Supplementary Materials for eFORGE v2.0: updated analysis of cell type-specific signal in epigenomic data

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eFORGE is a recently updated web tool for analysis of cell type-specific signal in Illumina BeadChip data. The updated version of eFORGE provides multiple improvements compared to the previous version, adding analysis options such as EPIC array support, chromatin state enrichment analysis, TF motif analysis and DNase I footprint analysis. eFORGE v2.0 is thus the first version of eFORGE to include EPIC array support, though this addressing the needs of a growing sector of the EWAS field. In addition, eFORGE adds a new probe-centric browser to facilitate assessment of TF binding at a particular locus. In this document we demonstrate an example eFORGE analysis for a particular EPIC dataset.

In this example we focus on the analysis of data from an EPIC array study by Moran and others (Moran *et al.*, 2016). This study compared DNAm profiles between colon and neuronal cells, providing a set of DMPs that separate both tissues.

We obtained the study probe list from supplementary table 7, and sorted all probes by DNAm difference (“dif” column) in descending order. We then took the probeids from the top 200 probes for subsequent analysis.

Given that eFORGE only requires probe location information to perform subsequent analysis, it is important to highlight that only probeids were analysed beyond this point, and location for these probeids was automatically assigned by eFORGE and compared to location and annotation from 1000 EPIC array background probe sets. In a preliminary analysis, we used eFORGE to test for enrichment of the Moran et al. probes in DNase I hotspots from the Roadmap Epigenomics Consortium (2015 release), compared to 1000 background sets of EPIC array probes. Results show a strong enrichment for brain DNase I hotspots (figure 1).



**Figure** 1: eFORGE Consolidated Roadmap DHS results for top 200 probes from Moran et al. 2016. (eFORGE link: <https://eforge.altiusinstitute.org/files/0x5B90C4B25FAD11E888B1D3F654000C8C/Unnamed.850k.erc2-DHS.chart.pdf>).

We then performed similar DHS enrichment analyses across datasets from the ENCODE, BLUEPRINT and 2012 Epigenomics Roadmap datasets. Results across these consortia support the brain DNase I hotspot enrichment, with enrichments in brain and spinal cord. No enrichment is observed for any other tissue (figure 2).





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**Figure** 2: eFORGE results for top 200 probes from Moran et al. 2016 across data from ENCODE (top), BLUEPRINT and 2012 Epigenomics Roadmap consortia (eFORGE links: ENCODE: <https://eforge.altiusinstitute.org/files/0xDA9ED6F45FAD11E884D880F754000C8C/Unnamed.850k.encode.chart.pdf>, BLUEPRINT: <https://eforge.altiusinstitute.org/files/0xEB7A16645FAD11E8BA92B6F754000C8C/Unnamed.850k.blueprint.chart.pdf>, 2012 Epigenomics Roadmap: <https://eforge.altiusinstitute.org/files/0xCDAB919E5FAD11E8A40F5BF754000C8C/Unnamed.850k.erc.chart.pdf>).

DHSs are markers for promoters, enhancers and other elements, constituting a general mark covering many cis regulatory element classes. To further dissect the underlying regulatory elements driving this brain signal we focused analysis on the 5 core histone marks mapped by the Epigenomics Roadmap consortium. Results reveal a brain H3K4me3 and H3K9me3 enrichment (figure 3). H3K4me3 is a mark enriched in active promoter elements and also present at active enhancers, and H3K9me3 is a mark enriched in heterochromatin and repressed regions.

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**Figure** 3: eFORGE results for top 200 probes from Moran et al. 2016 across 5 histone mark datasets from the Epigenomics Roadmap consortium (including H3K4me1, H3K4me3, H3K27me3, H3K9me3 and H3K36me3, eFORGE link: <https://eforge.altiusinstitute.org/files/0xBA8B48CA5FAD11E8AE2545F754000C8C/Unnamed.850k.erc2-H3-all.chart.pdf>)

To further characterise the H3K4me3 and H3K9me3 enrichment revealed by eFORGE histone mark analysis we sought to perform an additional analysis across 15 chromatin states. eFORGE results show enrichments for "enhancer" and "flanking active TSS" categories for brain, neuronal progenitors and neurosphere (figure 4).

