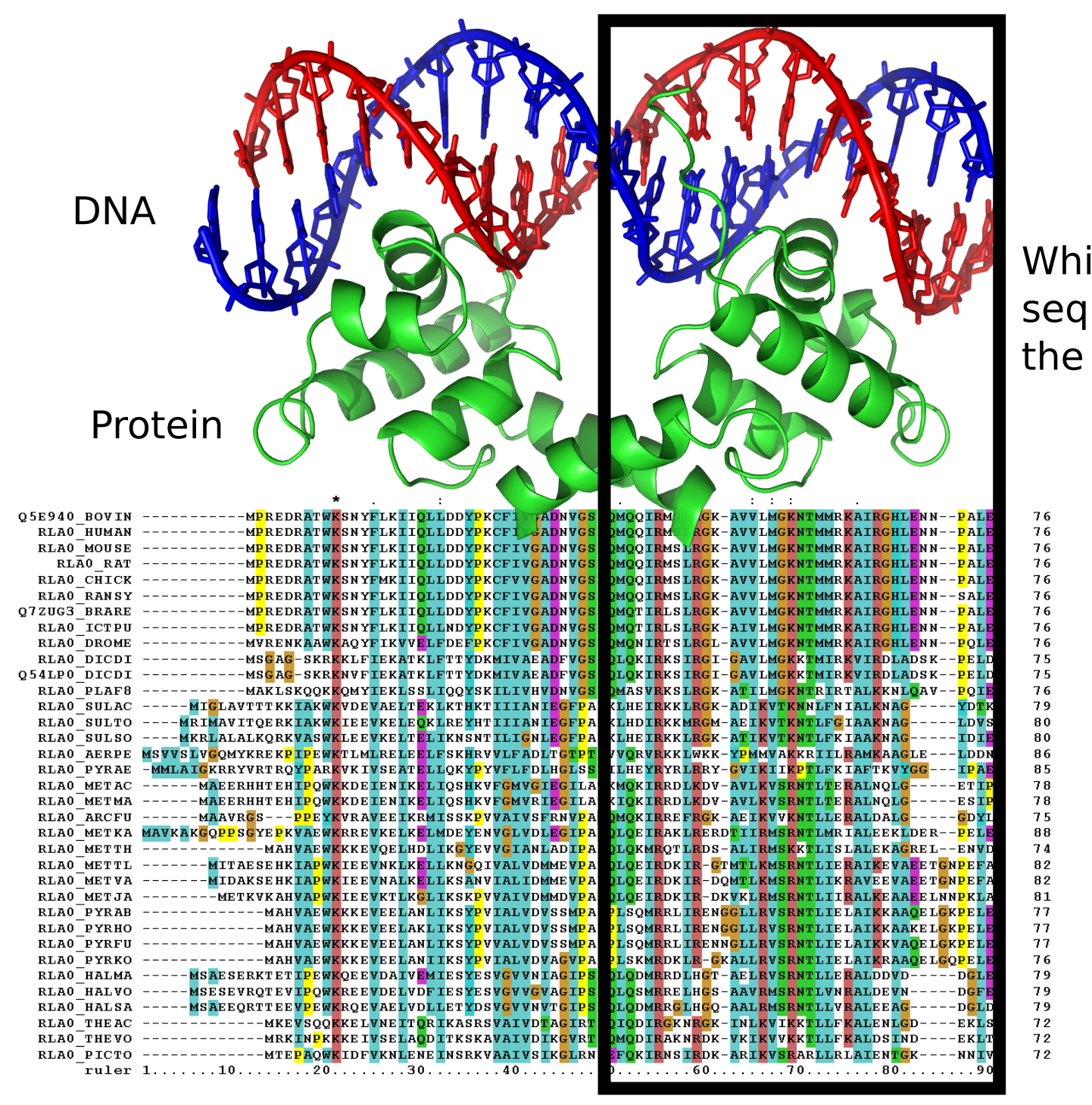
Sublogo dendrograms: visualizing correlation in biological sequence motifs

