

1 **Integration of human pancreatic islet genomic data refines** 2 **regulatory mechanisms at Type 2 Diabetes susceptibility loci**

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23

24 **Abstract**

25 Human genetic studies have emphasised the dominant contribution of
26 pancreatic islet dysfunction to development of Type 2 Diabetes (T2D). However,
27 limited annotation of the islet epigenome has constrained efforts to define the
28 molecular mechanisms mediating the, largely regulatory, signals revealed by
29 Genome-Wide Association Studies (GWAS). We characterised patterns of
30 chromatin accessibility (ATAC-seq, n=17) and DNA methylation (whole-genome
31 bisulphite sequencing, n=10) in human islets, generating high-resolution
32 chromatin state maps through integration with established ChIP-seq marks. We
33 found enrichment of GWAS signals for T2D and fasting glucose was concentrated
34 in subsets of islet enhancers characterised by open chromatin and
35 hypomethylation, with the former annotation predominant. At several loci
36 (including *CDC123*, *ADCY5*, *KLHDC5*) the combination of fine-mapping genetic
37 data and chromatin state enrichment maps, supplemented by allelic imbalance in
38 chromatin accessibility pinpointed likely causal variants. The combination of

39 increasingly-precise genetic and islet epigenomic information accelerates
40 definition of causal mechanisms implicated in T2D pathogenesis.

41

42 **1. Introduction**

43 T2D is a complex disease characterised by insulin resistance and reduced beta
44 cell function. Recent GWAS have identified a large number of T2D susceptibility
45 loci (Scott et al., 2017, Mahajan et al., 2014, Morris et al., 2012, Voight et al.,
46 2010), the majority of which affect insulin secretion and beta cell function
47 (Dimas et al., 2014, Wood et al., 2017). However, most GWAS signals map to the
48 non-coding genome and identification of the molecular mechanisms through
49 which non-coding variants exert their effect has proven challenging. Several
50 studies have demonstrated that T2D-associated variants map disproportionately
51 to regulatory elements, particularly those which influence RNA expression and
52 cellular function of human pancreatic islets. (Parker et al., 2013, Pasquali et al.,
53 2014, van de Bunt et al., 2015, Olsson et al., 2014, Dayeh et al., 2014, Volkov et
54 al., 2017, Varshney et al., 2017, Gaulton et al., 2015b, Gaulton et al., 2010).

55

56 Characterisation of the islet regulome has until now been limited in scope. The
57 use of DNA methylation and open chromatin data to further annotate ChIP-seq
58 derived chromatin states has successfully uncovered novel biology for other
59 diseases (Wang et al., 2016). Existing methylation studies in islets, however,
60 have either profiled a very small proportion of methylation sites using
61 methylation arrays (Olsson et al., 2014, Dayeh et al., 2014) or focused on T2D-
62 associated disease differentially methylated regions (dDMRs) rather than the
63 integration of DNA methylation status with T2D-relevant GWAS data (Volkov et
64 al., 2017). At the same time, assays of open chromatin in human islets have been
65 restricted to small sample numbers (limiting the potential to capture allelic
66 imbalance in chromatin accessibility for example): these have focussed
67 predominantly on the impact of clustered or “stretch” enhancers (Parker et al.,
68 2013, Pasquali et al., 2014, Gaulton et al., 2010, Varshney et al., 2017).

69

70 Most importantly, in part due to historical challenges in accessing human islet
71 material or authentic human cellular models, reference annotations of the islet

72 epigenome and transcriptome (in the context of projects such as GTex, ENCODE
73 and Epigenome Roadmap) have been largely absent. It is worth noting that islets
74 constitute only ~1% of the pancreas, and islet epigenomes and transcriptomes
75 cannot therefore be reliably assayed in analyses involving the entire organ.
76 Previous islet epigenome studies have, therefore, had only limited ability to
77 directly relate genetic variation to regulatory performance or to broadly
78 characterise the role of DNA methylation in these processes.

79
80 In this study, we set out to expand upon previous studies of the islet regulome in
81 several ways. First, we explored the human islet methylome in unprecedented
82 depth using Whole-Genome Bisulphite Sequencing (WGBS) applied to a set of 10
83 human islet preparations. Second, we explored both basal and genotype-
84 dependent variation in chromatin accessibility through ATAC-seq in 17 human
85 islet preparations. Third, we integrated these genome-wide data with existing
86 islet regulatory annotations to generate a high-resolution, epigenome map of this
87 key tissue. Finally, we used this detailed map to interpret GWAS signals for T2D
88 (and the related trait of fasting glucose) and deduce the molecular mechanisms
89 through which some of these loci operate.

90

91 **2. Results:**

92

93 **2.1 Characterising the DNA methylation landscape of human pancreatic** 94 **islets**

95

96 To characterise the human islet methylome and characterise the role of DNA
97 methylation with respect to T2D genetic risk, we performed WGBS (mean
98 coverage 13X) in human pancreatic islet DNA samples isolated from 10 non-
99 diabetic cadaveric donors of European descent. Methylation levels across the
100 genome were highly correlated across individual donors (mean CpG methylation
101 Spearman's rho across 10 individual WGBS donors=0.71, Figure 1-figure
102 supplement 1A): we pooled the WGBS results to generate a single high-pass
103 (mean coverage 85X) set of pooled human pancreatic islet methylation data
104 covering 23.3 million CpG sites (minimum pooled coverage 10X).

105

106 Most previous studies of the relationship between GWAS data and tissue-specific
107 methylation patterns (including those interrogating the relationship between
108 islet methylation and T2D predisposition (Dayeh et al., 2014, Olsson et al.,
109 2014)) had used data generated on the Illumina 450k methylation array
110 (Hannon et al., 2016, Mitchell et al., 2016, Kato et al., 2015, Ventham et al., 2016).
111 For comparative purposes, we generated 450k array methylation data from 32
112 islet samples ascertained from non-diabetic donors of European descent (5
113 overlapping with those from whom WGBS data were generated). As with the
114 WGBS data, methylation levels were highly correlated across individuals (mean
115 CpG methylation Spearman's rho across 32 individual 450k donor=0.98, Figure
116 1-figure supplement 1B). After pooling 450k array data across samples,
117 methylation profiles generated from the 450k array and WGBS were highly
118 correlated at the small subset of total CpG sites for which they overlap: this was
119 observed across pooled samples (pooled WGBS vs. 450k Spearman's rho=0.89,
120 Figure 1A) and across the 5 donors analysed by both methods (mean Spearman's
121 rho=0.80, not shown).

122

123 WGBS and 450k array data differed substantially in terms of genome-wide
124 coverage. The 450k array was designed to interrogate with high precision and
125 coverage ~480k CpG sites (approximately 2% of all sites in the genome),
126 selected primarily because they are located near gene promoters and CpG-island
127 regions. The focus of the 450k array on these regions, which tend to be less
128 variable in terms of methylation, explains the high 450k array correlation levels
129 between donors. In addition, this selective design results in marked differences
130 in the distributions of genome-wide methylation values between WGBS and the
131 450k array. Whilst the WGBS data revealed the expected pattern of widespread
132 high methylation levels with hypomethylation (<50%) restricted to 11.2%
133 (2.6M/23.3M CpG sites) of the genome, the array disproportionately
134 interrogated those hypomethylated sites (218k [46%] of all 450k CpG probes)
135 (Kolmogorov-Smirnov (KS) test for difference, $D=0.40$, $P<2.2\times 10^{-16}$) (Figure 1B).
136 These differences in methylation distribution were also evident within specific
137 islet regulatory elements from previously defined standard chromatin state

138 maps (Parker et al., 2013) (Figure 1C, Figure 1-figure supplement 1C-D). We
139 found significant (FDR<0.05) differences between the methylation levels of CpG
140 sites accessed on the array, and those interrogated by WGBS, across most islet
141 chromatin states: the largest differences were observed for weak promoters
142 (median WGBS=0.71 vs. median 450k=0.11, KS test D=0.51, $P<2.2\times 10^{-16}$,) and
143 weak enhancers (WGBS=0.87 vs. 450k median=0.76, D=0.39, $P<2.2\times 10^{-16}$, Figure
144 1-figure supplement 1D).

145

146 In terms of coverage, most chromatin states, apart from promoters, were poorly
147 represented by CpG sites directly interrogated by the array: for example the
148 array assayed only ~2.9% of CpG sites in strong enhancer states (2.7-3.8%
149 depending on strong enhancer subtype, Figure 1C). Although methylation levels
150 were previously reported to be highly correlated across short (0.1-2kb) genomic
151 distances (Zhang et al., 2015, Bell et al., 2011, Eckhardt et al., 2006, Guo et al.,
152 2017), the observed significant differences in the methylation distribution
153 (Figure 1C, Figure 1-figure supplement 1D) across chromatin states including
154 weak promoter (median size 600bp) and enhancer subtypes (median size ranges
155 from 200-1200bp) indicate that these correlative effects are not strong enough
156 to counterbalance the low coverage of the 450k array. These findings are
157 consistent with 450k array content being focused towards CpG-dense
158 hypomethylated and permissive promoter regions. This highlights the limited
159 capacity of the array to comprehensively interrogate the global DNA methylome,
160 in particular at distal regulatory states such as enhancers.

161

162 To understand the value of these data to reveal molecular mechanisms at GWAS
163 loci, where we and others had shown enrichment for islet enhancer states
164 (Pasquali et al., 2014, Gaulton et al., 2015a, Parker et al., 2013), we were
165 interested to see how the selective coverage of the array might impact on its
166 ability to interrogate methylation in GWAS-identified regions. We used the
167 largest currently available T2D DIAGRAM GWAS data set (involving 26.7k cases
168 and 132.5k controls of predominantly European origin, see dataset section for
169 details) to identify the “credible sets” of variants at each locus which collectively

170 account for 99% of the posterior probability of association (PPA) (Scott et al.,
171 2017, Maller et al., 2012).
172
173 To estimate the respective proportions of these T2D-associated variants
174 captured by CpG sites assayed by the 450k array and WGBS, we determined, for
175 each locus, the combined PPA of all 99% credible set variants mapping within
176 1000bp of any CpG site captured. This is based on evidence that across short
177 distances CpG methylation is highly correlated (Zhang et al., 2015, Bell et al.,
178 2011, Eckhardt et al., 2006, Guo et al., 2017) and may be influenced by genetic
179 variants associated with altered transcription factor binding (Do et al., 2016). We
180 found that coverage of this space of putative T2D GWAS variants by the 450k
181 array is low: across GWAS loci, the combined PPA attributable to variants within
182 regions assayed by the array ranged from 0-99% with a median PPA per locus of
183 16% (compared to a WGBS median PPA per locus=99%, KS-test $P < 2.2 \times 10^{-16}$,
184 Figure 1D, top). We estimated that the equivalent figure for a recently developed
185 upgrade of the 450k array, which captures ~850k CpG sites and aims to provide
186 better coverage of enhancer regions, would be ~39% (range 0%-99% Figure 1D,
187 top). For instance, at the *DGKB* T2D locus (centred on rs10276674), CpG sites
188 covered by the 450k array interrogated less than 1% of the PPA of associated
189 variants (vs. 99% captured by WGBS); the figure for the 850k array would be
190 23% (Figure 1E). We obtained similar results when we performed equivalent
191 analyses using GWAS data for fasting glucose (FG, from the ENGAGE consortium
192 (Horikoshi et al., 2015)), another phenotype dominated by islet dysfunction
193 (Figure 1D, bottom).
194
195 These data indicate that available methylation arrays provide poor genome-wide
196 coverage of methylation status and are notably deficient in capturing
197 methylation status around the distal regulatory enhancer regions most relevant
198 to T2D predisposition. For this reason, we focused subsequent analyses on the
199 WGBS data.
200
201
202

203 **2.2 Integration islet methylation and other epigenomic annotations**

204

205 Studies in a variety of other tissues have shown that hypomethylation is a strong
206 indicator of regulatory function (Stadler et al., 2011). More specifically,
207 continuous stretches of CpG-poor Low-Methylated Regions (LMRs, with
208 methylation ranging from 10-50% and containing fewer than 30 CpG sites)
209 denote potential distal regulatory elements such as enhancers, while stretches of
210 CpG-rich UnMethylated Regions (UMRs, containing more than 30 CpG sites) are
211 more likely to represent proximal regulatory elements including promoters
212 (Burger et al., 2013). We detected 37.1k LMRs, 13.6k UMRs (Figure 2A) and
213 10.7k Partially Methylated Domains (PMDs, Methods and Figure 2-figure
214 supplement 1A-B). PMDs represent large regions of unordered methylation
215 states associated with DNA sequence features (Gaidatzis et al., 2014). As
216 anticipated, we found significant enrichment of LMRs with weak and strong
217 enhancer states as defined by islet chromatin state maps derived from existing
218 ChIP-seq data (Parker et al., 2013) (69.2% of islet LMRs overlapped islet strong
219 and weak enhancer states, $\log_2FE=2.2-2.9$, Bonferroni $P<0.05$, (Figure 2B, Figure
220 1-figure supplement 1C). Similarly, UMRs were enriched for islet active promoter
221 chromatin states (90.8% of UMRs overlapped islet active promoters, $\log_2FE=3.9$,
222 $FDR < 0.05$, Figure 2B).

223

224 To further characterise these hypomethylation domains, we overlapped
225 information from analyses of islet cis-expression QTLs (eQTLs) (van de Bunt et
226 al., 2015) and islet ChIP-seq transcription factor binding sites (TFBS) (Pasquali
227 et al., 2014). We observed marked enrichment for eQTLs (LMR $\log_2FE=1.1$, UMR
228 $\log_2FE=2.7$, Bonferroni $P<0.05$) and TFBS (LMR $\log_2FE=4.1-4.6$; UMR $\log_2FE=2.4-$
229 3.9 , Bonferroni $P<0.05$, Figure 2B). These observations confirm that islet LMRs
230 and UMRs correspond to important tissue-specific regulatory regions,
231 overlapping cis-regulatory annotations known to be enriched for T2D GWAS
232 signals (Pasquali et al., 2014, Gaulton et al., 2015b).

233

234 We also considered the relationship between LMR and UMR regions defined in
235 our non-diabetic islet WGBS, and a complementary set of methylation-based

236 annotations previously derived from WGBS of islets from 6 T2D and 8 control
237 individuals (Volkov et al., 2017). In that study, comparisons between diabetic
238 and non-diabetic islets had been used to define a set of 25,820 “disease
239 differentially methylated regions” (dDMRs, min absolute methylation difference
240 5% and $P < 0.02$). We found only limited overlap between these dDMRs and the
241 UMRs and LMRs from our data: of the 25,820 dDMRs, 2.2% overlapped LMRs
242 and 2.4% UMRs. This overlap was slightly greater than expected by chance
243 (Bonferroni $P < 0.05$, LMR $\log_2FE = 1.0$ and promoter-like UMRs $\log_2FE = 1.1$, Figure
244 2B) but more modest than seen for the other regulatory annotations. Similarly,
245 we also observed that dDMRs showed more modest ($\log_2FE = 0.4-1.0$), but still
246 significant (Bonferroni $P < 0.05$) levels of enrichment with respect to all other
247 islet regulatory annotations (Figure 2B). The modest enrichment of dDMRs
248 indicates that only a fraction of these regions correspond to islet genomic
249 regulatory sites. Given that T2D risk variants preferentially map in islet
250 regulatory sites, the corollary is that most dDMRs are unlikely to directly
251 contribute to the mediation of genetic T2D risk.

252

253 **2.3 Refining islet enhancer function using methylation and open chromatin** 254 **data**

255

256 To further characterise the regulatory potential of hypomethylated regions,
257 including LMRs and UMRs, we combined the islet WGBS methylation data with
258 chromatin accessibility data generated from ATAC-seq assays of 17 human islet
259 samples (from non-diabetic donors of European descent; mean read count after
260 filtering = 130M, Figure 2-figure supplement 1C). We identified a total of 141k
261 open chromatin regions based on read depth, peak width and signal-to-noise
262 ratio (see Methods). These regions of islet open chromatin showed substantial
263 overlap (78%) with equivalent regions described in a recent study of two human
264 islets (Varshney et al., 2017) ($\log_2FE = 2.8$ compared to random sites, not shown).
265 In addition, our islet ATAC-Seq sites demonstrated substantial overlap with
266 LMRs: 53% of LMRs overlapped 16% of all ATAC-seq peaks (LMR $\log_2FE = 3.8$
267 compared to randomised sites, Figure 2B). Almost all UMRs (98%) were

268 contained within regions overlapping (13% of) ATAC-seq peaks (UMR
269 $\log_2FE=3.4$ compared to randomised sites, Figure 2B).
270
271 To fully leverage information across multiple overlapping islet epigenome
272 assays, we generated augmented chromatin state maps, using chromHMM (Ernst
273 and Kellis, 2012). These maps combined the WGBS methylation and ATAC-Seq
274 open chromatin data with previously generated ChIP-seq marks (Figure 3A,
275 Figure 3-figure supplement 1A). For these analyses, we initially used a single
276 definition for hypomethylated regions (methylation<60%) that captured both
277 UMRs and LMRs (see Methods).
278
279 This augmented and larger set of 15 islet chromatin states retained the broad
280 classification of regulatory elements that included promoters (positive for
281 H3K4me3), transcribed and genic regions (H3K36me3), strong enhancers
282 (H3K4me1; H3K27ac), weak enhancers (H3K4me1), insulators (CTCF) and
283 repressed elements (H3K27me) (Figure 3A). The addition of islet methylation
284 and open chromatin data expanded existing chromatin state definitions to
285 provide new subclasses, particularly amongst enhancer elements. Here, we
286 observed two subclasses of strong enhancers and three of weak enhancers
287 (Figure 3A). We denote the strong enhancer subtypes as “open” (n=32k genome-
288 wide), characterised by open chromatin and hypomethylation, and “closed”
289 (n=110k) with closed chromatin and hypermethylation (Figure 3A). The three
290 weak enhancer states we denote as “open” (n=38k: open chromatin,
291 hypomethylation), “lowly-methylated” (n=78k; closed chromatin,
292 hypomethylation) and “closed” (n=206k: closed chromatin, hypermethylation).
293 No equivalent class of “lowly-methylated” strong enhancers was observed in the
294 15-state model. When comparing these chromatin states to those identified
295 using only ChIP-seq marks ((Parker et al., 2013), Figure 1-figure supplement
296 1C), the two strong enhancer subclasses we identified subdivided the “strong
297 enhancer 1” state as described by Parker (defined by H3K27ac and H3K4me1).
298 Additional comparison to “stretch” enhancer clusters (Parker et al., 2013),
299 showed that there was considerable overlap between the “open” strong and
300 weak enhancer states we identify here and previously-described “stretch”

301 enhancer states (16.1k out of 23k stretch enhancer overlapped 32k out of 70.1k
302 “open” enhancers). Even so, most (55%) “open” enhancer states, and in
303 particular “open weak enhancers” (70%), were not captured within “stretch”
304 enhancer intervals, and we regard these as distinct islet enhancer subclasses.

