

Tumor type	Mutation class	Category	Num genes in sample	Unique official symbols matched	Number genes in cAMP pathway	p value	Genes	Ref	Source	Number genes in cGMP pathway	p value	Number genes in cAMP pathway (and not cGMP pathway)	p value	Genes	Number genes in cGMP pathway (and not cAMP pathway)	p value	Genes	Number genes common to cAMP and cGMP pathway	p value	Genes
Osteosarcoma	SNV	All	1707	1664	41	3.16E-22	ADCY1 ADRA1D ADRA2B AKAP1 AKAP3 AKAP5 AKAP6 ANXA1 ATP1A1 ATP2B1 CACNA1D CACNA1F CACNA1S CFTR CNGB1 DRD2 F2R GIPR GNAI3 GRIA2 GRIN2A GRIN2B GRIN3A HCN4 PDE10A PDE2A PDE4B PDE4D PDE6B PIK3C2B PIK3CG PIK3R4 PIK3R6 PLCL1 PPP2R2B PPP2R3A PRKCA PRKCB	Chen	validated SNVs table S3c	14	2.89E-05	33	2.14E-18	SSTR5	6	1.97E-02	ATP2A1 BDKRB1 KCNMB1 MEF2C	8	2.86E-05	ADCY1 ADRA1D ADRA2B CACNA1D CACNA1F CACNA1S CNGB1 PDE2A
Osteosarcoma	SNV	non silent	1506	1464	35	1.18E-18	ADRA1D ADRA2B AKAP1 AKAP5 AKAP6 ANXA1 ATP1A1 ATP2B1 CACNA1D CACNA1F CACNA1S CNGB1 DRD2 F2R GIPR GNAI3 GRIA2 GRIN2A GRIN2B GRIN3A HCN4 PDE10A PDE2A PDE4B PDE4D PDE6B PIK3C2B PIK3CG PIK3R6 PLCL1 PPP2R2B PRKCA PRKCB	Chen	validated SNVs table S3c (non silent)	13	2.89E-05	28	2.37E-15	AKAP1 AKAP5 AKAP6 ANXA1 ATP1A1 ATP2B1 DRD2 F2R GIPR GNAI3 GRIA2 GRIN2A GRIN2B GRIN3A HCN4 PDE10A PDE4B PDE4D PDE6B PIK3C2B PIK3CG PIK3R6 PLCL1 PPP2R2B PRKCA PRKCB PTGER3 SSTR5	6	1.04E-02	ATP2A1 BDKRB1 KCNMB1 MEF2C	7	7.97E-05	ADRA1D ADRA2B CACNA1D CACNA1F CACNA1S CNGB1 PDE2A
Ewings	SNV	All	1724	1683	26	2.22E-09	ADCY7 ADCY9 ADCYAP1R1 CACNA1D CACNA1S CCBL2 CNGB1 CREB5 GLP1R GRIA2 GRIN2A GRIN2B HCN4 NPY1R OXTR PIK3CG PRKCA PRKCB RYR2 SSTR1 TSHR	Triode	Table S2e: Tier1 SNVs	12	4.60E-04	20	9.36E-08	ADCYAP1R1 CCBL2 CNGA4 GLP1R GRIA2 GRIA4 GRIN2A GRIN2B GRIN3A HCN4 MLLT4 NPY1R OXTR PIK3CG PRKCA PRKCB RYR2 SLC9A1 SSTR1 TSHR	6	2.09E-02	ATP2A1 BDKRB1 IRS1 MEF2A MYLK PDE3A	6	4.60E-04	ADCY7 ADCY9 CACNA1D CACNA1S CNGB1 CREB5
Ewings	SNV	non silent	1470	1430	21	1.6399E-07	ADCY7 ADCY9 ADCYAP1R1 CACNA1D CACNA1S CCBL2 CNGB1 CREB5 GLP1R GRIA2 GRIN2A GRIN2B HCN4 NPY1R OXTR PIK3CG PRKCA PRKCB RYR2 SSTR1 TSHR	Triode	Table S2e: Tier1 SNVs (non silent)	12	9.48E-05	15	1.43E-05	ADCYAP1R1 CCBL2 GLP1R GRIA2 GRIN2A GRIN2B HCN4 NPY1R OXTR PIK3CG PRKCA PRKCB RYR2 SSTR1 TSHR	6	9.21E-03	ATP2A1 BDKRB1 IRS1 MEF2A MYLK PDE3A	6	1.20E-03	ADCY7 ADCY9 CACNA1D CACNA1S CNGB1 CREB5
Breast	SNV	All	2734	2608	33	7.29E-10	AKT1 BDNF BRAF BRD2 CACNA1F CCBL2 CHRM2 CNGA2 CNGA3 CNGA4 CREB5 EDNRA GLI3 GRIA4 GRIN2A GRIN3A JUN PPP1R12A PRKACG PRKCB RYR2 SOX9 ATP2B1 CACNA1D PIK3CG ROCK1 ROCK2 ADCY10 CREBBP GLP1R HCAR1 PDE10A RAF1 TNNI3	Ellis	Supplementary Table 5a: Tier1 SNVs	21	8.90E-07	25	1.94E-07	ADCY10 ATP2B1 BDNF BRAF BRD2 CCBL2 CHRM2 CNGA2 CNGA3 CNGA4 CREBBP GLI3 GLP1R GRIA4 GRIN2A GRIN3A HCAR1 JUN PDE10A PIK3CG PRKACG PRKCB RYR2 SOX9	12	2.96E-04	ATP2A1 EDNRB GNA13 GTF2I ITPR3 MEF2D MYLK NPR2 PDE3A PDE5A PRKCE PRKG1	9	0.0001737	ROCK2

Figure 7 – Figure supplement 1