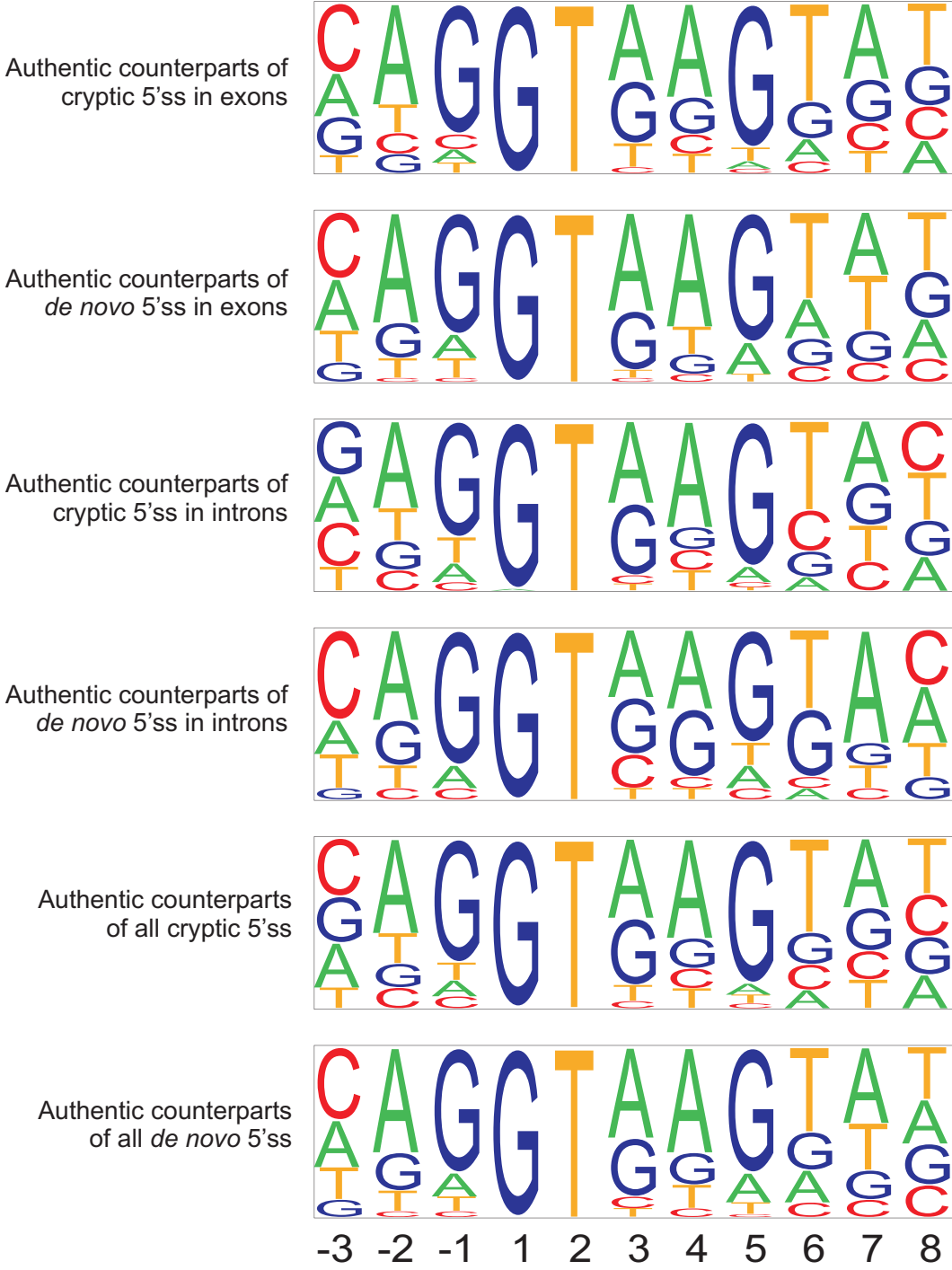