Toby Dylan Hocking - toby.hocking@etu.upmc.fr - useR! 2009 - July 7-10 - Rennes, France

Introduction: DNA-protein interactions motivate the study of sequence motifs



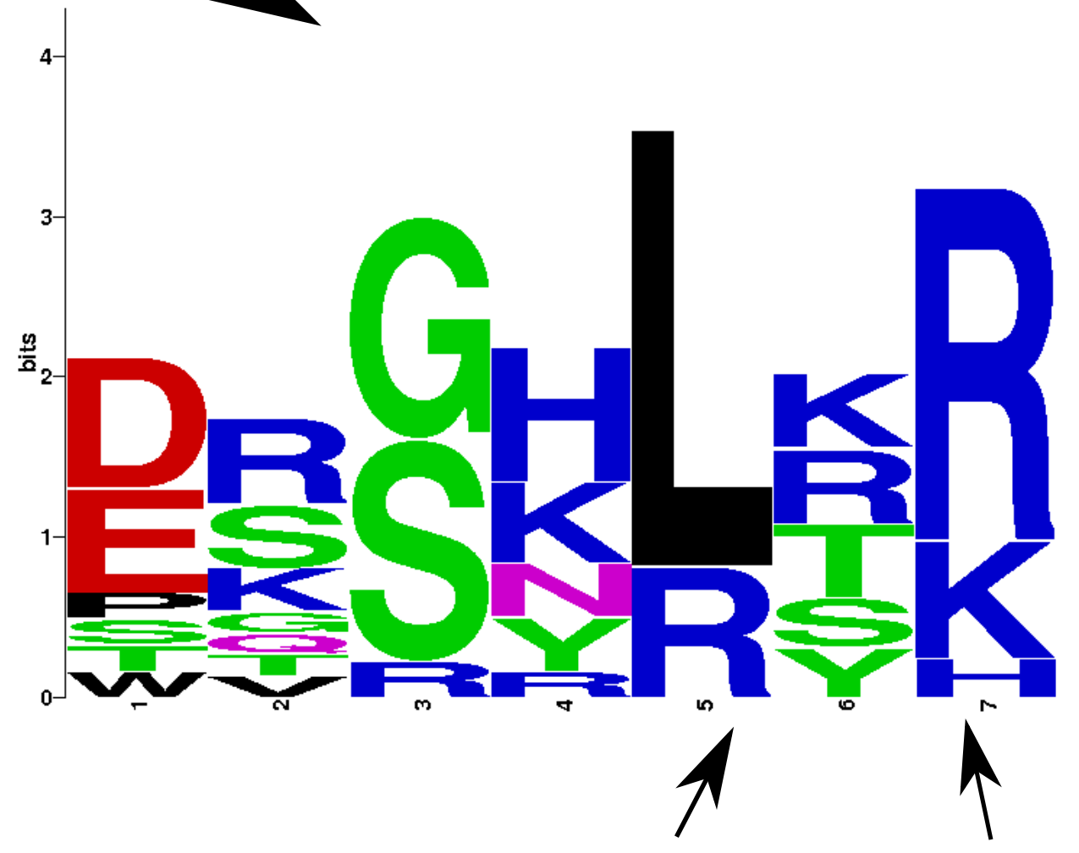
Which DNA and protein sequences coordinate the binding?

