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A genetic model for central chondrosarcoma evolution correlates with patient outcome

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Abstract

Background: Central conventional chondrosarcoma (CS) is the most common subtype of primary malignant bone tumour in adults. Treatment options are usually limited to surgery, and prognosis is challenging. These tumours are characterised by the presence and absence of *IDH1* and *IDH2* mutations, and recently, *TERT* promoter alterations have been reported in around 20% of cases. The effect of these mutations on clinical outcome remains unclear. The purpose of this study was to determine if prognostic accuracy can be improved by the addition of genomic data, and specifically by examination of *IDH1*, *IDH2*, and *TERT* mutations.

Methods: In this study, we combined both archival samples and data sourced from the Genomics England 100,000 Genomes Project ($n = 356$). Mutations in *IDH1*, *IDH2*, and *TERT* were profiled using digital droplet PCR ($n = 346$), whole genome sequencing ($n=68$), or both ($n = 64$). Complex events and other genetic features were also examined, along with methylation array data ($n = 84$). We correlated clinical features and patient outcomes with our genetic findings.

Results: *IDH2*-mutant tumours occur in older patients and commonly present with high-grade or dedifferentiated disease. Notably, *TERT* mutations occur most frequently in *IDH2*-mutant tumours, although have no effect on survival in this group. In contrast, *TERT* mutations are rarer in *IDH1*-mutant tumours, yet they are associated with a less favourable outcome in this group. We also found that methylation profiles distinguish *IDH1*- from *IDH2*-mutant tumours. *IDH* wild-type tumours rarely exhibit *TERT* mutations and tend to be diagnosed in a younger population than those with tumours harbouring *IDH1* and *IDH2* mutations. A major genetic feature of this group is haploidisation and subsequent genome doubling. These tumours evolve less frequently to dedifferentiated disease and therefore constitute a lower risk group.

Conclusions: Tumours with *IDH1* or *IDH2* mutations or those that are *IDHwt* have significantly different genetic pathways and outcomes in relation to *TERT* mutation. Diagnostic testing for *IDH1*, *IDH2*, and *TERT* mutations could therefore help to guide clinical monitoring and prognostication.

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Keywords: Chondrosarcoma, Sarcoma, Genetics, Genomics, Cancer evolution, IDH1, IDH2, TERT

Background

Central conventional chondrosarcoma (CS) is the most common primary malignant bone tumour in adults. Anatomical location, histopathology, and grading are the current criteria for determining treatment [1, 2], although providing prognoses remains challenging [1–3]; hence, a greater understanding of the disease, and its biomarkers is required to provide patients with a more personalised treatment plan. Well-differentiated cartilaginous tumours are referred to differently depending on where they develop: those presenting at sites, from where they can be excised fully with relative ease, including the phalanges and long bones they have an excellent prognosis, and are referred to as atypical cartilaginous tumours (ACT), the exception being if they are associated with a dedifferentiated (DD) component. In contrast, tumours with features of ACT that occur at sites where complete excision is difficult, such as the axial skeleton and pelvis, are referred to as CS grade (G) 1; these lesions often recur locally and are associated with transformation to higher tumour grade, with many patients eventually succumbing to their disease [4, 5]. G2 disease represents approximately 40% of central CS, and has a 5-year survival of approximately 70–99%, whereas G3 disease, comprising about 10% of all central CS, has a 5-year survival of approximately 30–77% [4, 5]. The most aggressive form of the disease is the DD subtype, which arises on the background of about 10% of all conventional central chondrosarcomas and has a 5-year survival of 7–24% [2, 4, 5]. In contrast high grade disease of the phalanges is uncommon and has little metastatic potential; DD CS rarely occurs at this site [6].

The cytosolic isocitrate dehydrogenase type 1 (*IDH1*) and mitochondrial isocitrate dehydrogenase type 2 (*IDH2*) enzymes are key components in the tricarboxylic acid cycle. Specific alterations at the R132 and R172 amino acid residues of these genes respectively occur in CS (amongst other cancers), disrupting normal functions and leading to the accumulation of 2-D-hydroxyglutarate (2HG), a competitive inhibitor of alpha KG-dependent dioxygenases. This results in downstream effects, including hypermethylation of CpG islands [7].

Close to 70% of central CS harbour an *IDH1* (60%) or an *IDH2* (10%) mutation [8], and these are considered key initiators of disease [8–11]. No recurrent initiating genetic drivers have been reported in the remaining 30% of *IDH1/2* wild type (IDHwt) cases [12, 13], although these tumours have been reported to exhibit different methylation profiles compared to *IDH1*

and *IDH2*-mutant tumours [14, 15], hereafter referred to as *IDH1* and *IDH2* tumours. Other key drivers include mutations in *COL2A1*, *CDKN2A/B*, and *TP53* [12, 13, 16, 17] as well as less common pathogenic alterations in cell cycle-related genes such as *RBI* [18] and *CDK4/6* [12, 19], alterations in the Indian Hedgehog pathway, and amplifications of *MYC* [12, 13]. Alterations in *CDKN2A* and *TP53* are more likely to occur in high grade disease (G2, G3, and DD CS) [12, 17, 19]. These alterations have limited value as markers for survival or risk stratification. Previously, near haploid karyotypes have been reported in CS [20–23], although the relationship with other mutations has not been reported.

The recently identified alterations in the *TERT* promoter locus (C228T) are thought to result in increased telomerase expression leading to immortalisation. These mutations rarely occur in well differentiated tumours, meaning they are a reliable prognostic marker for CS [24]. In contrast, the impact of *IDH1* and *IDH2* mutations on survival remains unclear [9, 25, 26] possibly reflecting the relatively small number of cases studied.

The aim of this study was to undertake a comprehensive analysis of a large set of CS genomes, leveraging data from the Genomics England 100,000 Genomes Project [27] combined with digital droplet PCR (ddPCR) and methylation profiling. A particular focus of our efforts was to identify mutations of relevance to patient outcome and identify recurrent driver mutations in those tumours that are wild type for *IDH1* and *IDH2* mutations (IDHwt).

