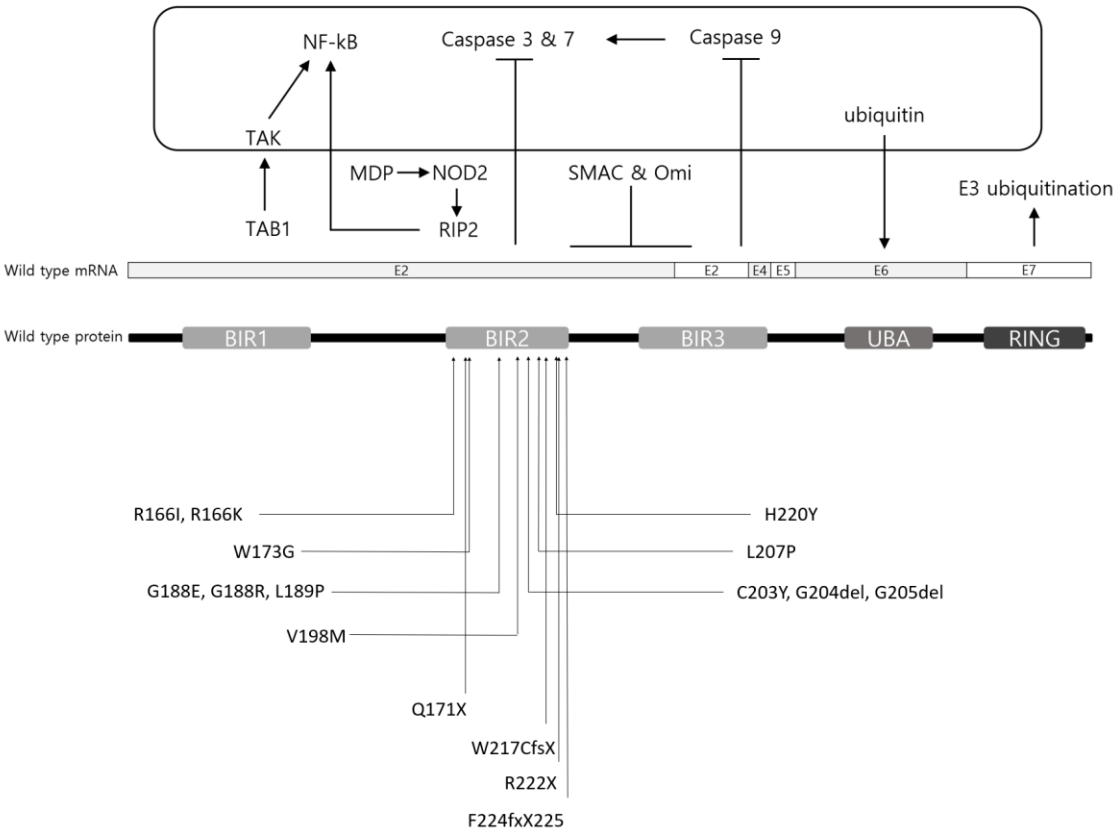
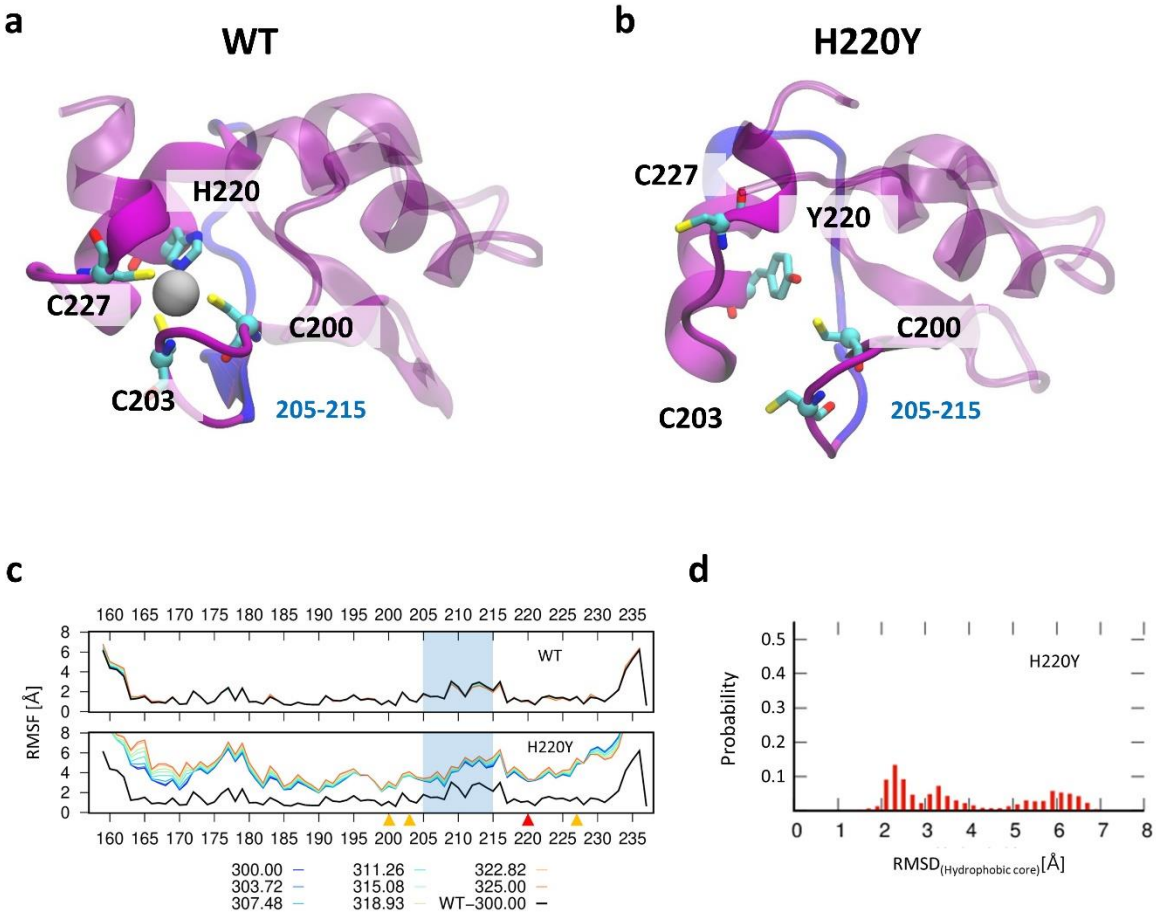
**Supplementary figure 1. Representative positions of pathogenic variants within the XIAP BIR2 domain on the schematic diagram of mutant XIAP proteins** [reference sequence: NM_001167.3]. Currently, 14 specific loci have been linked to pathogenic variants in the BIR2 domain, as confirmed in clinically established cases of XIAP deficiency.[1-6] Of them, eight loci had non-synonymous variants.



