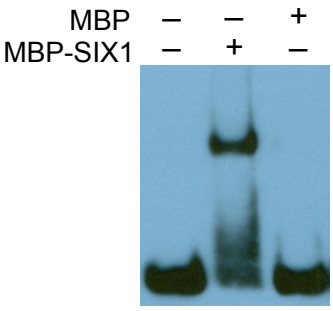
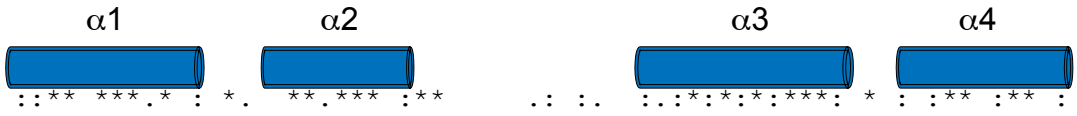

MBP – – +
MBP-SIX1 – + –

Supplemental Figure 1. MBP-SIX1 can bind DNA.
Electrophoretic mobility shift assay using an oligonucleotide containing the SIX1 MEF3 binding site from the myogenin promoter demonstrates that the MBP-fused SIX1-189 can still bind DNA.

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                 . : *: ::** ***.* : *.  **.*** :**     .: :.  :.:*:*:*:***: * : :** :** : *
hSix1      1  MSMLPSFGFTQEQVACVCEVLQQGGNLERLGRFLWSLP----ACDHLHKNESVLKAKAVVAFHRGNFRELYKILESHQFSP  77
mSix1      1  MSMLPSFGFTQEQVACVCEVLQQGGNLERLGRFLWSLP----ACDHLHKNESVLKAKAVVAFHRGNFRELYKILESHQFSP  77
hSix2      1  MSMLPTFGFTQEQVACVCEVLQQGGNIERLGRFLWSLP----ACEHLHKNESVLKAKAVVAFHRGNFRELYKILESHQFSP  77
mSix2      1  MSMLPTFGFTQEQVACVCEVLQQGGNIERLGRFLWSLP----ACEHLHKNESVLKAKAVVAFHRGNFRELYKILESHQFSP  77
so        95  RENLPSFGFTQEQVACVCEVLQQAGNIERLGRFLWSLP----QCDKLQLNESVLKAKAVVAFHRGQYKELYRLLEHHHFSA 171
hSix4    100  AAAQTPLAFSPDHVACVCEALQQGGNLDRLARFLWSLP----QSDLLRGNESLLKARALVAFHQGIYPELYSILESHSFES 176
mSix4     93  AAAQPPLAFSPDHVACVCEALQQGGNLDRLARFLWSLP----QSDLLRGNESLLKARALVAFHQGIYPELYSILESHSFES 169
hSix3     79  MFQLPTLNFSPEQVASVCETLEETGDIERLGRFLWSLPVAPGACEAINKHESILRARAVVAFHTGNFRDLYHILENHKFTK 159
mSix3     80  MFQLPTLNFSPEQVASVCETLEETGDIERLGRFLWSLPVAPGACEAINKHESILRARAVVAFHTGNFRDLYHILENHKFTK 160
hSix6      1  MFQLPILNFSPQQVAGVCETLEESGDVERLGRFLWSLPVAPAACEALNKNESVLRARAIVAFHGGNYRELYHILENHKFTK  81
mSix6      1  MFQLPILNFSPQQVAGVCETLEESGDVERLGRFLWSLPVAPAACEALNKNESVLRARAIVAFHGGNYRELYHILENHKFTK  81
hSix5     78  SEPPTGLRFSPEQVACVCEALLQAGHAGRLSRFLGALP----PAERLRGSDPVLRARALVAFQRGEYAELYRLLESRPFPA 154
mSix5     71  TEVPTGLRFSPEQVACVCEALLQAGHAGRLSRFLGALP----PAERLRGSDPVLRARALVAFQRGEYAELYQLLESRPFPA 147
                           +                                                               +
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                  *  ** :: .*:* ***: ***.**.*.***:*:*****::*****:. :****::*  *:  *  : **.* :** **
hSix1      78  HNHPKLQQLWLKAHYVEAEKLRGRPLGAVGKYRVRRKFPLPRTIWDGEETSYCFKEKSRGVLREWYAHNPYPSPREKRELA 158
mSix1      78  HNHPKLQQLWLKAHYVEAEKLRGRPLGAVGKYRVRRKFPLPRTIWDGEETSYCFKEKSRGVLREWYAHNPYPSPREKRELA 158
hSix2      78  HNHAKLQQLWLKAHYIEAEKLRGRPLGAVGKYRVRRKFPLPRSIWDGEETSYCFKEKSRSVLREWYAHNPYPSPREKRELA 158
mSix2      78  HNHAKLQQLWLKAHYIEAEKLRGRPLGAVGKYRVRRKFPLPRSIWDGEETSYCFKEKSRSVLREWYAHNPYPSPREKRELA 158
so        172  QNHAKLQALWLKAHYVEAEKLRGRPLGAVGKYRVRRKFPLPRTIWDGEETSYCFKEKSRSVLRDWYSHNPYPSPREKRDLA 252
hSix4     177  ANHPLLQQLWYKARYTEAERARGRPLGAVDKYRLRRKFPLPRTIWDGEETVYCFKEKSRNALKELYKQNRYPSPAEKRHLA 257
mSix4     170  ANHPLLQQLWYKARYTEAERARGRPLGAVDKYRLRRKFPLPRTIWDGEETVYCFKEKSRNALKELYKQNRYPSPAEKRHLA 250
hSix3     160  ESHGKLQAMWLEAHYQEAEKLRGRPLGPVDKYRVRKKFPLPRTIWDGEQKTHCFKERTRSLLREWYLQDPYPNPSKKRELA 240
mSix3     161  ESHGKLQAMWLEAHYQEAEKLRGRPLGPVDKYRVRKKFPLPRTIWDGEQKTHCFKERTRSLLREWYLQDPYPNPSKKRELA 241
hSix6      82  ESHAKLQALWLEAHYQEAEKLRGRPLGPVDKYRVRKKFPLPRTIWDGEQKTHCFKERTRHLLREWYLQDPYPNPSKKRELA 162