Methods

Patients and samples

Three hundred fifty-six cases of CS were included in the study. No enchondromas were included. These included 68 tumour-normal paired samples from four clinical sites (Royal National Orthopaedic Hospital Stanmore, Royal Orthopaedic Hospital Birmingham, Nottingham NHS Trust, Queen Elizabeth Hospital Birmingham) that were subjected to whole genome sequencing (WGS) as part of the Genomics England 100,000 Genomes Project (hereby referred to as the *100KGP* cohort, Additional file 1: Supplementary Table 1–2). The remaining cases were obtained from the archives of the Royal National Orthopaedic Hospital, Stanmore (Additional file 1: Supplementary Table 3). The pathology was reviewed Adrienne Flanagan, Fernanda Amary, and Roberto Tirabosco. For cases with clinical follow-up, the median surveillance time was 5.6 years (2059 days, range: 5–10,057 days). Nearly all patients received surgery as standard of care;

two died prior to receiving definitive treatment, and 6% ($n = 22$) of patients received adjuvant treatment in the form of doxorubicin/cisplatin or radiotherapy.

Bioinformatic pre-processing and statistical assessment

Single nucleotide variants (SNVs) and indels were called on WGS data and filtered using a panel of normal (PON) samples via the Genomics England analysis pipeline, which utilises Strelka and other tools [28] (Additional file 2: Supplementary Methods). To quality assess the 100KGP mutation calls, we performed orthogonal verification of hotspot mutations in *IDH1* (R132), *IDH2* (R172), and *TERT* (C228T) identified across 64 patients (59 mutations in total) using ddPCR, which yielded a recall rate of 100%. There was one instance (WGS_53) where a mutation was called by ddPCR but not in the WGS data (*IDH1* ddPCR, IDHwt WGS, later result used, Additional file 2: Supplementary Methods). Somatic copy number variants were called using Battenberg [29] and structural variants (SVs) were called using Delly (v0.8.5) [30]. Unless otherwise specified, comparisons between groups were performed using Wilcoxon tests for distributions and Fisher exact tests for group counts (i.e. in *IDH1/2/WT* group comparisons). Survival analysis utilised a Kaplan-Meier standard Cox proportional hazard model.

Identification of driver mutations, genome doubling, partial haploidisation, and analysis of mutational signatures

Driver mutations in SNVs and indels were identified using a combination of known hotspot locations published previously and available in Additional file 2: Supplementary Methods, the SIFT [31] and POLYPHEN [32] tools, plus visual inspection using integrative genomics viewer (IGV) of the *IDH1* R132, *IDH2* R172, and *TERT* mutations (Additional file 3: Supplementary Fig. 1, Note 1). Amplification events were designated as copy states of five or in diploid genomes and nine or more in those that are genome doubled. For the purposes of plotting, we classified copy states from Battenberg as either, diploid, trisomy or tetrasomy, copy neutral LOH (cnLOH), and the remaining copy states as 'other' (any remaining copy state). Tumours with genome doubling (GD) were identified using a clustering procedure based on the R package Mclust [33]. Cases with more than 50% LOH were marked as exhibiting partial haploidisation. We confirmed the ploidy status in 14 of the 100KGP cases using flow cytometry (Additional file 2: Supplementary Methods, Additional file 3: Supplementary Fig. 2, Note 2). To time the appearance of GD, we used a methodology based on molecular-clock principles [34, 35]. Ninety-six channel single-base substitution (SBS) mutational

signatures were extracted from the Strelka-called SNVs using SigProfilerExtractor [36] version 1.1.3 with default parameters.

Methylation data protocol and analysis

We analysed 84 cases using methylation arrays (Additional file 3: Supplementary Tables 4-6, Supplementary Fig. 3). Five hundred nanograms of DNA from frozen tumour samples were bisulphite converted using Zymo EZ DNA methylation Gold kit (Zymo Research Corporation Irvine, CA, USA) and hybridised to the Infinium HumanMethylationEPIC beadchip arrays (Illumina, San Diego, CA). The generated methylation data were analysed using the ChAMP R [37], normalised using BMIQ, and hierarchical clustering plots were constructed using the 'pheatmap' R package [38].

TERT promoter methylation status was determined by the methylation status of the cg11625005 probe as reported previously [39]. Raw DNA methylation data files have been deposited in the ArrayExpress database (<https://www.ebi.ac.uk/arrayexpress/experiments/E-MTAB-11031/>, accession: E-MTAB-11031).

Statistics and mathematical analysis

In all group comparison situations, such as *IDH1*, *IDH2*, and *IDH*-WT cases, with or without *TERT* mutations, we used Fisher test statistics as implemented in R (testing both 3x2 and 2x2 contingency tables). Distributions of data, as seen in the tests of timing for GD was performed using Wilcoxon tests, again implemented in R. Linear regressions were also implemented using the standard R methods. The cox proportional hazard model and Kaplan-Meier, were obtained via the *survminer* package [40]. For the chromosome arm frequency comparisons, we used Fisher tests and the Bonferroni multiple testing correction. For power calculations, please see Additional file 2: Supplementary Methods.

Results

Driver mutations in central conventional and dedifferentiated chondrosarcomas

Profiling a total of 350 CS cases for *IDH1* and *IDH2*, using ddPCR ($n = 282$) and WGS ($n = 68$), we verified previous findings that *IDH2* are less frequent than *IDH1* mutations (*IDH1*: 51%, *IDH2*: 14%, IDHwt: 35%) [16, 26, 41]. In cases with grading information ($n = 343$), we found that *IDH1* mutations were equally frequent across grades (ACT/G1: 51%, G2/3: 53%, DD CS: 55%; $p = 0.9$) and that *IDH2* mutations were more frequent in higher grade disease (ACT/G1: 7%, G2/3: 14%, DD: 25%; $p = 0.005$). IDHwt was negatively associated with increasing grade (%IDHwt; ACT/G1: 41%, G2/3: 32%, DD CS: 19%; $p = 0.01$). These data imply that the progression to DD

CS is more common in tumours with *IDH2* mutations and least common in IDHwt tumours.