Region of interest in the sequence alignment

Subsequences of interest

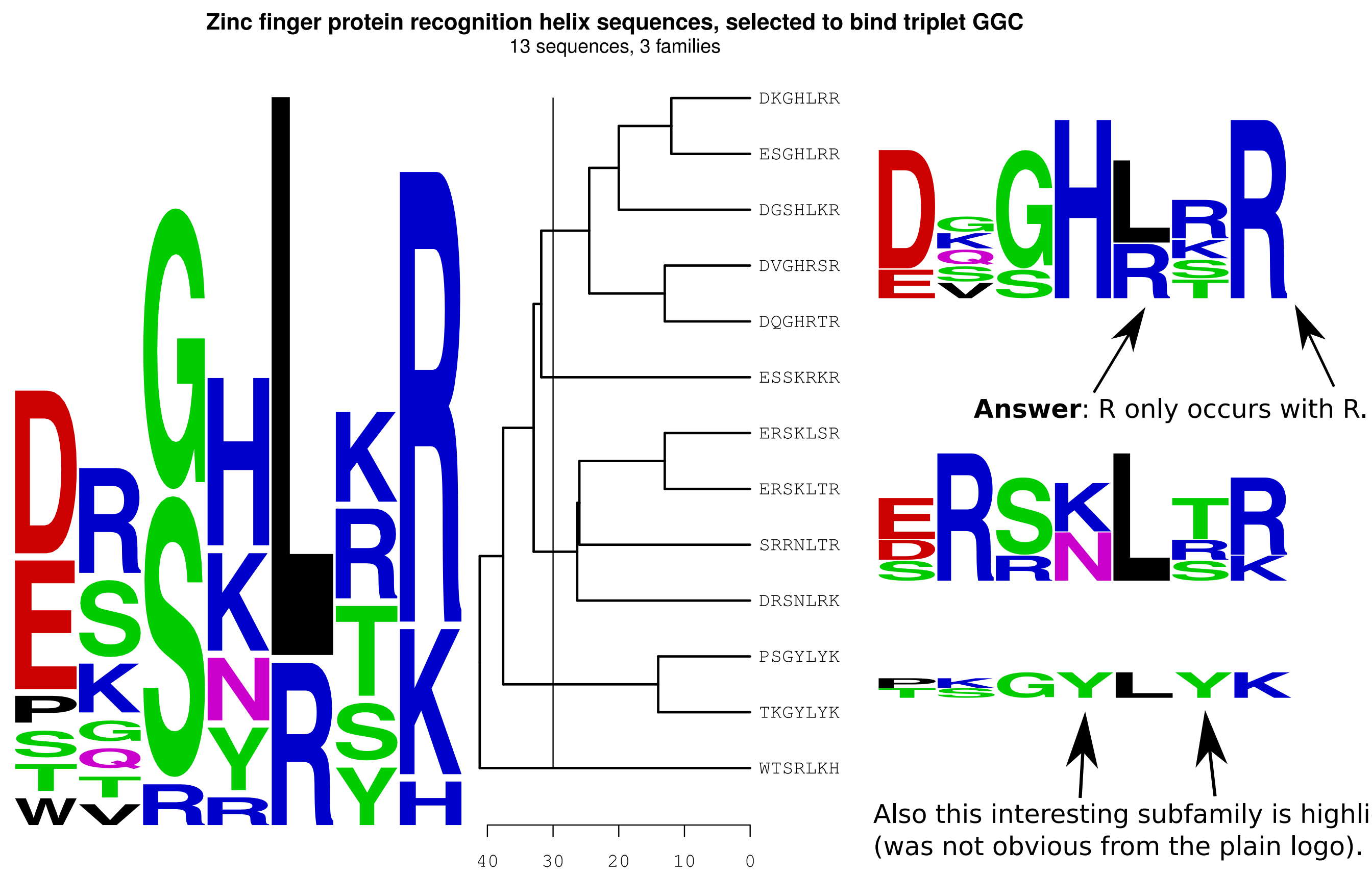
DQGHRTR
DVGHRSR
ESGHLRR
ESSKRKR
SRRNLTR
TKGYLYK
PSGYLYK
WTSRLKH
DKGHLRR
DGSHLKR
DRSNLRK
ERSKLTR
ERSKLSR

Visualize motif using Weblogo



Question: L/R goes with R/K/H?

> "A standard sequence logo does not provide any indication of correlations between different positions of the alignment."
> Crooks et al. 2004, authors of Weblogo



Zinc finger protein recognition helix sequences, selected to bind triplet GGC
13 sequences, 3 families

Answer: R only occurs with R.

Also this interesting subfamily is highlighted (was not obvious from the plain logo).

