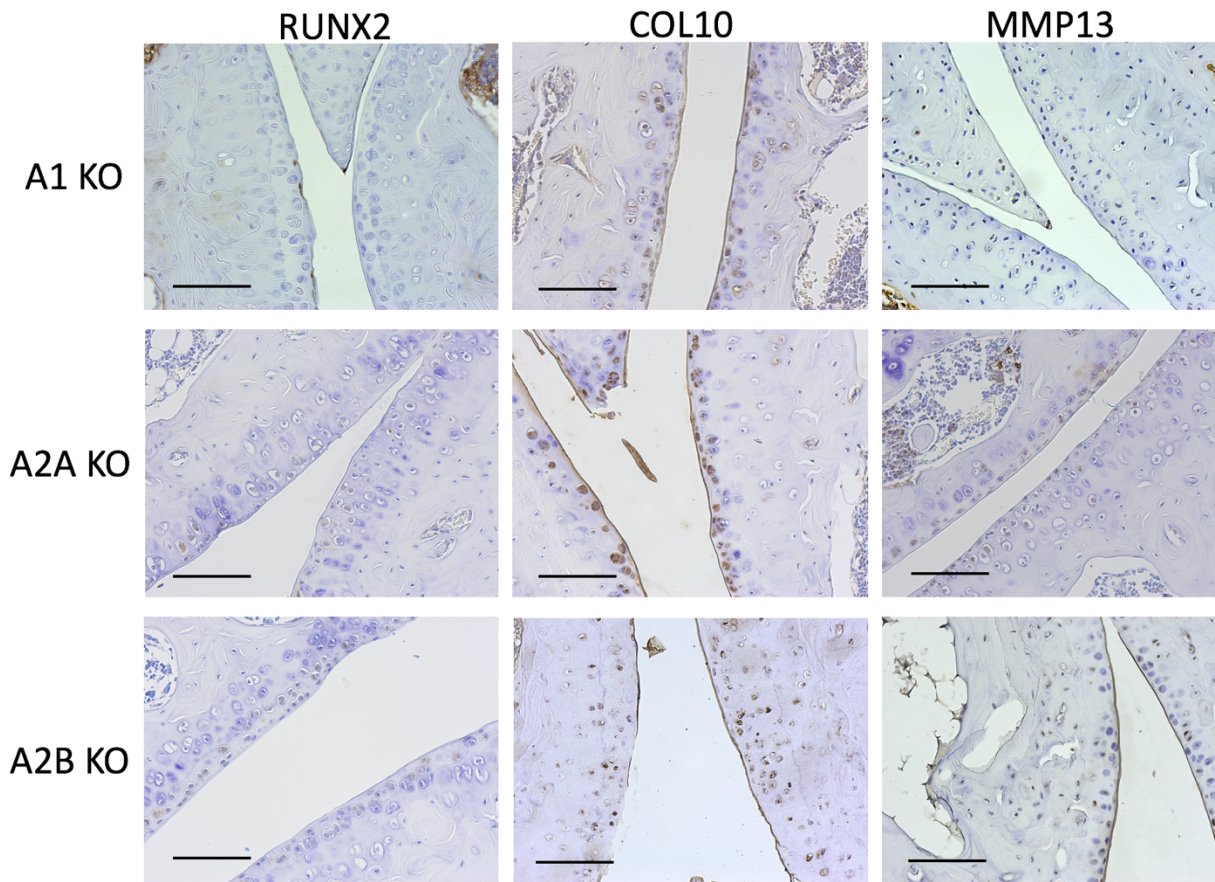


### Supplementary Figure 1

**Figure 1S. A3 receptor knockout shows no structural signs of progressive loss of articular cartilage in 12-week-old mice.** Representative images of Safranin O/Fast Green stained sections of 12-week-old mouse knee joint from wild type (WT) and A3 (ADORA3) genetic knockout (KO). **Both males (n=4) and females (n=4) were analyzed and no gender-specific differences noted.** Arrows delineate articular cartilage. No significant articular cartilage degradation and loss of glycosaminoglycans (GAGs) was present. Scale bars = 100  $\mu$ M.



### Supplementary Figure 2

**Figure 2S. Adenosine receptor knockout results in the upregulation of markers of osteoarthritis in mice.** Sections of A1 (ADORA1), A2A (ADORA2A) and A2B (ADORA2B) KO mouse knee joints were stained for various markers of osteoarthritis: Runx2, Collagen type X, and MMP13. Representative images are shown. Scale bar = 20  $\mu$ M.

**Supplementary Table 1. Antibodies used in the current study.**

<b>Antibody</b>	<b>Vendor</b>	<b>Catalog Number</b>
phospho-CaMKII	Abcam	Ab32678
Runx2	Cell Signaling	12556
Histone 3	Cell Signaling	4499
MMP13	Abgent	AP13706c
ADAMTS4	Abgent	AP7439b
Collagen X	Abcam	ab49945
Aggrecan Neo-epitope	Novus Biologicals	NB100-74350
Collagen II Neo-epitope	IBEX Pharmaceuticals Inc.	50-1035
ADORA3	Signalway Antibody	35615
AlexaFluor-594 Secondary (IHC)	Biolegend	406404
Rabbit IgG Secondary (IHC)	Vector Laboratories	I-1000
Mouse IgG Secondary (IHC)	Vector Laboratories	I-2000
Rabbit IgG Secondary Antibody	Thermo Fisher	31460
Mouse IgG Secondary Antibody	Thermo Fisher	31430

<b>GENETIC KO (8 mice/group) 64 weeks-72 weeks</b>	<b>HEALTH PROBLEM</b>	<b>Weight, gram MEAN +/- SD</b>
WT	NONE	28.075 +/- 4.05
A1	ENLARGED SPLEEN	29.56 +/- 3.21
A2A	TUMORS ENLARGED LIVER ENLARGED SPLEEN KIDNEY FAILURE	31.26 +/- 3.3
A2B	TUMORS OBESITY (>40g) CIRRHOSIS	45.85 +/- 4.38
A3 KO	ENLARGED LIVER	33.76 +/- 2.55

**Supplementary Table 2.** Health status and body weight of transgenic mice used in the current study