mSix6      82  ESHAKLQALWLEAHYQEAEKLRGRPLGPVDKYRVRKKFPLPRTIWDGEQKTHCFKERTRHLLREWYLQDPYPNPSKKRELA 162
hSix5     155  AHHAFLQDLYLRARYHEAERARGRALGAVDKYRLRKKFPLPKTIWDGEETVYCFKERSRAALKACYRGNRYPTPDEKRRLA 235
mSix5     148  AHHAFLQDLYLRARYHEAERARGRALGAVDKYRLRKKFPLPKTIWDGEETVYCFKERSRAALKACYRGNRYPTPDEKRRLA 228
                                        +   + +                 +   +
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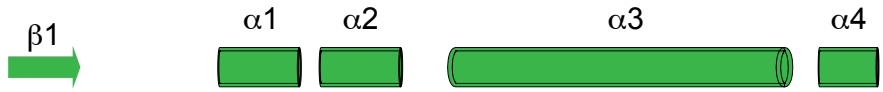
                  ***: ***.***********                .
hSix1      159  EATGLTTTQVSNWFKNRRQRDRAAEAK 185
mSix1      159  EATGLTTTQVSNWFKNRRQRDRAAEAK 185
hSix2      159  EATGLTTTQVSNWFKNRRQRDRAAEAK 185
mSix2      159  EATGLTTTQVSNWFKNRRQRDRAAEAK 185
so         253  EATGLTTTQVSNWFKNRRQRDRAAEHK 279
hSix4      258  KITGLSLTQVSNWFKNRRQRDRNPSET 284
mSix4      251  KITGLSLTQVSNWFKNRRQRDRNPSET 277
hSix3      241  QATGLTPTQVGNWFKNRRQRDRAAAAK 267
mSix3      242  QATGLTPTQVGNWFKNRRQRDRAAAAK 268
hSix6      163  QATGLTPTQVGNWFKNRRQRDRAAAAK 189
mSix6      163  QATGLTPTQVGNWFKNRRQRDRAAAAK 189
hSix5      236  TLTGLSLTQVSNWFKNRRQRDRTGAGG 262
mSix5      229  TLTGLSLTQVSNWFKNRRQRDRTGTGG 255
```

Supplemental Figure 2. Multiple sequence alignment of Six family members
Sequence alignment of human and mouse Six family members and *Drosophila so* was generated with CLUSTALW and annotated with secondary structure assigned with DSSP (shown above the alignment). Absolutely conserved residues among Six family members are indicated with "*". Residues with strongly similar properties are indicated with ":". Residues with weakly similar properties are indicated by ".". Residues that interact with the hydrophobic groove are colored orange, the surface patch green and those that are involved in salt-bridges/hydrogen bonds are colored magenta. Residues mutated in BOR are indicated by a "+" below the sequences.

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                ****:******:*:**:**:*::*.:* :* .  :  .: ****:*::****:***::*:***:*::**:********* *
hEya2       268 ERVFVWDLDETIIIFHSLLTGTFASRYGKDTTTSVRIGLMMEEMIFNLADTHLFFNDLEDCDQIHVDDVSSDDNGQDLSTY 348
mEya2       262 ERVFVWDLDETIIIFHSLLTGTFASRYGKDTTTSVRIGLMMEEMIFNLADTHLFFNDLEDCDQIHVDDVSSDDNGQDLSTY 342
hEya1       322 ERVFIWDLDETIIVFHSLLTGSYANRYGRDPPTSVSLGLRMEEMIFNLADTHLFFNDLEECDQVHIDDVSSDDNGQDLSTY 402
mEya1       321 ERVFIWDLDETIIVFHSLLTGSYANRYGRDPPTSVSLGLRMEEMIFNLADTHLFFNDLEECDQVHIDDVSSDDNGQDLSTY 401
hEya4       369 ERVFVWDLDETIIVFHSLLTGSYAQKYGKDPPMAVTLGLRMEEMIFNLADTHLFFNDLEECDQVHIDDVSSDDNGQDLSTY 449
mEya4       346 ERVFVWDLDETIIVFHSLLTGSYAQKYGKDPPMAVTLGLRMEEMIFNLADTHLFFNDLEECDQVHIDDVSSDDNGQDLSTY 426
hEya3       303 ERVFLWDLDETIIIFHSLLTGSYAQKYGKDPTVVIGSGLTMEEMIFEVADTHLFFNDLEECDQVHVEDVASDDNGQDLSNY 383
mEya3       256 ERVFLWDLDETIIIFHSLLTGSYAQKYGKDPTVVIGSGLTMEEMIFEVADTHLFFNDLEECDQVHVEDVASDDNGQDLSNY 336
eyes absent 493 ERVFVWDLDETLIIFHTLLSGSYANRYTKDHSSLMTIAFRMEEMVFNMADTHFFFNEIEECDQVHIDDVSSDDNGQDLSAY 573
                    +                                       +
```

