Dup, duplication; t2tInv, tail-to-tail inversion; h2hInv, head-to-head inversion), as well as the total and minor allele copy number. Zooming into three foci on chr1, chr8 and chr12, respectively, exemplifies distinct manifestations of

kataegis: (left) a novel process similar to Signature 17 with T>N mutations at CT or TT dinucleotides; (middle) the prototypical APOBEC3A/B type with C>T (Signature 2) and/or C>G/A (Signature 13) substitutions at TpC; (right) an alternative cytidine deaminase(s) with a preference for substitutions at C/GpC. Most of the SNVs in each of these foci can be phased to the same allele and no evidence of anti-phasing is observed. **(C)** Example of a chromothripsis event in a melanoma. The black points in the upper panel represent copy number estimates from individual genomic bins, with structural variants shown as coloured arcs (translocation in black, deletion in purple, duplication in brown, tail-to-tail inversion in cyan, head-to-head inversion in green), mostly demarcating copy number changes. The mate chromosomes are displayed above translocations. The lower panel shows the variant allele fraction (VAF) of somatic mutations distributed along the relevant chromosomal region.

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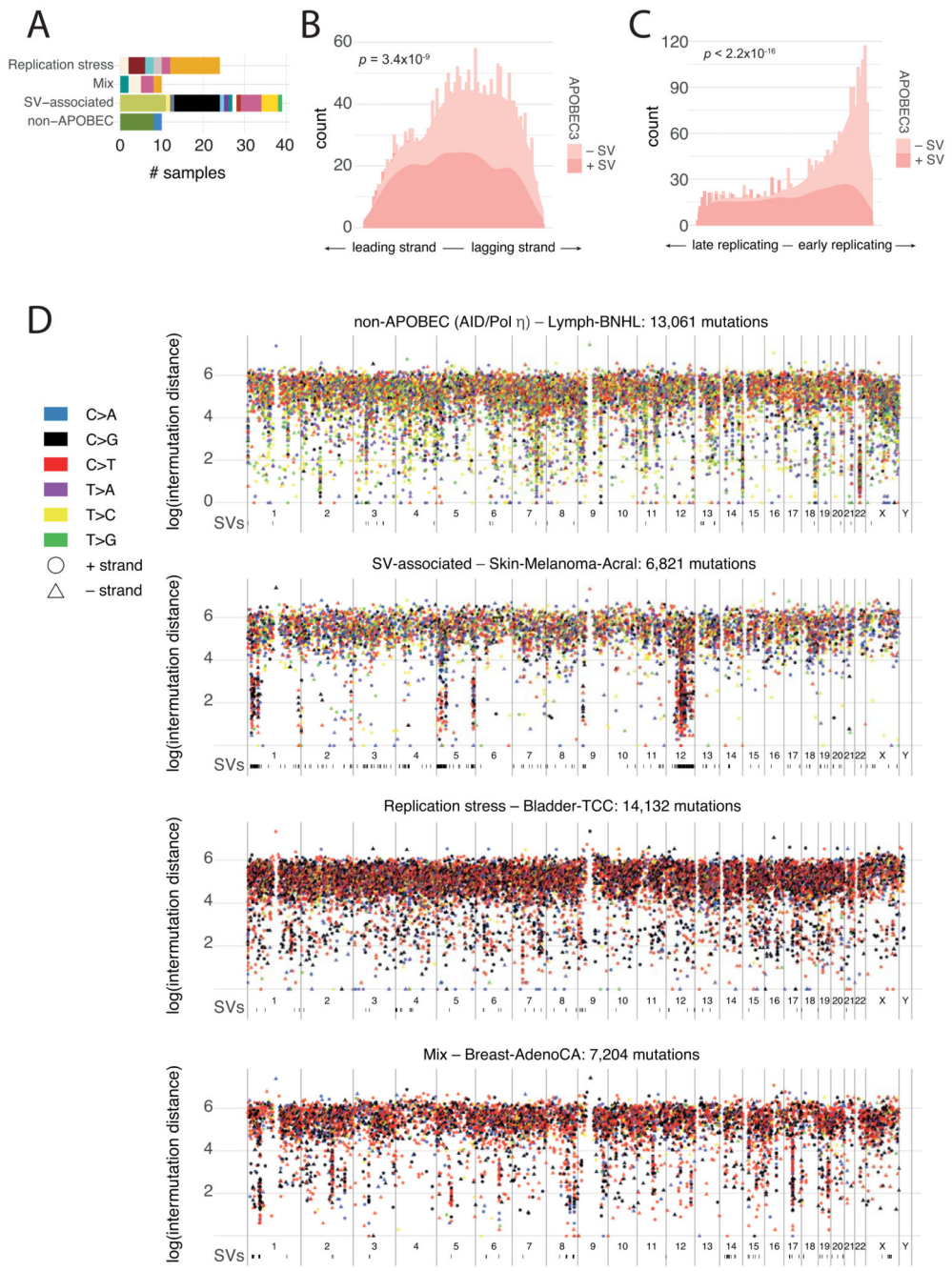

Extended Figure 6. Patterns of intense kataegis.

(A) Bar plot showing the tumour type distribution (colour-coded as in Extended Figure 3) of samples in the top 5% of kataegis intensity in each of the four genome-wide patterns identified: non-APOBEC, replication stress, rearrangement-associated and combination of the latter two. **(B,C)** Distribution of leading/lagging strand **(B)** and replication timing bias **(C)** for rearrangement-(in)dependent APOBEC kataegis, based on n=2,583 tumours. P-values were derived using a two-sided Mann–Whitney *U* test. **(D)** Example rainfall plots for each of the four kataegis patterns identified.

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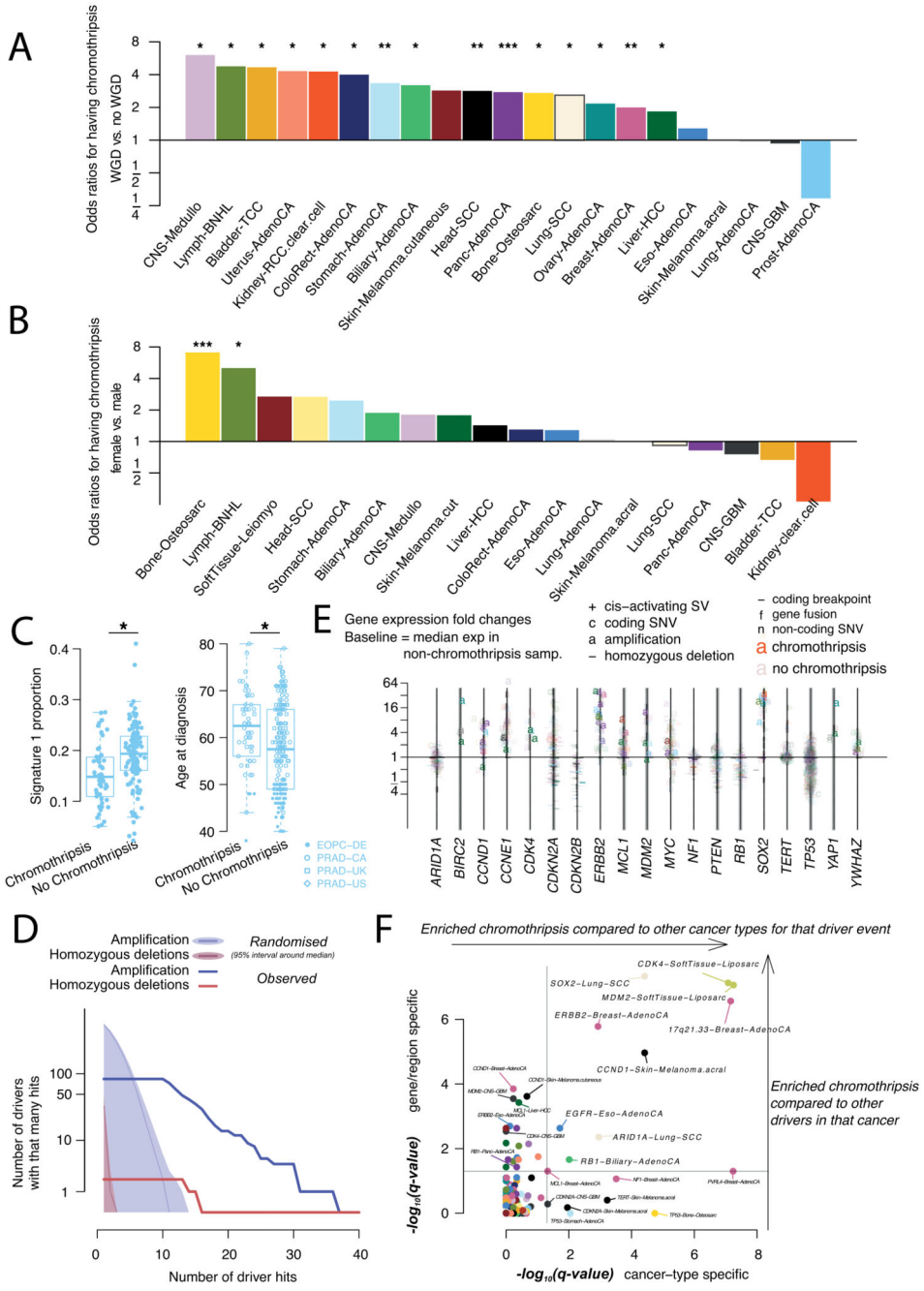

Extended Figure 7. Association of chromothripsis with covariates and driver events.

(A) Odds ratios per cancer type of harbouring chromothripsis in whole genome duplicated vs. diploid samples (n=2,583 patients). Asterisks represent significance level (***: q<0.001; **: q<0.01; *:q<0.05). Two-sided hypothesis testing was performed using Fisher-Boschloo tests, corrected for multiple-hypothesis testing. **(B)** Same as A for female vs. male. **(C)** Proportion of mutations explained by single base substitution signature 1 and age at diagnosis in prostate cancer samples (n=210 patients) with or without chromothripsis (q<0.05). The early-onset prostate cancer project drives the signal and was sequenced at

lower depth. For the box-and-whisker plots, the box denotes the interquartile range, with the median marked as a horizontal line. The whiskers extend as far as the range or 1.5x the interquartile range, whichever is less. Two-sided hypothesis testing was performed using Mann-Whitney U tests. **(D)** Counts of co-occurrence of chromothripsis with amplification (blue) and homozygous deletions (red) in driver regions: observed (thick line) vs. randomised (shaded area and thin line). The cumulative number of drivers hit is plotted as a function of the number of times those drivers are hit. **(E)** For each sample where chromothripsis coincided with a driver event in those genes, we show the gene expression fold change compared to the median expression of the gene in non-chromothripsis samples of the same cancer type, coloured by cancer type and shaped by the type of driver event. We show with added transparency the fold changes calculated the same way for samples with driver mutations hitting the same driver genes but no evidence for chromothripsis. Analysis is based on n=1,222 patients with RNA-sequencing data. **(F)** Enrichment of co-occurrence of chromothripsis with driver events. The x-axis indicates the association of chromothripsis with a driver in a given cancer type compared to its rate of association with that driver in all other cancer types. The y-axis show the association of chromothripsis with a driver in a given cancer type compared to its rate of association with all other drivers in that type. Exact binomial tests are used and p-values are corrected for multiple testing according to Benjamini and Hochberg.