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**Figure** 4: eFORGE results for top 200 probes from Moran et al. 2016 across 15 chromatin state datasets from the Epigenomics Roadmap consortium (eFORGE link: <https://eforge.altiusinstitute.org/files/0x55BB98285FAD11E88F9DC2F654000C8C/Unnamed.850k.erc2-chromatin15state-all.chart.pdf>)

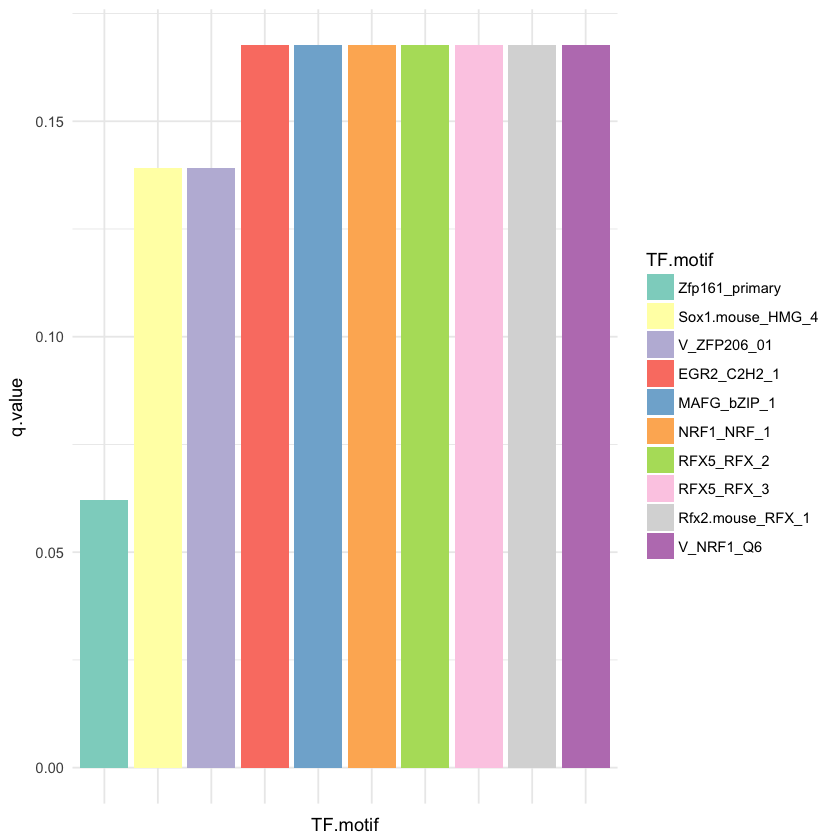
We have thus analysed the top 200 probes from Moran et al., 2016 across data for DHSs, histone mark broadpeaks and chromatin states. We have designed the tool in such a way that further datasets can be added to local installations of the eFORGE web database. The code to generate the eFORGE web database is available from <https://github.com/charlesbreeze/eFORGE/blob/master/docs/eforge-db-construction/>. In addition, a graphical schematic of the eFORGE web sqlite database structure is available from <https://github.com/charlesbreeze/eFORGE/blob/eforge.v2.0/docs/eforge_2.0.web.db.schematic.svg>.

As in previous versions, eFORGE v2 includes an optional 1kb proximity filter to avoid biases associated with repeatedly testing proximal probes that present a strong DNA methylation correlation (Eckhardt *et al.*, 2006). For the 850k EPIC array, we have observed this filter removing up to 0.7% of probes in a random input set (7 out of 1000 probes, 1000 background tests), suggesting that eFORGE probe filtering avoids proximal probe bias in a typical input set without removing an excessive number of probes from analysis for the larger EPIC array.