Canonical mutations and structural changes near the *TERT* promoter have been reported in approximately 20% of CS and found to correlate with high grade disease [24, 26, 42]. We found a similar frequency in our cohort (23%, 74 with C228T, one with C250T, four with structural changes near the *TERT* promoter (Additional file 3: Supplementary Fig. 1). *TERT* mutations were rare in well differentiated tumours and increased in frequency across grades (ACT/G1: 3%, G2/3: 22%, DD: 56%; $p = 2e-14$, Fig. 1A). We found that the *TERT* promoter was hypermethylated in 19/57 (33%) of cases analysed on methylation arrays, excluding DD CS cases (Fig. 1B). Seven of these cases, all high grade, also harboured *TERT* C228T promoter mutations. There was no significant difference between the number of cases with both *TERT* promoter mutations and hypermethylation across *IDH1* and *IDH2* tumours (Fig. 1B). Rare alterations involving *ATRX* have been reported previously [26], but in the 100KGP cohort ($n = 68$), we found no such alterations in this cohort. These data confirm that *TERT* mutations, and possibly methylation, have distinct roles in CS progression.

We next examined mutations in other key driver genes reported in CS, utilising the 100KGP cohort (Fig. 1A). Our findings were largely similar to those previously reported [13, 43]. Monosomies of 17p and pathogenic SNVs/indels in *TP53* were found in 22% of cases in line with previous reports [12]. *TP53* mutations were absent from all but one well-differentiated tumour. *COL2A1* mutations were common and marginally anti-correlated with increasing grade (ACT/G1: 100%, G2/3: 54%, DD CS: 44%; $p = 0.03$). As previously reported [17, 19, 21], pathogenic SNVs/indels and/or bi-allelic deletions of *CDKN2A* and *CDKN2B* were common in CS and enriched in G2/3 and DD CS, though not significantly in this dataset. Hypermethylation of these genes was not detected. *CDK4* and *CDK6* gains were found in 12 cases, and a single case had a pathogenic SNV in *CDK6*. These frequencies are similar to previous reports [12]. *MYC* amplifications were found in five high-grade tumours establishing its status as a driver of CS [44, 45]. *MDM2* alterations were identified in three high grade IDHwt cases, two of which were amplifications

(one 8 copies, one 31 copies, confirmed using fluorescence in situ hybridisation), and one was a structural alteration involving intron 7 of *MDM2* and an intragenic region on chr4q28.3. The latter did not result in amplification of *MDM2* but removal of the zinc finger binding domains, which has been suggested to have an oncogenic effect [46]. All three mutations were mutually exclusive of *TP53* mutations. These data support the premise that *MDM2* is a potential driver gene in CS [26], though any biological effects require further exploration. Homozygous deletions of *PTEN* were present in three high grade cases. *PTEN* promoter hypermethylation was found in 13/57 cases, all high grade. Analysis utilising dNdS [47] returned no previously unknown drivers, implying that all prominent somatically mutated genes driving CS have likely been identified (Additional file 2: Supplementary Methods, Additional file 3: Supplementary Fig. 2).

IDH1, IDH2, and TERT define key genetic subgroups

Analysis of all mutation calls ($n = 350$) revealed that the frequency of *TERT* mutations was different across *IDH1*, *IDH2*, and IDHwt cases (Fig. 1C). *IDH2* mutations were strongly associated with *TERT* mutations (IDHwt: 5%, *IDH1*: 24%, *IDH2*: 58%, $p = 6e-13$; *IDH1* vs *IDH2*: $p = 1e-5$). This association was observed in G2/3 (*IDH1* vs *IDH2*: $p = 7e-6$) but not in DD CS (*IDH1* vs *IDH2*: $p > 0.99$), implying that although *TERT* is associated with high-grade tumours, this is not equal in the context of IDH mutation status.

Hypermethylation across IDH1- and IDH2-mutated tumours

CpG island DNA hypermethylation has been reported to distinguish between cartilaginous *IDH* and IDHwt tumours [14, 15]. However, utilising the larger numbers available in this study, we found 3468 differentially methylated probes (DMPs) across *IDH1* and *IDH2* tumours, excluding DD CS ($n = 31$, $p = 0.002$, Additional file 3: Supplementary Fig. 2, Supplementary Tables 4–6). The overall methylation level across all probes also revealed significant differences between *IDH1* and *IDH2* tumours ($p = 0.002$) indicating that the former are globally hypermethylated compared to *IDH2* and IDHwt tumours.

(See figure on next page.)

Fig. 1 Summary of Genomics England Cohort. **A** Summary of driver mutations by grade. *IDH1* mutations are frequent across all grades, although *IDH2* and *TERT* mutations are enriched in G2/3 and DD CS tumours. **B** *TERT* mutation and methylation status (left) and overall genomic methylation levels (right) across IDH groups. **C** *TERT* mutation status across IDH groups. Canonical *TERT* promoter mutations are common in *IDH2*-mutant tumours but rare in IDHwt tumours (left plot). In G2/3 tumours, *TERT* alterations are more common in *IDH2* compared to *IDH1* tumours (middle plot), though equally common in DD CS (right plot). p -values for tests across all IDH groups above, *IDH1* vs *IDH2* are marked on plots. **D** Mutational calling showing driver calls, genome doubling (GD) and haploidisation (HP), Battenberg copy states (diploid, gain, copy neutral LOH, and any other copy state), and Delly structural variant calls (methods). **E** GD and HP overview by IDH status. Timing of GD shown on right (Additional file 1: Supplementary Methods). **F** Mutational signature analysis demonstrating commonality of SBS2, 5, and 8, and prominence of SBS40 in IDH groups.