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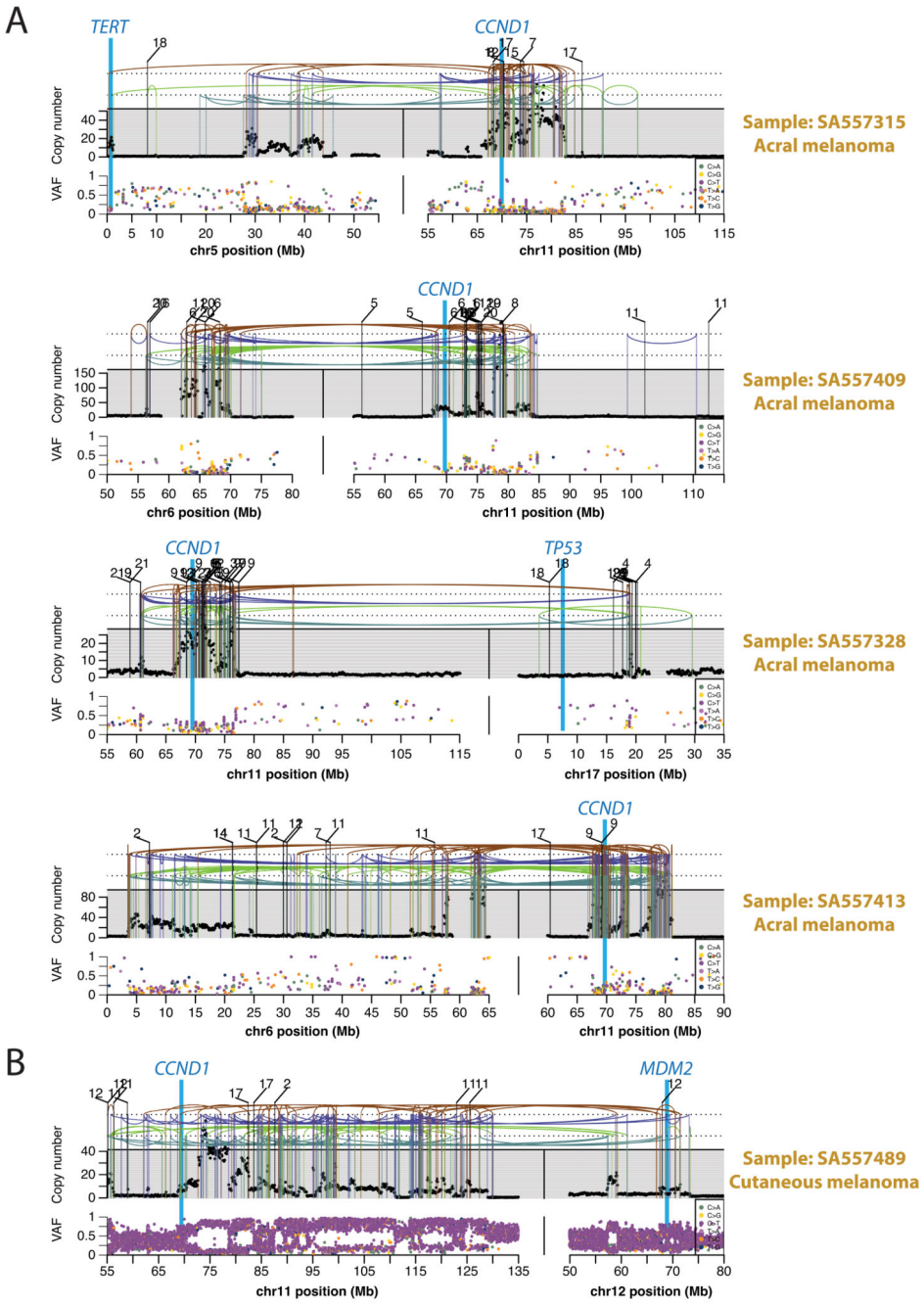

Extended Figure 8. Further examples of chromothripsis-induced amplification targeting multiple cancer genes simultaneously in melanoma.

(A) Examples of amplifications that occurred early in melanoma development. The black points in the upper panel represent copy number estimates from individual genomic bins, with structural variants shown as coloured arcs (translocation in black, deletion in purple, duplication in brown, tail-to-tail inversion in cyan, head-to-head inversion in green), mostly demarcating copy number changes. The mate chromosomes are displayed above translocations. The lower panel shows the variant allele fraction (VAF) of SNVs distributed

along the relevant chromosomal region. The paucity of somatic mutations at high variant allele fraction in the most heavily amplified regions indicates that these amplifications began very early in tumour evolution, before the lineage had had opportunity to acquire many SNVs. **(B)** Example of an amplification that occurred late in melanoma development. The large numbers of somatic mutations at high variant allele fraction in the most heavily amplified regions indicates that these amplifications began late in tumour evolution, after the lineage had already acquired many SNVs.

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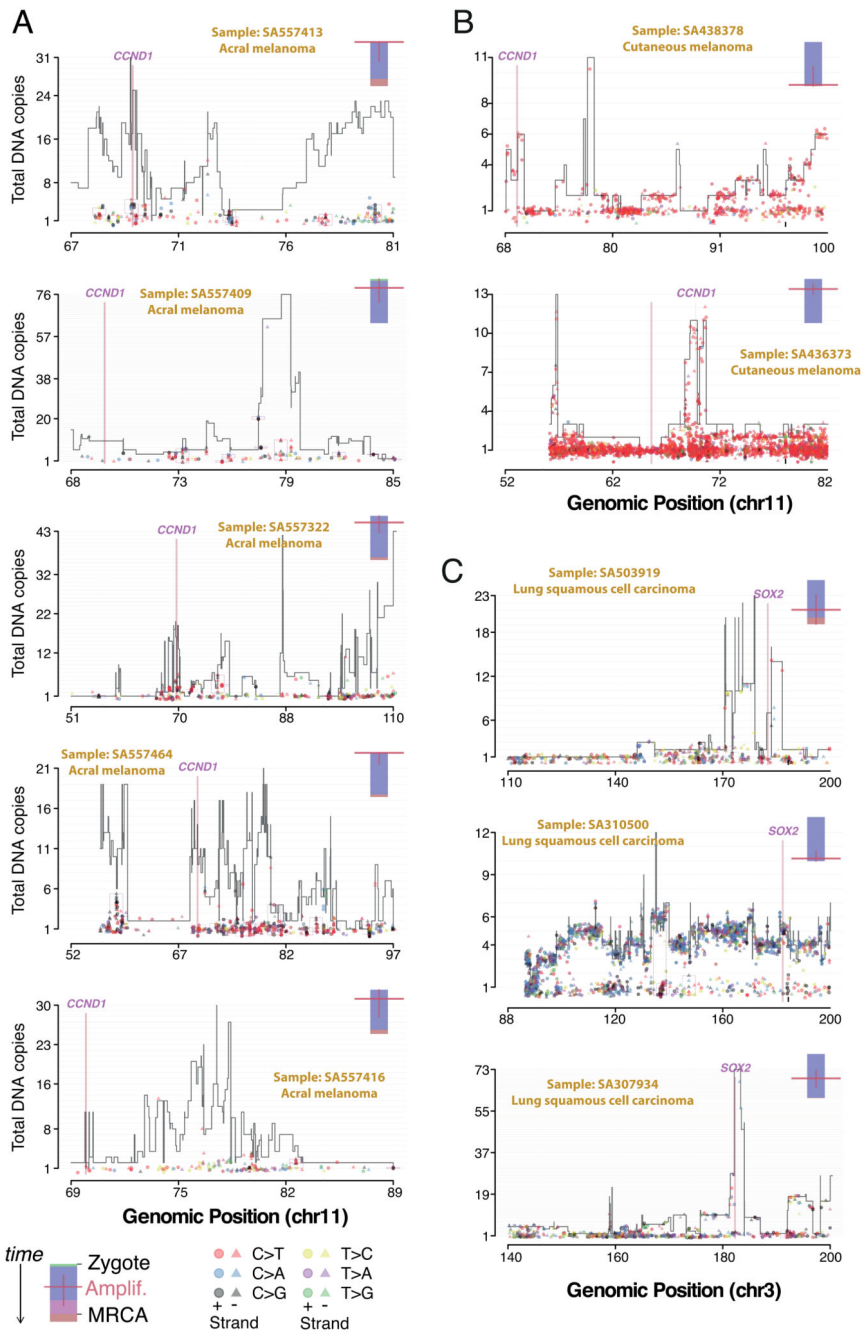

Extended Figure 9. Timing the amplifications following chromothripsis in molecular time – 10 selected cases.

(A) Copy number plot of chromothriptic regions categorised as "liposarc-like" in 5 acral melanomas showing *CCND1* amplification. Segments indicate the copy number of the major allele. Points represent SNV multiplicities, i.e. the estimated number of copies carrying them, coloured by base change and shaped by strand. Small vertical arrows link SNVs to their corresponding copy number segment. Kataegis foci are shown within black boxes, and show typical strand-specificity (all triangles or all circles), similar multiplicities and base

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changes of signatures 2 and 13 (red and black). A coloured bar on the top right represents the molecular timing of the amplification (red bar; high is early, low is late) and is coloured by the fraction of total SNVs assigned to timing categories clonal[early], clonal[NA], clonal[late] and subclonal. **(B)** Same as A in 2 cutaneous melanomas, one shows an early amplification, the other a late one. **(C)** Same as A-B for 3 lung squamous cell carcinomas and late amplification of *SOX2*.

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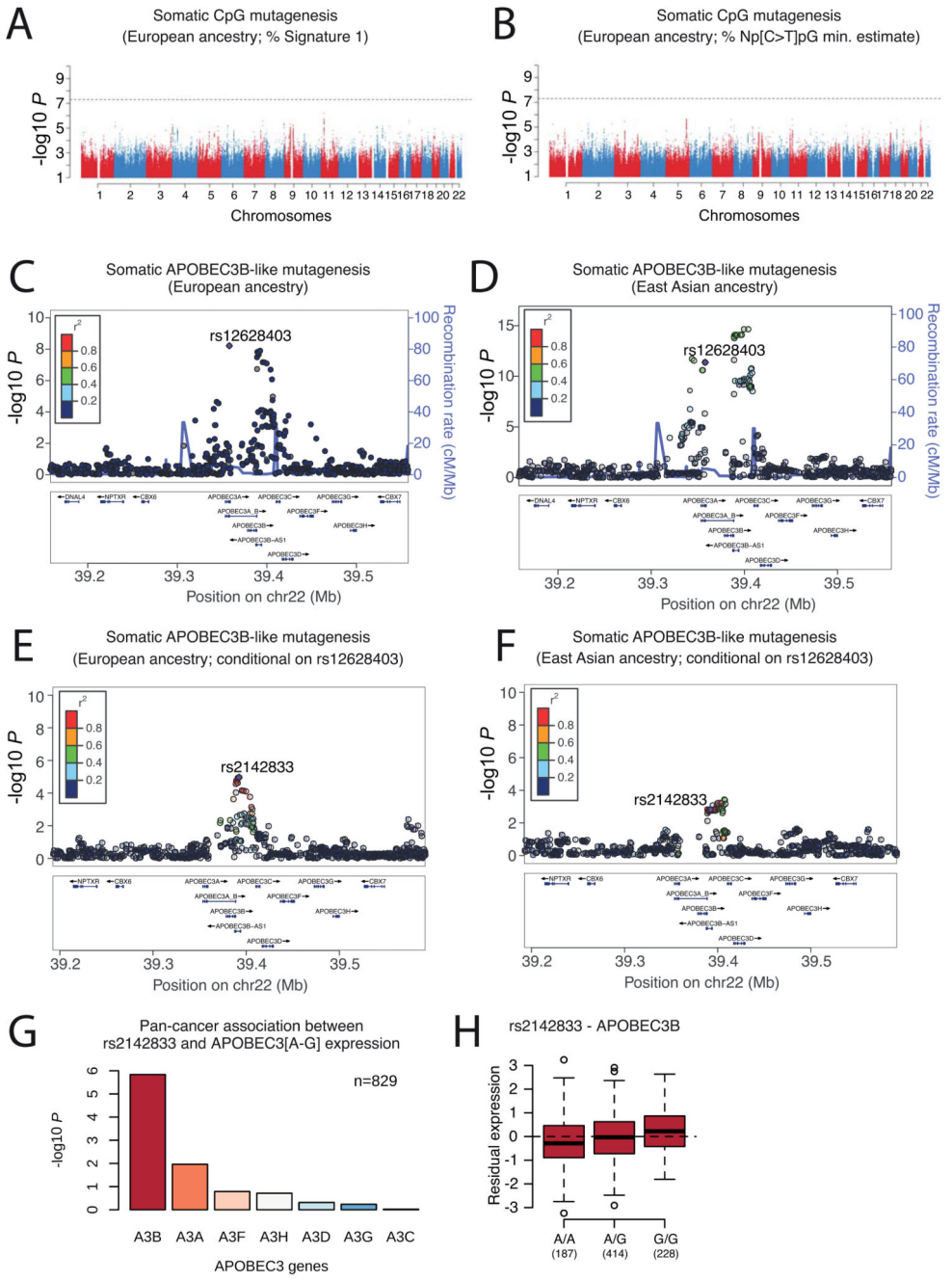

Extended Figure 10. Association between common germline variants and endogenous mutational processes.