Methods Implemented in http://sublogo.r-forge.r-project.org

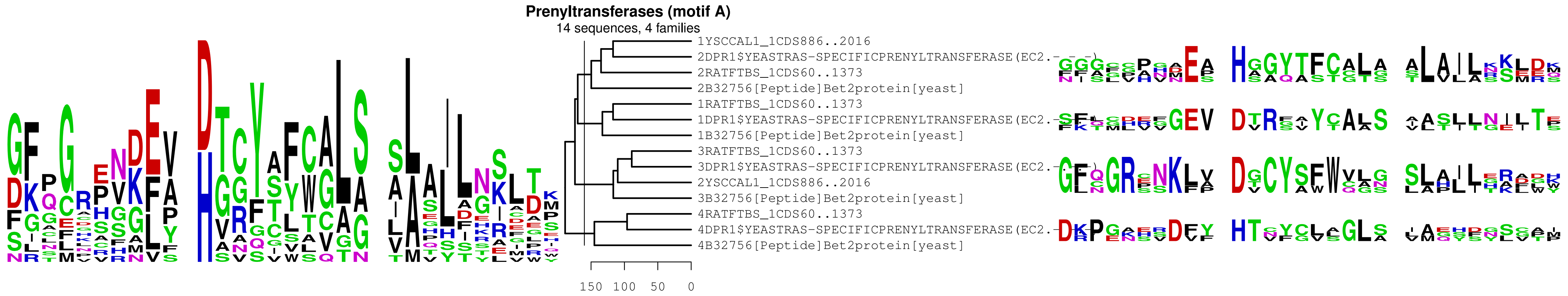
```
> sublogo(c("DQGHRTR","DVGHRSR","ESGHLRR",...),cutline=30,main="Zinc finger...")
```

will generate the sublogo dendrogram in the lower left.
If the vector of sequences has names, the names will be used to label the dendrogram.

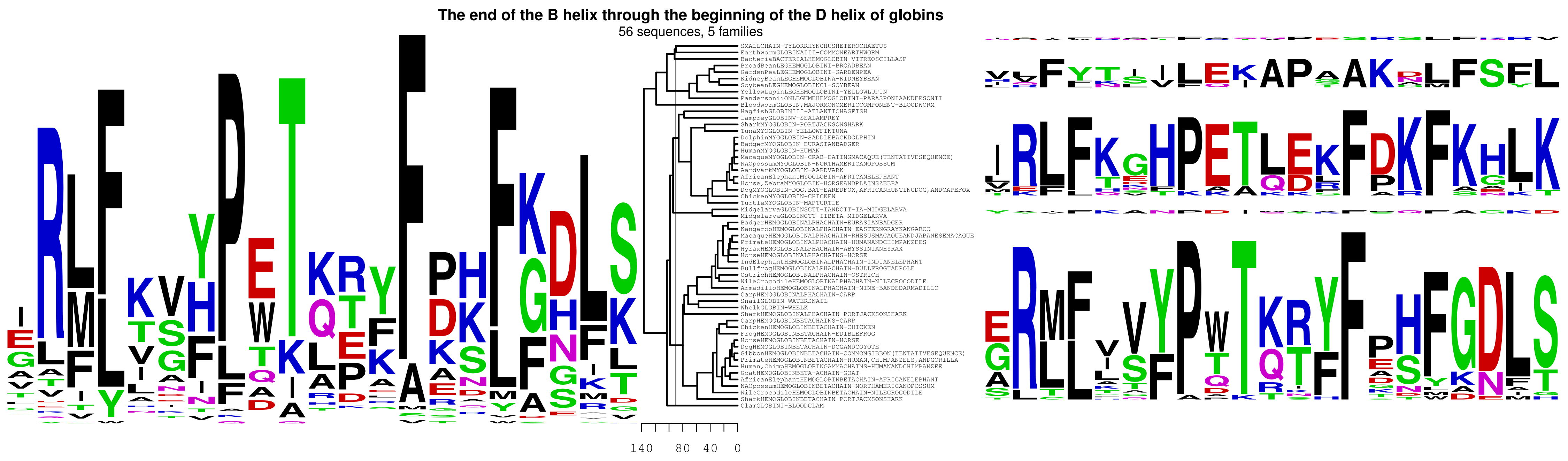
0. **Alignment**. Data input to sublogo() function is a character vector of aligned input sequences.
1. **Difference matrix calculation**. A substitution matrix (BLOSUM62 for protein, identity for DNA) is used to calculate a difference between each pair of sequences.
2. **Clustering**. The difference matrix is used with hclust() to perform a hierarchical clustering.
3. **Cutting**. User selects level to cut the tree, yielding several subfamilies of sequences.
4. **Logos**. Sequences exported to plain text files for input to Weblogo, which saves PS logo images.
5. **Drawing**. R package grImport used to import logo PS files, gridBase used to combine logos (grid graphics) with dendrogram (base graphics).