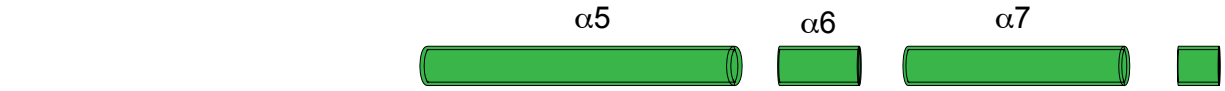


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                .*.:***     ..   .     **:***************:::::*:.::.*** *:.. ::::  ::*:*:*  ** *
hEya2       349 NFSADGFHS---SAPGANLCLGSGVHGGVDWMRKLAFRYRRVKEMYNTYKNNVGGLIGTPKRETWLQLRAELEALTDLWLT 426
mEya2       343 NFSTDGFHS---TAPGASLCLGTGVHGGVDWMRKLAFRYRRVKEMYNTYRNNVGGLIGAPKRETWLQLRAELEALTDLWLT 420
hEya1       403 NFGTDGFPA---AATSANLCLATGVRGGVDWMRKLAFRYRRVKEIYNTYKNNVGGLLGPAKREAWLQLRAEIEALTDSWLT 480
mEya1       402 NFGTDGFPA---AATSANLCLATGVRGGVDWMRKLAFRYRRVKEIYNTYKNNVGGLLGPAKREAWLQLRAEIEALTDSWLT 479
hEya4       450 SFATDGFHA---AASSANLCLPTGVRGGVDWMRKLAFRYRRVKELYNTYKNNVGGLLGPAKRDAWLQLRAEIEGLTDSWLT 527
mEya4       427 SFATDGFHA---AASSANLCLPTGVRGGVDWMRKLAFRYRRVKELYNTYKNNVGGLLGPAKRDAWLQLRAEIEGLTDSWLT 504
hEya3       384 SFSTDGFSG---SGGSGSHGSSVGVQGGVDWMRKLAFRYRKVREIYDKHKSNVGGLLSPQRKEALQRLRAEIEVLTDSWLG 461
mEya3       337 SFSTDGFSG---SGGSGSHGSSVGVQGGVDWMRKLAFRYRKVREIYDKHKSNVGGLLSPQRKEALQRLRAEIEVLTDSWLG 414
eyes absent 574 NFATDGFHTNTPPGAPPNLCLPTGVRGGVDWMRKLAFRYRKIKDIYNSYRGNVGTLLGPGKREAWLQIRSEIEVATDNWAT 654
                                          +  +          +