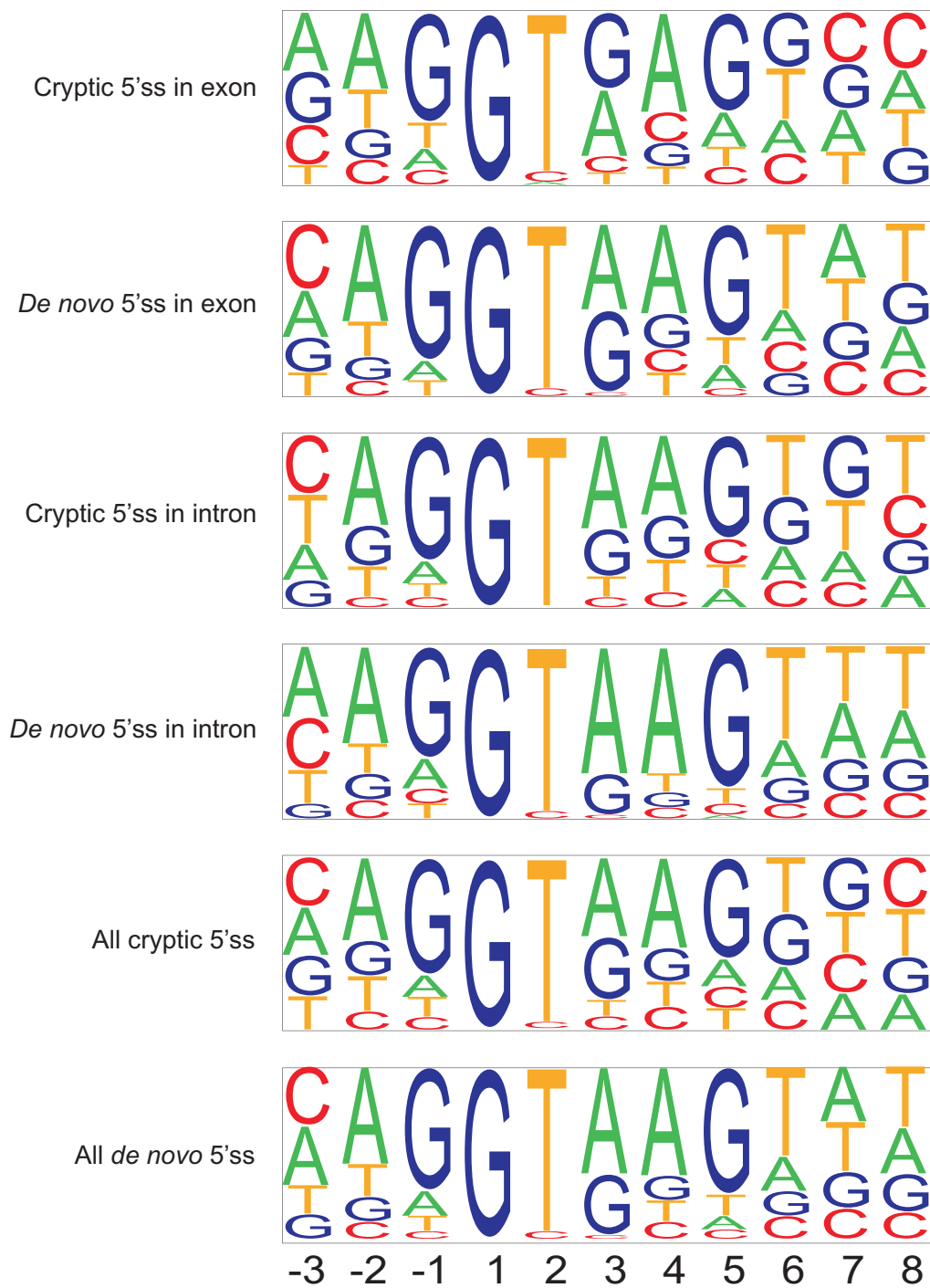