**Supplementary Figure 2. Effect of H220Y mutation on Zn-finger.** (a) Baculovirus IAP repeat 2 domain of X-linked inhibitor of apoptosis protein (XIAP BIR2) Zn-finger structure. Zn ion indicated using a gray ball. (b) H220Y mutation-mediated structural changes causing Zn loss. (c) The root mean square fluctuation (RMSF) of wild-type XIAP BIR2 (XIAP BIR2-WT) and -H200Y. Zn-fingers and mutation point are indicated in yellow and red arrows, respectively, 205–215 loop region highlighted in blue. (d) The root mean square deviation (RMSD) of XIAP BIR2-H220Y mutant hydrophobic core.



**Supplementary figure 3. Characterization of X-linked inhibitor of apoptosis protein (XIAP) ubiquitination sites by mass spectroscopy.** (a) Amino acid sequence of XIAP. Possible ubiquitination sites are indicated in red font. (b) Di-glycine-lysine (GG) remnants after trypsin digestion indicate possible ubiquitination sites. Note that K168 ubiquitination was confirmed by the described method, however quantitatively assessing the extent of ubiquitination at this site was not feasible.

**a**

►BIR1 31
MTFNSFEGSK TCVPADINKE EEFVEEFNRL KTFANFPSGS PVSASTLARA GFLYTGEGDT VRCFSCHAAV DRWQYGDSAV GRHRKVSPNC RFINGFYLEN SATQSTNSGI QNGQYKVENYLGS 123
►BIR2 168
RDHFALD RPSETHADYL LRTGQVVDIS DTIYPRNPAM YSEEARLKSF QNWPDYAHLT PRELASAGLY YTGIGDQVQC FCCGGKLKNW EPCDRAWSEH RRHFPNCFFV LGRNLNIRSE 240
►BIR3 297
SDAVSSDRNF PNSTNLPRNP SMADYEARIF TFGTWIYSVN KEQLARAGFY ALGEGDKVKC FHCGGGLTDW KPSEDPWEQH AKWYPGCKYL LEQKGQEYIN NIHLTHSLEE CLVRTT 356
►UBA
EKTPSLTRRIDDTI FQNPMVQEAI RMGFSFKDIK KIMEEKIQIS GSNYKSLEVL VADLVNAQKD SMQDESSQ 428
►RING
TS LQKEISTEEQ LRRLQEEKLC KICMDRNIAI VFVPCGHLVT CKQCAEAVDK CPMCYTVITF KQKIFMS 497

**b**

| Position | Target | Modification | Sequence |
|---|---|---|---|
| 31 | K | GG | (R)LKTFANFPSGSPVSASTLAR |
| 168 | K | GG | SEEARLKSFQNWP |
| 297 | K | GG | (R)AGFYALGEGDKVK |

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