Genome-wide association of somatic CpG mutagenesis in individuals of European ancestry (n=1,201 patients) based on mutational signature analysis **(A)** and NpCpG motif analysis **(B)**. Two-sided hypothesis-testing was performed using PLINK v1.9. To mitigate multiple hypothesis-testing, the significance threshold was set at genome-wide significance ($p<5x10^{-8}$). **(C,D)** Locuszoom plot for somatic APOBEC3B-like mutagenesis association results, LD, and recombination rates around the genome-wide significant 22q13.1 locus in

individuals with European **(C)** and East Asian **(D)** ancestry (n=1,201 and 318 patients respectively). Locuszoom plot for somatic APOBEC3B-like mutagenesis association results around the 22q13.1 locus in individuals of European **(E)** and East Asian **(F)** ancestry after conditioning on rs12628403. **(G,H)** Association between rs2142833 and expression of *APOBEC3* genes in PCAWG tumour samples (adjusted for sex, age at diagnosis, histology, and population structure in linear regression models with two-sided hypothesis testing not corrected for multiple tests). For the box-and-whisker plot, the box denotes the interquartile range, with the median marked as a horizontal line. The whiskers extend as far as the range or 1.5x the interquartile range, whichever is less. Outlier patients are shown as points.

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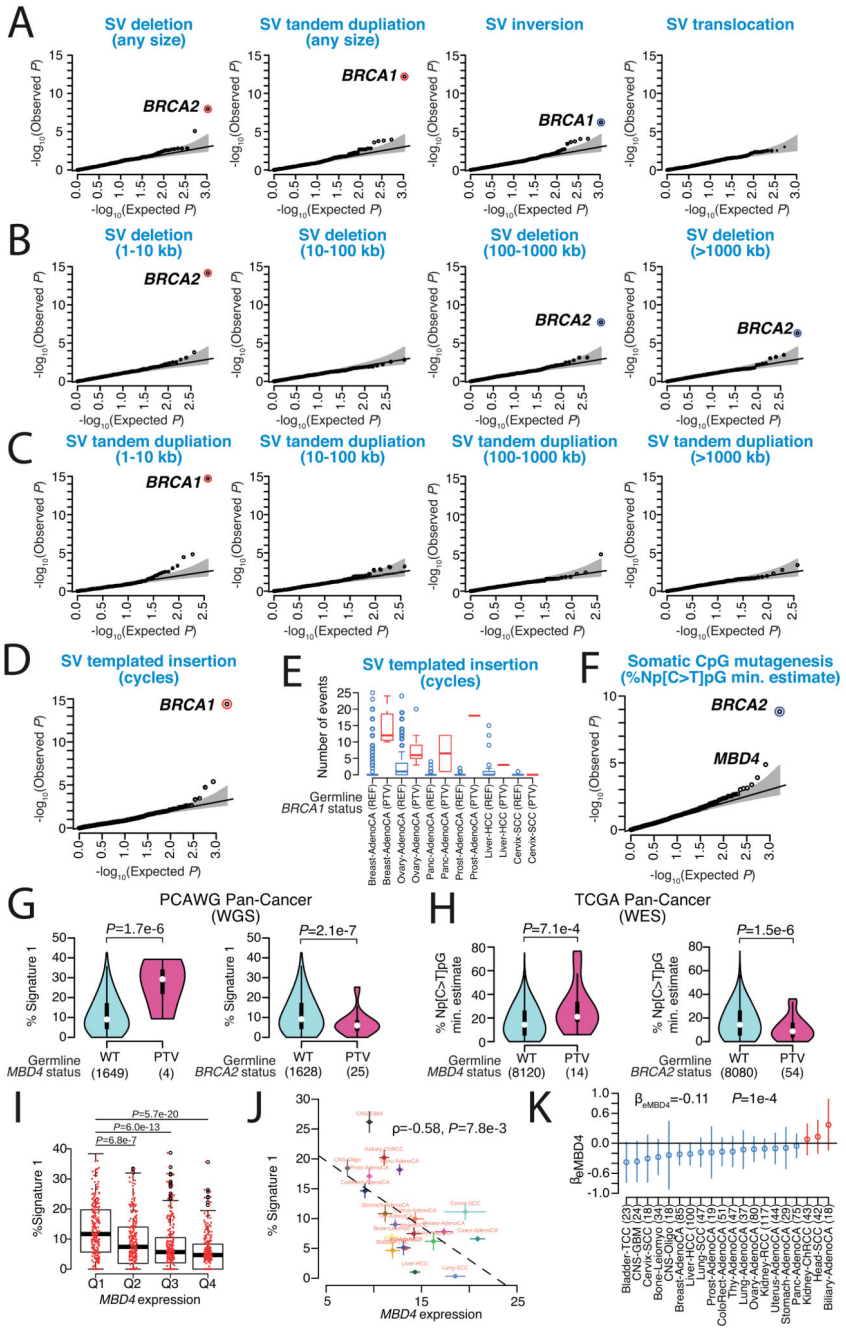

Extended Figure 11. Association between rare germline PTVs in protein-coding genes and somatic mutational phenotypes.

For panels **A-D** and **F**, the data are based on two-sided rare-variant association testing across n=2,583 patients, with a stringent p-value threshold of $P<2.5x10^{-6}$ used to mitigate multiple hypothesis testing (significant genes marked with coloured circles). Blue/red circles mark genes that decrease/increase somatic mutation rates. The black line represents the identity line which would be followed if the observed p values followed the null expectation, with the shaded area showing 95% confidence intervals. **(A)** QQ plots for proportion of somatic

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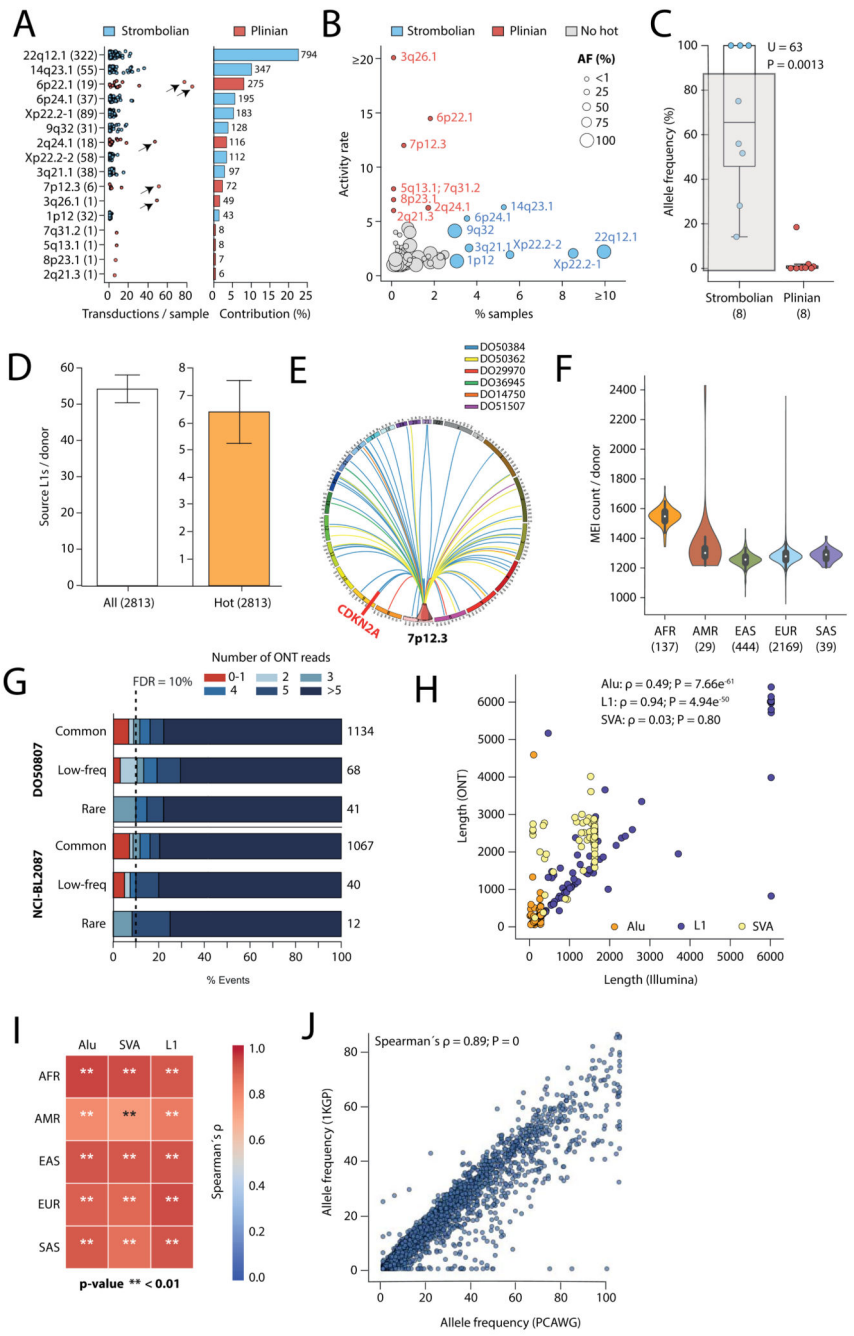
SV deletions, tandem duplications, inversions, and translocation in cancer genomes. **(B)** QQ plots for proportion of somatic SV deletions in cancer genomes stratified by four size groups (1-10 kb; 10-100 kb; 100-1000 kb; >1000 kb). **(C)** QQ plots for proportion of somatic SV tandem duplications in cancer genomes stratified by four size groups (1-10 kb; 10-100 kb; 100-1000 kb; >1000 kb). **(D)** QQ plot for presence/absence of somatic SV templated insertion (cycles) in cancer genomes. **(E)** Number of SV templated insertion cycles in PCAWG tumours with germline *BRCA1* PTVs. Only histologies with at least one germline *BRCA1* PTV carrier are shown (n=1,095 patients combined). The box denotes the interquartile range, with the median marked as a horizontal line. The whiskers extend as far as the range or 1.5x the interquartile range, whichever is less. Outlier patients are shown as points. **(F)** QQ plot for somatic CpG mutagenesis in cancer genomes based on NpCpG motif analysis. **(G)** Violin plots show estimated density of the proportion of somatic CpG mutations in PCAWG donors with germline *MBD4* and *BRCA2* PTVs. The box denotes the interquartile range, with the median marked as a white point. The whiskers extend as far as the range or 1.5x the interquartile range, whichever is less. Two-sided hypothesis testing, not corrected for multiple testing, was performed using linear regression models. **(H)** Replication of germline *MBD4* and *BRCA2* PTV associations with somatic CpG mutagenesis in TCGA WES donors. Violin plots show estimated density of the proportion of somatic CpG mutations in TCGA exomes with germline *MBD4* and *BRCA2* PTVs. The box denotes the interquartile range, with the median marked as a white point. The whiskers extend as far as the range or 1.5x the interquartile range, whichever is less. Two-sided hypothesis testing, not corrected for multiple testing, was performed using linear regression models. **(I)** Correlation between *MBD4* expression and somatic CpG mutagenesis in primary solid PCAWG tumours. Hypothesis testing was two-sided and not corrected for multiple testing, using linear regression models. The box denotes the interquartile range, with the median marked as a horizontal line. The whiskers extend as far as the range or 1.5x the interquartile range, whichever is less. **(J)** Points represent means across n=20 tumour types and error bars represent standard error of the mean. The dashed black line shows the fitted line to the data, estimated with linear regression models. Hypothesis testing was two-sided and not corrected for multiple testing, performed with Spearman's rank correlation method. **(K)** *MBD4* effect sizes (open circles) with 95% confidence intervals (error bars) for individual cancer types were estimated with linear regression analysis after (if available) accounting for sex, age at diagnosis (low/high), and ICGC project. Hypothesis testing was two-sided and not corrected for multiple testing.