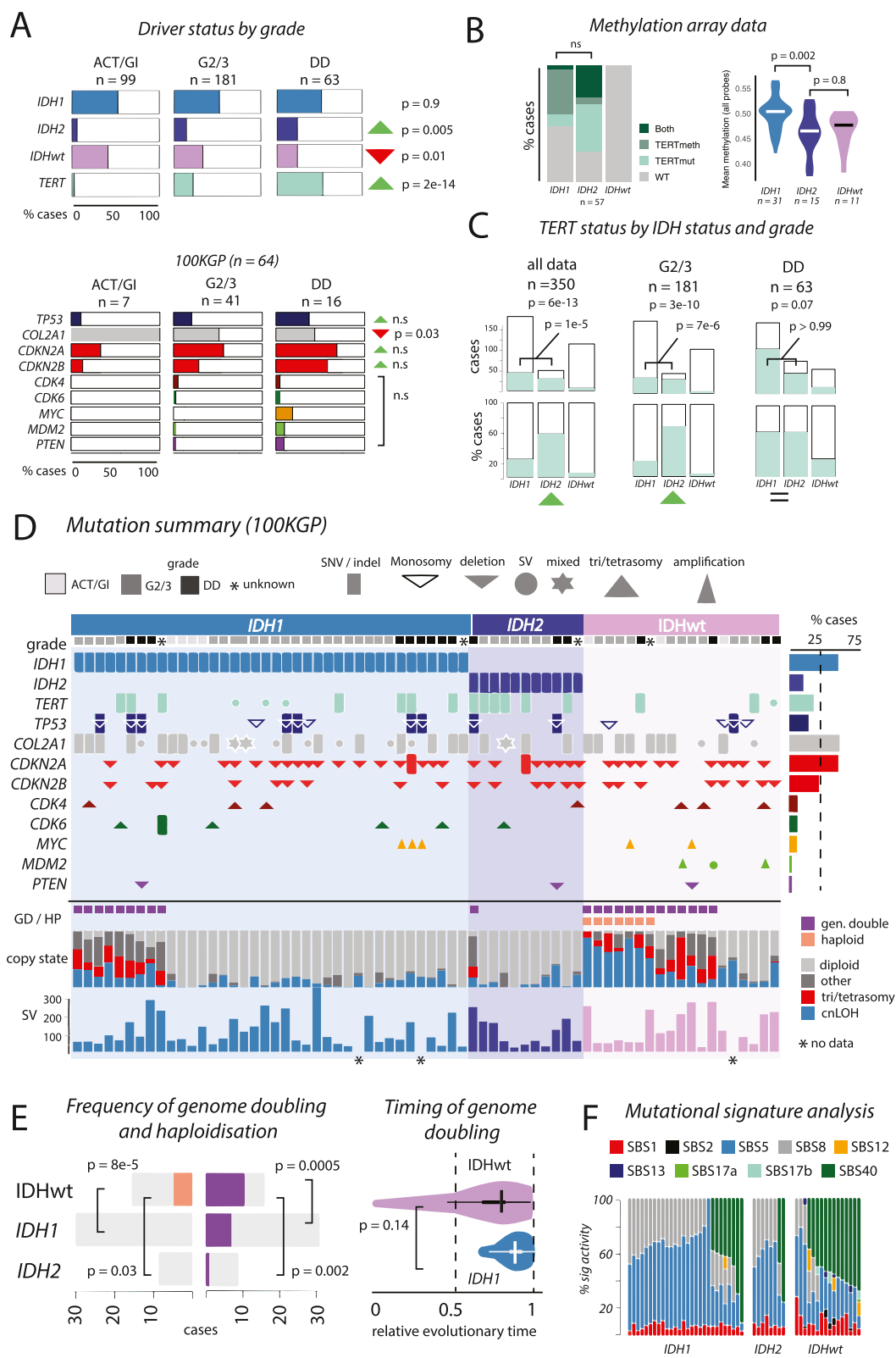


Fig. 1 (See legend on previous page.)

Partial haploidisation followed by genome doubling is common in IDHwt tumours

We compared the mutational profiles across each IDH group (complete summary of 100KGP data shown in Fig. 1D) and found that the frequency of common drivers, excluding *TERT*, was similar across *IDH1* and *IDH2* and IDHwt tumours. We did not find that mutations in *CDKN2A/B* and *TP53* were enriched in *IDH1/2* cases, as previously reported [48] but contrasting another study [26]. The total number of SVs was not statistically different across the *IDH* groups nor was the number of SVs that fell into gene regions. We did not find any common structural variants affecting the same gene more than 25% of cases, although none of these were cancer-related genes (Additional file 2: Supplementary Methods).

The genetic alterations initiating development of IDHwt CS remains unknown, but previous reports of near-haploid (HP) and hyperhaploidy in CS and in other sarcoma subtypes including undifferentiated sarcomas and malignant peripheral nerve sheath tumours prompted us to investigate this [21, 22, 49, 50]. We found 23 tumours with GD and seven with HP in the 100KGP cohort ($n=68$, Additional file 3: Supplementary Fig. 4, Additional file 2: Supplementary Methods). Most GD events (16/23, 69%) occurred in the absence of HP, whereas HP always occurred with GD (Fig. 1D). GD was highly enriched in IDHwt tumours (GD%, *IDH1*: 24%, *IDH2*: 9%, IDHwt: 63%, IDHwt vs *IDH1* $p = 0.0005$, Fig. 1E), and HP was exclusive to this group (HP%, *IDH1*: 0%, *IDH2*: 0%, IDHwt: 37%, IDHwt vs *IDH1* $p = 8e-5$, Fig. 1E). Timing analysis demonstrated that GD events tended to occur at a similar relative time in IDHwt and *IDH1* cases implying that it could be an intermediate or late event in evolutionary timelines of both tumour groups (Fig. 1E, Additional file 2: Supplementary Methods). The six cases of IDHwt tumours without HP/GD events, harboured mutations in *TP53* and *CDKN2A*, although alterations in these genes were not mutually exclusive with the absence of GD and HP (*TP53*: 3/6, 50%, *CDKN2A/B*: 5/6, 83%, Fig. 1D). One of these cases was ACT/G1, pointing to a possible initiating role of *TP53* and *CDKN2A* in some IDHwt tumours.