```


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                 :**.* :*  * ** *:*:*:*** ********:.**  * ******* * *:*:*:***: *** : .*:*****
hEya2       427 HSLKALNLINSRPNCVNVLVTTTQLIPALAKVLLYGLGSVFPIENIYSATKTGKESCFERIMQRFGRKAVYVVIGDG 503
mEya2       421 HSLKALNLINSRPNCVNVLVTTTQLIPALAKVLLYGLGSVFPIENIYSATKTGKESCFERIMQRFGRKAVYIVIGDG 497
hEya1       481 LALKALSLIHSRTNCVNILVTTTQLIPALAKVLLYGLGIVFPIENIYSATKIGKESCFERIIQRFGRKVVYVVIGDG 557
mEya1       480 LALKALSLIHSRTNCVNILVTTTQLIPALAKVLLYGLGIVFPIENIYSATKIGKESCFERIIQRFGRKVVYVVIGDG 556
hEya4       528 NALKSLSIISTRSNCINVLVTTTQLIPALAKVLLYSLGGAFPIENIYSATKIGKESCFERIMQRFGRKVVYVVIGDG 604
mEya4       505 NALKSLSIISTRSNCVNVLVTTTQLIPALAKVLLYSLGGAFPIENIYSATKIGKESCFERIVSRFGTNITYVVIGDG 581
hEya3       462 TALKSLLLIQSRKNCVNVLITTTQLVPALAKVLLYGLGEIFPIENIYSATKIGKESCFERIVSRFGKKVTYVVIGDG 538
mEya3       415 TALKSLLLIQSRKNCANVLITTTQLVPALAKVLLYGLGEIFPIENIYSATKIGKESCFERIVSRFGKKVTYVVIGDG 491
eyes absent 655 LALKCLSMISQRENCVNVLVTSTQLAPALAKVLLFGLGGIFNIENIYSAHKIGHETCYERIVTRFGRKSTYVVIGDG 731
                      +    +           +      ++            +                          +  +
```
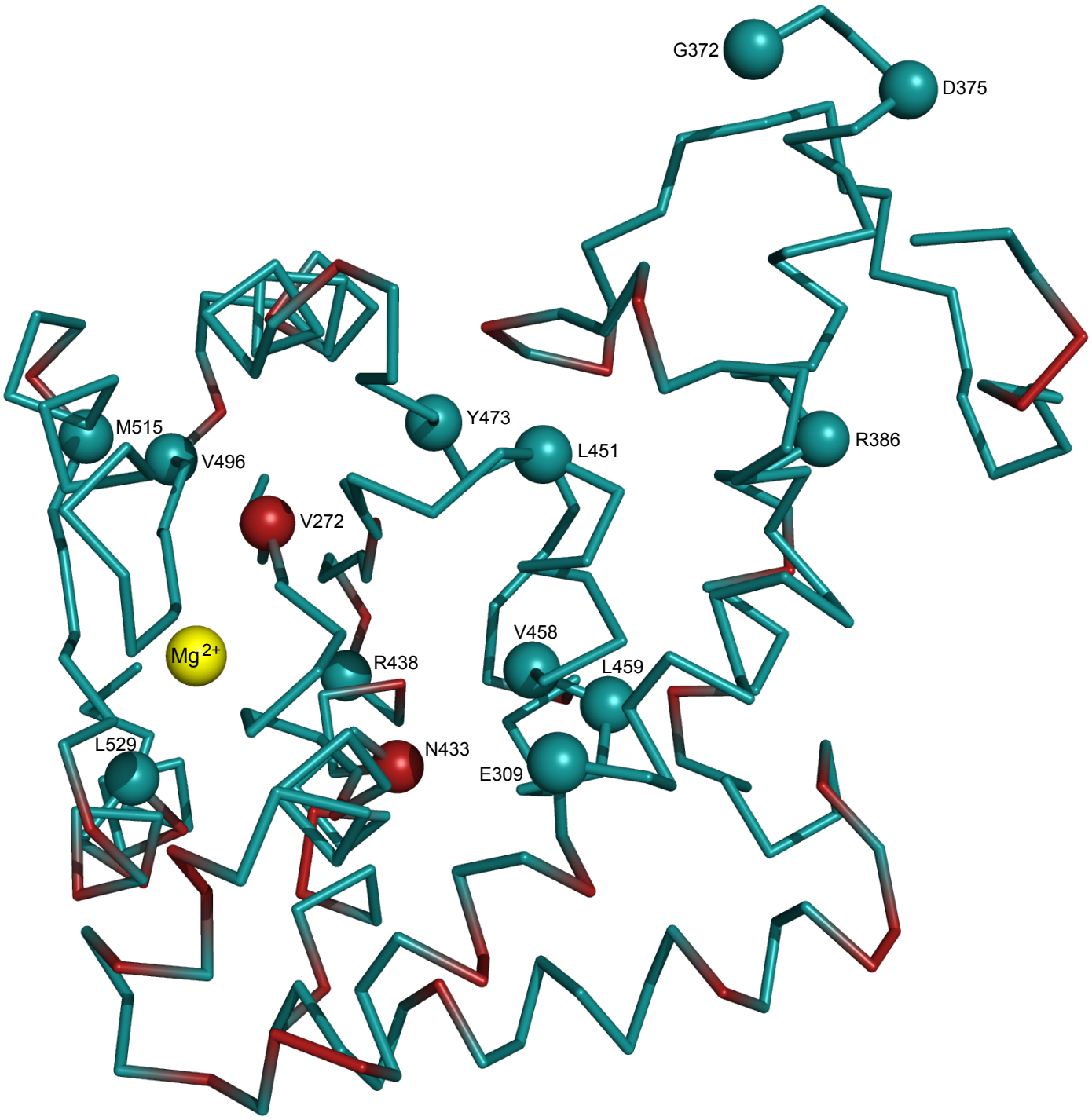