Extended Figure 12. Germline mobile element insertion (MEI) callset.

(A) On the left, dots show the number of transductions promoted by each hot element in individual samples. Arrows highlight retrotransposition burst. On the right, the contribution of each hot locus is represented. The total number of transductions mediated by each source element is shown on the right side. **(B)** Source L1 activity rate (*i.e.,* measured as the average number of transductions mediated by an element) versus the percentage of samples with retrotransposition activity in which the germline element is active. For visualization purposes, extreme points observed for a source L1 with an activity rate of 49 and for a L1

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active in 31% of the samples are shown at “≥20” and “≥10”, respectively. **(C)** Contrasting allele frequencies for Strombolian and Plinian source loci (sample sizes shown under each axis label). The box denotes the interquartile range, with the median marked as a white point. The whiskers extend as far as the range or 1.5x the interquartile range, whichever is less. Hypothesis-testing was performed using two-sided Mann-Whitney tests without correction for multiple tests. **(D)** Number of active and hot source L1 elements per donor. The bar height represents the mean number of elements per donor and error bars the standard deviation. **(E)** Novel Plinian source element on 7p12.3 mediates 72 transductions amongst only six cancer samples. This includes a transduction that induces the deletion of the tumour suppressor gene *CDKN2A*. **(F)** Violin plots show estimated number of distinct germline MEI alleles per PCAWG donor. The box denotes the interquartile range, with the median marked as a white point. The whiskers extend as far as the range or 1.5x the interquartile range, whichever is less. Donors are grouped according to their genetic ancestry: AFR, African; AMR, Ad Mixed American; EAS, East Asian; EUR, European; SAS, South Asian. Sample sizes are shown under each axis label. **(G)** For each type of MEI (L1, Alu and SVA) identified both in PCAWG and in the 1000 Genomes Project (1KGP), the correlations between allele frequency estimates per ancestry derived from both projects are displayed in a blue (0) to a red (1) coloured gradient. Sample size was n=2,583 PCAWG patients. Two-sided hypothesis-testing was performed using Spearman’s rank correlation without correction for multiple tests. **(H)** Example displaying the correlation between PCAWG and 1KGP derived MEI allele frequencies in individuals with European ancestry (n=1201 patients in PCAWG). Two-sided hypothesis-testing was performed using Spearman’s rank correlation without correction for multiple tests. **(I)** Evaluation of TraFiC-mem false discovery rate on a liver hepatocellular carcinoma donor (DO50807) and a cell-line (NCI-BL2087) sequenced through single-molecule sequencing with MinION (Oxford Nanopore). For each allele frequency bin (common, >5%; low-freq, 1-5%; rare, <1%), the percentage of events supported by N long-reads is represented (N from 0-1 to more than 5). MEIs supported by at least two Nanopore reads were considered true positives (blue palette) and false positives (red), otherwise. The total number of germline MEIs per allele frequency bin is shown on the right side of the panels. **(J)** Correlation between predicted MEI lengths from Illumina and Nanopore data. Two-sided hypothesis testing was performed using Spearman’s rank correlation without correction for multiple testing.

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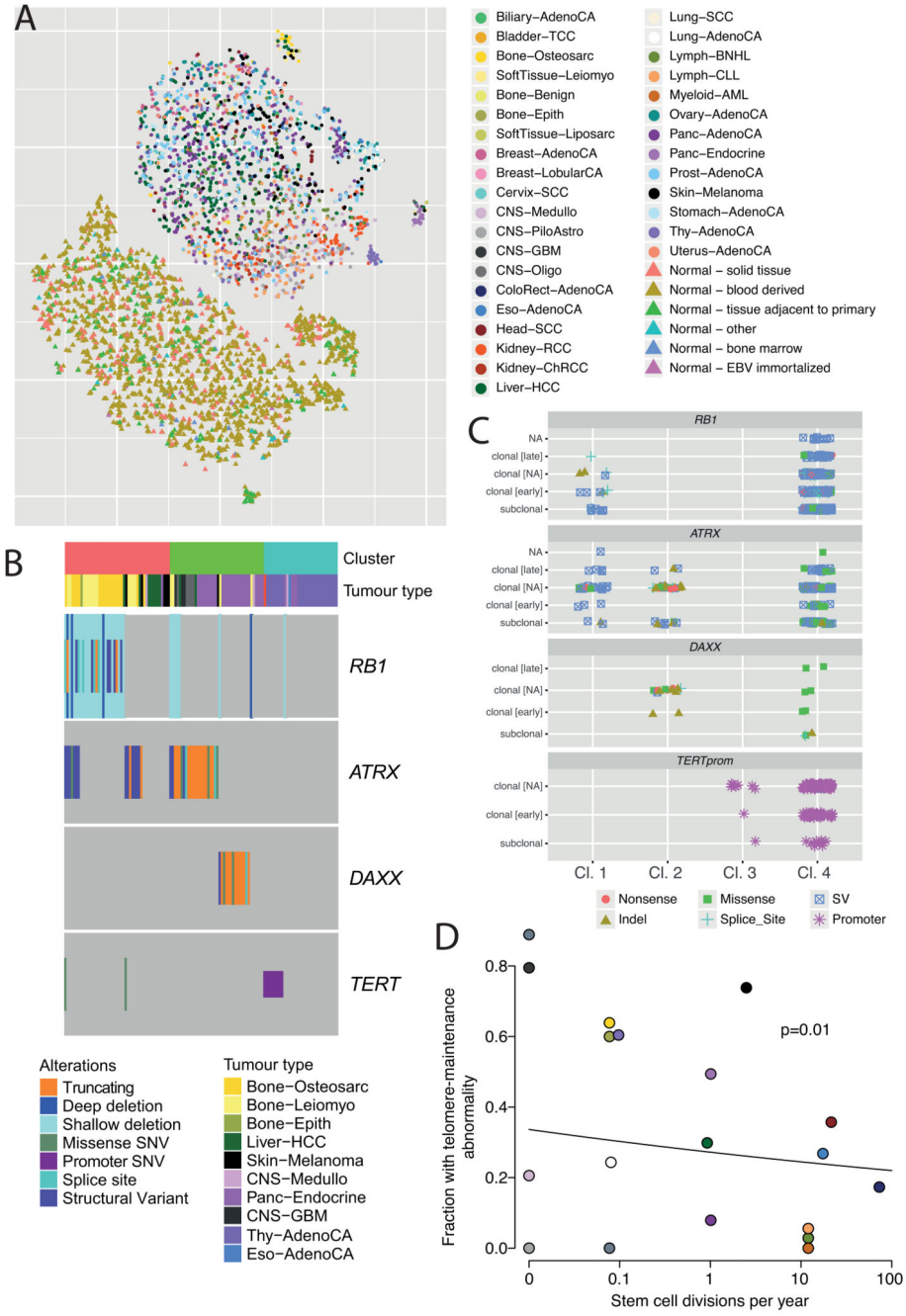

Extended Figure 13. Different mechanisms of telomere lengthening in cancer.

(A) Scatter plot showing the four clusters of tumour-specific telomere patterns identified across PCAWG samples, together with the clusters of matched normal samples, generated by t-Distributed Stochastic Neighbour Embedding. Circles represent tumour samples and triangles represent matched normal samples. Points are coloured by tissue of origin. Data are based on n=2,518 tumour samples and their matched normal samples. **(B)** Patterns of co-mutation of the relevant driver mutations across individual patients. Columns in plot represent individual patients, coloured by type of abnormality observed. **(C)** Clonal [early]

denotes clonal mutations occurring before duplications involving the relevant chromosome (including whole genome duplications); clonal [late] to clonal mutations occurring after such duplications; and clonal [NA] to mutations occurring when no duplication was observed. **(D)** Relationship between estimated number of stem cell divisions per year and rate of telomere maintenance abnormalities across tumour types. The analysis uses data on estimated rates of stem cell division per year across n=19 tissue types previously collated from the literature[86]. Tumour types are coloured according to the scheme shown in Extended Figure 3. Two-sided hypothesis testing was performed using likelihood ratio tests on Poisson regression models with no correction for multiple tests.

Extended Table 1
Overview of tumour types included in PCAWG project.

Med, Median; F, Female; M, Male; 10-90th, 10-90th centile; Adeno., Adenocarcinoma; Comb., Combined; SCC, squamous cell carcinoma; HCC, hepatocellular carcinoma; Ca. Carcinoma.