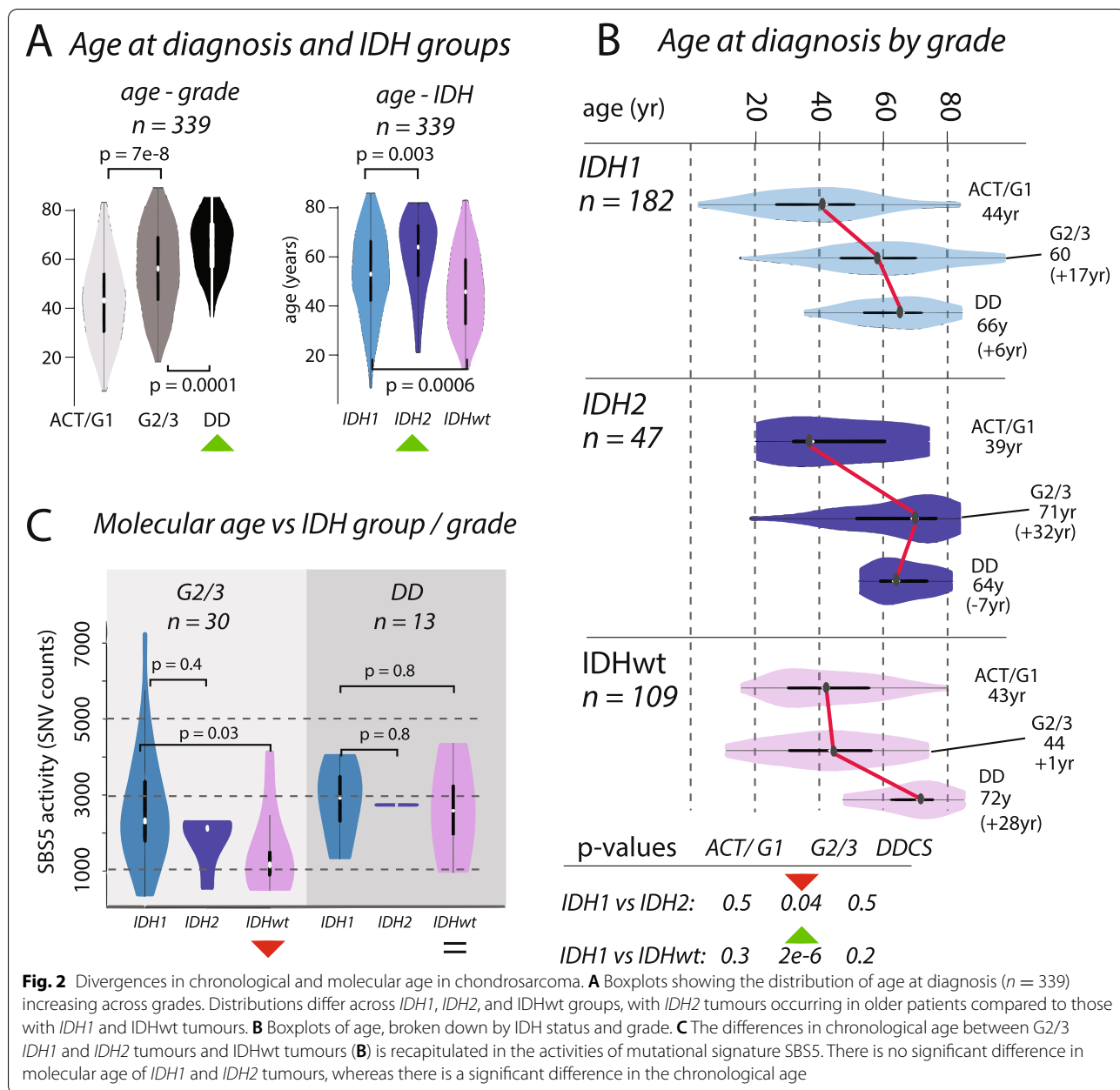
Mutational signatures across IDH1, IDH2, and IDHwt groups

Analysis of mutational signatures in the 100KGP cohort ($n = 52$, Fig. 1F, Additional file 3: Supplementary Fig. 5) revealed nine active signals, with SBS1, SBS5, and SBS8 being ubiquitous and most prominent across *IDH1*, *IDH2*, and IDHwt tumours. Five signatures (SBS2, SBS12, SBS13, and SBS17a/b) were principally exclusive to IDHwt tumours. SBS2 and SBS13 have been associated

with APOBEC and were simultaneously active in five IDHwt cases (18%). We did not observe any difference in SNV burden in tumours with active SBS2 and SBS13. SBS12 was found in one *IDH1* case and three IDHwt cases. SBS17a/b, signatures with unknown aetiology, were found only in IDHwt cases. SBS40, also of unknown aetiology, was found in 28% of *IDH1* cases, 25% of *IDH2* cases, and 81% of IDHwt. These data demonstrate that *IDH1* and *IDH2* tumours are comparable in terms of mutational signatures, whereas IDHwt tumours exhibit more heterogeneous mutational processes.