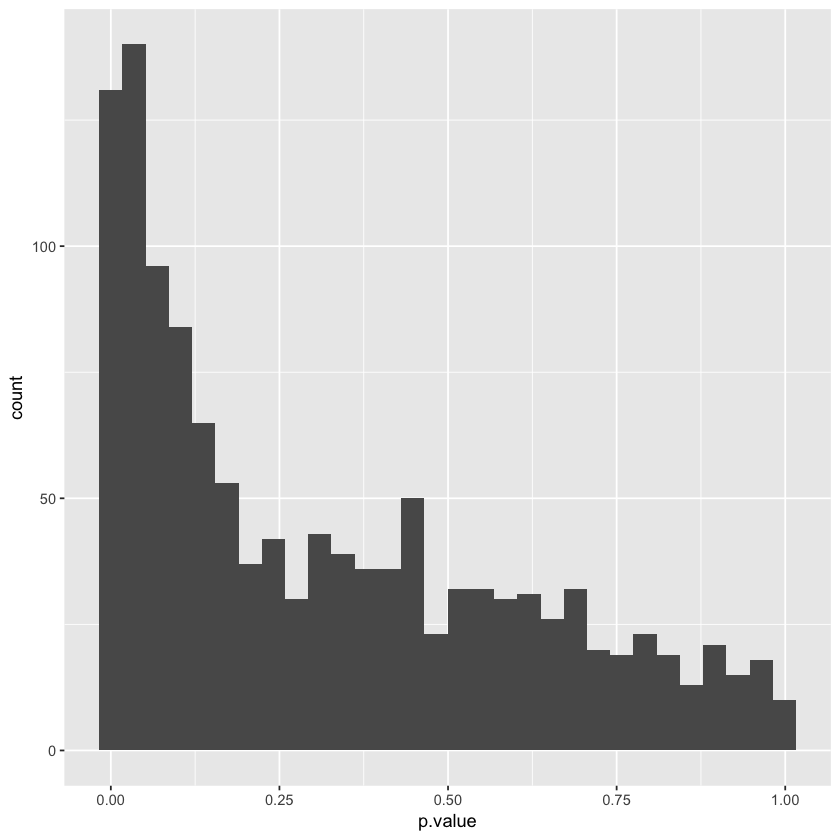
In addition, eFORGE v2.0 currently contains 815 individual datasets (493 individual DHS datasets included the previous eFORGE publication, 195 individual histone mark datasets and 127 individual chromatin state datasets). Our online datatable includes all 815 individual datasets present in eFORGE (available at <https://docs.google.com/spreadsheets/d/1S1GCZmaPRXYHjFHCpY9XPWO_9NBlS0oi29uoq7weTbI/edit?usp=sharing>, column 1 indicates whether the datasets were added in eFORGE v2.0 or were added previously).

eFORGE v2 corresponds to developments in eFORGE web, which can also be set up for automated use in a cluster environment. For a simpler command line setup, eFORGE standalone remains in its original design for users to modify and experiment with new datasets.

Given that DNAm changes can result as a consequence of the binding of sequence-specific TFs, and that TFs are also involved in the formation of enhancers and other regulatory elements, we sought to identify TF motifs associated with the top 200 probes from Moran et al. 2016. We therefore performed an enrichment analysis across all 2256 TF motifs in eFORGE-TF. Results did not identify significant motifs at q<0.05 (figure 5). However, a p-value histogram shows evidence of anti-conservative p-values (figure 6), and we anticipated that testing a higher number of probes could reveal significant enrichments at q<0.05.