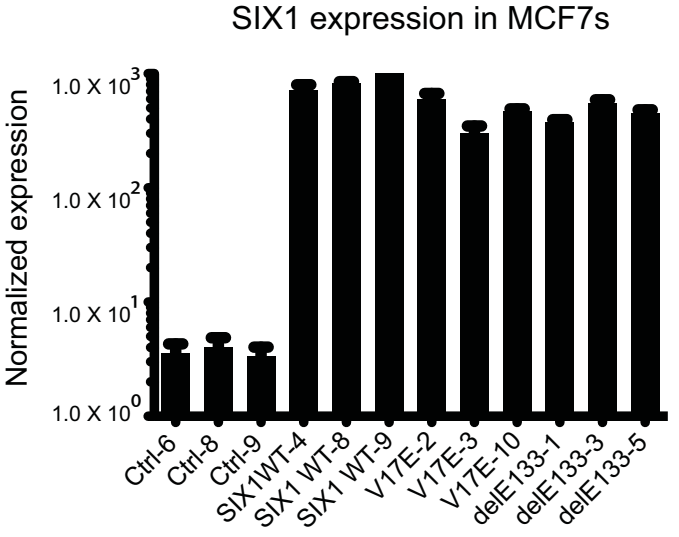
```
                 :** .*:   :****:: *.*: :*  **:: :*
hEya2       504 VEEEQGAKKHNMPFWRISCHADLEALRHALELEYL 538
mEya2       498 VEEEQGAKKHNMPFWRISCHADLEALRHALELEYL 532
hEya1       558 VEEEQGAKKHAMPFWRISSHSDLMALHHALELEYL 592
mEya1       557 VEEEQGAKKHAMPFWRVSSHSDLMALHHALELEYL 591
hEya4       605 VEEEQAAKKHNMPFWRISSHSDLLALHQALELEYL 639
mEya4       582 RDEEHAANQHNMPFWRISSHSDLLALHQALELEYL 616
hEya3       539 RDEEIAAKQHNMPFWRITNHGDLVSLHQALELDFL 573
mEya3       492 RDEEIAAKQHNMPFWRITNHGDLVSLHQALELDFL 526
eyes absent 732 NEEETAAKAMNFPFWRISAHSDIRALYTALDMGFL 766
                          +           +
```