305

306 To understand the relationship of these various state definitions to genetic
307 variants influencing T2D risk, we applied the hierarchical modelling approach
308 FGWAS to the same sets of large-scale GWAS data for T2D (from DIAGRAM (Scott
309 et al., 2017)) and FG (ENGAGE (Horikoshi et al., 2015)) described in section 2.1.
310 FGWAS allowed us to combine GWAS and genomic data to determine the
311 genome-wide enrichment within islet regulatory features for variants associated
312 with T2D risk. These enrichment priors were then used to generate credible
313 variant sets that are informed by both GWAS and genomic data, as described in
314 section 2.4.

315

316 In single-feature analyses, we found significant enrichment (lower limit of
317 Confidence Interval (CI)>0) limited to four enhancer states (open weak
318 enhancers, both types of strong enhancer and H3K36me3 marked genic
319 enhancers) (Figure 3B, Table 1). To take into account protein-coding variant and
320 conserved sequence effects, we also included CoDing exon Sequence (CDS)
321 (Carlson and Maintainer, 2015) and CONServed sequence (CONS) (Lindblad-Toh
322 et al., 2011) as additional annotations which were previously found to be
323 strongly enriched for T2D GWAS signal (Finucane et al., 2015). We observed
324 significant enrichment for CDS and CONS sequence in the single state results
325 (Figure 3B, Table 1). FGWAS multi-feature analyses for T2D, incorporating all
326 annotations positive in single-element analyses, retained both subclasses of
327 strong enhancer, the subclass of open weak enhancers, genic enhancers and CDS
328 in the joint model (Figure 3C and Methods). Conserved sequence annotations
329 were not retained in the joint model.

330

331 We observed markedly different levels of enrichment for T2D association
332 between and within open and closed enhancer states (Figure 3B-3C, Table 1).
333 Using these augmented chromatin state maps, we demonstrated clear

334 enrichment for T2D association for the subset of “open” weak enhancers (12% of
335 all weak enhancer sites) with no evidence of enrichment in the remaining
336 subclasses (“closed” and “lowly-methylated”) (Figure 3B and Table 1). This
337 concentration of enrichment amongst a relatively small subset of the weak
338 enhancers was consistent with the lack of enrichment across all weak enhancers
339 defined solely on the basis of H3K4me1 signal ((Parker et al., 2013), single state
340 $\log_2FE=0.9$, $CI=-2.5$ to 2.0 , Table 1, Figure 1-figure supplement 1C). We also saw
341 differences in enrichment signal between open and closed strong enhancers,
342 with the most marked enrichment amongst open strong enhancers (22% of the
343 total, Figure 3B-C, Table 1). This effect was particularly obvious in the joint-
344 analysis (open strong enhancer joint $FE=4.1$, $CI=3.3$ to 4.8 vs. closed strong
345 enhancer joint $\log_2FE=2.4$, $CI=0.5$ to 3.3 , Figure 3C).

346

347 Hypomethylation and open chromatin are highly correlated, but the observed
348 difference in T2D enrichment between the weak enhancer states (particularly
349 between “lowly-methylated” and “open” which differ markedly with respect to
350 chromatin status) points to a primary role for open chromatin. To test this
351 further, we regenerated chromatin state maps using different subsets of the data
352 (ChIP-only, with optional addition of methylation and/or open chromatin
353 information, see Methods and Figure 3-figure supplement 1A-3B). These
354 analyses confirmed that the T2D GWAS enrichment signal was predominantly
355 driven by the distribution of islet open chromatin (Figure 3-figure supplement
356 1C).

357

358 We further evaluated the role of subclasses of DNA methylation regulatory
359 region with respect to T2D GWAS enrichment. We divided hypomethylated
360 (<60% methylated) sequence into enhancer-like LMRs (6.5% of all
361 hypomethylated sequence), promoter-like UMRs (7.5% of hypomethylated
362 sequence), as well as PMDs (61% of hypomethylated sequence). The remaining
363 25% of hypomethylated sequence did not fit any category. LMRs were
364 significantly ($CI>0$) enriched ($\log_2FE=3.2$, $CI=2.3$ to 3.9) for T2D association
365 signals consistent with their co-localisation with distal regulatory elements, and
366 displayed modestly increased enrichment compared to enhancer states derived

367 from CHIP-seq alone (Figure 3D, Figure 3-source data 1). In contrast, no
368 significant enrichment was found for human islet (promoter-like) UMRs
369 ($\log_2FE=1.4$, $CI=-0.6$ to 2.5) or PMDs ($\log_2FE=-0.8$, $CI=-1.7$ to -0.1). We also found
370 no evidence that recently-described regions of T2D-associated differential
371 methylation (dDMRs: derived from comparison of WGBS data from islets of
372 diabetic and non-diabetic individuals) were enriched for genome-wide T2D
373 association signals ($\log_2FE=-24.6$, $CI=-44.6$ to 3.7) (Figure 3D, Figure 3-source
374 data 1).

375

376 Finally, since the hypomethylation signal for T2D enrichment was concentrated
377 in LMRs (Figure 3D, Figure 3-source data 1), we reran a FGWAS joint-analysis
378 combining open chromatin peaks, LMRs and CHIP-only states using a nested
379 model (Figure 3E, Figure 3-figure supplement 1D-E, see Methods). This
380 confirmed that the improvement in enrichment was mainly driven by open
381 chromatin but showed that LMRs also contributed significantly and
382 independently to the enrichment (Figure 3E, Figure 3-source data 2).

383

384 FGWAS analysis for FG corroborated the observations from T2D analysis.
385 Despite reduced power of the FG GWAS data due to a lower number of
386 significantly associated FG GWAS loci, both single feature and joint-model
387 analyses of human islet epigenome data found significant enrichment in strong
388 enhancer states with the strongest enrichment in enhancers with open
389 chromatin and hypomethylation (Figure 3-figure supplement 2A-B and Table 1).
390 In addition, evaluation of the relative contributions of ATAC-seq open chromatin
391 and DNA methylation to FG GWAS enrichment across both single-feature (Figure
392 3-figure supplement 2C-D) and joint-model analysis (Figure 3-figure supplement
393 2E-F and Figure 3-source data 3) indicated that open chromatin was primarily
394 responsible for the enhanced enrichment.

395

396 Overall, these analyses demonstrate that the addition of open chromatin and
397 DNA methylation data to CHIP-seq marks enhances the resolution of regulatory
398 annotation for human islets. In particular, it defines subsets of weak and strong
399 enhancers that differ markedly with respect to the impact of genetic variation on

400 T2D risk. Although DNA accessibility and hypomethylation status are strongly
401 correlated and provide broadly similar enrichments, the effects of the former
402 predominate. In line with the dominance of open chromatin status for T2D GWAS
403 enrichment, we observed that T2D risk in relation to methylation status is
404 primarily invested in hypomethylated LMRs (i.e. enhancers) rather than UMRs,
405 dDMRs or PMDs.

406

407 **2.4 Augmented chromatin maps and open chromatin allelic imbalance** 408 **refine likely causal variants at *ADCY5*, *CDC123*, and *KLHDC5***

409

410 We next deployed the insights from the global FGWAS enrichment analyses to
411 define the molecular mechanisms at individual T2D susceptibility loci, refining
412 T2D causal variant localisation using the combination of genetic data (from fine-
413 mapping) and the genome-wide patterns of epigenomic enrichment.

414

415 Specifically, we applied FGWAS to the T2D DIAGRAM GWAS data (Scott et al.,
416 2017) under the joint model (Figure 3C) derived from the augmented chromatin
417 state maps. We divided the genome into 2327 segments (average size 5004 SNPs
418 or 1.2Mb) and identified 52 segments significantly associated with T2D genome-
419 wide (segmental FGWAS PPA ≥ 0.9 or single variant GWAS $P < 5 \times 10^{-8}$, see
420 Methods for details). These corresponded to 49 known T2D associated regions
421 representing that subset of the ~ 120 known T2D GWAS loci which passed those
422 significance/filtering criteria in this European-only dataset. We then calculated
423 reweighted PPAs for each variant within each segment and generated
424 reweighted 99% credible sets. (Of note, in line with traditional GWAS
425 nomenclature, locus names were defined based on proximity between the lead
426 variant and the closest gene and does not, of itself, indicate any causal role for
427 the gene in T2D susceptibility).

428

429 Consistent with the increased T2D GWAS enrichment of states including open
430 chromatin and DNA methylation information, we found that analyses using
431 enrichments from the augmented chromatin state model (combining ChIP-seq,
432 ATAC-seq and WGBS data) were associated with smaller 99% credible sets

433 (median of 17 SNPs) than those derived from FGWAS enrichment derived from
434 ChIP-seq data alone (median 23). In parallel, the PPA for the best variant per
435 locus increased (median 0.39 vs 0.31). Individual T2D GWAS locus results are
436 shown in Figure 4A-B. We also expanded the FGWAS PPA analysis to investigate
437 open chromatin and DNA methylation effects on fine-mapping and found that the
438 reduction in 99% credible set size and increase in maximum variant PPA was
439 driven predominantly by open chromatin (Figure 4-figure supplement 1, Figure
440 4-source data1). This demonstrates that the inclusion of open chromatin maps
441 helps to improve prioritisation of causal variants at many T2D GWAS loci.

442

443 A subset of T2D GWAS signals are known to influence T2D risk through a
444 primary effect on insulin secretion, whilst others act primarily through insulin
445 resistance. We used previous categorisations of T2D GWAS loci based on the
446 patterns of association with quantitative measurements of metabolic function
447 and anthropometry (Wood et al., 2017, Dimas et al., 2014), to define a set of
448 15/48 loci most clearly associated with deficient insulin secretion (and therefore
449 most likely to involve islet dysfunction). At 11 of these 15 loci, we found that islet
450 “open strong enhancer” states, and to a lesser extent “open weak enhancer” and
451 “closed strong enhancer”, captured more than 60% of the PPA (median 92%,
452 Figure 4C). Variants in these islet enhancer subclasses also captured at least 95%
453 of the PPA at 4 T2D GWAS loci that could not be classified according to
454 physiological association data but which have been previously implicated in
455 human islet genome or functional regulation based on islet eQTL (van de Bunt et
456 al., 2015) or mQTL (Olsson et al., 2014) data (Figure 4C, genes highlighted in
457 bold). In contrast, at 3/6 of the insulin resistance and all but 5 unclassified loci,
458 the PPA was mostly (>50%) attributable to other non-islet enhancer states
459 (across all insulin resistance and unclassified loci, DNA not overlapping islet
460 enhancers and defined as “Other” capture a median PPA of 64%). Thus, islet
461 regulatory annotations are particularly useful for fine-mapping T2D GWAS loci
462 that affect insulin secretion and beta-cell function.

463

464 To obtain additional evidence to support the localisation of causal variants, we
465 tested for allelic imbalance in ATAC-seq open chromatin data. We selected 54

466 variants within 33 T2D-associated GWAS segments for testing of allelic
467 imbalance on the basis of (a) a reweighted variant PPA $\geq 10\%$ and (b) overlap
468 with an enriched regulatory state within the FGWAS T2D joint-model (Figure 4D,
469 Figure 4-source data 2). Of these, 20 variants (at 16 loci) had sufficient numbers
470 of heterozygous samples (>2) and ATAC-Seq read depth (depth >9 and at least 5
471 reads for each allele). After correcting for mapping bias using WASP, we
472 observed the strongest evidence for allelic imbalance (FDR < 0.05) at 3 out of the
473 20 variants (rs11257655 near *CDC123* and *CAMK1D*, rs10842991 near *KLHDC5*
474 and rs11708067 at *ADCY5*) (Table 2). All three overlapped refined islet open
475 strong or open weak enhancer regions characterised by open chromatin and
476 hypomethylation.

477

478 Variant rs11257655 accounts for 95% of the reweighted PPA (compared to a
479 PPA of 20% from genetic data alone) at the *CDC123/CAMK1D* locus, overlaps an
480 “open strong enhancer” region (Figure 5A) and the risk allele correlates with
481 increased chromatin accessibility. The same variant is in high LD ($r^2=0.82$) with
482 the lead variant for a cis-eQTL for *CAMK1D* in islets (van de Bunt et al., 2015). In
483 experimental assays (Fogarty et al., 2014), the T2D-risk allele has been shown to
484 be associated with increased *CAMK1D* gene expression and enhanced binding of
485 the FOXA1 and FOXA2 transcription factors. These data all point to rs11257655
486 as the causal variant at this locus.

487

488 At *KLHDC5*, no clear causal variant emerged based on genetic fine-mapping data
489 alone as the credible set contained 23 variants in high mutual LD ($r^2>0.8$, top
490 variant PPA $<5\%$, Figure 5B). Of these, variants rs10771372 (genetic fine-
491 mapping PPA= 5%), rs10842992 (genetic fine mapping PPA=5%) and
492 rs10842991 (genetic fine-mapping PPA=3%) overlapped “open strong
493 enhancer” regions (Figure 5B), such that their reweighted PPAs rose to 21%
494 (rs10771372), 21% (rs10842992) and 13% (rs10842991), respectively. We
495 observed allelic imbalance only at rs10842991 with the T2D-risk C allele
496 showing greater chromatin accessibility (binomial $P=4.1\times 10^{-3}$, Table 2). This
497 variant further overlapped a predicted TFBS motif for PAX6 as determined by
498 the software tool FIMO (Grant et al., 2011): the T2D-risk allele was predicted to

499 enhance PAX6 transcription factor binding consistent with the allelic effects on
500 increasing chromatin accessibility (Figure 5-figure supplement 1A). This strong
501 enhancer region is almost exclusively found in islets, with strong enhancer
502 H3K27ac states overlapping rs10842991 in only two non-islet (heart and
503 smooth muscle) Epigenome Roadmap tissues (out of 99 tissues with 18-state
504 chromatin state information, Figure 5B)(Roadmap Epigenomics et al., 2015).
505 Islet eQTL data (Varshney et al., 2017) also links rs10842991 and close proxy
506 SNPs (including rs7960190) to islet transcription with the risk allele increasing
507 *KLHDC5* expression. These data prioritise rs10842991 as the likely causal
508 variant at the *KLHDC5* T2D GWAS locus, and indicate a likely molecular
509 mechanism involving modified PAX6 transcription factor binding and an impact
510 on *KLHDC5* expression and islet function.

511

512 The third example of allelic imbalance mapped to the *ADCY5* locus. Fine-mapping
513 based solely on genetic data could not prioritise a distinct causal variant due to
514 multiple variants in high LD (range for top 5 variants=12-26%, Figure 5C).
515 However, reweighting of variants based on epigenomic annotation clearly
516 prioritised variant rs11708067: this SNP overlapped an “open weak enhancer”
517 and captured most of the reweighted PPA (PPA=92%). Allelic imbalance analysis
518 also showed that the T2D-risk A allele was associated with decreased chromatin
519 accessibility (binomial $P=1.2 \times 10^{-6}$, Table 2). The same lead variant maps to an
520 islet cis-eQTL and methylation QTL (Figure 5C, Figure 5-figure supplement 1B)
521 at which the T2D-risk allele is associated with reduced *ADCY5* expression and
522 increased *ADCY5* gene body DNA methylation.

523

524 To further understand the role of the rs11708067 variant, we performed ATAC-
525 seq and Next Generation Capture-C, in the glucose-responsive human beta-cell
526 line EndoC- β H1 (n=3). We targeted the *ADCY5* promoter to define distal regions
527 interacting with the promoter, and confirmed physical contact with the
528 hypomethylated open chromatin enhancer region harbouring rs11708067
529 (Figure 5C, Figure 5-figure supplement 1C). To resolve the significance of the
530 interaction between the restriction fragment encompassing rs11708067 and the
531 *ADCY5* promoter, we used the programme peakC(de Wit and Geeven, 2017)

532 (<https://github.com/deWitLab/peakC>) to evaluate the interactions of 12
533 fragments covering the lead SNP rs11708067 and 15 SNPs in high LD ($r^2 > 0.8$)
534 across a region of 47kb. After adjusting for multiple testing using FDR correction,
535 only two fragments yielded a significant normalised read number over
536 background. This included the open-chromatin overlapping fragment containing
537 rs11708067 and another fragment harbouring rs2877716, rs6798189,
538 rs56371916 (Figure 5-figure supplement 1D). These SNPs fall into a region that
539 did not show evidence of open chromatin.

540

541 These findings support rs11708067 as the likely causal variant affecting islet
542 accessible chromatin (in line with another recent study (Roman et al., 2017)),
543 and link the open and hypomethylated enhancer element in which it sits to
544 regulation of *ADCY5* expression in islets.

545

546 **3. Discussion**

547

548 A key challenge in the quest to describe the molecular mechanisms through
549 which GWAS signals influence traits of interest, involves the identification of the
550 causal variants responsible and, given that most lie in non-coding sequence, the
551 characterisation of the regulatory elements which they perturb. This underpins
552 efforts to define the effector genes through which these variants operate and to
553 reconstruct the biological networks that are central to disease pathogenesis.

554

555 Genetic and physiological studies have highlighted the singular importance of
556 pancreatic islet dysfunction in type 2 diabetes, but epigenomic characterisation
557 of this tissue has been limited in large-scale community projects such as ENCODE
558 and GTex. The present study seeks to address this deficit by describing, in
559 unprecedented detail, genome-wide patterns of methylation and chromatin
560 accessibility in human islet material. We have combined these data with existing
561 islet epigenomic marks to generate a refined regulatory map which, based on the
562 evidence of improved enrichment for T2D association signals, offers more
563 granular annotation of functional impact.

564

565 Our data show that, for DNA methylation, the signal of T2D predisposition is
566 primarily associated with enhancer-like LMRs rather than other categories of
567 methylation elements including UMRs, dDMRs or PMDs. We highlight the strong
568 correlation between islet methylation status and chromatin accessibility but
569 demonstrate that open chromatin predominantly contributes to defining the
570 regulatory impact associated with genetic T2D risk. Finally, we demonstrate
571 how these enhanced epigenomic annotations, when analysed in concert with
572 genetic fine-mapping data and information from allelic imbalance in chromatin
573 accessibility allow us to home in on likely causal variants at T2D association
574 signals such as those near *ADCY5*, *CDC123* and *KLHDC5*.