Organ	Abbrevation	Included subtypes	Cases	Sex		Age	
Neural Crest			**Num.**	**F**	**M**	**Med.**	**10th-90th**
CNS	CNS-GBM	Glioblastoma	41	13	28	60	43-72
CNS	CNS-Medullo	Medulloblastoma and variants	146	67	79	9	3-28
CNS	CNS-Oligo	Oligodendroglioma	18	9	9	41	21-62
CNS	CNS-PiloAstro	Pilocytic astrocytoma	89	47	42	8	2-17
Skin	Skin-Melanoma	Malignant melanoma	107	38	69	57	37-78
Endoderm							
Biliary	Biliary-AdenoCA	Papillary cholangiocarcinoma	34	15	19	64	53-76
Bladder	Bladder-TCC	Transitional cell carcinoma	23	8	15	65	52-80
Colon/Rectum	ColoRect-AdenoCA	Adenocarcinoma; Mucinous adeno.	60	30	30	67	46-81
Oesophagus	Eso-AdenoCA	Adenocarcinoma	98	14	84	70	56-79
Liver	Liver-HCC	Hepatocellular carcinoma; Comb. HCC/cholangio	317	89	228	67	50-78
Lung	Lung-AdenoCA	Adenocarcinoma; Adenocarcinoma *in situ*	38	20	18	66	47-77
Lung	Lung-SCC	Squamous cell carcinoma; Basaloid SCC	48	10	38	68	54-77
Pancreas	Panc-AdenoCA	Adeno.; Acinar cell Ca.; Mucinous adeno.	239	119	120	67	50-79
Pancreas	Panc-Endocrine	Neuroendocrine carcinoma	85	30	55	59	38-75
Prostate	Prost-AdenoCA	Adenocarcinoma	210	0	210	59	47-71
Stomach	Stomach-AdenoCA	Adenocarcinoma; Mucinous; Papillary; Tubular	75	18	57	65	47-79
Thyroid	Thy-AdenoCA	Adenocarcinoma; Columnar cell; Follicular type	48	37	11	51	26-75
Mesoderm							

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Organ	Abbrevation	Included subtypes	Cases	Sex		Age	
Bone/Soft Tissue	Bone-Benign	Osteoblastoma; Osteofibrous dysplasia	7	4	3	18	12-30
Bone/Soft Tissue	Bone-Benign	Chondroblastoma; Chrondromyxoid fibroma	9	2	7	16	14-38
Bone/Soft Tissue	Bone-Epith	Adamantinoma; Chordoma	10	4	6	60	37-67
Bone/Soft Tissue	Bone-Osteosarc	Osteosarcoma	38	20	18	20	9-58
Bone/Soft Tissue	SoftTissue-Leiomyo	Leiomyosarcoma	15	10	5	61	51-78
Bone/Soft Tissue	SoftTissue-Liposarc	Liposarcoma	19	5	14	n/a	n/a
Cervix	Cervix-AdenoCA	Adenocarcinoma	2	2	0	39	33-46
Cervix	Cervix-SCC	Squamous cell carcinoma	18	18	0	39	25-58
Head/Neck	Head-SCC	Squamous cell carcinoma	57	10	47	53	34-71
Kidney	Kidney-ChRCC	Adenocarcinoma, chromophobe type	45	19	26	47	34-69
Kidney	Kidney-RCC	Clear cell adenocarcinoma; papillary type	144	54	90	60	48-75
Lymphoid	Lymph-BNHL	Burkitt; Diffuse large B-cell; Follicular; Marginal	107	51	56	57	10-74
Lymphoid	Lymph-CLL	Chronic lymphocytic leukaemia	95	31	64	62	46-78
Myeloid	Myeloid-AML	Acute myeloid leukaemia	10	3	7	50	35-56
Myeloid	Myeloid-MDS	Myelodysplastic syndrome	2	1	1	76	74-77
Myeloid	Myeloid-MPN	Myeloproliferative neoplasm	26	14	12	56	38-75
Ovary	Ovary-AdenoCA	Adenocarcinoma; Serous cystadenocarcinoma	113	113	0	60	48-74
Uterus	Uterus-AdenoCA	Adeno., endometrioid; Serous cystadeno.	51	51	0	69	57-81
Ectoderm							
Breast	Breast-AdenoCA	Infiltrating duct carcinoma; Medullary; Mucinous	198	197	1	56	39-76
Breast	Breast-DCIS	Duct micropapillary carcinoma	3	3	0	55	43-60
Breast	Breast-LobularCA	Lobular carcinoma	13	13	0	53	42-69
Total			**2658**	**1189**	**1469**	**59**	**21-76**

Extended Table 2

Ethical considerations of genomic cloud computing.

Ethical Considerations of Genomic Cloud Computing

The PCAWG project represents the first large-scale use of distributed cloud computing in genomics. The project involved the movement of large quantities of personal health information across multiple legal jurisdictions and responsible use of this data by several hundred international researchers. Donor consents were written to explicitly allow for broad research use of the data and for international data sharing. PCAWG was granted permission by the leads of each of the tumour data providers to store, analyse and distribute the data on academic and/or commercial compute clouds.

To ensure that the PCAWG personal data were handled in a manner consistent with the donor consents, authorised representatives of each of the academic clouds and high-performance computing facilities signed a commitment not to access controlled tier data beyond the minimum needed to administer it. We negotiated similar contractual terms with commercial cloud partners. Prior to accessing the data, each PCAWG researcher was required to obtain local Institutional Review Board approval for their proposed analytic projects, and obtained controlled tier authorisation from dbGaP (National Center for Biotechnology Information) and the ICGC DACO (Centre of Genomics and Policy at McGill University). To handle the data securely, we encrypted it while in motion and at rest. We used a central authentication and digital token generating system to enforce a strong data access protocol that required researchers to provide their TCGA and/or ICGC credentials prior to accessing controlled tier data. No data breach or other compromise of donor confidentiality is known to have occurred over the course of the PCAWG project, despite its extensive use of cloud computing.

Extended Table 3

Scientific output using PCAWG data, in bite-size chunks.

Scientific	Key findings	Citation
Driver mutations		
Discovery of non-coding drivers	• Estimated ~10-fold more coding than non-coding driver point mutations. • Variation in point mutation density in non-coding regions influenced more by mutational processes than selection.	4
Drivers by pathways and networks	• Both coding and non-coding alterations contribute to cancer pathways. • Some pathways, such as RNA splicing, are primarily driven by non-coding mutations.	16
Evolution and heterogeneity		
Timing of cancer evolution	• Each tumour type has a distinct pattern of early and late-occurring driver events. • Earliest somatic mutations may occur decades prior to diagnosis, providing opportunities for early diagnosis. • Intra-tumour heterogeneity is widespread and tumour subclones contain drivers that are under positive selection.	7
Structural variants		
Patterns of structural variation	• Replication-based mechanisms of genome rearrangement frequent in many cancers, often causing driver structural variants. • 16 signatures of SV, including break-and-ligate patterns and copy-and-insert patterns, varying by size range, replication timing, tumour type and patient.	6
Functional consequence of structural variation	• 52 regions with recurrent structural breakpoints and 90 recurrently fused pairs of loci show evidence of positive selection. • Oncogenic fusions are shaped by juxtaposition of proto-oncogenes with tissue-specific regulatory elements.	4
Patterns of retrotransposition	• Many flavours of somatic retrotransposition in many cancers: LINE element mobilisation; transductions, pseudogenes, Alu elements.	10

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Scientific	Key findings	Citation
	• Retrotranspositions can induce genomic instability, including large deletions and breakage-fusion-bridge cycles amplifying cancer genes.	
Chromothripsis	• Chromothripsis pervasive across cancers, with frequency > 50% in several tumour types. • Replicative processes and templated insertions contribute to rearrangement.	18
Mutational signatures		
Signatures of point mutations	• >70 distinct mutational signatures, encompassing SNVs, doublet subs and indels. • Multiple signatures from unknown processes of DNA damage, repair and replication.	5
Mutation distribution across genome	• Uneven distribution of somatic mutations and structural variants across the genome explained by epigenetic state of tissue, cell of origin and topological associated domains. • Can be used to identify a tumour‘s type and presumed tissue/cell of origin.	11,12,15
Transcriptional consequences of somatic mutation		
RNA effects of somatic mutation	• Genomic basis for RNA alterations across ~1200 tumours, including quantitative trait loci, allele specific expression and alternative splicing. • Link between mutational signatures and expression; classification of gene fusions; identification of genes recurrently altered at RNA level.	8,9
Others		
Tumour subtypes from genome sequencing	• Genomic distribution of somatic mutations, mutational signatures and driver mutations accurately distinguish major tumour types of primaries and metastases.	12
Mitochondrial DNA mutations	• Somatic mitochondrial truncating mutations frequent in certain cancer types, associated with activation of critical signaling pathways.	14
Telomere biology and sequences	• Activating *TERT* promoter mutations are the single most frequent non-coding driver. • In *ATRX/DAXX*-mutant tumours, aberrant telomere variant repeat distribution is common.	4,13

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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BOX 1

Online resources for data access, visualisation and analysis

The PCAWG Landing Page at http://docs.icgc.org/pcawg provides links to several data resources for interactive online browsing, analysis and download of PCAWG data and results (Supplementary Table 4).

Direct download of PCAWG data

Aligned PCAWG read data in BAM format are also available at the European Genome Phenome Archive (EGA; https://www.ebi.ac.uk/ega/search/site/pcawg under accession EGAS00001001692). In addition, all open tier PCAWG genomics data, as well as reference data sets used for analysis, can be downloaded from the ICGC Data Portal at http://docs.icgc.org/pcawg/data/. Controlled tier genomic data, including SNVs and indels that originated from TCGA projects (in VCF format), and aligned reads (in BAM format) can be downloaded using the Score (https://www.overture.bio/) software package, which implements accelerated and secure file transfer, as well as BAM slicing facilities to selectively download defined regions of genomic alignments.

PCAWG computational pipelines

The core alignment, somatic variant-calling, quality control and variant consensus generation pipelines used by PCAWG have each been packaged into portable cross-platform images using the Dockstore system[88] and released under an Open Source license that allows for unrestricted usage and redistribution. All PCAWG Dockstore images are available to the public at https://dockstore.org.

ICGC Data Portal (https://dcc.icgc.org).

The ICGC Data Portal[89] serves as the main entry point for accessing PCAWG datasets with a single uniform web interface and a high-performance data download client. This uniform interface gives users easy access to the myriad of PCAWG sequencing data and variant calls that reside in many repositories and compute clouds worldwide. Streaming technology[90] gives users high-level visualisations in real time of BAM and VCF files stored remotely on the Cancer Genome Collaboratory.

UCSC Xena (https://pcawg.xenahubs.net)

UCSC Xena[91] visualises all PCAWG primary results, including copy number, gene expression, gene fusion, promoter usage, simple somatic mutations, large somatic structural variation, mutational signatures and phenotypic data. These open-access data are available through a public Xena hub, while consensus simple somatic mutations can be loaded into a user's local computer private Xena hub. Kaplan-Meier plots, histograms, boxplots, scatterplots and transcript-specific views offer additional visualisation options and statistical analyses.

Expression Atlas (https://www.ebi.ac.uk/gxa/home)

The Expression Atlas contains RNAseq and expression microarray data for querying gene expression across tissues, cell types, developmental stages and/or experimental

conditions[92]. Two different views of the data are provided: summarised expression levels for each tumour type and gene expression at the level of individual samples, including reference gene expression datasets for matching normal tissues.

PCAWG-Scout (http://pcawgscout.bsc.es/)

PCAWG-Scout provides a framework for ‘omics workflow and website templating to make on-demand, in-depth analyses over the PCAWG data openly available to the whole research community. Views of protected data are available that still safeguard sensitive data. Through the PCAWG-Scout web interface, users can access an array of reports and visualisations that leverage on-demand bioinformatic computing infrastructure to produce results in real-time, allowing users to discover trends as well as form and test hypotheses.

Chromothripsis Explorer (http://compbio.med.harvard.edu/chromothripsis/)

Chromothripsis Explorer is a portal that allows structural variation in the PCAWG dataset to be explored on an individual patient basis through the use of circos plots. Patterns of chromothripsis can also be explored in aggregated formats.