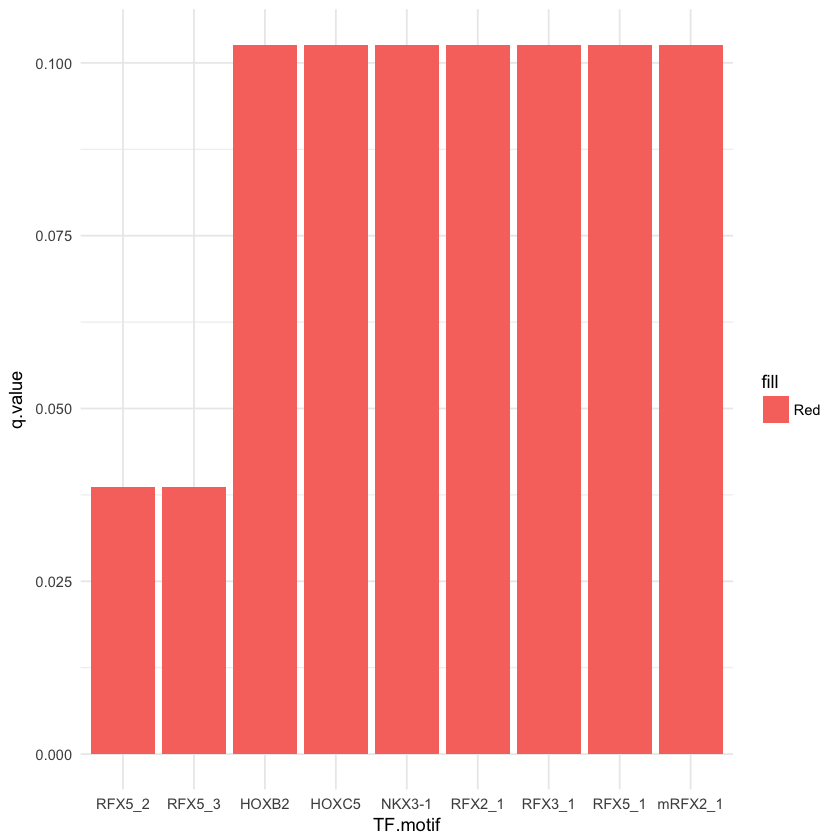


**Figure 5:** 10 most enriched TF motifs from eFORGE-TF analysis on the top 200 probes from Moran et al. 2016. No significant TF motifs are detected at q<0.05.



**Figure 6**: eFORGE-TF p-value histogram for top 200 probes from Moran et al. 2016 tested across 2256 TF motifs from the JASPAR, UniPROBE, TRANSFAC and Taipale DATABASES.

We therefore tested the top 1000 study probes (table 1) for enrichment analysis across 2256 TF motifs in eFORGE-TF. Results indicate a significant enrichment for motifs associated with transcription factor RFX5 (figure 7).