Results: visualization method applied to data sets from Crooks et al.

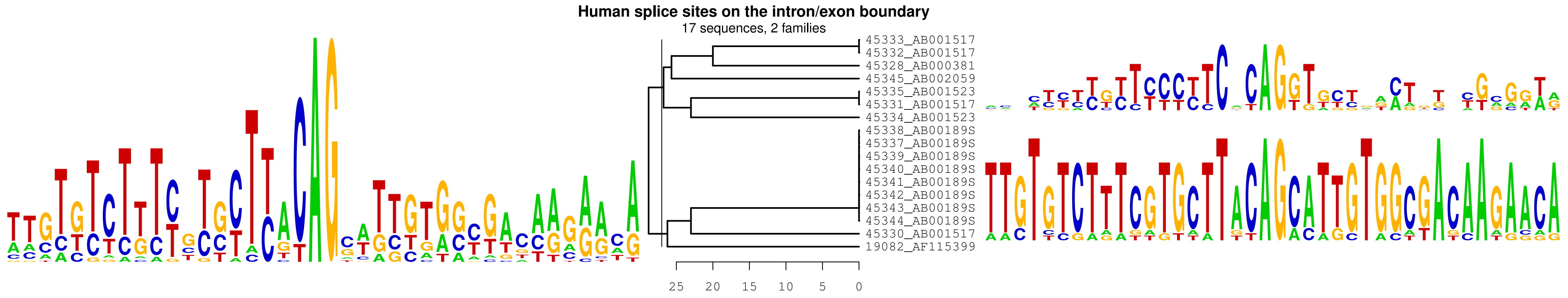
- Visualizes effectively subfamilies which are not readily visible from logo alone.
- Can inform about sequence correlation (or lack thereof).



Prenyltransferases (motif A)
14 sequences, 4 families



The end of the B helix through the beginning of the D helix of globins
56 sequences, 5 families