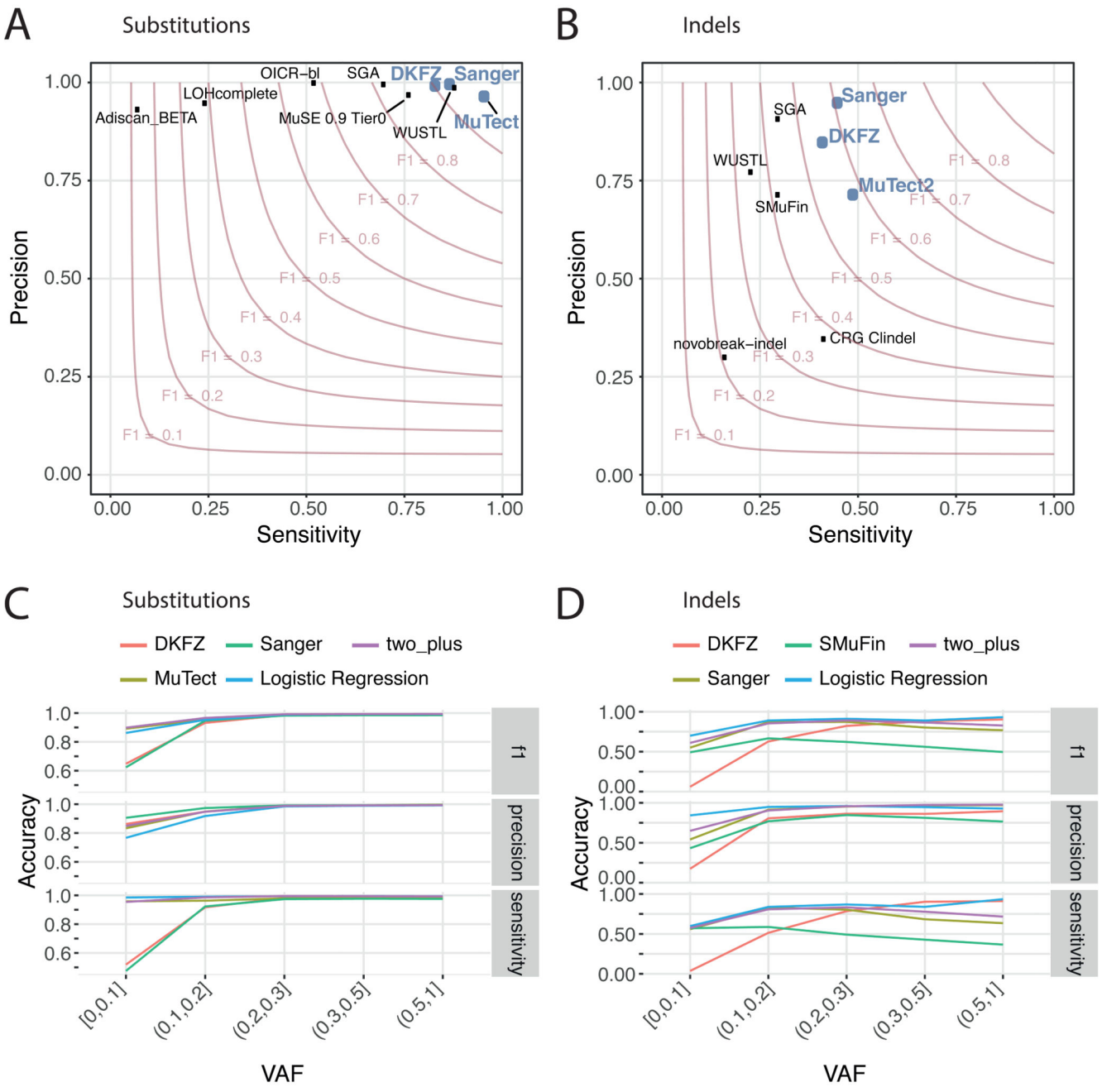

Figure 1. Validation of variant-calling pipelines in PCAWG.

(A) Scatter plot of estimated sensitivity and precision for somatic SNVs across individual algorithms assessed in the validation exercise across n=63 PCAWG samples. Core algorithms included in the final PCAWG call-set are shown in blue. **(B)** Sensitivity and precision estimates across individual algorithms for somatic indels. **(C)** Accuracy (F_1 score, precision and sensitivity) of somatic SNV calls across variant allele fractions (VAF) for the core algorithms. Also shown is the accuracy for two methods of combining variant calls

(two-plus, which was used in the final data-set, and logistic regression). **(D)** Accuracy of indel calls across VAFs.

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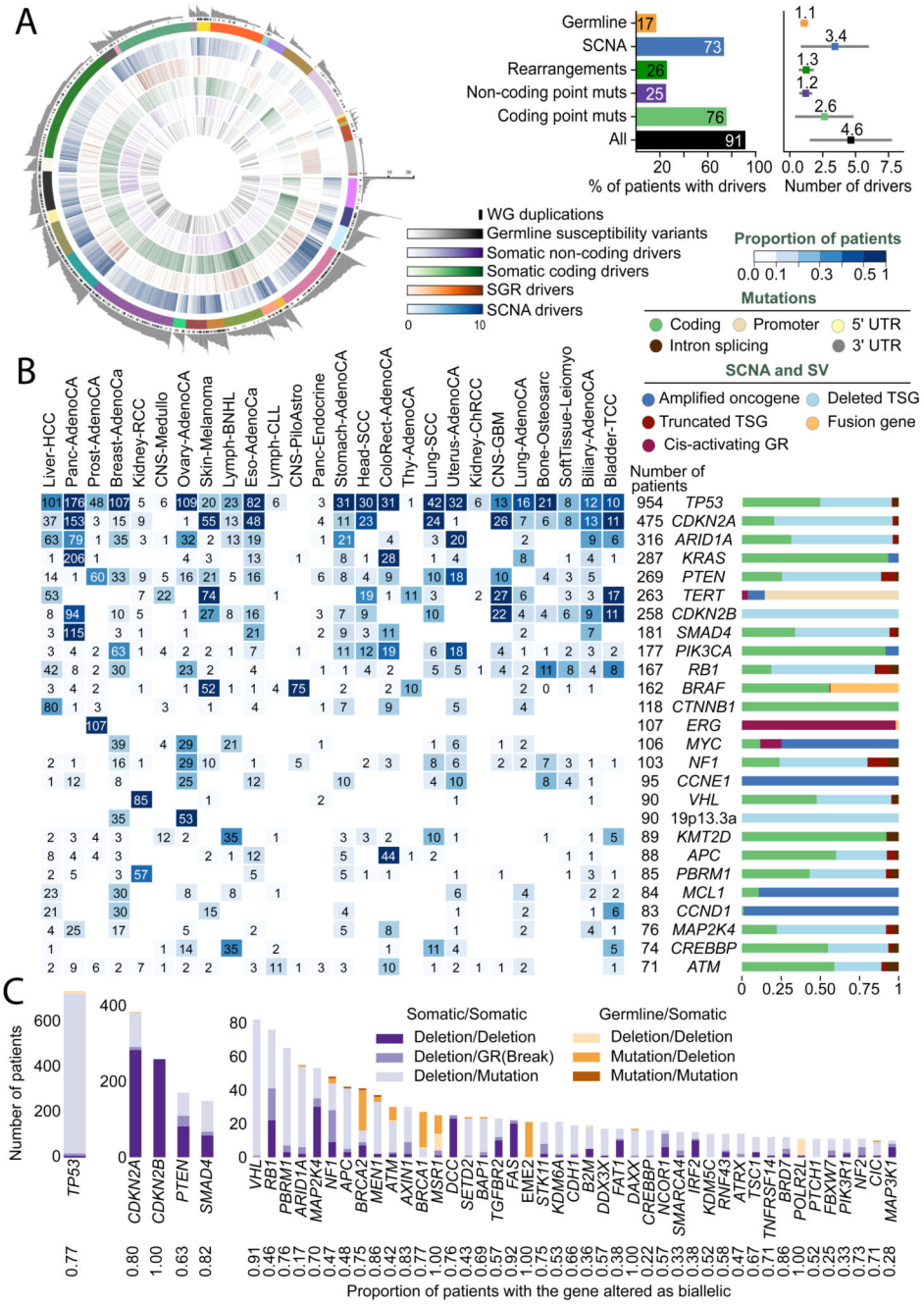

Figure 2. Panorama of driver mutations in PCAWG.

(A) Left panel: putative driver mutations in PCAWG, represented as a circos plot. Each sector represents a tumour in the cohort. From the periphery to the centre of the plot the concentric rings represent: i) the total number of driver alterations; ii) presence of whole genome duplication; iii) the tumour type; iv) the number of driver copy number alterations; v) the number of driver genomic rearrangements; vi) driver coding point mutations; vii) driver non-coding point mutations; and viii) pathogenic germline variants. **Right panel**: Snapshots of the panorama of driver mutations. The horizontal bar plot at the left represents

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the proportion of patients with different types of drivers. The dot plot at the right represents the mean number of each type of driver mutation across tumours with at least one event (the square dot), and its standard deviation (gray whiskers), based on n=2,583 patients. **(B)** Genomic elements targeted by different types of mutations in the cohort in more than 65 tumours. Both germline and somatic variants are included. The heatmap shows the recurrence of alterations experienced across cancer types (with the colour indicating the proportion, and the number indicating the absolute count of mutated tumours); the barplot at the right reflects the proportion of each type of alteration affecting each genomic element. **(C)** Tumour suppressor genes with biallelic inactivation in 10 or more patients. The values quoted under the gene labels represent the proportions of patients who have biallelic mutations of the gene out of all patients with a somatic mutation in that gene.

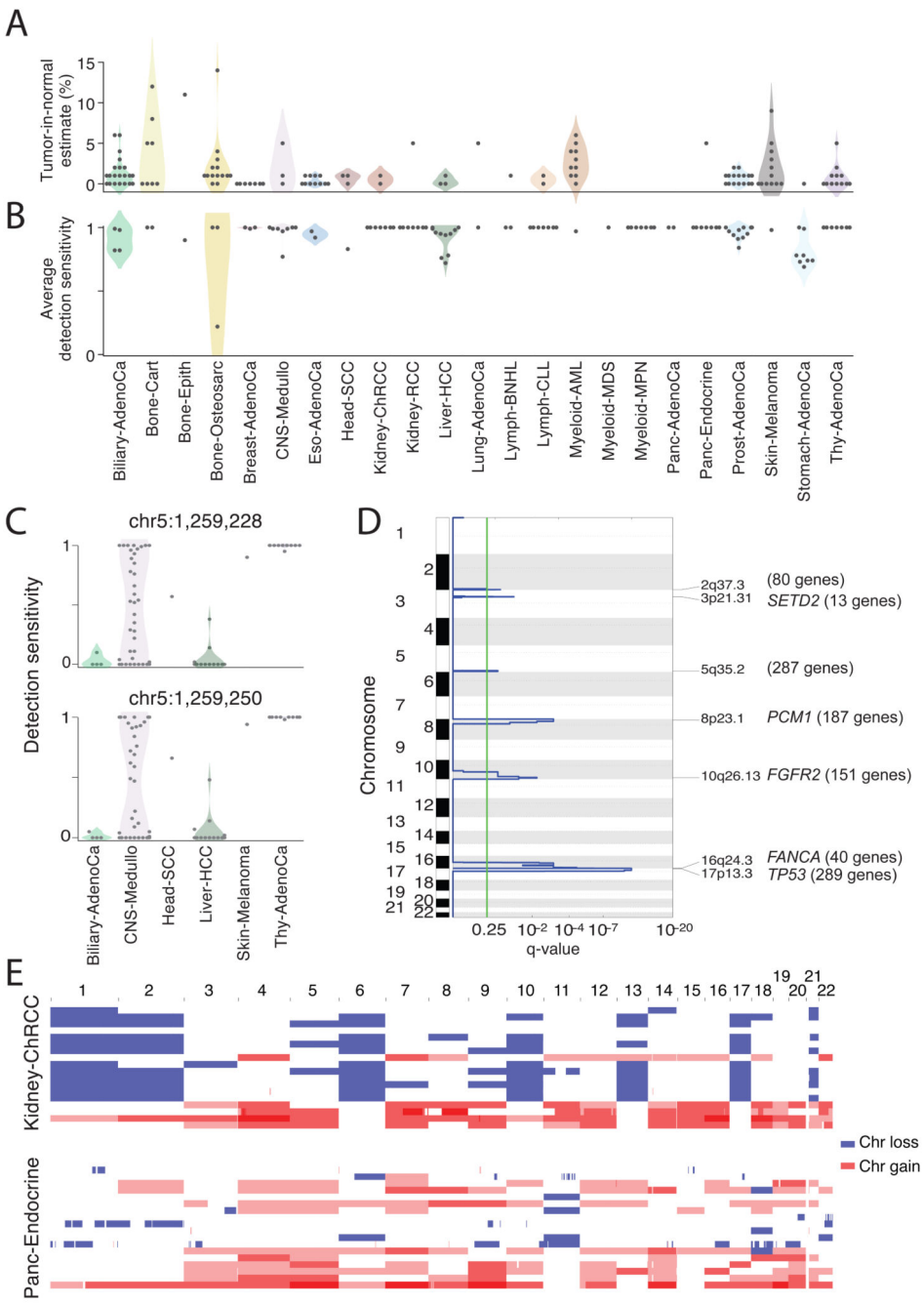

Figure 3. Analysis of patients with no detected driver mutations.