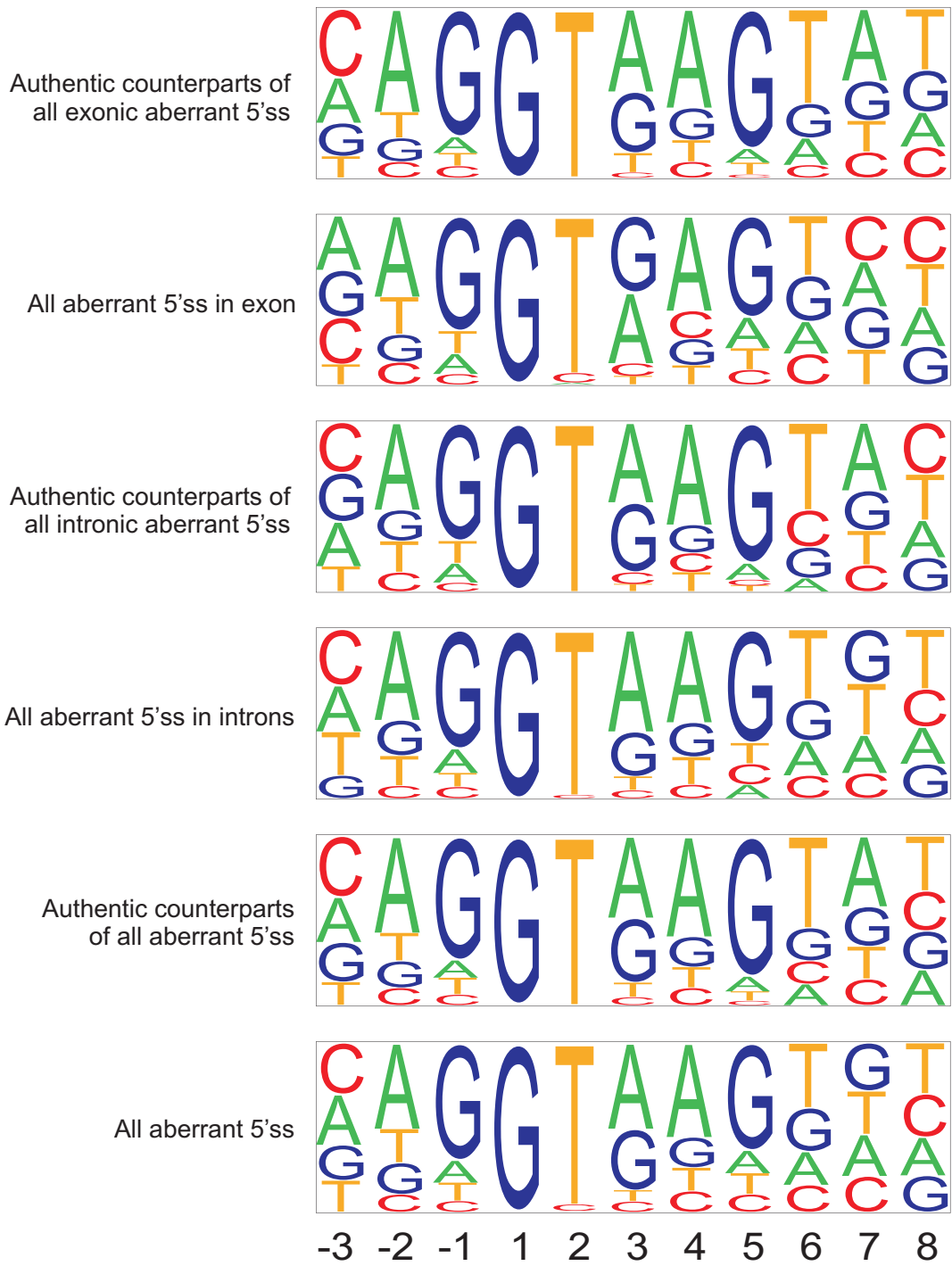
# Supplementary Fig. 1



# Supplementary Fig. 2



# Supplementary Fig. 3



# Supplementary Fig. 4

A

B

| Gene                                                  | HMBS                                                                                                                                                                                                                                                                                                                                                                                                                                                          | Location of Aberrant 5' Splice Site                         | Exon         |
|-------------------------------------------------------|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-------------------------------------------------------------|--------------|
| Phenotype                                             | Acute intermittent porphyria                                                                                                                                                                                                                                                                                                                                                                                                                                  | Distance between Authentic and Aberrant 5' Splice Site (nt) | -9           |
| Mutation                                              | E10+114G>T                                                                                                                                                                                                                                                                                                                                                                                                                                                    | Change in the Reading Frame                                 | 0            |
| Splice Site Strength                                  |                                                                                                                                                                                                                                                                                                                                                                                                                                                               | Authentic 5'ss                                              | Cryptic 5'ss |
| Shapiro & Senapathy Matrix Score <sup>[1]</sup>       |                                                                                                                                                                                                                                                                                                                                                                                                                                                               | 84.05                                                       | 69.33        |
| Maximum Entropy Mode <sup>[2]</sup>                   |                                                                                                                                                                                                                                                                                                                                                                                                                                                               | 9.46                                                        | 3.69         |
| Maximum Dependence Decomposition Model <sup>[3]</sup> |                                                                                                                                                                                                                                                                                                                                                                                                                                                               | 13.08                                                       | 7.88         |
| First-Order Markov Mode <sup>[2]</sup>                |                                                                                                                                                                                                                                                                                                                                                                                                                                                               | 9.04                                                        | 5.1          |
| Weight Matrix Model <sup>[2]</sup>                    |                                                                                                                                                                                                                                                                                                                                                                                                                                                               | 6.11                                                        | 6.11         |