Supplemental Figure 3. Multiple sequence alignment of Eya family members
Sequence alignment of human and mouse Eya family members and *Drosophila* eyes absent. Annotations are identical to Supplemental Figure 2. Residues that make up the hydrophobic binding pocket are colored orange, the surface patch green and those that are involved in salt-bridges/hydrogen bonds are colored magenta. Residues mutated in BOR are indicated by a "+" below the sequences.

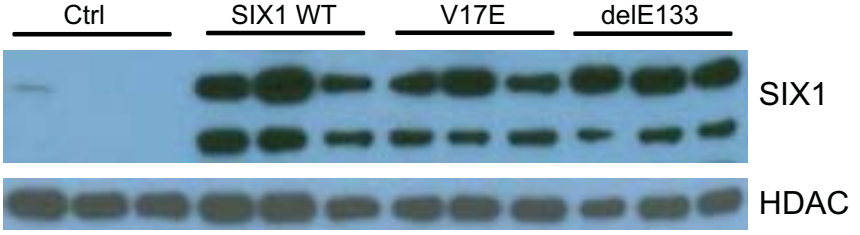

G372
D375
M515
V496
Y473
L451
R386
V272
Mg 2+
R438
V458
L459
L529
N433
E309

Supplemental Figure 4. The Eya domain of EYA1 and EYA2 are highly conserved
Amino acid residues that are identical between EYA1 and EYA2 are colored teal, while non-identical residues are colored red. Residues mutated in BOR are shown as spheres where 12 of the 14 mutations are identical between EYA1 and EYA2.

A


SIX1 expression in MCF7s
Normalized expression
1.0 X 10^3
1.0 X 10^2
1.0 X 10^1
1.0 X 10^0
Ctrl-6
Ctrl-8
Ctrl-9
SIX1WT-4
SIX1 WT-8
SIX1 WT-9
V17E-2
V17E-3
V17E-10
delE133-1
delE133-3
delE133-5

B


Ctrl
SIX1 WT
V17E
delE133
SIX1
HDAC

Supplemental Figure 5. *SIX1* WT and mutant expression levels are similar in MCF7 cell lines.

(A) 10 clonal isolates of each of the MCF7-SIX1 transfectents (WT, V17E, delE133) were screened for *SIX1* expression levels by qRT-PCR. Shown are the expression levels of *SIX1* in the three selected MCF7 clonal isolates each for Ctrl, SIX1 WT, V17E and delE133.

(B) SIX1 WT and the SIX1 mutant MCF7 lines express similar levels of the SIX1 protein. Western blot was performed on nuclear extracts generated after 12h of treatment with 25μM proteasome inhibitor MG132 to enrich for SIX1 protein. The MG132 treated SIX1 protein migrates between 37 and 50 kD, likely representative of ubiquitinated SIX1.

Supplementary Table 1.
Supplementary Table 1 is presented as a separate Excel file and references cited in the Excel file are presented below titled “Supplementary Table 1 references”.

Supplementary Table 1 references

The Cancer Genome Atlas. TCGA Data Portal Overview, https://tcga-data.nci.nih.gov/tcga/. Accessed April 1, 2012

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