575

576 While previous studies had explored the candidacy of selected variants at the
577 *CDC123* (Fogarty et al., 2014) and *ADCY5* (Olsson et al., 2014, Hodson et al., 2014,
578 van de Bunt et al., 2015) loci with respect to islet regulation and T2D
579 predisposition, our integrative analysis of T2D GWAS and epigenetic data has
580 enabled a detailed and comprehensive analysis that considers the regulatory
581 impact of all variants at these loci across multiple islet samples. Our analysis
582 implicates the rs11257655 and rs11708067 variants as the most likely causal
583 variants at the *CDC123* and *ADCY5* loci respectively and highlights their
584 relationship to islet enhancer activity. The findings at *ADCY5* are supported by a
585 recent paper that found allelic imbalance in H3K27 acetylation involving the
586 rs11708067 variant in a single human islet sample, and which observed that
587 deletion of the relevant enhancer element led to reduction in both *ADCY5* gene
588 expression and insulin secretion (Roman et al., 2017).

589

590 At the *KLHDC5* locus, local LD frustrated efforts to define the causal variant using
591 genetic data alone, but the integration of genetic and epigenetic data pinpointed
592 rs10842991 as the likely culprit based on its impact on chromatin accessibility in
593 an open enhancer region. Evidence that this variant co-localises with an islet cis-
594 eQTL signal points to *KLHDC5* as the likely downstream target (Varshney et al.,
595 2017). Overall, our integrative approach provides useful insights into the
596 functional mechanisms through which T2D GWAS signals operate. Our findings
597 mirror those from other studies, which have, in various ways, and for other

598 complex traits, combined diverse epigenomic annotations to explore the basis of
599 genetic risk (Wang et al., 2016).

600

601 The whole genome methylation data generated in the present study also allowed
602 us to evaluate the likely contribution of previously identified T2D-associated
603 dDMRs (Volkov et al., 2017) with respect to T2D predisposition. These dDMRs,
604 defined on the basis of observed differences in methylation between islets
605 recovered from diabetic and non-diabetic donors, cover a substantial part of the
606 genome, but we were able to show that only a small minority of these overlap
607 functional islet regulatory regions. As a consequence, dDMR regions as a whole
608 had no significant enrichment for T2D association signals. This suggests that
609 most of the dDMR signal involves stochastic effects and/or the secondary
610 consequences on methylation of the diabetic state. However, we cannot exclude
611 that some of the dDMR signals are causal contributors to the diabetic phenotype
612 either because they reflect environmental rather than genetic predisposition, or
613 because they accelerate further perturbation of islet dysfunction as diabetes
614 develops.

615

616 Although we provide highly detailed functional fine-mapping of T2D genetic
617 variants to uncover causal variants, the FGWAS approach applied in this study is
618 limited in its ability to determine the effect of multiple variants at individual loci.
619 Specifically, FGWAS relies on the assumption of a single causal variant within
620 each region, which may not necessarily be true for all loci. This assumption could
621 be violated where there are multiple independent signals at a given locus, or
622 where there are multiple (small effect size) variants on a single risk haplotype
623 which jointly impact the phenotype. Analysis methods that combine functional
624 fine-mapping with conditional analysis and consider LD and haplotype patterns
625 are likely to provide a more complete overview of the causal interactions at T2D
626 GWAS loci.

627

628 In addition, while the present study characterises islet epigenome status and
629 variability in chromatin accessibility in substantially larger numbers of islet
630 samples than those previously reported (Gaulton et al., 2015b, Parker et al.,

631 2013, Pasquali et al., 2014, Varshney et al., 2017), the number of islet
632 preparations for which these data were available was still limited. As a result,
633 our power to detect allelic imbalance in chromatin accessibility was restricted to
634 sites with common variants and relatively large effects. We anticipate that
635 expansion of these sample numbers will extend our capacity to detect such allelic
636 imbalance, and offer more granular insights into the relationships between
637 genetic variation and methylation status. A further limitation is that the genomic
638 data we analysed was generated only from islet samples from non-diabetic
639 donors. Whilst causal inference is possible through the integration of basal
640 epigenomic annotations with genetic data, addition of epigenomic data from
641 islets recovered from diabetic donors has the potential to add a further
642 dimension to such analyses, and to unravel what are likely to be complex causal
643 relationships between genetic variants, epigenomic phenotypes and disease
644 states (Gutierrez-Arcelus et al., 2013). Finally, future work should also focus on
645 experimental validation of likely causal variants and mechanisms e.g. differential
646 binding of the TF PAX6 could be tested at the *KLHDC5* rs10842991 variant
647 through electrophoretic mobility shift assays. Our ongoing research efforts are
648 now concentrated on improving the fine-mapping analysis and expanding these
649 genomic enrichment analyses in larger numbers of human islet samples from
650 healthy and diabetic islets. By coupling the integration of these data with
651 empirical functional studies, we expect to provide an increasingly complete
652 description of the causal interactions between DNA methylation, chromatin
653 state, RNA expression and T2D susceptibility.

654

655 **4. Methods**

656

657 **4.1 Human Pancreatic islet samples**

658

659 **4.1.2 WGBS and 450k array human pancreatic islet sample collection**

660 Human islets were retrieved from deceased Caucasian non-diabetic donors from
661 the Oxford DRWF Human Islet Isolation Facility (n=34) and at the Alberta
662 Diabetes Institute in Edmonton in Canada (n=10). For the analysis only samples
663 with a purity >70% were used as determined by dithizone labeling. The Human

664 Research Ethics Board at the University of Alberta (Pro00001754), the
665 University of Oxford's Oxford Tropical Research Ethics Committee (OxTREC
666 Reference: 2-15), or the Oxfordshire Regional Ethics Committee B (REC
667 reference: 09/H0605/2) approved the studies. All organ donors provided
668 informed consent for use of pancreatic tissue in research.

669

670 For all WGBS (n=10) and a subset of 450k array samples (n=18) human
671 pancreatic islet DNA was extracted from 100,000-150,000 islet cells using Trizol-
672 (Ambion, UK or Sigma Aldrich, Canada) as described previously (van de Bunt et
673 al., 2015). For the remaining 23 samples islet DNA was extracted using the
674 ReliaPrep gDNA Tissue Miniprep system (Promega). Extracted DNA was stored
675 at -80°C before further use.

676

677 **4.1.2 ATAC-seq human pancreatic islet sample collection**

678 Human pancreatic islets preparations (n=18) were retrieved from 17 deceased
679 non-diabetic donors of European descent from the Oxford DRWF Human Islet
680 Isolation Facility and stored for 1-3 days in CMRL or UW media. The latter were
681 reactivated in CMRL for 1h before processing them further. Approximately
682 50,000 islet cells per sample were hand-picked and immediately processed for
683 ATAC-seq as described previously (Buenrostro et al., 2013), however, an
684 additional round of purification was performed using Agencourt AMPure XP
685 magnetic beads (Beckman Coulter).

686

687

688 **4.2. WGBS data generation**

689

690 **4.2.1 Bisulphite conversion**

691 400ng of DNA per human islet samples (n=10) were sent as part of a
692 collaborative effort to the Blizard Institute, Queen Mary University, London, UK
693 and bisulphite- converted using the Ovation Ultralow Methyl-Seq DR Multiplex
694 System 1-8 (Nugen) and purified using Agencourt AMPure beads (Beckman
695 Coulter) as described previously (Lowe et al., 2013).

696

697 **4.2.2 Library generation and processing of reads**

698 The libraries were sequenced by members of the High-Throughput Genomics
699 group at the Wellcome Trust Centre for Human Genetics, University of Oxford,
700 Oxford, UK. Samples were sequenced as multiplex libraries across 3 HiSeq2000
701 lanes with 100bp paired-end read length (including a PhIX spike-in of 5%) to
702 obtain high-coverage read data. The obtained reads were trimmed using a
703 customized python3 script (10bp at the start and 15bp at the end) and aligned to
704 hg19 using the software Bismark (settings: L,0,-0.6, version 0.12.5,
705 RRID:SCR_005604)(Krueger and Andrews, 2011). Specifically, paired-end
706 alignment of trimmed reads was performed and unmapped reads from read 1
707 were realigned using Bismark and merged with the paired-end alignment using
708 samtools (Li et al., 2009) (version 0.1.19, RRID:SCR_002105) in order to increase
709 mapping efficiency. Coverage for the merged paired-end and realigned HiSeq
710 read alignments was estimated for the human mappable genome (NCBI hg19 2.8
711 billion base pairs excluding gaps and unmappable and blacklisted regions
712 according to UCSC and Encode(EncodeProjectConsortium, 2012)) using bedtools
713 (version v2.21.0) (Quinlan, 2014).

714

715 **4.2.3 WGBS DNA methylation quantification and prediction of** 716 **hypomethylated regulatory regions**

717 CpG methylation levels were determined for each sample by calculating the ratio
718 of unmodified C (methylated) and bisulphite converted T (unmethylated) alleles
719 using BiFAST (first described here (Lowe et al., 2013)). High-pass pooled WGBS
720 data was generated by adding methylated and unmethylated read counts across
721 individual low-pass samples to then estimate the average beta methylation
722 levels.

723

724 Regulatory regions were identified using the R package methylseek
725 (RRID:SCR_006513) (Burger et al., 2013). After removing PMDs, which represent
726 highly heterogenous methylation states determined by DNA sequence features
727 (Gaidatzis et al., 2014), LMRs (<30 CpGs) and UMRs (>30 CpGs) were predicted
728 in hypomethylated regions (<50%) at an FDR of 0.05. The methylation level and

729 FDR parameter was inferred from the data as suggested by the methylseek
730 workflow (Burger et al., 2013).

731

732 **4.3 450k DNA methylation array data generation**

733 In total, 41 samples were processed for the Illumina Infinium
734 HumanMethylation450 BeadChip (Illumina, San Diego, CA). Of these 18 samples
735 were bisulphite-converted and processed as part of a collaboration at the UCL
736 Cancer Institute, University College London, London, UK while the remaining 23
737 samples were processed in OCDEM, University of Oxford, Oxford, UK. The DNA
738 was bisulphite converted using the EZ DNA Methylation™ Kit (© Zymogen
739 Research Corp, Irvine, CA) and hybridised to the Illumina 450k array and
740 scanned with iScan (Illumina) according to the manufacturer's protocol.

741

742 The resulting data was analysed using the Package minfi (RRID:SCR_012830)
743 (Aryee et al., 2014) and custom R scripts ((RCoreTeam), R version 3.0.2,
744 RRID:SCR_001905). Specifically, CpG sites with a detection P-value >0.01 were
745 removed from the analysis and samples with >5% of CpG sites failing this
746 threshold (n=9) were also removed from the analysis.

747

748 Following separate quantile normalisation of signal intensities derived from
749 methylated and unmethylated Type I probes and Type II probes, methylation
750 levels (β) were estimated, based on the intensities of the methylated (M) and
751 unmethylated (U) signal in the following way: $\beta = M/(M+U+100)$. To correct for
752 batch effects the ComBat function implemented in the sva (Johnson et al., 2007,
753 Leek et al.) package was used (Figure 1-figure supplement 2).

754

755 **4.4 ATAC-seq data generation**

756

757 **4.4.1 Sequencing of ATAC-seq reads**

758 ATAC-seq libraries were sequenced at the High-Throughput Genomics group
759 which is part of the Wellcome Trust Centre for Human Genetics, University of
760 Oxford, Oxford, UK. Samples were sequenced as 4-6plex libraries across 1-3
761 HiSeq2500 lanes with 50bp paired-end read length.

762

763 **4.4.2 Processing of ATAC-seq reads**

764 Raw FASTQ reads were processed with an in-house pipeline (first described in
765 (Hay et al., 2016) and on the website
766 <http://userweb.molbiol.ox.ac.uk/public/telenius/PipeSite.html>). Specifically,
767 library and sequencing quality was checked with FASTQC (RRID:SCR_014583)
768 (<http://www.bioinformatics.babraham.ac.uk/projects/fastqc>) and reads were
769 mapped to the human genome (hg19) via bowtie (Langmead et al., 2009)
770 (version 1.1.0, RRID:SCR_005476) with default settings but -m 2, and maxins
771 2000 which allows mapping of reads with a maximum number of 2 alignments
772 and a maximum insert size of 2000bp. For reads that could not be aligned the
773 first time, adapters were removed with Trim Galore at the 3 prime end
774 (RRID:SCR_011847, settings -length 10, -qualFilter 20,
775 http://www.bioinformatics.babraham.ac.uk/projects/trim_galore/) to enhance
776 the chance of mapping. The resulting trimmed reads were then mapped again
777 with bowtie. Any remaining unmapped and trimmed reads were processed with
778 FLASH (Magoc and Salzberg, 2011) (version 1.2.8, RRID:SCR_005531, settings -m
779 9 -x 0.125) which combines overlapping read pairs and reconstructs read pairs
780 without overlap. These are then realigned a third time using bowtie. PCR
781 duplicates are then removed from the mapped bam files using samtools rmdup
782 function (Li et al., 2009). Additionally, all reads overlapping any of the
783 "unmappable" UCSC Duke blacklisted hg19 regions (EncodeProjectConsortium,
784 2012) are also removed from the final bam file.

785 Open chromatin peaks were called through the aforementioned in-house
786 pipeline by applying sample-specific read depth and width parameters, which
787 were chosen based on the signal to noise ratio of a given sample.

788

789 **4.5 ChIP-seq data and identification of chromatin states**

790

791 **4.5.1 Processing of available ChIP-seq data**

792 Human islet ChIP-seq histone mark and TFBS data were obtained from various
793 sources: H3K4me1, *CTCF* and H3K27ac (Pasquali et al., 2014), H3K36me3 and
794 H3K4me3 (Moran et al., 2012) and H3K27me3 (Roadmap Epigenomics et al.,

795 2015). Available raw fastq files were aligned to hg19 using bowtie1 (version
796 1.1.1) with modified default settings (-m 1 which removes reads with more than
797 1 valid alignment and -n 1 which defines the maximum number of mismatches in
798 seed) and PCR duplicates were removed from the aligned bam files with Picard
799 tools (RRID:SCR_006525, v1.119, <http://broadinstitute.github.io/picard/>). The
800 resulting reads were converted into bed format using the bedtools bamToBed
801 function (Quinlan, 2014) (RRID:SCR_006646, version v2.21.0) and extended by
802 200bp towards the 3' end to account for fragment size.

803

804 **4.5.2 Identification of chromatin states using chromHMM**

805

806 Binarised 200bp density maps from the bed files of the 6 ChIP-seq marks were
807 created using a Poisson distribution implemented in the BinaryBed function of
808 the ChromHMM software as described in (Ernst and Kellis, 2012, Ernst et al.,
809 2011). From these epigenomic density maps, 11 ChIP-only chromatin states
810 were derived using a multivariate Hidden Markov Model implemented in the
811 Learnmodel function (standard settings, h19 genome) of the software
812 ChromHMM (Ernst and Kellis, 2012).

813

814 To generate additional sets of chromatin states based on ChIP-seq, ATAC-seq and
815 DNA methylation data, ATAC-seq open chromatin and DNA methylation status
816 were binarised. Specifically, ATAC-seq peaks (presence/absence) and whole-
817 genome CpG methylation status (hypermethylation/hypomethylation based on a
818 threshold of 60% methylation) were binarised across 200bp windows of the
819 genome.

820

821 These binarised 200bp ChIP-seq, ATAC-seq and DNA methylation maps were
822 combined and used to generate 3 sets of chromatin states derived from ChIP and
823 DNA methylation data (ChIP+Meth), ChIP and ATAC-seq data (ChIP+ATAC) or
824 ChIP, ATAC-seq and DNA methylation data (ChIP+ATAC+Meth) using the
825 Learnmodel ChromHMM function (Figure 3A and Figure 3-figure supplement
826 1A-B) . As suggested by (Ernst et al., 2011), after evaluating models with up to 20

827 chromatin states, a 15 state model was chosen based on the resolution provided
828 by identified states

829

830 **4.6 *ADCY5* Capture C analysis and ATAC-seq in EndoC-βH1**

831 Next-generation Capture-C was performed in order to map physical chromatin
832 interactions with the *ADCY5* promoter in EndoC-βH1 (RRID:CVCL_L909) cell
833 lines (n = 3) (see protocol in Methods in (Davies et al., 2016)).

834 In brief, chromatin conformation capture (3C) libraries were generated by
835 formaldehyde fixation prior to DpnII restriction enzyme digestion and
836 subsequent DNA ligation. Following cross-link reversal, DNA extraction and
837 sonication, sequencing adapters were added to sonicated fragments (~200bp).
838 Library fragments were subjected to a double capture through hybridisation
839 with a biotinylated oligonucleotide probes encompassing the *ADCY5* promoter
840 and enriched using streptavidin bead pulldown. PCR amplified fragments were
841 then sequenced through paired-end sequencing (Illumina Next-Seq). An *in silico*
842 restriction enzyme digestion was performed on the set of reconstructed
843 fragments (from paired-end sequenced reads) using the DpnII2E.pl script
844 (Davies, 2015)(<https://github.com/Hughes-Genome-Group/captureC>).

845 Uncaptured reads and PCR duplicates were removed prior to mapping to the
846 human genome (hg19) with Bowtie (Langmead et al., 2009)(v 1.1.0). Removal of
847 PCR duplicates and classification of fragments as 'capture' (i.e. including the
848 *ADCY5* promoter) or 'reporter' (outside the capture fragment on exclusion
849 region) was performed with the CCanalyser2.pl wrapper (Davies,
850 2015)(<https://github.com/Hughes-Genome-Group/captureC>). Unique mapped
851 interactions were normalized to the total number of *cis* interactions (i.e. same
852 chromosome) per 100,000 interactions. Significant chromatin interactions were
853 determined from a rank-sum test implemented in the program peakC (de Wit
854 and Geeven, 2017)(<https://github.com/deWitLab/peakC>). Specifically, we
855 evaluated interactions involving all SNPs in high LD ($r^2 > 0.8$) with the lead
856 rs11708067. The lead variant (rs11708067) was in high LD with 15 SNPs
857 (mapping to 12 DpnII fragments) that spanned a region of 47kb. We applied the
858 Benjamini-Hochberg correction to control the false discovery rate for the set of

859 p-values corresponding to each restriction fragment within the 47kb region at
860 the ADCY5 locus.

861

862 In addition, ATAC-seq was performed in 50,000 cells of EndoC- β H1 cell lines
863 (n=3) and the data was analysed in the same way as described above for human
864 islet samples.

865

866 Endo- β H1 cells were obtained from Endocells and have been previously
867 authenticated (Ravassard et al., 2011). In addition, the cell line was tested and
868 found negative for mycoplasma contamination.