The genetic distinction between central conventional and dedifferentiated chondrosarcoma

We next analysed the DD CS for specific alterations that may explain their histological phenotype and their poor clinical outcomes. We confirmed that metastatic disease was most common in DD CS (60%, compared to 27% in G2/3 and <1% in ACT/G1 (G2/3 vs DD: $p = 1e-5$). Analysing the 100KGP data (DD: $n = 16$, G2/3: $n = 41$), the frequency of identified known drivers in DD CS and G2/3 revealed no difference except for *IDH2* and *TERT*, which were enriched in DD (*IDH2*: $p = 0.05$, *TERT*: $p = 3e-6$). However, we found differences in total driver burden ($p = 2e-8$), SNV burden ($p = 0.009$), number of chromosome segments ($p = 0.01$), and SV burden ($p = 0.01$) (Additional file 3: Supplementary Fig. 6). We next explored whether the increased segment counts were attributable to chromothripsis. Using a previously published method [51], we found only one instance of chromothripsis (WGS_21) which overlapped with the SV identified at the *TERT* loci (Fig. 1D, Additional file 3: Supplementary Fig. 1). Examining the number more broadly, the average number of chromosomes with high breakage was higher in DD CS compared to G2/3 (median, G2/3: 0, DD CS: 2.5, $p = 0.03$, see Additional file 2: Supplementary Methods). There were no specific chromosome arms enriched amongst those with high fragmentation, although three cases (19%) had fragmentation across chromosome 12q, which has also been reported in dedifferentiated liposarcoma [52]. Previous studies have reported that aberrations of chromosome 5q and trisomy of chromosome 19 distinguish G2/3 from DD CS [53]. Twenty-five per cent DD CS harboured 19p/q gains which is less than the 50% previously reported [53]. Examining losses and gains across all chromosome arms revealed no events unique to DD CS although losses at 15q were more common in this subtype (15q loss, G2/3, 10%, DD CS: 38%, $p = 0.05$). Together, these analyses suggest that the primary genetic difference between G2/3 and DD CS is the number of accrued SNVs and the degree of chromosomal instability.



Age at diagnosis as a clinical factor in chondrosarcoma

Previous studies of CS have treated IDH1 and IDH2 tumours as one group [14, 54]. Our results, leveraging hundreds of cases, provide evidence that IDH1 and IDH2 mutations lead to distinct downstream genetic events, with differences in the frequency of TERT mutations, GD/HP, methylation profiles, and the number and types of mutational signatures.

We examined the effect of the presence or absence of IDH1 and IDH2 mutations on the clinical behaviour of CS (n = 339, Fig. 2). We showed that patient age at

diagnosis increased across grades in these groups and that the median age was highest in those with IDH2 tumours (IDH1: 55 year, IDH2: 67 year, IDHwt: 47 year, IDH1 vs IDH2: p = 0.003, IDH1 vs IDHwt: p = 0.0006, Fig. 2A). The age at diagnosis for each IDH group was similar for ACT/G1 and DD CS, and the difference in age of the G2/3 tumours explained the overall difference in ages (median age G2/3, IDH1: 60 year, IDH2: 71 year, IDHwt: 44 year, IDH1 vs IDH2: p = 0.04, IDH1 vs IDHwt: p = 2e-6, Fig. 2B). We considered whether these differences in chronological age at diagnosis were reflected

in the mutational signatures active in each group. The total SNV burden correlated with age at diagnosis, as did SBS5, previously been reported as clock-like [55], SBS8, but not SBS1. In G2/3 tumours, the activity of SBS5 was similar in *IDH1* and *IDH2*, but lower in IDHwt (*IDH1* vs *IDH2* $p = 0.4$, *IDH1* vs IDHwt: $p = 0.03$, Fig. 2C). By contrast, SBS5 activity was similar in all DD cases (*IDH1* vs *IDH2* $p = 0.7$, *IDH1* vs IDHwt: $p = 0.8$, Fig. 2C). These same results were recapitulated when using SBS8 and total SNV burden (Additional file 3: Supplementary Fig. 7). Together, these data imply further differences in the rate of evolution from G2/3 to DD CS across *IDH1*, *IDH2*, and IDHwt tumours.

Divergent outcomes in *IDH1*, *IDH2* and IDHwt tumours

Using all available clinical information ($n = 342$), we found that *IDH2* tumours tended to be larger at time of presentation (*IDH1* vs *IDH2*: $p = 0.001$, *IDH1* vs IDHwt: $p = 0.4$, Fig. 3A), supporting the premise that these tumours evolve over longer time periods, and present in older people. Development in specific anatomical locations was not significantly different (Fig. 3A).

Using all cases with available follow-up data ($n = 328$), a Cox proportional hazard model demonstrated that ACT/G1 tumours nearly always had a good outcome with no metastatic events being recorded and only one of 98 patients, with a pelvic tumour, succumbing to disease. No patients with tumours in the small bones of the hands and feet died of disease (Fig. 3B). We found that DD CS had a higher frequency of metastatic disease compared with G2/3 disease (G2/3 vs DD CS, $p = 9e-7$). There were no significant differences in the frequency of metastatic or recurrent disease across *IDH1*, *IDH2*, and IDHwt DD CS tumours. However, metastases or recurrent disease appeared to occur less frequently in patients with *IDH2* G2/3 tumours compared to *IDH1* and IDHwt tumours (% metastases/recurrence, *IDH1*: 37%, *IDH2*: 13%, IDHwt: 23%, *IDH1* vs *IDH2*: $p = 0.04$, Fig. 3B). We also found that the time interval between diagnosis and detection of metastatic disease six months following presentation of the primary tumour was shorter in *IDH2* tumours compared to *IDH1* ($p = 0.04$, Fig. 3B). Finally, we found no differences in outcome related to the different *IDH1* mutation contexts (R132C/G/H/L/S) but noted that R132S/L variants found in only a minority number of cases, making statistical analysis difficult (Additional file 3: Supplementary Table 3, Supplementary Fig. 8).

Canonical *TERT* promoter mutations (g.1295113) had an independent hazard ratio (HR) that was equal to that of grade (*TERT*: HR = 2.2, $p = 0.003$, tumour grade: HR = 2.2, $p = 2e-13$, Additional file 3: Supplementary Fig. 8), pointing to the benefit of *TERT* as a biomarker. We also found that overall outcomes were worse

in patients whose tumours had *TERT* hypermethylation ($n = 68$, HR = 3.4, $p = 0.01$). Restricting our analyses to high-grade tumours and excluding tumours in the hands and feet, we found that patients whose tumour harboured both *IDH1* and *TERT* mutations had significantly worse outcomes than those with an *IDH1* mutation alone. *TERT* mutations had no effect on outcome in patients with *IDH2* tumours, even though these mutations are found more frequently in combination with *IDH2* mutations (Fig. 3C, Additional file 3: Supplementary Methods). This suggests that *TERT* mutations are context specific and only relevant to outcome predictions in *IDH1* tumours.

