Supplementary Figure legends

Supplementary Figure S1

Principal component analysis of six substitutions in chondrosarcoma. No significant association was observed between substitution patterns and tumor subtype (P=0.89) and the presence of *IDH1* mutation (P=0.13).

Supplementary Figure S2

Ratio of each somatic substitution and its association with histological subtype or *IDH1* mutation status. (A) Somatic cytosine substitutions were classified into those at CpG and non-CpG sites. Ratio of each substitution to total number of substitutions in each case was shown. (B) No significant association was observed between substitution patterns and tumor subtype (P=0.90) and the presence of *IDH1* mutation (P=0.11).

Supplementary Figure S3

Disproportional number of somatic substitutions on transcribed and untranscribed strands in chondrosarcoma. Number of each substitution on transcribed (blue) and untranscribed (red) strands were plotted. Significant difference in number between the two strands was indicated by asterisks. *; P<0.05, **; P<0.02, ***; P<0.001, ****; P<0.0001.

Supplementary Figure S4

Frequencies of mutation portraits (combination of immediate 5' and 3' bases with

six substitutions) in chondrosarcoma cases. Frequency of each mutation portrait (combination of immediate 5' and 3' bases with six substitutions) is indicated by different color columns.

Supplementary Figure S5

Frequencies of 96 mutation portraits (combination of immediate 5' and 3' bases with six substitutions) in chondrosarcoma and other cancer types. Frequencies of each mutation portrait (combination of immediate 5' and 3' bases with six substitutions) are indicated by different color columns.

Supplementary Figure S6

Principal component analysis of 96 mutation portraits (combination of immediate 5' and 3' bases with six substitutions) in chondrosarcoma and other cancer types. Red, green, orange and purple dots indicate each case of chondrosarcoma, prostate cancer, chronic lymphocytic leukemia and liver cancer. Blue dots indicate melanoma and smoking-associated lung cancers. Note that remarkable overlap of chodrosarcoma and prostate cancer cases.

Supplementary Figure S7

Characteristic base contexts at C>A and C>T mutations in chondrosarcoma

Sequence logos of consensus surrounding sequences enriched at C>A (A) and C>T (B) mutations in chondrosarcoma and other tumor types. X-axis indicates base position

from the mutation site (center: mutation position, left: 5' position of the mutation, right: 3' position of the mutation). Y-axis indicates the information content at each position in the sequence.

Supplementary Figure S8

Circos plot of chondrosarcoma cases

Structural alterations (Red line: deletion, Green line; inversion, Blue line: tandem duplication, Purple line; translocation) are shown in the inner circle. Copy number changes (Green; copy gain/amplification, Red: copy loss) are shown in the outer circle. Arrowed lines indicate regions of localized accumulation of structural alterations.

Supplementary Figure S9

Complex rearrangements in chondrosarcoma

Copy numbers were calculated by comparing read depth in tumor and normal samples in the 5 kb window.

Supplementary Figure S10

Association between *IDH1*/*COL2A1* mutation status and patients' prognosis

Kaplan-Meier plot of overall survival (A) and metastasis-free survival (B) segregated by *IDH1* (left) and *COL2A1* (right) mutation status. Green and blue line indicate mutation-positive and mutation negative cases respectively.

Supplementary Figure S11

Validation of *FN1-ACVR2A* gene fusion by whole transcriptome sequencing (WTS). Eighty-one WTS reads which overlapped the fusion point of *FN1* and *ACVR2A* genes are shown.

Supplementary Figure S12

Estimation of *FN1* gene expression at nucleotide resolution by counting RNA sequencing reads. An arrow indicates the fusion point.

Supplementary Figure S13

Nucleotide variations in *FN1-ACVR2A* fusion transcripts between chondrosarcoma (CS6T) and osteochondromatosis (1804T) cases. Alignment of *FN1-ACVR2A* fusion cDNA obtained from CS6T (top) and 1804T (bottom). There are two distinctive SNPs between the two transcripts, which clearly demonstrates that the two transcripts are derived from different samples.

Supplementary Figure S14

Schematic presentation of step-wise genetic alterations in chondrosarcomagenesis. Molecules involved in chondrocyte differentiation and epigenetic regulation together with *TP53* are causative of benign and malignant cartilaginous tumors. MSC: mesenchymal stem cell.

Supplementary Table S1

Germline mutations of *EXT1* and *EXT2* genes in peripheral chondrosarcoma cases

Supplementary Table S2

Summary of clinical data and somatic alterations of 10 chondrosarcoma cases analyzed by whole-genome sequencing.

Supplementary Table S3

Somatic mutations and indels detected in this analysis

Supplementary Table S4

Gene set enrichment analysis of genes with non-synonymous mutations in chondrosarcoma

Supplementary Table S5

Genes affected by amplifications detected in this analysis

Supplementary Table S6

Structural alterations predicted in this analysis

Direction indicates the relative orientation of the paired reads on either side of the breakpoint. Class indicates the category of the structural alteration predicted by direction.

Supplementary Table S7

Significantly mutated gene in discovery set

Supplementary Table S8

Clinical data of validation set cohort

Supplementary Table S9

Mutations detected in a validation cohort

Red backgrounds indicate mutations documented somatically acquired.

Supplementary Table S10

Expression level of *COL2A1*, *ACVR2A* and *YEATS2* genes calculated by RNA sequences (RPKM: number of reads per kb per million sequences)

Supplementary Table S11

Primers used in validation study