(A) Individual estimates of percentage of tumour-in-normal contamination across no-driver patients in PCAWG (n=181). No data were available for Myeloid-MDS and Myeloid-AML. Points represent estimates for individual patients, and the coloured areas beneath the points are estimated density distributions (violin plots). **(B)** Average detection sensitivity by tumour type for tumours without known drivers (n=181). Each dot represents a given sample and represents the average sensitivity for detecting clonal substitutions across the genome. Coloured areas beneath the points are estimated density distributions, shown for cohorts

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with ≥5 cases. **(C)** Detection sensitivity for *TERT* promoter hotspots in tumour types where *TERT* is frequently mutated. Coloured areas beneath the points are estimated density distributions. **(D)** Significant copy number losses identified by two-sided hypothesis testing using GISTIC2.0, corrected for multiple hypothesis testing. Numbers in parentheses are the number of genes in significant regions when analysing missing-driver tumours (n=181). Significant regions with known cancer genes are labelled with a representative cancer gene. **(E)** Aneuploidy in Kidney-ChRCC and Panc-Endocrine cancers without known drivers. Patients are ordered in the y axis by tumour type and then by presence of whole genome duplication (bottom) or not (top).

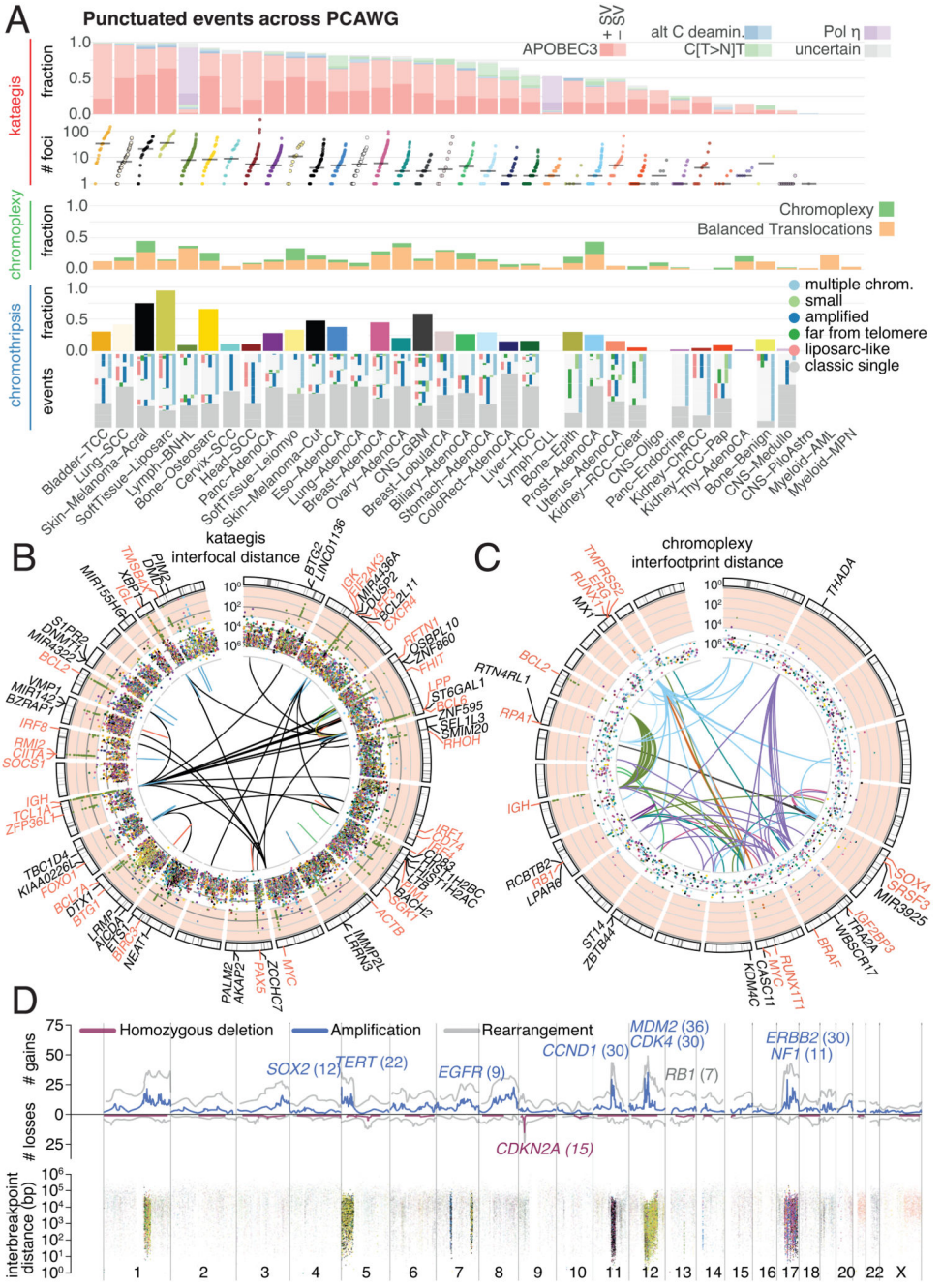

Figure 4. Patterns of clustered mutational processes in PCAWG.

(A) Kataegis. Prevalence of different types of kataegis and their association with SVs (≤1kb from the focus). The distribution of number of foci of kataegis per sample is given below. **Chromoplexy.** Prevalence of chromoplexy across cancer types, subdivided into balanced translocations and more complex events. **Chromothripsis.** Frequency of chromothripsis across cancer types. For each cancer type, a column is shown below, in which each row is a chromothripsis region represented by 5 coloured rectangles relating to its categorisation. **(B)** Circos rainfall plot showing the distances between consecutive kataegis events across

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PCAWG vs their genomic position. Lymphoid tumours (khaki for Lymph-BNHL and orange for Lymph-CLL) harbour hypermutation hot spots (≥3 foci with distance ≤1kb; pale red zone), many near known cancer genes (red annotations) and with associated SVs (≤10kb from the focus; shown as internal arcs). **(C)** Circos rainfall plot as in **B** showing distance vs position for consecutive chromoplexy and reciprocal translocation footprints across PCAWG. Lymphoid, prostate and thyroid cancers exhibit recurrent events (≥2 footprints with distance ≤10kb; pale red zone) likely to be driver structural variants and are annotated with nearby genes and associated SVs shown as bold and thin arcs for chromoplexy and reciprocal translocations, respectively (colours as in **A**). **(D)** Impact of chromothripsis along the genome and involvement of PCAWG driver genes. **Top.** Number of chromothripsis-induced gains/losses (grey) and amplifications/deletions (blue/red). Within the identified chromothripsis regions, selected recurrently rearranged (light grey), amplified (blue) and homozygously deleted (red) driver genes are indicated. **Bottom.** Inter-breakpoints distance between all subsequent breakpoints within chromothripsis regions across cancer types, coloured by cancer type. Regions with an average inter-breakpoint distance <10kb are highlighted.

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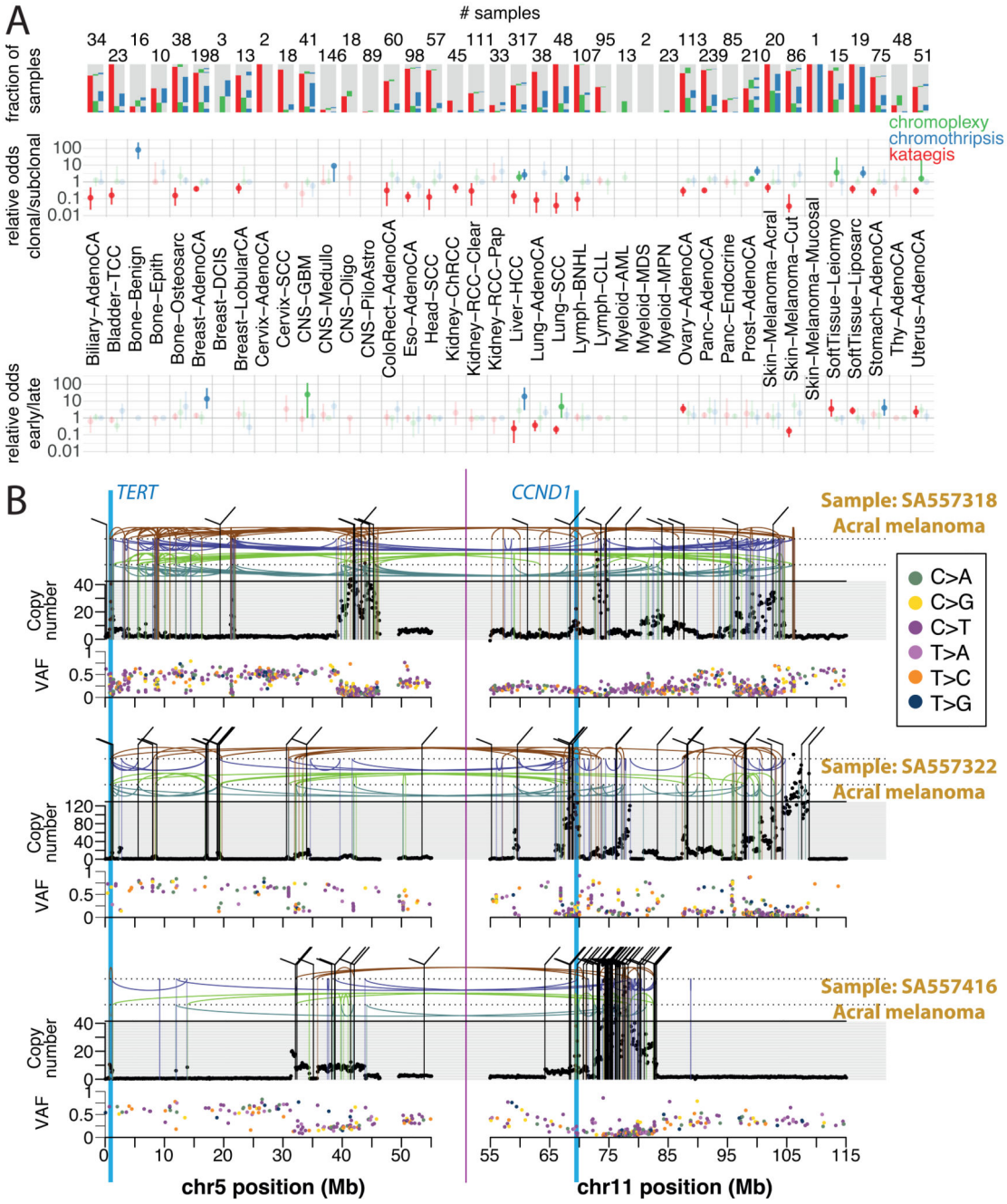

Figure 5. Timing of clustered events in PCAWG.