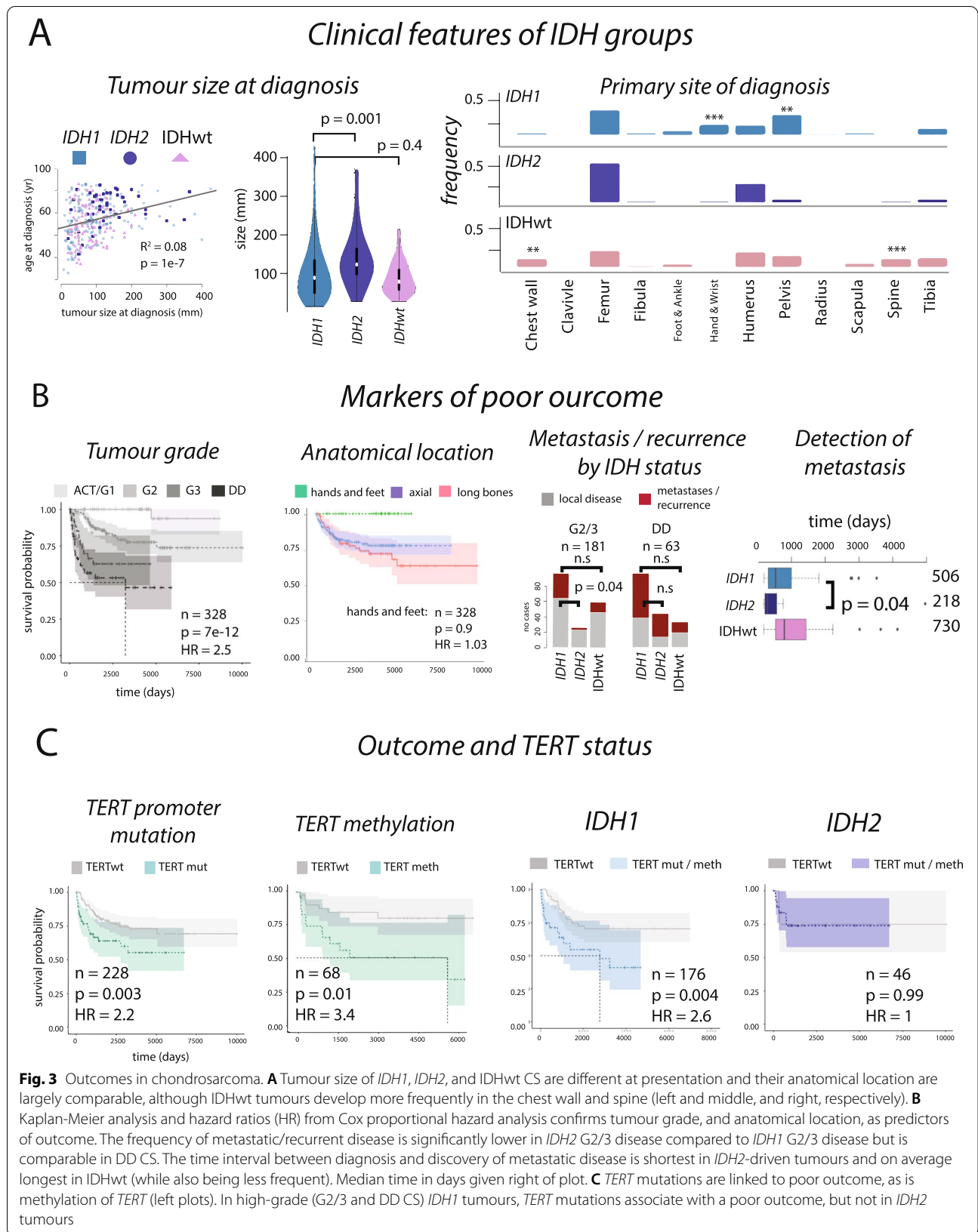
Given these findings, identification of tumours with *IDH1* and *TERT* mutations has clinical value.

Discussion

In this study of patients with CS, involving targeted, whole genome, and methylation data, we provide significant insights into the genetic pathways and dynamics underlying disease progression. Here, with the benefit of large sample numbers, we have been able to study tumours with *IDH1* and *IDH2* mutations independently and shown that they represent distinct genetic and clinical groups.

In addition to confirming that *IDH2* tumours represent the minority group with 14% of cases, we report that they are highly represented in DD CS. They also present as larger tumours and on average over a decade later than *IDH1* tumours. Despite this, *IDH1* and *IDH2* tumours have similar molecular ages suggesting that on average, tumours with *IDH2* mutations have slower cell division rates. Therefore, we speculate that many of these tumours go into growth arrest and become calcified, representing at least a proportion of calcified enchondromas, a lesion commonly detected, when medical imaging is undertaken for unrelated symptoms. This would account for the comparatively lower frequency of *IDH2* tumours. Furthermore, the high incidence of *TERT* mutations and *TERT* promoter methylation in high grade *IDH2* tumours, suggests that these events, through activation of telomerase, have prevented the senescent phenotype and bring about high-grade *IDH2* tumours. This finding could potentially account for the presentation at the relatively late age of these tumours.