869

870 **4.7 Overlaying generated epigenomic datasets generated here with other** 871 **genomic regulatory regions**

872

873 CpG sites and/or hypomethylated regulatory regions identified from the WGBS
874 and/or 450k array data were overlapped with existing islet chromatin state
875 maps (Parker et al., 2013), islet transcription factor binding sites (*FOXA2*, *MAFB*,
876 *NKX2.2*, *NKX6.1*, *PDX1*), T2D-associated islet dDMRs (Dayeh et al., 2014) and
877 eQTLs (van de Bunt et al., 2015). Similarly, ATAC-seq open chromatin peaks
878 generated here were overlapped with publicly available ATAC-seq peaks
879 (Varshney et al., 2017).

880

881 In addition, we also obtained the 850k array manifest file to determine overlap
882 of 850k array CpG sites with GWAS credible set regions

883 ([https://support.illumina.com/downloads/infinium-methylationepic-v1-0-](https://support.illumina.com/downloads/infinium-methylationepic-v1-0-product-files.html)
884 [product-files.html](https://support.illumina.com/downloads/infinium-methylationepic-v1-0-product-files.html)).

885

886 **4.8 Genetic datasets used in this study**

887 Credible sets from the DIAGRAM (Scott et al., 2017)(involving 26.7k cases and
888 132.5k controls of predominantly European origin, imputed to the 1000G March
889 2012 reference panel) and ENGAGE (Horikoshi et al., 2015)(including 46.7k
890 individuals, imputed to the 1000G March 2012 reference panel) consortium

891 were used to compare the ability of the 450k, 850k and WGBS methylation array
892 to interrogate T2D and FG GWAS regions.

893

894 The DIAGRAM and ENGAGE GWAS SNP summary level data was used for the
895 FGWAS analysis to determine enrichment of regulatory annotations in T2D and
896 FG GWAS signal.

897

898 Furthermore, data from (Wood et al., 2017) and (Dimas et al., 2014) were used
899 to categories T2D GWAS loci into physiological groups of insulin secretion,
900 insulin resistance or unclassified loci.

901

902 **4.9 Statistical and computational analysis**

903

904 **4.9.1 Enrichment analysis of identified regulatory annotations in other** 905 **genomic annotations**

906

907 Enrichment of hypomethylated regulatory regions (LMRs and UMRs, result
908 section 2.2.) and ATAC-seq open chromatin peaks (result section 2.3) in the
909 aforementioned genomic annotations (method section 4.6) was determined
910 through 100,000 random permutations. P-values and fold enrichment was
911 determined by comparing the true overlap results to the permuted overlap
912 results. The resulting P-values were multiple testing corrected using Bonferroni
913 correction (an adjusted P-value < 0.05 was considered significant).

914

915 **4.9.2 FGWAS enrichment analysis**

916 FGWAS (Pickrell, 2014) (version 0.3.6) applied a hierarchical model that
917 determined shared properties of loci affecting a trait. The FGWAS model used
918 SNP-based GWAS summary level data and divided the genome into windows
919 (setting "k"=5000 which represents the number of SNPs per window), which are
920 larger than the expected LD patterns in the population. The model assumed that
921 each window either contained a single SNP that affected the trait or that there
922 was no SNP in the window that influenced the trait. The model estimated the
923 prior probability of a window to contain an association and the conditional prior

924 probability that a SNP within the window was the causal variant. These prior
925 probabilities were variable, dependent on regional annotations and estimated
926 based on enrichment patterns of annotations across the genome using a Bayes
927 approach.

928

929

930

931 **4.9.2.1 FGWAS Single state analysis**

932 FGWAS was used with standard settings to determine enrichment of individual
933 islet chromatin states, LMRs, UMRs, PMDS and ATAC-seq open chromatin peaks,
934 CDS and CONS sequence in DIAGRAM (setting "cc" was applied for use with T2D-
935 case-control GWAS data) and ENGAGE GWAS SNP summary level data.

936

937 For each individual annotation, the model provided maximum likelihood
938 enrichment parameters and annotations were considered as significantly
939 enriched if the parameter estimate and 95% CI was above zero.

940

941 **4.9.2.2 FGWAS Joint model analysis**

942 To determine the maximum likelihood model the following approach suggested
943 by (Pickrell, 2014) was used for each set of chromatin states (ChIP-only,
944 ChIP+ATAC, ChIP+Meth and ChIP+ATAC+Meth), separately. In addition, CDS and
945 CONS sequenced were used as well for each set of chromatin states in the joint
946 analysis. Firstly, a model was fitted for each annotation individually to identify
947 all annotations that were significantly enriched with the trait. Secondly, the
948 annotation with the highest increase (and enrichment) in the maximum log-
949 likelihood was added to the model and the analysis was repeated with the
950 additional annotation. Thirdly, annotations were added as long as they increase
951 the maximum log-likelihood of the newly tested model. Fourthly, a 10-fold cross-
952 validation approach was used after determining a penalty parameter based on
953 the maximum likelihood of a penalised log-likelihood function to avoid
954 overfitting. Fifthly, each annotation was dropped from the model and the
955 maximum cross-validation likelihood was evaluated. If a reduced model has a
956 higher cross-validation maximum likelihood, additional annotations are dropped

957 until the model cannot be further improved. This model was described as the
958 best fitted model and used for the remaining analysis. The maximum likelihood
959 enrichment parameters and 95% CI for each annotation of the best model were
960 reported (independent of significance).

961

962 **4.9.2.3 Comparing FGWAS enrichment parameter across chromatin states**

963 Initially, similar enhancer chromatin states derived from the 4 different
964 ChromHMM analyses (ChIP-only, ChIP+ATAC, ChIP+Meth, ChIP+ATAC+Meth)
965 were compared. Similarity was determined based on shared histone chromatin
966 marks according to the chromHMM emission parameters. Further comparisons
967 between the ChIP-only and ChIP+ATAC+Meth model were performed based on
968 the reweighted FGWAS maximum variant PPA and the number of reweighted
969 99% credible set variants per T2D locus (for details regarding FGWAS PPA see
970 next section).

971

972 However, considering that the chromatin states were derived from distinct sets
973 of annotations across different analyses of ChromHMM, a direct comparison was
974 not fully possible. Hence, a nested model approach was used to further dissect
975 the contribution of open chromatin and DNA methylation to the enrichment.
976 Specifically, an FGWAS analysis was performed that combined the ChIP-only
977 chromHMM states with raw LMRs (representing DNA methylation) and ATAC-
978 seq peaks (representing open chromatin). After determining the best maximum-
979 likelihood cross-validation model (combining ChIP-only, ATAC-seq and LMR
980 states) a nested model and log-likelihood ratio test were used to determine the
981 contribution of each annotation to the model (Figure 3-figure supplement 1D).

982

983 **4.9.3 Reweighting of variant PPA and testing of allelic imbalance**

984 The enrichment priors derived from the FGWAS maximum likelihood model
985 were used as a basis for evaluating both the significance and functional impact of
986 associated variants in GWAS regions; allowing variants that map into
987 annotations that show global enrichment to be afforded extra weight.

988

989

990 Specifically, variants at significant GWAS regions with a high FGWAS PPA (PPA
991 $\geq 10\%$) and overlapping open enhancer states were prioritised for further
992 follow-up. Genome-wide significance of loci was determined based on P-values
993 ($P < 5 \times 10^{-8}$) or a regional FGWAS PPA $\geq 90\%$ (representing the sum of the PPAs
994 of all SNPs in a given region). The latter threshold is based on a recommendation
995 from (Pickrell, 2014) who observed that a regional PPA of 90% or above can be
996 used to identify sub-threshold GWAS loci.

997

998 Of the prioritised variants, only variants with at least 2 heterozygous samples
999 and ATAC_Seq read depth of at least 9 reads (minimum 5 reads for each allele)
1000 were tested for allelic imbalance.

1001

1002 To avoid read-mapping and reference allele bias the software WASP (van de
1003 Geijn et al., 2015)(Version 0.2261) was used to remove reads associated with
1004 mapping bias. In short, reads of the unfiltered bam file that overlapped the
1005 variant of interest were identified. For each read overlapping an SNP, the
1006 genotype of that SNP was changed to the alternative allele and the read was
1007 remapped using bwa (Li and Durbin, 2009) (version 0.5.8c). Any read that failed
1008 to realign in the same position in the genome was discarded. Ultimately, PCR
1009 duplicates were filtered using the WASP "rmdup_pe.py" script, which removed
1010 duplicated reads randomly (independent of the mapping score) to avoid any
1011 bias.

1012

1013 Allelic imbalance was determined using a binomial test as implemented in R.

1014

1015 **4.9.4 Identification of TFBS at SNPs that display allelic imbalance**

1016

1017 The tool "Fimo"(Grant et al., 2011) implemented in the "meme" software
1018 package (RRID:SCR_001783) was applied to identify TF motifs that significantly
1019 (FDR < 0.05) matched the sequence overlapping a SNP variant showing allelic
1020 imbalance (20bp up and downstream).

1021

1022 **4.9.5 Overlap of regulatory regions**

1023 Overlap between genomic regulatory regions was performed using bedtools
1024 intersectBed function (Quinlan, 2014) (version 2.21.0). Summary statistics
1025 across 200bp windows were determined using bedtools mapBed function.
1026 Random permutations of regulatory regions were performed by applying the
1027 bedtools shuffleBed function.

1028

1029 **4.9.6 Statistical analysis**

1030 All statistical analysis (unless otherwise stated) was performed using R (version
1031 3.0.2) including Spearman's correlation analysis to compare the 450k and WGBS
1032 array, the KS-test to compare 450k and WGBS DNA methylation distributions,
1033 the binomial test to evaluate allelic imbalance and principal component analysis
1034 to identify batch effects in the 450k data. Significance is defined as $P < 0.05$ unless
1035 otherwise stated.

1036

1037 **4.9.7 Visualisation and figure generation**

1038 All figures unless otherwise stated were generated using R (version 3.0.2)
1039 and/or ggplot2(Wickham, 2009). Figure 1E was generated using locuszoom
1040 (Pruim et al., 2010). Chromatin state ChIP-seq enrichment maps (Figure 3A,
1041 Figure 3-figure supplement 1A-B) were generated using chromHMM (Ernst and
1042 Kellis, 2012). The genome-browser views (Figure 5) were generated using the
1043 UCSC genome browser tool (Kent et al., 2002).

1044

1045 **5. Acknowledgements**

1046 We thank the High-Throughput Genomics Group at the Wellcome Trust Centre
1047 for Human Genetics (funded by Wellcome Trust grant reference 090532) for the
1048 generation of the Sequencing data.

1049 MT was supported by a Wellcome Trust Doctoral Studentship. MvdB was
1050 supported by a Novo Nordisk postdoctoral fellowship run in partnership with
1051 the University of Oxford. JMT is supported by Wellcome Trust Strategic Award.
1052 VN is funded by the European Union Horizon 2020 Programme (T2DSYSTEMS).
1053 SB was supported by a Royal Society Wolfson Research Merit Award
1054 (WM100023). ALG is a Wellcome Trust Senior Fellow in Basic Biomedical
1055 Science (095101/Z/10/Z and 200837/Z/16/Z) and MIM is a Wellcome Trust

1056 Senior Investigator. The research was supported by the National Institute for
1057 Health Research (NIHR) Oxford Biomedical Research Centre (BRC). This work
1058 was also supported by EU (HEALTH-F4-2007-201413), Wellcome Trust
1059 (090367, 090532, 106130, 098381 and 099673/Z/12/Z) and NIH (U01-
1060 DK105535, U01-DK085545, R01-DK098032 and R01-MH090941) grants. The
1061 views expressed are those of the author(s) and not necessarily those of the NHS,
1062 the NIHR or the Department of Health.

1063 **6. Competing interests**

1064 The authors do not have any competing interest.

1065

1066 **7. Main table information and associated titles/legends.**

Chromatin States	Total number of states	T2D log2FE (CI)	FG log2FE (CI)
1. Active Promoter	20k	1.6 (-0.8 to 2.7)	2.7 (0 to 4.1)
2. Weak Promoter	33k	1.7 (-4.8 to 2.9)	2.7 (-0.1 to 4.2)
3. Transcriptional Elongation	71k	-0.4 (-20 to 1.1)	-26.1 (-46.1 to 1)
4. Low Methylation	73k	-1.5 (-3.1 to -0.6)	-1.7 (-4.2 to -0.3)
5. Closed Weak Enhancer	206k	1.2 (-0.1 to 2)	1.7 (0 to 2.9)
6. Lowly-methylated Weak Enhancer	78k	-0.5 (-20 to 1.6)	-26.7 (-46.7 to 1.6)
7. Open Weak Enhancer	38k	3.4 (2.5 to 4.2)	3.1 (-0.6 to 4.6)
8. Closed Strong Enhancer	110k	2.7 (1.8 to 3.4)	3.3 (2 to 4.4)
9. Open Strong Enhancer	32k	3.8 (3.1 to 4.5)	4.3 (2.8 to 5.5)
10. Genic Enhancer	39k	2.5 (1.3 to 3.4)	2.9 (0.8 to 4.3)
11. Accessible chromatin	14k	-25.2 (-45.2 to 2.5)	-28.4 (-48.4 to 3.7)
12. Insulator	31k	0.9 (-20 to 2.6)	-0.6 (-20 to 3.6)
13. Heterochromatin	216k	2.3 (-20 to 3.9)	1.8 (-1.5 to 4)
14. Polycomb Repressed	71k	-25.5 (-45.5 to 0.9)	-33.2 (-53.2 to 1.5)
15. Quiescent State	1.7k	-1 (-2.2 to -0.1)	-28.6 (-48.6 to -0.6)
CDS	NA	2.6 (1.2 to 3.5)	2.7 (-0.2 to 4.3)
CONS	NA	2.1 (1.1 to 2.9)	1.9 (0.2 to 3.2)
Parker Weak Enhancer	119k	0.9 (-2.5 to 2.0)	-2.0 (-20.0 to 2.4)
Parker Strong Enhancer (all)	123k	2.7 (2.0 to 3.3)	3.1 (2.0 to 4.4)
Parker Strong Enhancer (open)	64k	3.1 (2.4 to 3.7)	3.6 (2.3 to 4.8)
Parker Strong Enhancer (closed)	59k	1.9 (0.8 to 2.7)	2.3 (0.5 to 3.5)

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TABLE 1. Single FGWAS annotation enrichment in T2D and FG GWAS data.

For each annotation (chromatin state and CDS) the total number of sites and the single state FGWAS log2 Fold Enrichment (log2FE) in T2D and FG is shown. 95% Confidence Intervals (CI) for log2FE are shown in brackets and significantly enriched states are highlighted in bold (CI>0).

Variant	Locus	DIAGRAM P-value	FGWAS T2D PPA	Allelic imbalance Allele Ratio (Allele #)	Allelic imbalance WASP P-value	Direction of effect (T2D)
rs11708067	ADCY5	8.8E-13	0.92	0.29 (38 A VS 94 G alleles)	1.2E-06	risk allele A closed
rs11257655	CDC123	4.0E-08	0.95	0.39 (278 C VS 435 T alleles)	4.5E-09	risk allele T open
rs10842991	KLHDC5	7.3E-07	0.13	0.64 (75 C VS 43 T alleles)	4.1E-03	risk C allele open

TABLE 2. T2D-associated variants with allelic imbalance in open chromatin.

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8. Legends and titles for main figures.

FIGURE 1. Comparison of human pancreatic islet WGBS and 450k

methylation data across the genome. A) Smooth Scatter plot shows Spearman's rho correlation between the 450k array (x-axis) and WGBS (y-axis) at overlapping sites. Darker colour indicates higher density of sites. B) Comparison of the 450k array (orange) and WGBS (yellow) methylation levels (x-axis) of all CpGs genome-wide assayed by either method (y-axis shows density). The P-value shown is derived using a Kolmogorov-Smirnov (KS) test. C) For each chromatin state from Parker et al 2013 the methylation levels of all CpG sites independent of overlap (diamond indicates the median) are shown as violin plots (left y-axis) and the CpG probe percentage per state for the 450k array (orange) and WGBS (yellow) are shown as bar-plot (right y-axis). The 450k probes represent the percentage of the total number of CpG sites which is determined by the number of WGBS CpG sites detected (WGBS=100%). D) Distribution of GWAS Posterior Probabilities (Type 2 Diabetes and Fasting Glucose) captured by CpG sites on the 450k array (orange), 850k array (green) and WGBS (yellow/black line). E) Locuszoom plot showing CpG density and credible set SNPs. SNPs are shown with P-values (dots, y-axis left), recombination rate (line, y-axis right) and chromosome positions (x-axis) while CpG and gene annotations are shown below. These annotations include CpGs identified from WGBS (yellow strips), 450k CpG probes (orange stripes), 850k CpG probes (green stripes) and gene overlap (*DGKB* label). The highlighted region in blue captures the 99% credible set region plus additional 1000bp on either side. At the very bottom the position on chromosome 7 is shown in Megabases (Mb).

FIGURE 2. Overlap of WGBS hypomethylation and ATAC-seq open

chromatin peaks with regulatory annotation . A) Methylation levels in percent (y-axis) and log₂ CpG density (x-axis) of UMR and LMR regulatory regions with the dashed line indicating the CpG-number (30 CpGs) that distinguishes LMRs and UMRs. B) Log₂ Fold Enrichment (log₂FE) of LMRs (green shape), UMRs (blue shape) in various islet annotations is shown. These annotations include islet chromatin states, islet relevant TFBS (FOXA2, MAFB, NKX2.2, NKX.61, PDX1), islet eQTLs, WGBS derived T2D-associated islet disease DMRs (dDMRs) and ATAC-seq open chromatin peaks. The dDMRs were derived from 6 T2D and 8 non-diabetic individuals by Volkov et al 2017 and dDMRs (orange shape) were also tested for enrichment in the aforementioned islet regulatory annotations. For all annotations, the empirically determined Bonferroni adjusted P-value is ≤0.00032 unless otherwise indicated by the

1116 shape: a dot corresponds to an Bonferroni adjusted P-value <0.00032 while the 3
1117 triangles indicates Bonferroni adjusted P-values > 0.00032: UMR enrichment
1118 adjusted P-value for weak enhancers=1; dDMR enrichment adjusted P-value for
1119 MAFB=0.006 and dDMR enrichment adjusted P-value for islet eQTLs=0.01.