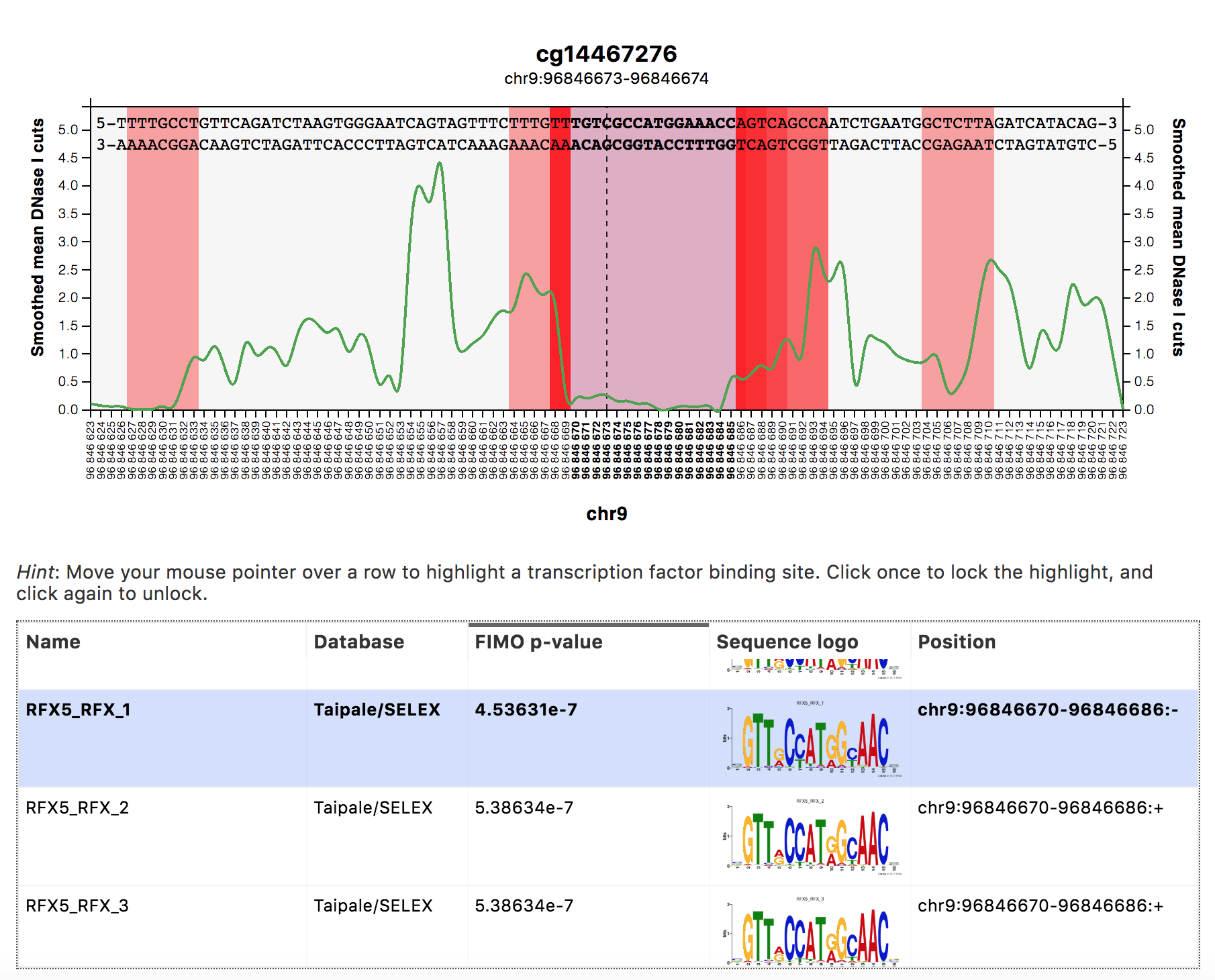
**Figure 7**: eFORGE-TF motif analysis reveals significant enrichment in two RFX5 motifs for top 1000 probes from Moran et al. 2016, and, in addition, low q-values for 4 additional motifs of TFs belonging to the RFX family.