(A) Extent and timing of chromothripsis, kataegis and chromoplexy across PCAWG. (top) Stacked bar-charts illustrate co-occurrence in samples. (middle) Relative odds of clustered events being clonal vs subclonal are plotted with bootstrapped 95% confidence intervals. Point estimates are highlighted when they do not overlap 1:1 odds. (bottom) Relative odds of the events being early vs late clonal are plotted as above. Sample sizes (number of patients) are shown across the top panel. **(B)** Three representative patients with melanoma and chromothripsis-induced amplification simultaneously affecting *TERT* and *CCND1*. The

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black points in the upper panel represent sequence coverage from individual genomic bins, with structural variants shown as coloured arcs (translocation in black, deletion in purple, duplication in brown, tail-to-tail inversion in cyan, head-to-head inversion in green). The lower panel shows the variant allele fraction (VAF) of somatic point mutations.

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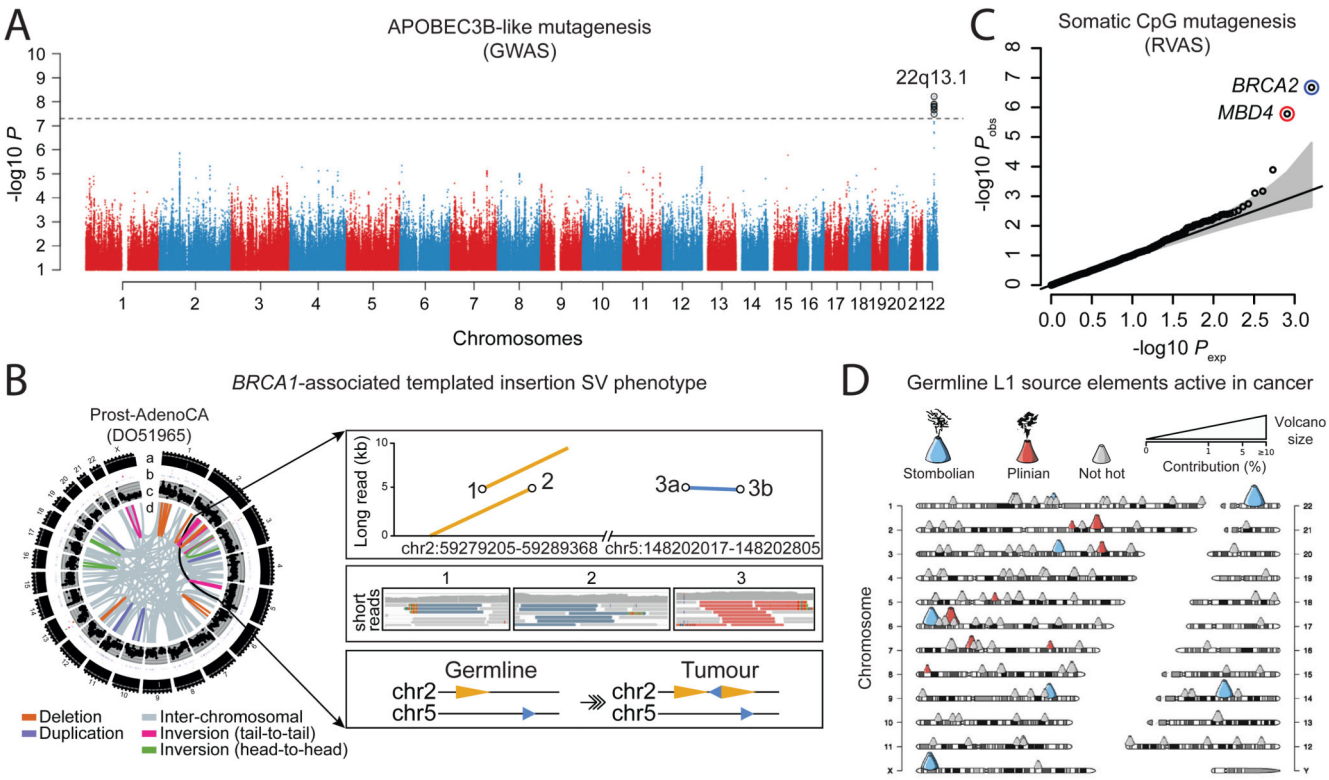

Figure 6. Germline determinants of the somatic mutation landscape.

(A) Association between common (MAF>5%) germline variants and somatic APOBEC3B-like mutagenesis in individuals of European ancestry (n=1201). Two-sided hypothesis testing was performed with PLINK v1.9. To mitigate multiple hypothesis-testing, the significance threshold was set at genome-wide significance ($p<5x10^{-8}$). **(B)** Templated insertion SVs in a *BRCA1*-associated prostate cancer. Left panel: chromosome bands (a); SVs ≤10Mbp (b); 1kb read-depth from CN 0-6 (c); inter- and intra-chromosomal SVs (>10Mbp) (d). Right panel: complex somatic SV composed of a 2.2 kb tandem duplication on chr2 together with a 232 bp inverted templated insertion SV that is derived from chr5 and inserted in-between the tandem duplication (bottom panel). Consensus sequence alignment of locally assembled ONT long-reads to chrs 2 and 5 of the human reference genome (top panel). Breakpoints are circled and marked as 1 (beginning of tandem duplication), 2 (end of tandem duplication), and 3 (inverted templated insertion). For each breakpoint, the middle panel shows Illumina short reads at SV breakpoints. **(C)** Association between rare germline PTVs (MAF<0.5%) and somatic CpG mutagenesis (approx. with Signature 1) in individuals of European ancestry (n=1201). Genes highlighted in blue/red were associated with lower/higher somatic mutation rates. Two-sided hypothesis testing was performed using linear regression models with sex, age at diagnosis, and ICGC project as variables. To mitigate multiple hypothesis-testing, the significance threshold was set at exome-wide significance ($p<2.5x10^{-6}$). The black line represents the identity line which would be followed if the observed p values followed the null expectation, with shaded area showing 95% confidence intervals. **(D)** Catalogue of polymorphic germline L1 source elements active in cancer. Chromosomal map shows germline source L1 elements as volcano symbols. Each volcano is

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colour-coded according to the type of source L1 activity. The contribution of each source locus (expressed as percentage) to the total number of transductions identified in PCAWG tumours is represented in a size gradient, with top contributing elements exhibiting larger sizes.

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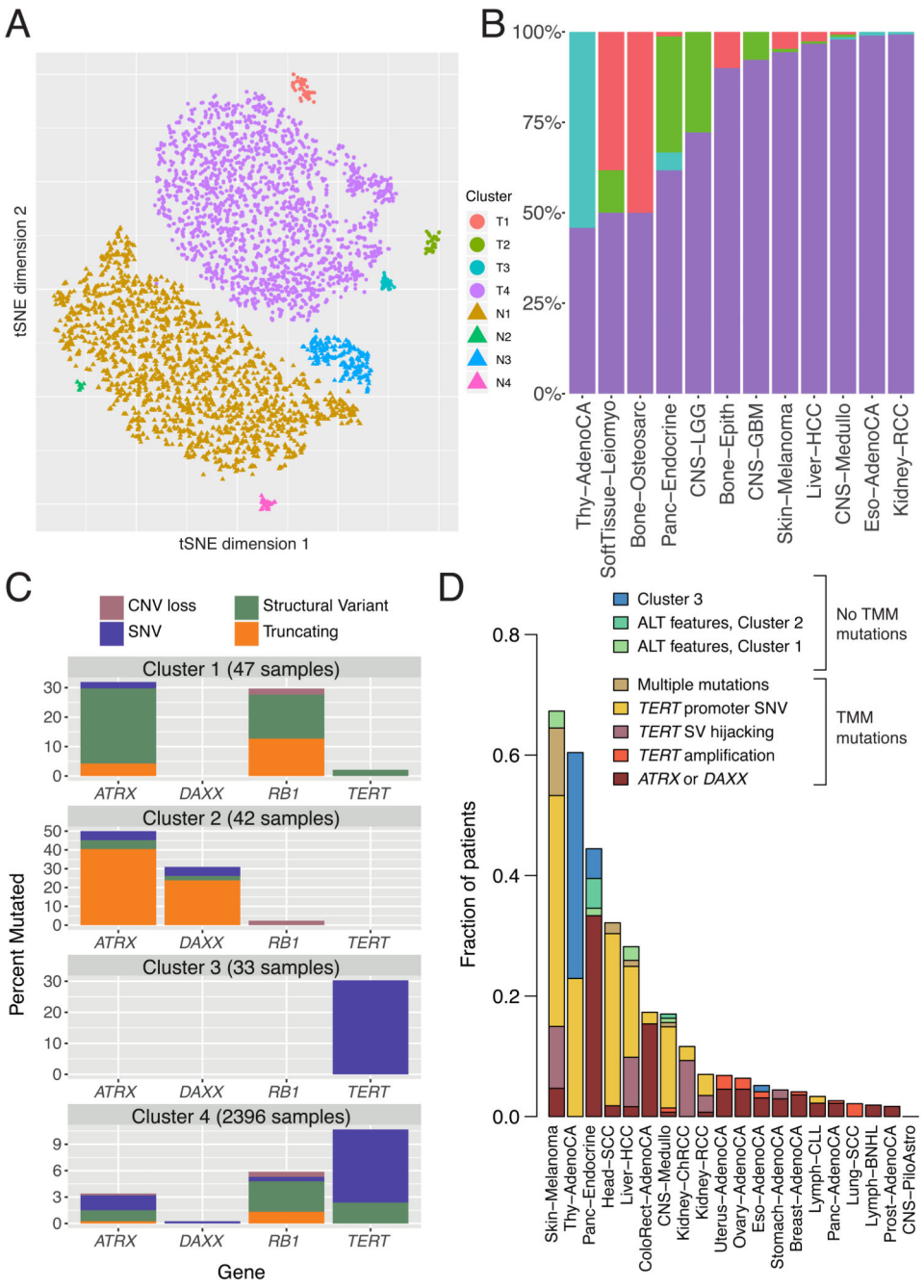

Figure 7. Telomere sequence patterns across PCAWG.

(A) Scatter-plot showing clusters of telomere patterns identified across PCAWG by t-Distributed Stochastic Neighbour Embedding (tSNE), based on n=2,518 tumour samples and their matched normal samples. Axes have arbitrary dimension such that samples with similar telomere profiles are clustered together and samples with dissimilar telomere profiles are far apart with high probability. **(B)** Distribution of the four tumour-specific clusters of telomere patterns in selected tumour types from PCAWG. **(C)** Distribution of relevant driver mutations associated with alternative lengthening of telomere and normal telomere

maintenance across the four clusters. **(D)** Distribution of telomere maintenance abnormalities across tumour types with more than 40 patients in PCAWG. Samples classified as tumour cluster 1-3 if they fall into a relevant cluster without mutations in *TERT*, *ATRX* or *DAXX* and have no ALT phenotype.

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