No significant differences in the type or number of mutations were identified that accounted for the different clinical findings associated with *IDH1* and *IDH2*. However, we show that *IDH1* tumours are globally more methylated at CpG islands compared to both the *IDH2* and IDHwt tumours. The small numbers of cases studied to date is likely to account for this being unrecognised previously [14, 15]. Indeed, even *IDH1* and *IDH2* gliomas,



which are considerably more common than CS, are generally studied together because of their small numbers. Nevertheless, although all *IDH* mutations result in accumulation of 2-HG there is growing evidence that the impact of the different mutations exerts different biological effects. Studies utilising human oligodendroglioma cells have shown that the *IDH1* R132 mutation leads to higher enzymatic activity than that brought about by *IDH2* R172 [56]. Other studies of *IDH1* and *IDH2* mutations in gliomas point to them as having distinct mutational and clinical patterns [57]. Furthermore, different biological effects of 2HG are also seen as a consequence of different *IDH2* mutations [58]. As it is known that 2HG exerts diverse biological functions including regulation of DNA hydroxymethylation, it is feasible that the *IDH1* and *IDH2* mutations explain our different methylation array findings and mediate the different behaviour of the tumour subgroups. However, further research is required to establish this.

The limitation of the study remains the small numbers of cases when broken down by grade, particularly grade 3. Hence, the need to build prospective collaborative studies with detailed clinical outcome over a long period. Previous studies have suggested different effects of *IDH* mutations on clinical outcome in patients with CS [9, 25, 26]. Here, with the benefit of a large patient cohort, we show that although *IDH2* tumours are more commonly associated with *TERT* mutations, only *IDH1* mutations in combination with *TERT* mutations are associated with significantly reduced survival.

Conclusions

The underlying mutational pathways of tumours with *IDH1* or *IDH2* mutations, or those that are IDHwt, differ significantly. Based on the finding that *TERT* leads to different outcomes in *IDH1*- and *IDH2*-mutant tumours, we propose that genetic testing for *IDH1*, *IDH2*, and *TERT* promoter mutations in the context of other clinical factors, could be useful in patient stratification.

Supplementary Information

The online version contains supplementary material available at <https://doi.org/10.1186/s13073-022-01084-0>.

Additional file 1: Supplementary Tables 1-6.

Additional file 2: Supplementary Methods.

Additional file 3: Supplementary Figs. 1-8, Notes 1-3.

Acknowledgements

We are grateful to the Biobank Team at the RNOH and RJA, and all healthcare workers who cared for the patients. We specifically wish to thank the patients for engaging in our research.

We acknowledge the work of the Genomics England research consortium:

John Ambrose¹; Prabhu Arumugam¹; Roel Bevers¹; Marta Bleda¹; Freya Boardman-Pretty^{1,2}; Christopher Boustred¹; Helen Brittain¹; Mark Caulfield^{1,2}; Georgia Chan¹; Greg Elgar^{1,2}; Tom Fowler¹; Adam Giess¹; Angela Hamblin¹; Shirley Henderson^{1,2}; Tim Hubbard¹; Rob Jackson¹; Louise Jones^{1,2}; Dalia Kasperaviciute^{1,2}; Melis Kayikci¹; Athanasios Kousathanas¹; Lea Lahnstein¹; Sarah Leigh¹; Ivonne Leong¹; Javier Lopez¹; Fiona Maleady-Crowe¹; Meriel McEntagart¹; Federico Minneci¹; Loukas Moutsianas^{1,2}; Michael Mueller^{1,2}; Nirupa Murugaesu¹; Anna Need^{1,2}; Peter O'Donovan¹; Chris Odhams¹; Christine Patch^{1,2}; Mariana Buongiorno Pereira¹; Daniel Perez-Gil¹; John Pullinger¹; Tahrira Rahim¹; Augusto Rendon¹; Tim Rogers¹; Kevin Savage¹; Kushmita Sawant¹; Richard Scott¹; Afshan Siddiq¹; Alexander Sieghart¹; Samuel Smith¹; Alona Sosinsky^{1,2}; Alexander Stuckey¹; Mélanie Tanguy¹; Ana Lisa Taylor Tavares¹; Ellen Thomas^{1,2}; Simon Thompson¹; Arianna Tucci^{1,2}; Matthew Welland¹; Eleanor Williams¹; Katarzyna Witkowska^{1,2}; Suzanne Wood^{1,2}.

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Authors' contributions

Conceptualization AMF. Data curation WC, SH, AS, RT, AM, CD, SW, Genomics England. Investigation WC, IL, TB, CS, DO, HY, TL, LA, SH, SH-F, GB, DB, PC, NP, PVL, AMF. Writing WC, IL, PC, PVL, AMF. All authors read and approved the final manuscript.

Availability of data and materials

All ddPCR results are included in Supplementary Table 3. The SNV, indel, and structural calls produced from the WGS data are available in Additional File 1: Supplementary Table 2. The bam and vcf files of the WGS data are covered by the Genomics England participant consent policy, which has a legally obligation to protect personal identity. Raw data available on application for access to Genomics England and the Clinical Interpretation Partnership (GeCIP) and reviewed by the Access Review Committee. Please see <https://www.genomicsengland.co.uk/patients-participants/data> for further information. The raw methylation array files are available via the ArrayExpress database (<https://www.ebi.ac.uk/arrayexpress/experiments/E-MTAB-11031/>, accession: E-MTAB-11031). Code is available via the Github page: <https://doi.org/10.5281/zenodo.6800685>.

Declarations

Ethics approval and consent to participate

Informed consent was obtained for all patients either as part of the Genomics England 100,000 Genomes Project (WGS data), as determined by the Genomics England Ethics Advisory Committee, or under the generic biobank consent at the Royal National Orthopaedic Hospital. The Royal National Orthopaedic Hospital (RNOH) Biobank is a satellite of the UCL/UCLH Biobank for Health and Disease, which is approved by the National Research Ethics Committee of the Health Research Committee (reference: Integrated Research Application System (IRAS) project identifier: 272816). This project (EC17.14) was approved by the National Research Ethics Committee UCL/UCLH Biobank Ethics Committee. The ethical principles of the Helsinki Declaration for medical research are included as core principles.

Consent for publication

Not applicable

Competing interests

The authors declare that they have no competing interests.

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Received: 2 November 2021 Accepted: 7 July 2022
Published online: 30 August 2022

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