1120

1121 **FIGURE 3. Integration of islet epigenetic data to refine chromatin**
1122 **regulatory states and enrichment of these states in T2D GWAS data.** A) 15
1123 chromatin states (y-axis) were derived from ChIP histone marks, DNA
1124 methylation and ATAC-seq open chromatin annotations (x-axis) using
1125 chromHMM. For each state the relevant marks characterising the state are
1126 shown. The colour is based on the chromHMM emission parameters and a darker
1127 colour indicates a higher frequency of a mark at a given state. Weak enhancers
1128 (marked by H3K4me1 alone, red) and strong enhancers (marked by H3K27ac
1129 and H3K4me1, green) were subdivided by the chromHMM analysis according to
1130 methylation and ATAC-seq status (highlighted in red and green box). The black
1131 bar at the x-axis highlights the most important marks for characterising
1132 enhancer subtypes. B-C) FGWAS Log₂ Fold Enrichment including 95% CI (log₂FE,
1133 x-axis) of all chromatin states (y-axis) in T2D GWAS regions is shown which
1134 demonstrate differential enrichment amongst enhancer subclasses in single-
1135 feature enrichment analysis. In addition, log₂FE of Coding Sequence (CDS) and
1136 Conserved Sequence (CONS) annotations are shown to include the effect of
1137 protein-coding and conserved regions. Significantly enriched annotations are
1138 shown in black while non-significant annotations are shown in grey. C) T2D
1139 FGWAS maximum likelihood model determined through cross-validation. Log₂FE
1140 and 95% CI (x-axis) of annotations included in the maximum likelihood model
1141 (y-axis) also demonstrate differential enrichment amongst enhancer subclasses.
1142 *Analysis for Genic Enhancers (state 10) did not converge and hence, only a
1143 point log₂FE estimate is provided. D) Single feature log₂FE including 95% CI (x-
1144 axis) results are shown highlighting the differences in T2D GWAS enrichment of
1145 various annotations. These include ATAC-seq open chromatin peaks (red),
1146 WGBS methylation regions (including enhancer-like LMRs, promoter-like UMRs
1147 and Partially Methylated Domains, blue), ChIP-seq chromatin states (orange) and
1148 CDS (green). E) Chi-square distribution (curved black line) with the indicated
1149 results of a maximum likelihood ratio test based on the maximum likelihood
1150 difference between a model including LMRs or ATAC-seq peaks compared to the
1151 ChIP-only model. The dashed red line indicates significance (P-value<0.05). For
1152 all FGWAS enrichment plots the axis has been truncated at -6 to facilitate
1153 visualisation and accurate values are provided in the supplementary tables.

1154

1155 **FIGURE 4. Evaluating Posterior Probabilities (PP) derived from the FGWAS**
1156 **maximum likelihood model at significant T2D GWAS loci.** (A) Per locus the
1157 difference in the number of 99% credible set variants between ChIP+ATAC+Meth
1158 and ChIP-only model is shown (positive values indicate a reduction in the
1159 number of 99% credible set variants in the ChIP_ATAC_Meth model). B) Per
1160 locus the difference in the maximum single variant PPA between the
1161 ChIP+ATAC+Meth and ChIP-only model is shown (positive values indicate an
1162 increase in the maximum single variant PPA in the ChIP+ATAC+Meth model). C)
1163 T2D GWAS loci were classified into insulin secretion (ISR), insulin resistance (IR)
1164 or unclassified loci based on genetic association with physiological traits derived

1165 from Dimas et al 2014 and Wood et al 2017. In addition, loci with known role in
1166 islet genomic regulation or function are highlighted in bold. These include loci
1167 with islet eQTLs (*ZMIZ1*, *CDC123*) and mQTLs (*WFS1*, *KCNJ11*). D) Identification
1168 of T2D GWAS loci and variants enriched for enhancer chromatin states using
1169 FGWAS PP. Per locus the highest PPA variant is shown (y-axis) and the number
1170 of variants with PPA >0.01 (x-axis). Loci with high PPA variants (min PPA >0.1,
1171 dashed horizontal line) that overlap one of the enhancer states (green) are
1172 highlighted and the high PPA variants (PPA>0.1) were tested for allelic
1173 imbalance in open chromatin.

1174

1175 **FIGURE 5. Epigenome Landscape of selected loci with allelic imbalance.** For
1176 each locus A) *CDC123*, B) *KLHDC5* and C) *ADCY5* the following information is
1177 shown: 3 ATAC-seq Endo β tracks (green, top), variant level information
1178 (depending on the region GWAS lead SNP red, credible set black, eQTL blue and
1179 high LD SNPs with $r^2 > 0.8$ black), WGBS methylation data (black, middle), 4
1180 human islet ATAC-seq tracks (green, middle), islet chromatin states (from this
1181 study as well as Parker et al 2013 and Pasquali et al 2014) and Encode
1182 chromatin states from 9 cell types (bottom). For *ADCY5* the Capture C results in
1183 the Endo β cell line are shown as well (middle blue). Abbreviation for cell types:
1184 B-lymphoblastoid cells (GM12878), embryonic stem cells (H1 ES), erythrocytic
1185 leukaemia cells (K562), hepatocellular carcinoma cells (HepG2), umbilical vein
1186 endothelial cells (HUVEC), mammary epithelial cells (HMEC), skeletal muscle
1187 myoblasts (HSMM), normal epidermal keratinocytes (NHEK) and normal lung
1188 fibroblasts (NHLF).

1189

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1191

1192 **9. Data accessibility and supplementary file information:**

1193 **9.1 Sequencing data:**

1194 ATAC-seq and WGBS sequencing data has been deposited at the EBI hosted
1195 European Genome-phenome Archive (EGA, <http://www.ebi.ac.uk/ega/>) and is
1196 accessible via the EGA accession number: EGAS00001002592.

1197

1198 **9.2 Supplementary figure information:**

1199

1200 Figure 1-figure supplement 1 is associated with primary figure 1 (uploaded on
1201 eLife submission website with label: "Figure 1-figure supplement 1")

1202

1203 **FIGURE 1-FIGURE SUPPLEMENT 1. Correlation of DNA methylation across**
1204 **WGBS and 450k sites and comparison of WGBS and 450k methylation**
1205 **levels across chromatin states** A-B) Spearman's rho correlation of DNA
1206 methylation across 10 individual (A) WGBS and (B) 10 selected (out of 32) 450k
1207 samples on the x-axis and y-axis. C) Islet chromatin state definitions based on
1208 ChIP-seq data reproduced from Parker et al 2013. TSS: Transcription Start Site
1209 D) The differences in the 450k and WGBS methylation level distribution
1210 measured as D statistic, which represents the difference in the cumulative
1211 distributions and is derived from the Kolmogorov-Smirnov test, are shown for
1212 each chromatin state separately.

1213

1214

1215 Figure 2-figure supplement 1 is associated with primary figure 2 (uploaded on
1216 eLife submission website with label: "Figure 2-figure supplement 1")

1217

1218 **FIGURE 2-FIGURE SUPPLEMENT 1. Identification and removal of Partially**
1219 **Methylated Domains (PMDs)** A-B) Density distribution of the alpha value (A)
1220 before and (B) after removing PMDs (green curve in (A)) on chromosome 22.
1221 Alpha values represent a summary statistic derived from DNA methylation of
1222 windows of 100 CpGs and represents an indication of the polarisation status of
1223 methylation values in the genome which is expected to contain either highly
1224 methylated or unmethylated regions. Distributions with $\alpha < 1$ indicate
1225 methylation levels that are bimodal with either 0 or 1 methylation. $\alpha = 1$
1226 corresponds to a uniform distribution of methylation; and distributions with
1227 $\alpha > 1$ tend to have primarily intermediate methylation levels. The red and
1228 green curve in (A) represent the non-PMD (red) and PMD regions (green) in the
1229 genome. C) Number of peaks (x-axis) and mapped and filtered reads (y-axis) per
1230 ATAC-seq islet preparation. The dashed line indicates the mean read number. D)
1231 \log_2 Fold Enrichment (\log_2 FE, x-axis) and associated $-\log_{10}$ Bonferroni adjusted
1232 P-values (y-axis) of LMRs (circle), UMRs (triangle) in various islet annotations
1233 (colours) is shown. These annotations include islet chromatin states, islet
1234 relevant TFBS (FOXA2, MAFB, NKX2.2, NKX.61, PDX1), islet eQTLs, WGBS
1235 derived T2D-associated islet disease DMRs (dDMRs) and ATAC-seq open
1236 chromatin peaks. dDMRs (square) were also tested for enrichment in the
1237 aforementioned islet regulatory annotations. The results cluster near $-\log_{10}$ P-
1238 value of 3.5 since most Bonferroni adjusted P-values were more extreme than
1239 0.00032.

1240

1241 Figure 3-figure supplement 1 is associated with primary figure 3 (uploaded on
1242 eLife submission website with label: "Figure 3-figure supplement 1")

1243

1244 **FIGURE 3-FIGURE SUPPLEMENT 1. Prediction of regulatory regions using**
1245 **WGBS data and testing these regions for enrichment in T2D GWAS regions.**

1246 A) Different combinations of epigenomic data (top) were combined to generate
1247 different sets of refined chromatin states (middle, 11 ChIP-only and 15
1248 ChIP+Meth, ChIP+ATAC and ChIP+ATAC-Meth states, see figure S3B and 3A-B for
1249 actual states) using chromHMM. These sets of chromatin states were then tested
1250 for enrichment in T2D-related GWAS traits using FGWAS to compare enrichment
1251 across states (bottom). B) ChromHMM (I) 11 ChIP-only and 15 state (II)
1252 ChIP+ATAC state and (III) ChIP+Meth models. C) Single feature log₂FE (x-axis)
1253 for different enhancer states (grey panels) defined from different combinations
1254 of epigenetic marks (y-axis) including ChIP+ATAC+Meth, ChIP+ATAC, ChIP+Meth
1255 and ChIP+only. The grey-dashed line indicates the enrichment value of CDS as
1256 reference. Enhancers are defined as follows: Strong enhancers are marked by
1257 both H3K4me1 and H3K27ac, weak Enhancers are defined by H3K4me1 only,
1258 gene enhancers are marked by H3K4me1 and H3K36me3, other enhancers are
1259 marked by H3K4me1, H3K4me3 and H3K27ac and are often referred to as TSS
1260 upstream regions (only included in the FGWAS T2D model for ChIP-only and
1261 ChIP+Meth chromatin states). D) Since chromatin states defined from a different
1262 set of epigenomic marks (ChIP-only, ChIP+Meth, ChIP+ATAC and
1263 ChIP+ATAC+Meth), as described in S3A-B, are not equivalent and the enrichment
1264 can not be easily compared across models, a nested model approach was applied.
1265 That is, ChIP-only chromatin states were generated and after evaluating the
1266 individual enrichment of each annotation (see Figure 3D), FGWAS maximum
1267 likelihood models were defined using ChIP-only, hypomethylated and/or ATAC-
1268 seq peak regulatory regions. The combination of all these annotations
1269 represented a nested linear model and the changes in maximum likelihood by
1270 adding/removing hypomethylated regulatory and ATAC-seq states could be
1271 statistically evaluated using a Loglikelihood Ratio Test (LRT) as shown in Figure
1272 3E. E) Maximum likelihood FGWAS nested model combining ChIP-only, ATAC-
1273 peaks and LMR states (y-axis) showing log₂FE enrichment (x-axis) which was
1274 used for the LRT in Figure 3E. For all FGWAS enrichment plots the axis has been
1275 truncated at -6 to facilitate visualisation and accurate values are provided in the
1276 supplementary tables.

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1279 Figure 3-figure supplement 2 is associated with primary figure 3 (uploaded on
1280 eLife submission website with label: "Figure 3-figure supplement 2")

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1282 **FIGURE 3-FIGURE SUPPLEMENT 2. Enrichment of refined islet regulatory**
1283 **states in FG GWAS data** A) FGWAS Log₂ Fold Enrichment including 95% CI
1284 (log₂FE, x-axis) of all chromatin states (y-axis) in FG GWAS regions. In addition,
1285 CDS is shown to also include the effect of protein-coding regions. Significantly
1286 enriched annotations are shown in black. B) FG FGWAS maximum likelihood
1287 model determined through cross-validation. log₂FE and 95% CI (x-axis) of
1288 annotations included in the maximum likelihood model (y-axis) are shown. C)

1289 Single feature \log_2FE (x-axis) for different enhancer states (grey panels) defined
1290 from different combinations of epigenetic marks (y-axis) including
1291 ChIP+ATAC+Meth, ChIP+ATAC, ChIP+Meth and ChIP-only. Enhancers are defined
1292 as follows: Strong enhancers are marked by both H3K4me1 and H3K27ac, weak
1293 Enhancers are defined by H3K4me1 only, gene enhancers are marked by
1294 H3K4me1 and H3K36me3, other enhancers are marked by H3K4me1, H3K4me3
1295 and H3K27ac and are often referred to as TSS upstream regions (only included in
1296 the FGWAS T2D model for ChIP-only and ChIP+Meth chromatin states). D) Single
1297 feature \log_2FE including 95% CI (x-axis) results of various annotations derived
1298 from ChIP-seq (ChIP-only), ATAC-seq, WGBS methylation status and CDS are
1299 shown. E) Maximum likelihood FGWAS nested model combining ChIP-only,
1300 ATAC-peaks and LMR states (y-axis) showing \log_2FE enrichment (x-axis) which
1301 was used for the LRT in Supplementary Figure S3F. F) Chi-square distribution
1302 (black curved line) with the indicated results of a maximum likelihood ratio test
1303 based on the maximum likelihood difference between a model including LMRs or
1304 ATAC-seq peaks compared to the ChIP-only model. The dashed line indicates
1305 significance (P -value <0.05). For all FGWAS enrichment plots the axis has been
1306 truncated at -6 to facilitate visualisation and accurate values are provided in the
1307 supplementary tables.

1308
1309 Figure 4-figure supplement 1 is associated with primary Figure 4 (uploaded on
1310 eLife submission website with label: "Figure 4-figure supplement 1")

1311

1312 **Figure 4-figure supplement 1. Evaluating annotation effect on Posterior**
1313 **Probabilities (PPA) derived from the FGWAS maximum likelihood model at**
1314 **significant T2D GWAS loci.** (A) Violin plot showing the distribution of 99%
1315 credible set variant size (y-axis, \log_{10} scale) of different annotation types used
1316 (x-axis, ChIP-only, ChIP+Meth, ChIP+ATAC, ChIP+ATAC+Meth, ATAC-only and
1317 LMR-only model). B) Violin plot showing the distribution in the maximum single
1318 variant PPA (y-axis) of different annotation types used (x-axis, ChIP-only,
1319 ChIP+Meth, ChIP+ATAC, ChIP+ATAC+Meth, ATAC-only and LMR-only model).
1320 Dots indicate mean value. C) Median 99% credible set variant size (x-axis) and
1321 median top variant PPA (y-axis) information for ChIP-only, ChIP+Meth,
1322 ChIP+ATAC, ChIP+ATAC+Meth, ATAC-only and LMR-only models.

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1325 Figure 5-figure supplement 1 is associated with primary Figure 6 (uploaded on
1326 eLife submission website with label: "Figure 5-figure supplement 1")

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1328 **FIGURE 5-FIGURE SUPPLEMENT 1.** A) Predicted *PAX6* Transcription factor
1329 binding motif likely affected by allelic imbalance of the variant rs10842991
1330 (highlighted in purple). B) The *ADCY5* rs11708067 risk A allele was associated
1331 with increased methylation levels (y-axis, while genotypes are shown on the x-
1332 axis). C) Chromatin Capture (Capture C) in the human beta-cell line Endo β H1
1333 showed interactions between the *ADCY5* promoter (peak) and the flanking
1334 regions of the promoter. The x-axis shows the position on the chromosome in Mb
1335 while the y-axis indicates mapped reads per fragment. D) Chromatin Capture
1336 (Capture C) in the human beta-cell line Endo β H1 focussed at the genomic region
1337 (~47kb) near the variant rs11708067 (highlighted) and variants in high LD

1338 (r2>0.8) with it (variants are depicted as black dots). Fragments containing
1339 rs11708067 (red) or other high LD variants (dark grey) are highlighted. The x-
1340 axis shows the position on the chromosome in bp while the y-axis indicates
1341 normalised mapped reads per fragment. The two fragments with P-values have a
1342 significant (FDR <0.05) number of normalised read counts over background: The
1343 fragment with the P-value on the left (in red) contains rs11708067 while the
1344 fragment with the P-value on the right harbours rs2877716, rs6798189,
1345 rs56371916.

1346
1347 Figure 1-figure supplement 2 is mentioned in the methods section and
1348 associated with primary Figure 1 (uploaded on eLife submission website with
1349 label: "Figure 1-figure supplement 2")

1350
1351 **FIGURE 1-FIGURE SUPPLEMENT 2.** A-B) PCA analysis of 450k DNA methylation
1352 data of 32 human islet samples coloured according to the location of origin and
1353 processing (A) before correction for Sample-location and (B) after correction for
1354 Sample-location using the ComBat function included in the sva package. The
1355 shape indicates sex. Sample location **EDM_OX**: samples obtained from the
1356 Alberta Diabetes Institute in Edmonton (Canada) and processed at the University
1357 of Oxford. **OX_OX**: samples obtained from Oxford DRWF Human Islet Isolation
1358 Facility and processed at the University of Oxford. **OX_UCL**: samples obtained
1359 from Oxford DRWF Human Islet Isolation Facility and processed at University
1360 College London.

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1363 **9.3 Supplementary table information (uploaded as source files):**

1364
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1366
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Figure 3-source data 1 is associated with primary Figure 3 (uploaded on eLife
submission website with label: "Figure 3- source data 1")

1368 **FIGURE 3-SOURCE DATA 1. Annotation enrichment in T2D GWAS data.** For
1369 each annotation the data source and the log₂ Fold Enrichment (log₂FE) in T2D is
1370 shown. 95% Confidence Intervals (CI) for log₂FE are shown in brackets and
1371 significantly enriched states are highlighted in bold (CI>0).

1372
1373

1374 Figure 3-source data 2 is associated with primary Figure 3 (uploaded on eLife
1375 submission website with label: "Figure 3-source data 2")

1376

1377 **FIGURE 3-SOURCE DATA 2. Evaluating enrichment in T2D GWAS data.** For
1378 each annotation the single feature and joint-model log₂ Fold Enrichment
1379 (log₂FE) in T2D is shown. 95% Confidence Intervals (CI) for log₂FE are shown in
1380 brackets. In addition, the LRT statistic and P-value of a nested joint-model
1381 excluding a given annotation is shown.

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1383

1384 Figure 3-source data 3 is associated with primary Figure 3 (uploaded on eLife
1385 submission website with label: "Figure 3-source data 3")

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1387 **FIGURE 3-SOURCE DATA 3. Evaluating enrichment in FG GWAS data.** For
1388 each annotation the single feature and joint-model log₂ Fold enrichment
1389 (log₂FE) in FG is shown. 95% Confidence Intervals (CI) for log₂FE are shown in
1390 brackets. In addition, the LRT statistic and P-value of a nested joint-model
1391 excluding a given annotation is shown.