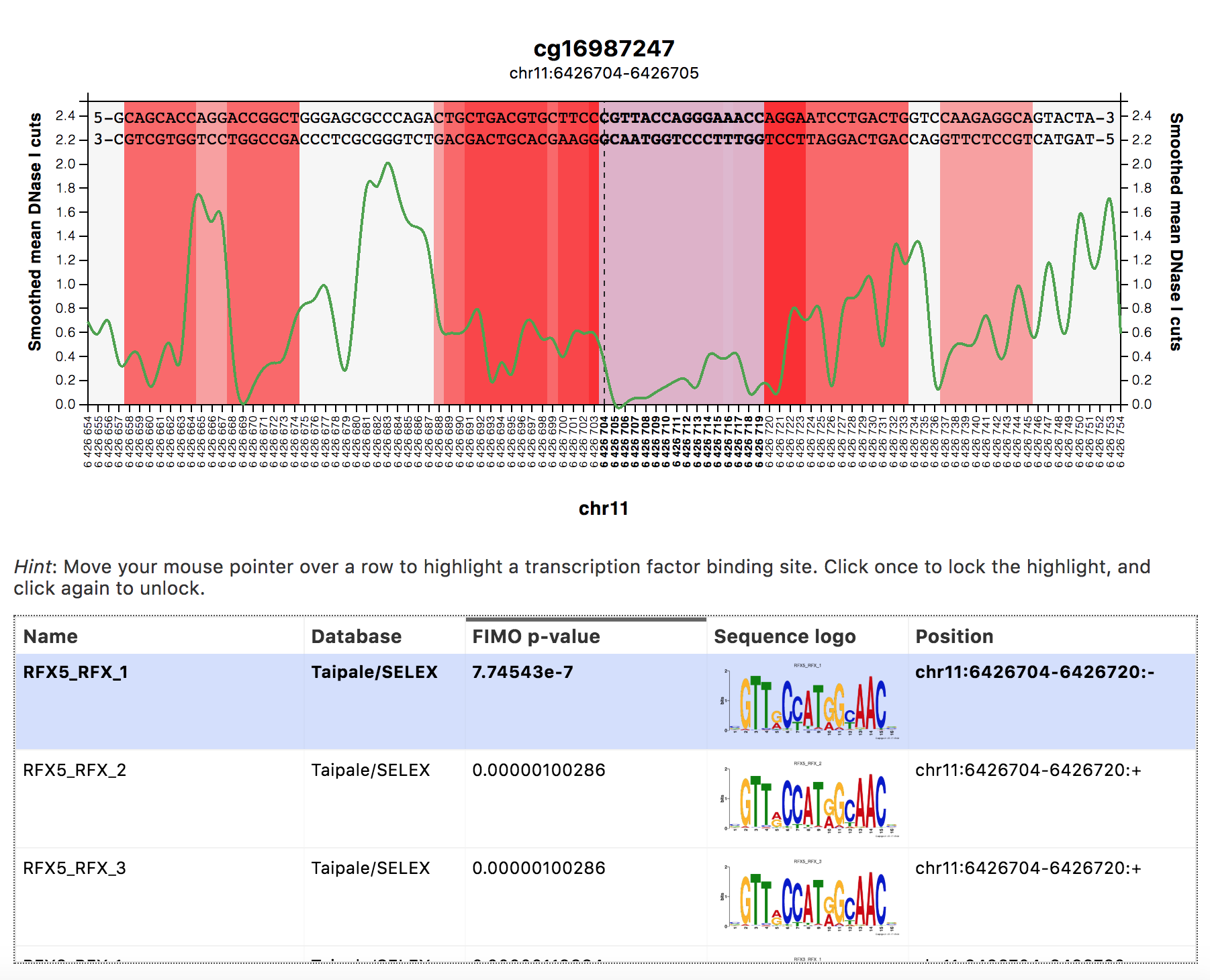
eFORGE-TF analysis therefore points to RFX5 as a TF associated with several DMPs in this study. To better understand the role of DNAm changes at RFX5 sites we sought to characterise DMP location across the RFX5 footprint profile in brain. eFORGE-TF cumulative footprint analysis reveals that DMPs for the study by Moran et al. overlap several different positions covering most the RFX5 motif (figure 8).



**Figure 8:** Distribution of study sites and aggregated RFX5 footprints in brain. 6 of the 1000 top study probes overlap 5 different positions within the RFX5 motif. The RFX family is widely expressed in many tissues, including brain (Uhlén *et al.*, 2015) and has been associated with the regulation of genes linked to conditions such as dyslexia (Tammimies *et al.*, 2016) and bare lymphocyte syndrome (Mach *et al.*, 1996).

To improve our knowledge on the DMP-associated genes potentially regulated by RFX5 binding we sought to characterise RFX5 binding at specific study loci. An eFORGE-TF gallery was generated for RFX5 binding sites overlapping the top 1000 probes from Moran et al. (two of these sites are show in figure 9). Close examination of results suggests that RFX5 is likely to be bound at several of these loci, highlighting at least four binding sites likely to affect the differential methylation of CpG sites from this study.



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**Figure 9:** eFORGE-TF gallery examples for cg14467276 and cg16987247, two of the six probes from table 1 that overlap RFX5 motifs. [cg14467276, upper panel]: red regions indicate DNase I footprints, and the green line represents smoothed cutcount data. Probe location is indicated by a vertical dashed line in the centre of the graph. [cg14467276, lower panel]: TF motifs, including motifs for RFX5, are included in the lower panel. Given the interactive nature of the plot, hovering the cursor on a given motif in the lower panel will highlight its position on the graph in the upper panel. [cg16987247, upper panel]: same as for the upper panel of cg14467276. [cg16987247, lower panel]: same as for the lower panel of cg14467276.