| H-Bond Score <sup>[4]</sup>                           |                                                                                                                                                                                                                                                                                                                                                                                                                                                               | 15.7                                                        | 9.5          |
| Free Energy <sup>[5]</sup>                            |                                                                                                                                                                                                                                                                                                                                                                                                                                                               | -9.2                                                        | -8.6         |
| Base Pairing with U1 snRNA <sup>[4]</sup>             |                                                                                                                                                                                                                                                                                                                                                                                                                                                               | 8                                                           | 8            |
| Neural Network <sup>[7]</sup>                         |                                                                                                                                                                                                                                                                                                                                                                                                                                                               | 0.63                                                        | 0.13         |
| Reference(s)                                          | Delfau, M. H., Picot, C., De Rooij, F., Voortman, G., Deybach, J. C., Nordmann, Y., and Grandchamp, B. (1991). Molecular heterogeneity of acute intermittent porphyria: identification of four additional mutations resulting in the CRM-negative subtype of the disease. <i>Am J Hum Genet</i> 49, 421-428. Pub Med Article # 1714233                                                                                                                        |                                                             |              |
| Comments                                              | -                                                                                                                                                                                                                                                                                                                                                                                                                                                             |                                                             |              |
| Nucleotide Sequence <sup>[6]</sup>                    | <p>cattaagctg agagctgaa gatgactgaa gtcagccag ctagagaggy aaagacagac tcaggcagag ggaaccgac gggcccccag attgcccag actggtgtc ttgcaactc tccacgCG GGAACCTCA ACACCGGCT TCGAAGCTG GACGACAGC AGGATTCAG TCCGATCATC CTGGAAACG CTGGCTTGA GCGATGGG TGGCAACAC CG-CTGGGAC A(G-T)gtag ggcctggccc tctcctctcc ccagctcctc tgcattcct tctgctta cagtcaccc caatttaga ttttagact ttatgattg gtaagagca taccgttca gtagaaactg tacttagtac ccatcagcc atctgtttt ttactttac tacagtattc attaca</p> |                                                             |              |
| Terminal Exon?                                        | No                                                                                                                                                                                                                                                                                                                                                                                                                                                            |                                                             |              |
| Percent Utilisation                                   | Not determined                                                                                                                                                                                                                                                                                                                                                                                                                                                |                                                             |              |

**Legend**  
*i*, cryptic or *de novo* splice sites; > nucleotide substitutions (in parentheses); [], deletions; [], duplications or insertions. Intronic sequences are in lower case (in blue), exons are in upper case.