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1394 Figure 4-source data 1 is associated with primary Figure 4 (uploaded on eLife
1395 submission website with label: "Figure 4-source data 1")

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1397 **FIGURE 4-SOURCE DATA 1. Comparison of variant variant PPA and 99%
1398 credible set size across annotations.** For each set of annotations used the
1399 median segment top variant PPA (higher values indicate better performance),
1400 the median segment 99% credible set size (lower values indicate better
1401 performance) and the number of significant segments (higher number indicates
1402 better performance) is shown. Significant loci were defined solely on a combined
1403 segmental PPA of at least 0.90.

1404

1405

1406 Figure 4-source data 2 is associated with primary Figure 4 (uploaded on eLife
1407 submission website with label: "Figure 4-source data 2")

1408

1409 **Figure 4-source data 2. Information for variants overlapping a genomic
1410 annotation included in the FGWAS T2D-joint model.** For each variant that
1411 overlaps a genomic annotation included in FGWAS T2D-joint model the following
1412 information is provided: rsID; FGWAS PPA; T2D GWAS P-value; FGWAS segment
1413 number; T2D locus name; tested for allelic imbalance (Yes/No). If available, the
1414 following eQTL information from Varshney et al 2017 is shown as well: eQTL
1415 allele1 (effector), eQTL allele 2, eQTL q-value, eQTL effect and eQTL gene.

1416

1417

1418 **9.4 Source data bed file information:**

1419

1420 **Figure 2-source data 1.** LMR_UMR_source_MThurner_Oct_2017.tds is
1421 associated with primary Figure 2 Bed file providing coordinates of WGBS
1422 hypomethylated regulatory regions defined as UMRs and LMRs.

1423

1424 **Figure 3-source data 4.** Merged_ATAC_seq_peaks_MThurner_Oct_2017.tds is
1425 associated with primary Figure 3 (uploaded on eLife submission website with
1426 label: "Figure 3-source data bed file 1"). Bed file providing coordinates of ATAC-
1427 seq open chromatin peaks merged across all samples.

1428

1429 **Figure 3-source data 5.**

1430 Pancreatic_islet_15_chromatin_states_MThurner_Oct_2017.tds.zip is associated
1431 with primary Figure 3. Zipped bed file providing coordinates of human
1432 pancreatic islet chromatin states.

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1435 **10. List of abbreviations:**

1436		
1437	450k array	Infinium Human Methylation 450K BeadChip
1438	850 array	Infinium MethylationEPIC BeadChip
1439	ATAC-seq	Assay for Transposase-Accessible Chromatin using sequencing
1440	CDS	CoDing Sequence
1441	ChIP	Chromatin ImmunoPrecipitation
1442	CI	Confidence Interval
1443	CONS	CONSeRved sequence
1444	dDMRs	disease Differentially Methylated Regions
1445	DIAGRAM	DIABetes Genetics Replication And Meta-analysis
1446	DNA	DeoxyriboNucleic Acid
1447	ENGAGE	European Network for Genetic and Genomic Epidemiology
1448	eQTL	expression Quantitative Trait Locus
1449	FE	Fold Enrichment
1450	FG	Fasting Glucose
1451	GWAS	Genome-Wide Association Studies
1452	KS-test	Kolmogorov–Smirnov test
1453	LD	Linkage Disequilibrium
1454	LMRs	Low-Methylated Regions
1455	log2FE	log2 Fold Enrichment
1456	mQTL	methylation Quantitative Trait Locus
1457	P	P-value
1458	PMDs	Partially Methylated Domains
1459	PPA	Posterior Probability of Association
1460	RNA	RiboNucleic Acid
1461	SNP	Single-Nucleotide Polymorphism
1462	T2D	Type 2 Diabetes
1463	TFBS	Transcription Factor Binding Site
1464	UMRs	UnMethylated Regions
1465	WGBS	Whole-Genome Bisulphite Sequencing

1466

1467 **11. References**

1468

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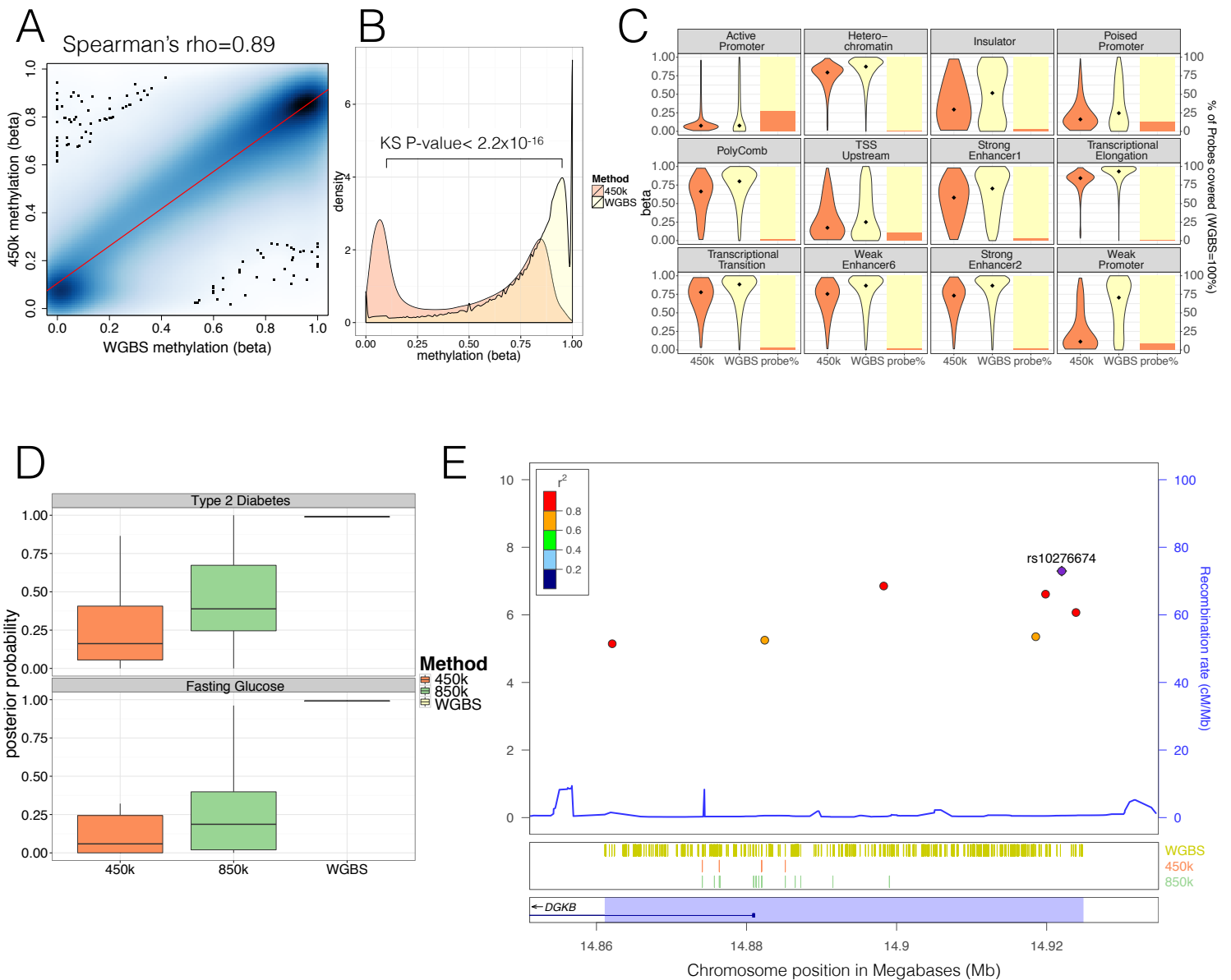


FIGURE 1. Comparison of human pancreatic islet WGBS and 450k methylation data across the genome. A) Smooth Scatter plot shows Spearman's rho correlation between the 450k array (x-axis) and WGBS (y-axis) at overlapping sites. Darker colour indicates higher density of sites. B) Comparison of the 450k array (orange) and WGBS (yellow) methylation levels (x-axis) of all CpGs genome-wide assayed by either method (y-axis shows density). The P-value shown is derived using a Kolmogorov-Smirnov (KS) test. C) For each chromatin state from Parker et al 2013 the methylation levels of all CpG sites independent of overlap (diamond indicates the median) are shown as violin plots (left y-axis) and the CpG probe percentage per state for the 450k array (orange) and WGBS (yellow) are shown as bar-plot (right y-axis). The 450k probes represent the percentage of the total number of CpG sites which is determined by the number of WGBS CpG sites detected (WGBS=100%). D) Distribution of GWAS Posterior Probabilities (Type 2 Diabetes and Fasting Glucose) captured by CpG sites on the 450k array (orange), 850k array (green) and WGBS (yellow/black line). E) Locuszoom plot showing CpG density and credible set SNPs. SNPs are shown with P-values (dots, y-axis left), recombination rate (line, y-axis right) and chromosome positions (x-axis) while CpG and gene annotations are shown below. These annotations include CpGs identified from WGBS (yellow strips), 450k CpG probes (orange stripes), 850k CpG probes (green stripes) and gene overlap (*DGKB* label). The highlighted region in blue captures the 99% credible set region plus additional 1000bp on either side. At the very bottom the position on chromosome 7 is shown in Megabases (Mb).

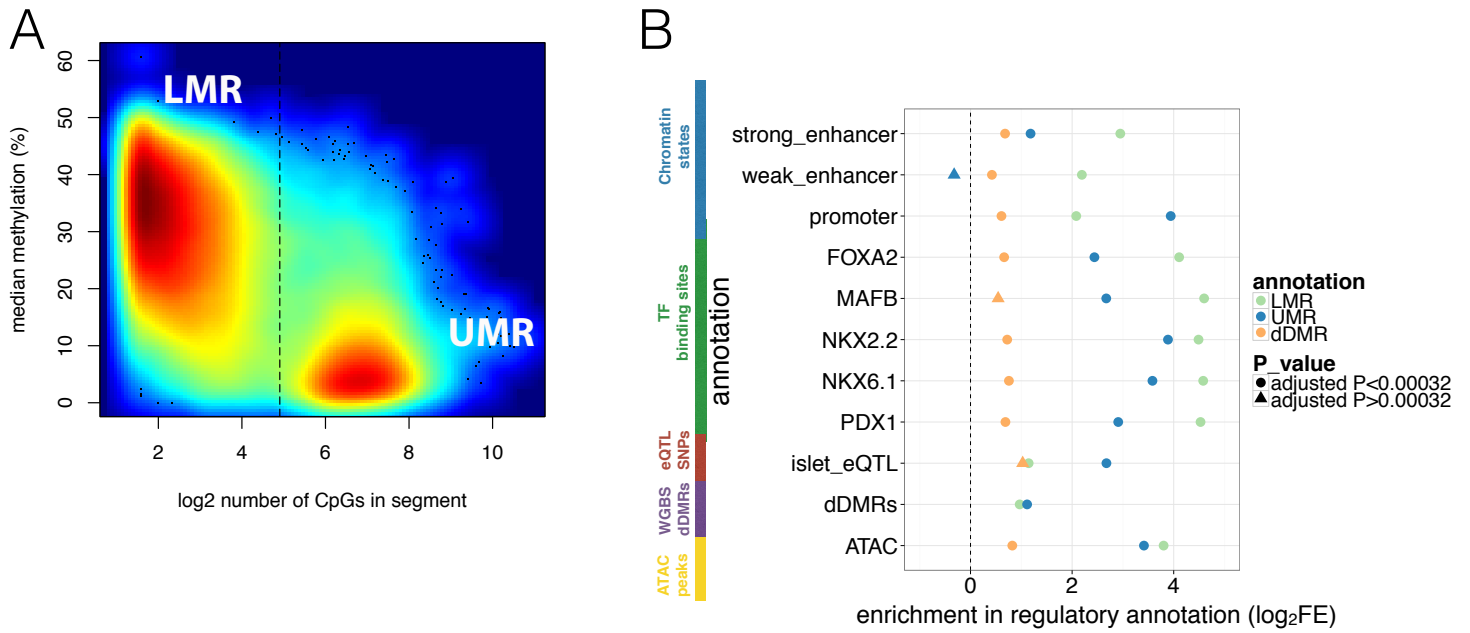


FIGURE 2. Overlap of WGBS hypomethylation and ATAC-seq open chromatin peaks with regulatory annotation . A) Methylation levels in percent (y-axis) and log₂ CpG density (x-axis) of UMR and LMR regulatory regions with the dashed line indicating the CpG-number (30 CpGs) that distinguishes LMRs and UMRs. B) Log₂ Fold Enrichment (log₂FE) of LMRs (green shape), UMRs (blue shape) in various islet annotations is shown. These annotations include islet chromatin states, islet relevant TFBS (FOXA2, MAFB, NKX2.2, NKX.61, PDX1), islet eQTLs, WGBS derived T2D-associated islet disease DMRs (dDMRs) and ATAC-seq open chromatin peaks. The dDMRs were derived from 6 T2D and 8 non-diabetic individuals by Volkov et al 2017 and dDMRs (orange shape) were also tested for enrichment in the aforementioned islet regulatory annotations. For all annotations, the empirically determined Bonferroni adjusted P-value is ≤ 0.00032 unless otherwise indicated by the shape: a dot corresponds to an Bonferroni adjusted P-value < 0.00032 while the 3 triangles indicates Bonferroni adjusted P-values > 0.00032 : UMR enrichment adjusted P-value for weak enhancers=1; dDMR enrichment adjusted P-value for MAFB=0.006 and dDMR enrichment adjusted P-value for islet eQTLs=0.01.

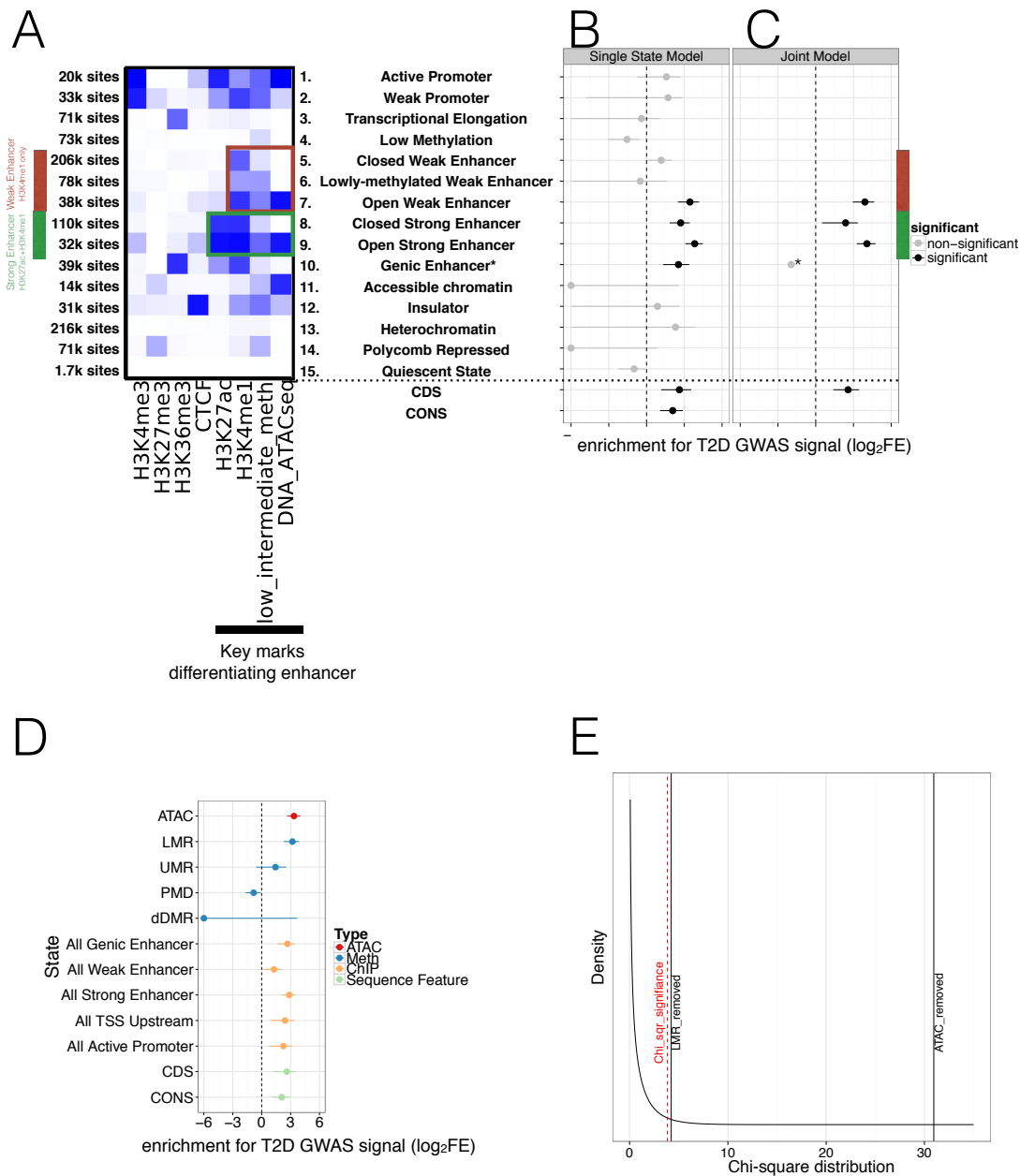


FIGURE 3. Integration of islet epigenetic data to refine chromatin regulatory states and enrichment of these states in T2D GWAS data. A) 15 chromatin states (y-axis) were derived from ChIP histone marks, DNA methylation and ATAC-seq open chromatin annotations (x-axis) using chromHMM. For each state the relevant marks characterising the state are shown. The colour is based on the chromHMM emission parameters and a darker colour indicates a higher frequency of a mark at a given state. Weak enhancers (marked by H3K4me1 alone, red) and strong enhancers (marked by H3K27ac and H3K4me1, green) were subdivided by the chromHMM analysis according to methylation and ATAC-seq status (highlighted in red and green box). The black bar at the x-axis highlights the most important marks for characterising enhancer subclasses. B-C) FGWAS Log₂ Fold Enrichment including 95% CI (\log_2FE , x-axis) of all chromatin states (y-axis) in T2D GWAS regions is shown which demonstrate differential enrichment amongst enhancer subclasses in single-feature enrichment analysis. In addition, \log_2FE of Coding Sequence (CDS) and Conserved Sequence (CONS) annotations are shown to include the effect of protein-coding and conserved regions. Significantly enriched annotations are shown in black while non-significant annotations are shown in grey. C) T2D FGWAS maximum likelihood model determined through cross-validation. \log_2FE and 95% CI (x-axis) of annotations included in the maximum likelihood model (y-axis) also demonstrate differential enrichment amongst enhancer subclasses. *Analysis for Genic Enhancers (state 10) did not converge and hence, only a point \log_2FE estimate is provided. D) Single feature \log_2FE including 95% CI (x-axis) results are shown highlighting the differences in T2D GWAS enrichment of various annotations. These include ATAC-seq open chromatin peaks (red), WGBS methylation regions (including enhancer-like LMRs, promoter-like UMRs and Partially Methylated Domains, blue), ChIP-seq chromatin states (orange) and CDS (green). E) Chi-square distribution (curved black line) with the indicated results of a maximum likelihood ratio test based on the maximum likelihood difference between a model including LMRs or ATAC-seq peaks compared to the ChIP-only model. The dashed red line indicates significance (P-value<0.05). For all FGWAS enrichment plots the axis has been truncated at -6 to facilitate visualisation and accurate values are provided in the supplementary tables.