We have thus used eFORGE-TF to characterise TF motifs and TF footprints associated with top probes from an EPIC array study by Moran et al. (2016). While eFORGE-TF currently only supports EPIC array analysis (<https://github.com/charlesbreeze/eFORGE-TF>), we intend to extend support for 450k arrays in the near future.

cg07823492

cg09787504

cg15760474

cg16490124

cg22664298

cg15365500

cg23298862

cg27628891

cg06688803

cg24525461

cg06032337

cg01248385

cg19113686

cg13144059

cg01589353

cg17008486

cg22029015

cg22346032

cg09010067

cg08407901

cg14114910

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cg16669455

cg13514954

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cg06345712

cg24335070

cg07517358

cg22381686

cg19220825

cg00701253

cg05940455

cg11571741

cg01091938

cg12952703

cg01895882

cg17738733

cg17758652

cg00655552

cg12512875

cg25920545

cg16217908

cg00897144

cg00912518

cg09631193

cg06881639

cg04494298

cg02518245

cg20920163

cg10014112

cg07821424

cg00197389

cg26528623

cg01985330

cg01292980

cg10778113

cg14051805

cg16230724

cg05660656

cg13943731

cg21211480

cg11479223

cg02580085

cg09306641

cg07907474

cg22614142

cg15287092

cg22202558

cg02640104

cg06027584

cg06484274

cg11280732

cg14608770

cg10566963

cg23144722

cg27207809

cg11879444

cg03141232

cg15647296

cg00552684

cg06060137

cg15461431

cg26537443

cg06228138

cg20267559

cg07934856

cg20983004

cg26363053

cg06239350

cg05293861

cg06484075

cg14344550

cg05190033

cg05203113

cg01875106

cg05191655

cg02090171

cg03078551

cg17572196

cg24875518

cg19080354

cg14962296

cg10019684

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cg13957558

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cg18556792

cg22457769

cg03190140

cg24953428

cg14033341

cg05014660

cg19391247

cg11571304

cg24413842

cg21223843

cg11622164

cg23920953

cg07985890

cg18175247

cg04208750

cg22478240

cg12050641

cg11953749

cg00466071

cg14282114

cg02852182

cg19789466

cg10077311

cg07340719

cg19780831

cg11827097

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cg14084907

cg00807353

cg01288089

cg15237757

cg13500480

cg17394978

cg01201120

cg17148219

cg05826162

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cg09328979

cg16327891

cg25557277

cg26711732

cg11855710

cg23676869

cg10236838

cg14425468

cg11576424

cg04694633

cg10187421

cg23516953

cg02821484

cg03336270

cg17445840

cg25621667

cg01622399

cg04844987

cg18811155

cg26305062

cg27102304

cg14480249

cg17252260

cg06711306

cg05907835

cg23837191

cg12441242

cg23005102

cg18174005

cg09225373

cg27628372

cg03617435

cg09948687

cg11619961

cg12190219

cg11125851

cg12258368

cg13084525

cg01155450

cg22515971

cg26477511

cg13679714

cg03639185

cg00994306

cg08731961

cg22854836

cg18448570

cg03857571

cg20893039

cg01948202

cg06221000

cg16469353

cg25504086

cg04048517

cg24982491

cg00589251

cg22797514

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cg07754492

cg18680612

cg15179566

cg19651159

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cg23889684

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cg00924017

cg06267197

cg26959257

cg00700039

cg00695955

cg15258711

cg25543264

cg16933147

cg18443412

cg13573375

cg26758857

cg08469834

cg26266789

cg00698602

cg18577326

cg24380163

cg04331561

cg07713361

cg16271200

cg10078415

cg14882150

cg27064692

cg22396868

cg17825438

**Table 1**: top 1000 probes from Moran et al., Supplementary Table 7, when sorted in descending order by differential methylation (“dif” column). These probes (including the set of top 200 probes in this table) were used as input in the eFORGE v2.0 analyses presented in this document.

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