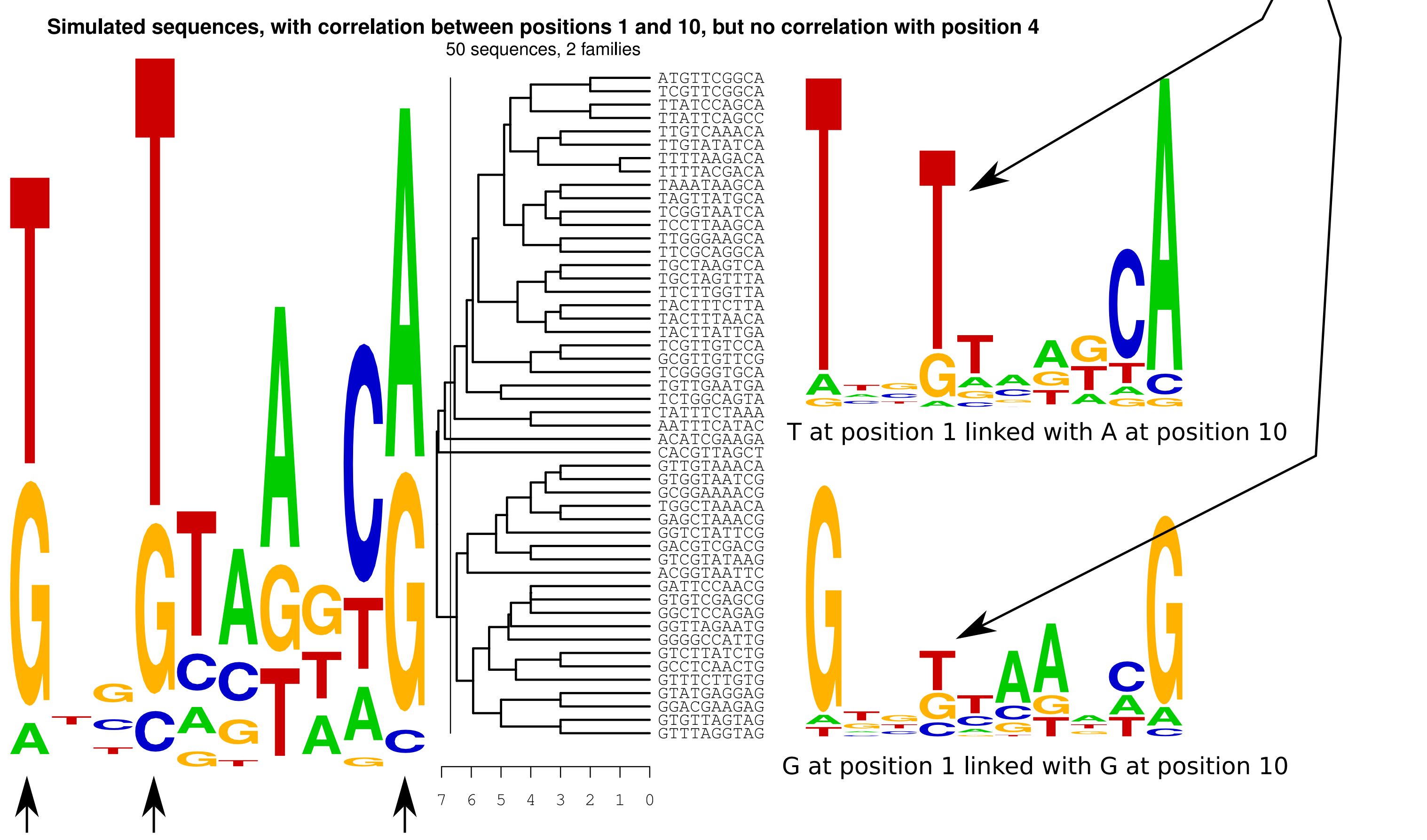


Human splice sites on the intron/exon boundary
17 sequences, 2 families

Simulation

This is a randomly generated dataset with all positions independent, except that position 10 is dependant on position 1.

Both T and G appear in both subfamilies, implying no correlation at position 4.



Simulated sequences, with correlation between positions 1 and 10, but no correlation with position 4
50 sequences, 2 families

T at position 1 linked with A at position 10

G at position 1 linked with G at position 10

Strong signals, is there any correlation?

Conclusions

Sublogo dendrograms are useful for characterizing
1. subfamily structure
2. sequence correlation

Future work

- Deploy on a webserver.
- Use SeqinR package for sequence IO.
- Find or write a function for drawing dendrograms using grid graphics.
- Use seqLogo package to draw logos instead of weblogo/grImport.
- Automatically pick cutline and family structure.
- Allow position weights, for clearer partitions.
- Adapt for large (N>100) data sets.

References

Schneider TD Stephens RM (1990). Sequence Logos: A New Way to Display Consensus Sequences. Nucleic Acids Res., 18, 6097–6100.

Crooks GE, Hon G, Chandonia JM, Brenner SE (2004). WebLogo: A sequence logo generator. Genome Research, 14, 1188–1190, http://weblogo.berkeley.edu

Paul Murrell (2009). Importing Vector Graphics: The grImport Package for R. Journal of Statistical Software, 30(4), 1-37. URL http://www.jstatsoft.org/v30/i04/.