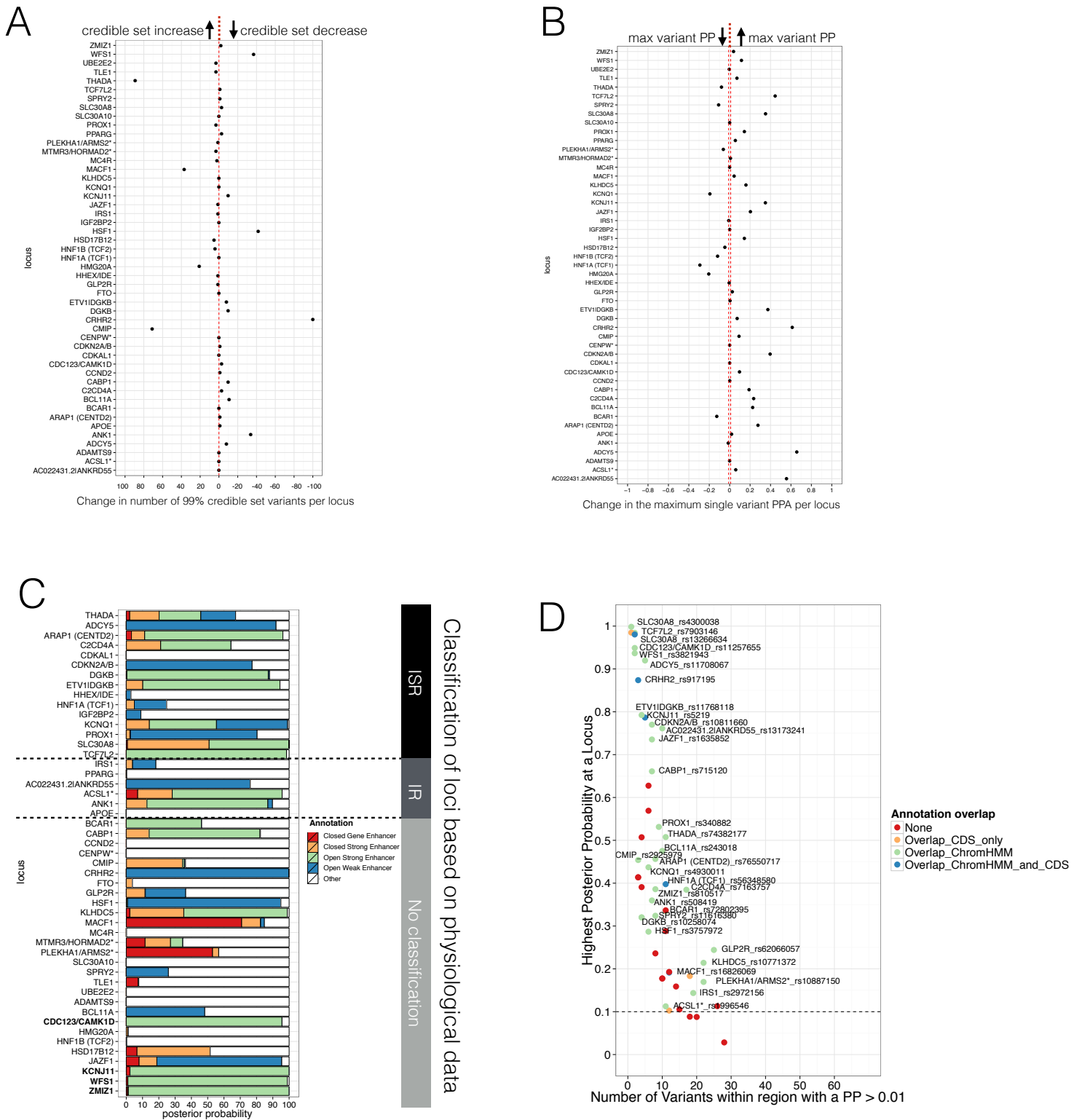


FIGURE 4. Evaluating Posterior Probabilities (PP) derived from the FGWAS maximum likelihood model at significant T2D GWAS loci. (A) Per locus the difference in the number of 99% credible set variants between ChIP+ATAC+Meth and ChIP-only model is shown (positive values indicate a reduction in the number of 99% credible set variants in the ChIP_ATAC_Meth model). (B) Per locus the difference in the maximum single variant PPA between the ChIP+ATAC+Meth and ChIP-only model is shown (positive values indicate an increase in the maximum single variant PPA in the ChIP+ATAC+Meth model). (C) T2D GWAS loci were classified into insulin secretion (ISR), insulin resistance (IR) or unclassified loci based on genetic association with physiological traits derived from Dimas et al 2014 and Wood et al 2017. In addition, loci with known role in islet genomic regulation or function are highlighted in bold. These include loci with islet eQTLs (*ZMIZ1*, *CDC123*) and mQTLs (*WFS1*, *KCNJ11*). (D) Identification of T2D GWAS loci and variants enriched for enhancer chromatin states using FGWAS PP. Per locus the highest PPA variant is shown (y-axis) and the number of variants with PPA > 0.01 (x-axis). Loci with high PPA variants (min PPA > 0.1, dashed horizontal line) that overlap one of the enhancer states (green) are highlighted and the high PPA variants (PPA > 0.1) were tested for allelic imbalance in open chromatin.

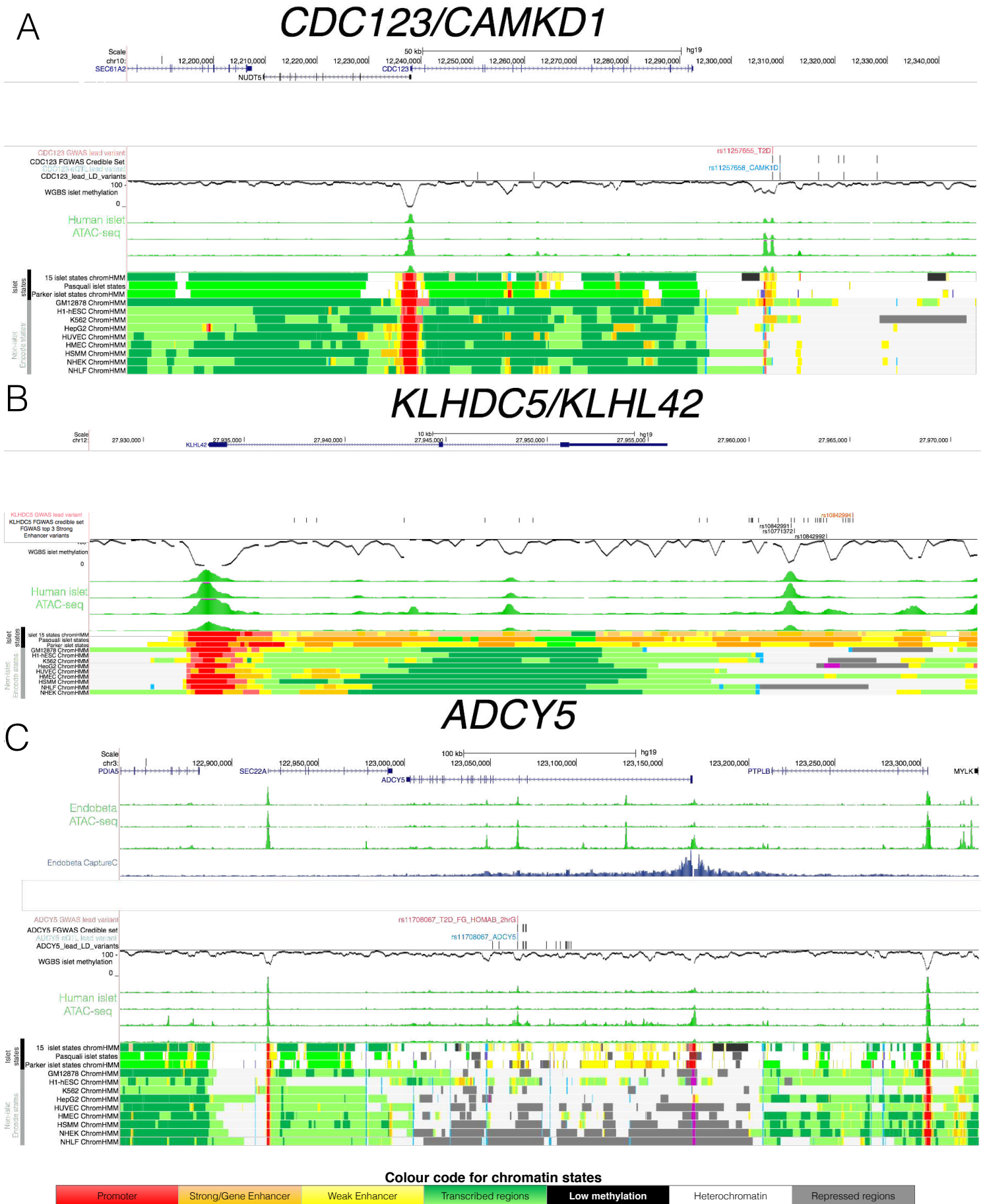
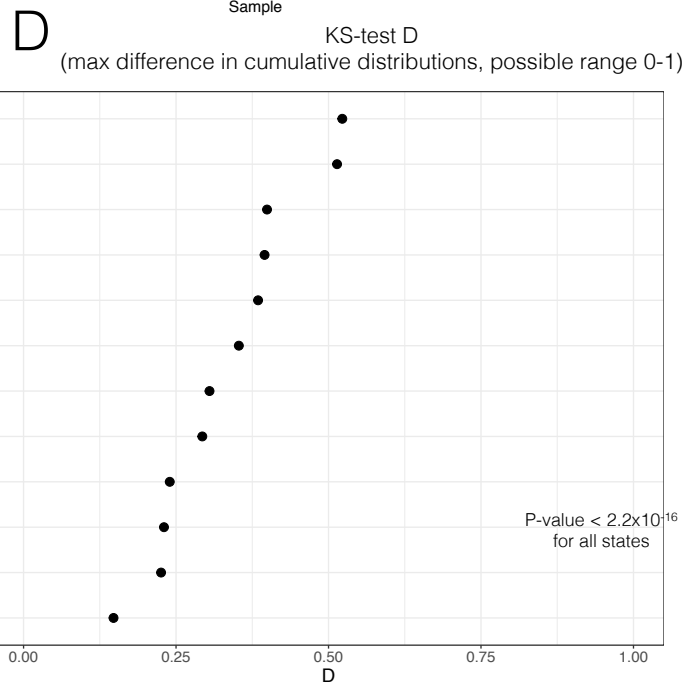
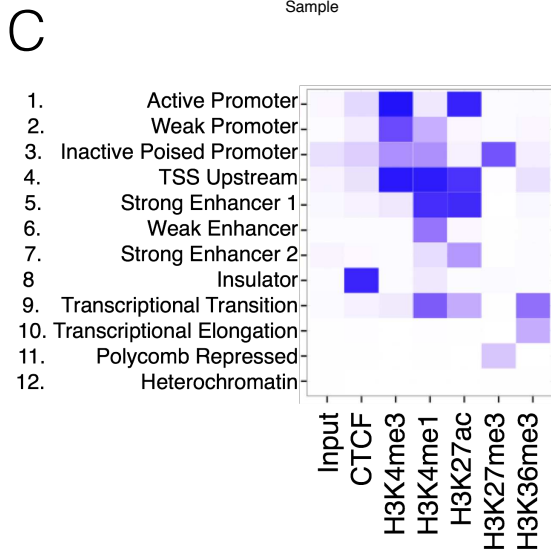
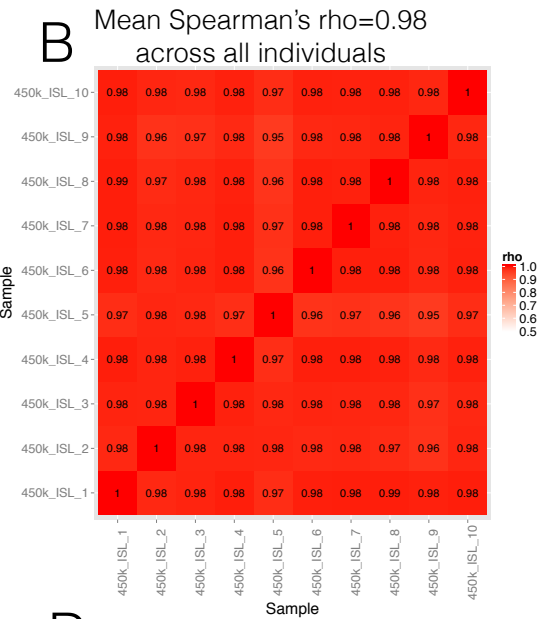
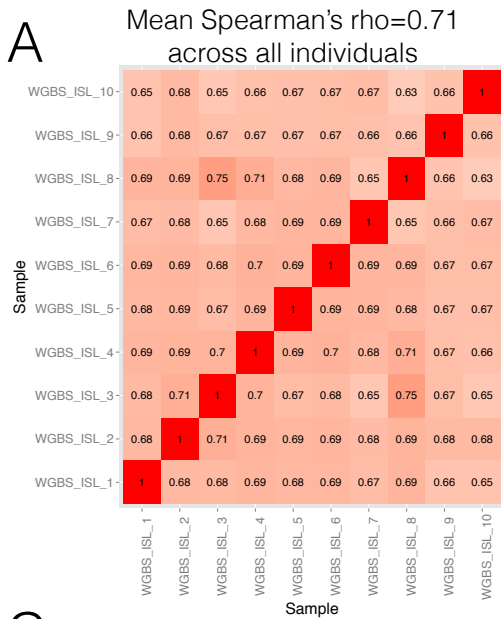
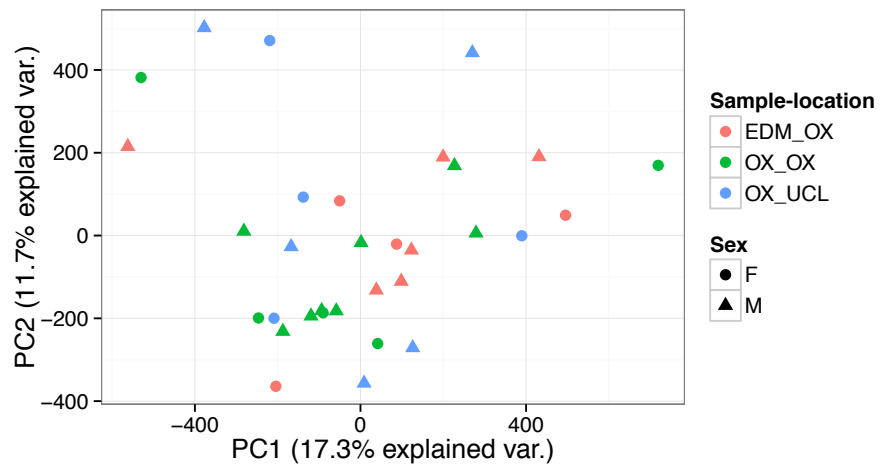
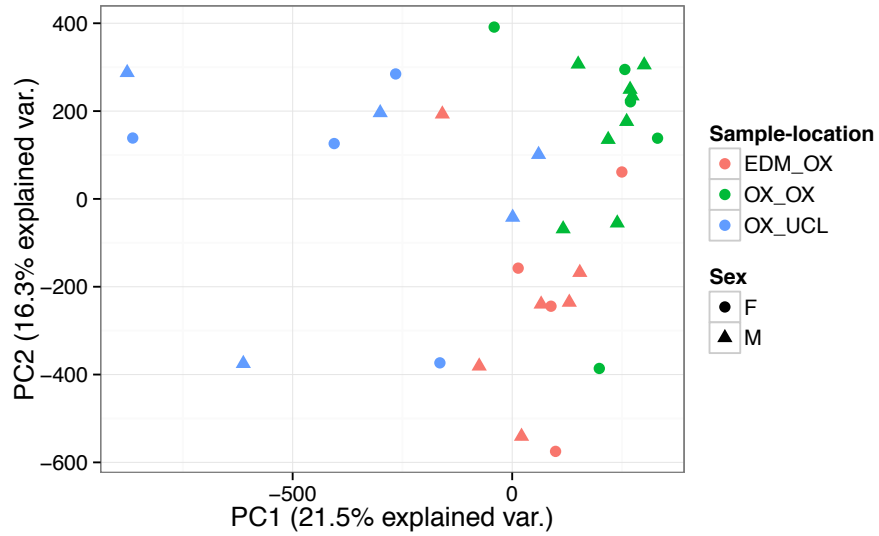


FIGURE 5. Epigenome Landscape of selected loci with allelic imbalance. For each locus A) *CDC123*, B) *KLHDC5* and C) *ADCY5* the following information is shown: 3 ATAC-seq Endo β tracks (green, top), variant level information (depending on the region GWAS lead SNP red, credible set black, eQTL blue and high LD SNPs with $r^2 > 0.8$ black), WGBS methylation data (black, middle), 4 human islet ATAC-seq tracks (green, middle), islet chromatin states (from this study as well as Parker et al 2013 and Pasquali et al 2014) and Encode chromatin states from 9 cell types (bottom). For *ADCY5* the Capture C results in the Endo β cell line are shown as well (middle blue). Abbreviation for cell types: B-lymphoblastoid cells (GM12878), embryonic stem cells (H1 ES), erythrocytic leukaemia cells (K562), hepatocellular carcinoma cells (HepG2), umbilical vein endothelial cells (HUVEC), mammary epithelial cells (HMEC), skeletal muscle myoblasts (HSMM), normal epidermal keratinocytes (NHEK) and normal lung fibroblasts (NHLF).

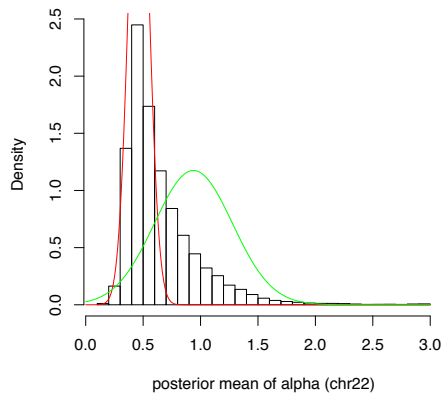


SUPPLEMENTARY FIGURE 1. Correlation of DNA methylation across WGBS and 450k sites and comparison of WGBS and 450k methylation levels across chromatin states A-B) Spearman's rho correlation of DNA methylation across 10 individual (A) WGBS and (B) 10 selected (out of 32) 450k samples on the x-axis and y-axis. C) Islet chromatin state definitions based on ChIP-seq data reproduced from Parker et al 2013. TSS: Transcription Start Site D) The differences in the 450k and WGBS methylation level distribution measured as D statistic, which represents the difference in the cumulative distributions and is derived from the Kolmogorov-Smirnov test, are shown for each chromatin state separately.

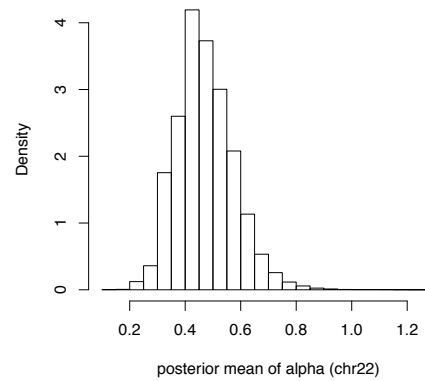


SUPPLEMENTARY FIGURE 7. A-B) PCA analysis of 450k DNA methylation data of 32 human islet samples coloured according to the location of origin and processing (A) before correction for Sample-location and (B) after correction for Sample-location using the ComBat function included in the sva package. The shape indicates sex. Sample location **EDM_OX**: samples obtained from the Alberta Diabetes Institute in Edmonton (Canada) and processed at the University of Oxford. **OX_OX**: samples obtained from Oxford DRWF Human Islet Isolation Facility and processed at the University of Oxford. **OX_UCL**: samples obtained from Oxford DRWF Human Islet Isolation Facility and processed at University College London.

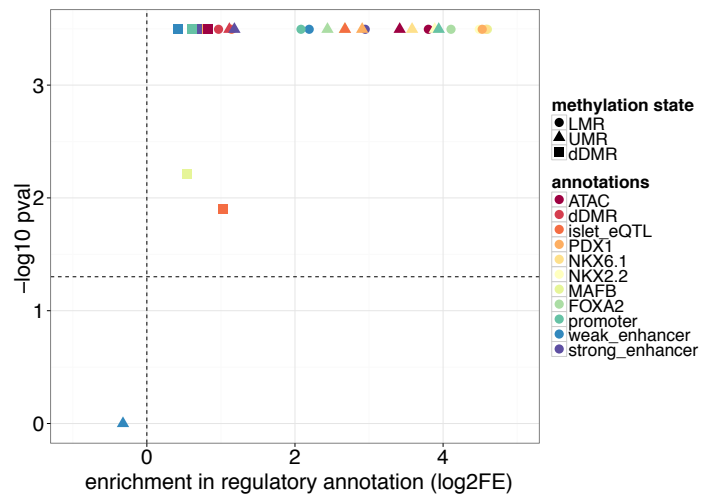
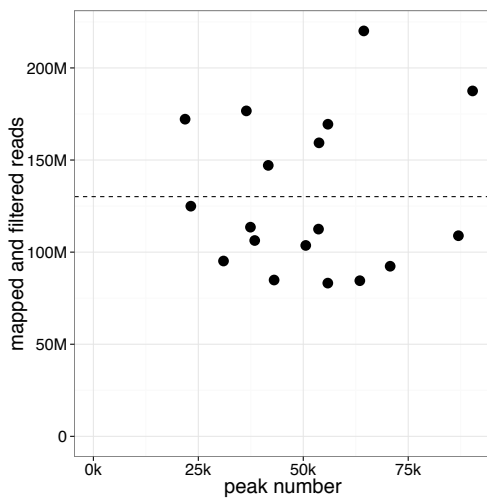
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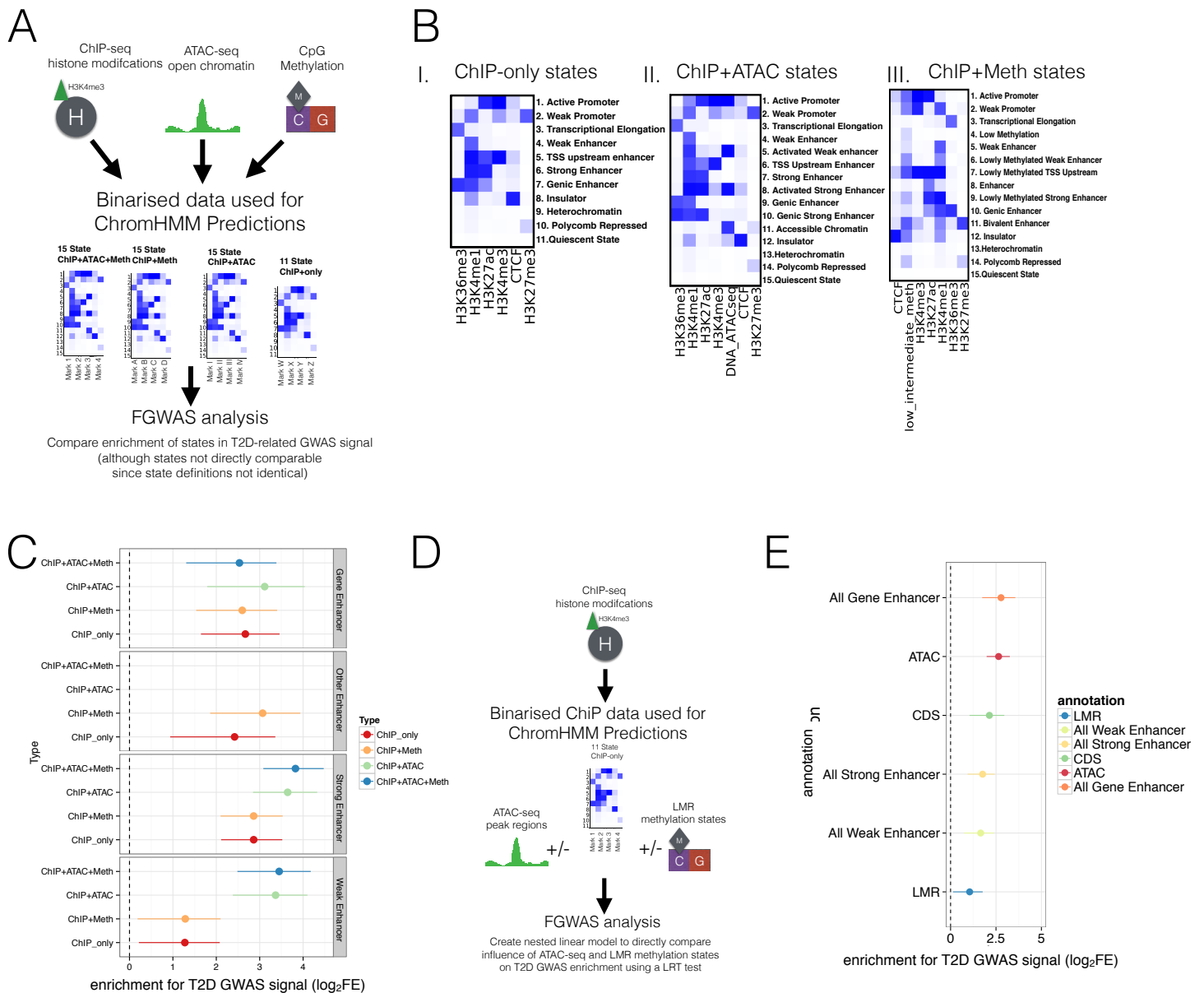
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SUPPLEMENTARY FIGURE 2. Identification and removal of Partially Methylated Domains (PMDs) A-B) Density distribution of the alpha value (A) before and (B) after removing PMDs (green curve in (A)) on chromosome 22. Alpha values represent a summary statistic derived from DNA methylation of windows of 100 CpGs and represents an indication of the polarisation status of methylation values in the genome which is expected to contain either highly methylated or unmethylated regions. Distributions with $\alpha < 1$ indicate methylation levels that are bimodal with either 0 or 1 methylation. $\alpha = 1$ corresponds to a uniform distribution of methylation; and distributions with $\alpha > 1$ tend to have primarily intermediate methylation levels. The red and green curve in (A) represent the non-PMD (red) and PMD regions (green) in the genome. C) Number of peaks (x-axis) and mapped and filtered reads (y-axis) per ATAC-seq islet preparation. The dashed line indicates the mean read number. D) \log_2 Fold Enrichment (\log_2FE , x-axis) and associated $-\log_{10}$ Bonferroni adjusted P-values (y-axis) of LMRs (circle), UMRs (triangle) in various islet annotations (colours) is shown. These annotations include islet chromatin states, islet relevant TFBS (FOXA2, MAFB, NKX2.2, NKX.61, PDX1), islet eQTLs, WGBS derived T2D-associated islet disease DMRs (dDMRs) and ATAC-seq open chromatin peaks. dDMRs (square) were also tested for enrichment in the aforementioned islet regulatory annotations. The results cluster near $-\log_{10}$ P-value of 3.5 since most Bonferroni adjusted P-values were more extreme than 0.00032.



SUPPLEMENTARY FIGURE 3. Prediction of regulatory regions using WGBS data and testing these regions for enrichment in T2D GWAS regions.

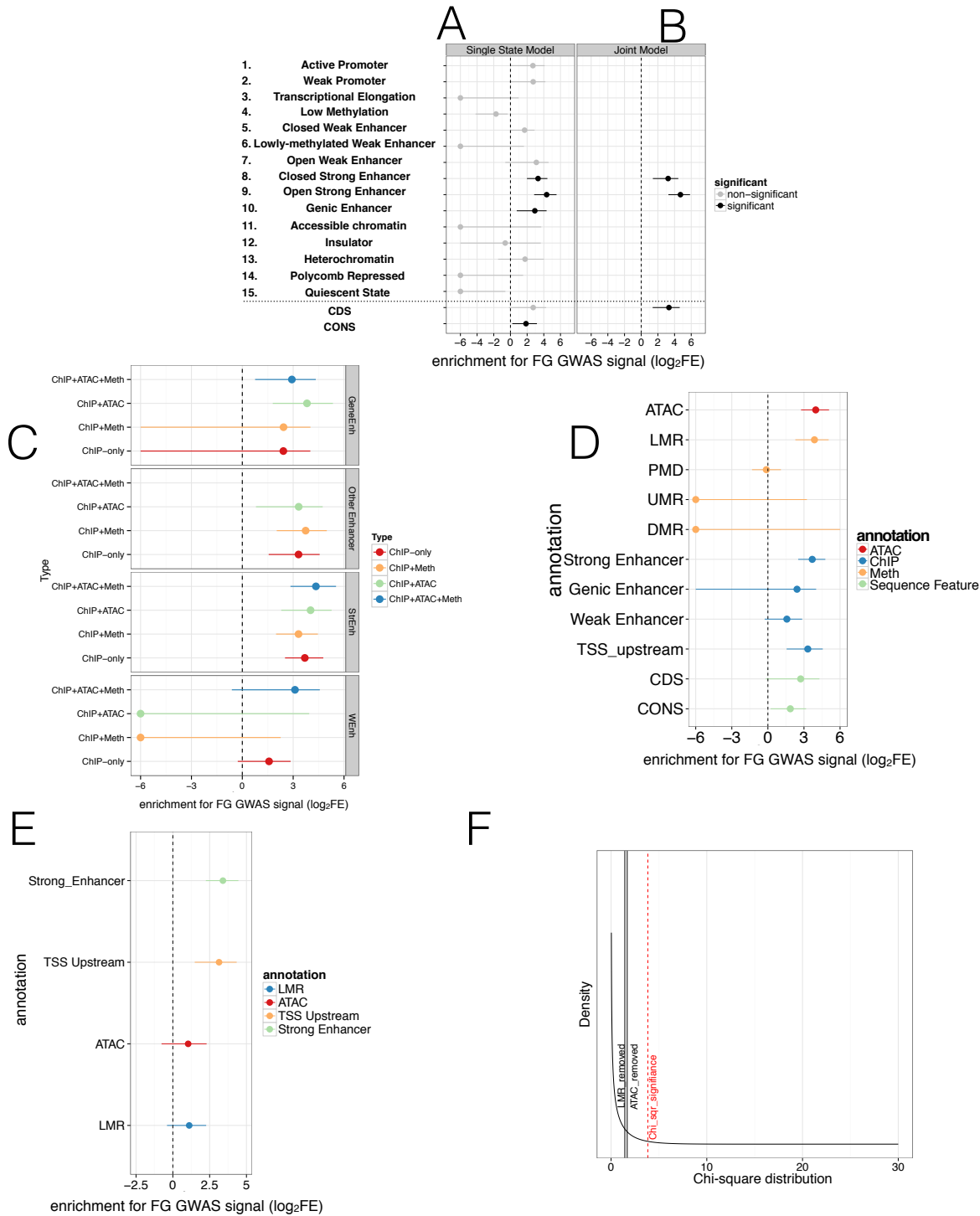
A) Different combinations of epigenomic data (top) were combined to generate different sets of refined chromatin states (middle, 11 ChIP-only and 15 ChIP+Meth, ChIP+ATAC and ChIP+ATAC-Meth states, see figure S3B and 3A-B for actual states) using chromHMM. These sets of chromatin states were then tested for enrichment in T2D-related GWAS traits using FGWAS to compare enrichment across states (bottom).

B) ChromHMM (I) 11 ChIP-only and 15 state (II) ChIP+ATAC state and (III) ChIP+Meth models.

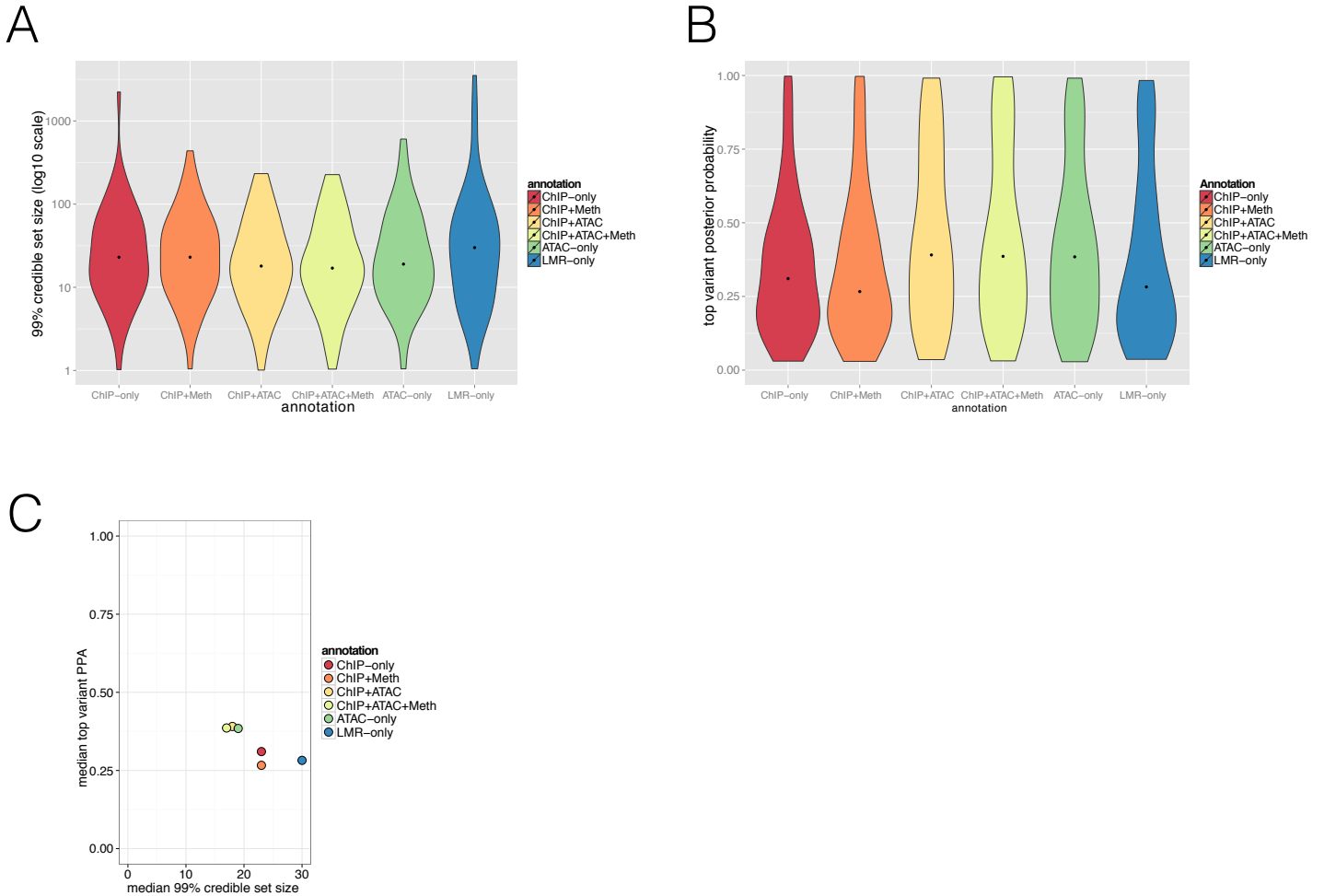
C) Single feature \log_2FE (x-axis) for different enhancer states (grey panels) defined from different combinations of epigenetic marks (y-axis) including ChIP+ATAC+Meth, ChIP+ATAC, ChIP+Meth and ChIP-only. The grey-dashed line indicates the enrichment value of CDS as reference. Enhancers are defined as follows: Strong enhancers are marked by both H3K4me1 and H3K27ac, weak Enhancers are defined by H3K4me1 only, gene enhancers are marked by H3K4me1 and H3K36me3, other enhancers are marked by H3K4me1, H3K4me3 and H3K27ac and are often referred to as TSS upstream regions (only included in the FGWAS T2D model for ChIP-only and ChIP+Meth chromatin states).

D) Since chromatin states defined from a different set of epigenomic marks (ChIP-only, ChIP+Meth, ChIP+ATAC and ChIP+ATAC+Meth), as described in S3A-B, are not equivalent and the enrichment can not be easily compared across models, a nested model approach was applied. That is, ChIP-only chromatin states were generated and after evaluating the individual enrichment of each annotation (see Figure 3D), FGWAS maximum likelihood models were defined using ChIP-only, hypomethylated and/or ATAC-seq peak regulatory regions. The combination of all these annotations represented a nested linear model and the changes in maximum likelihood by adding/removing hypomethylated regulatory and ATAC-seq states could be statistically evaluated using a Loglikelihood Ratio Test (LRT) as shown in Figure 3E.

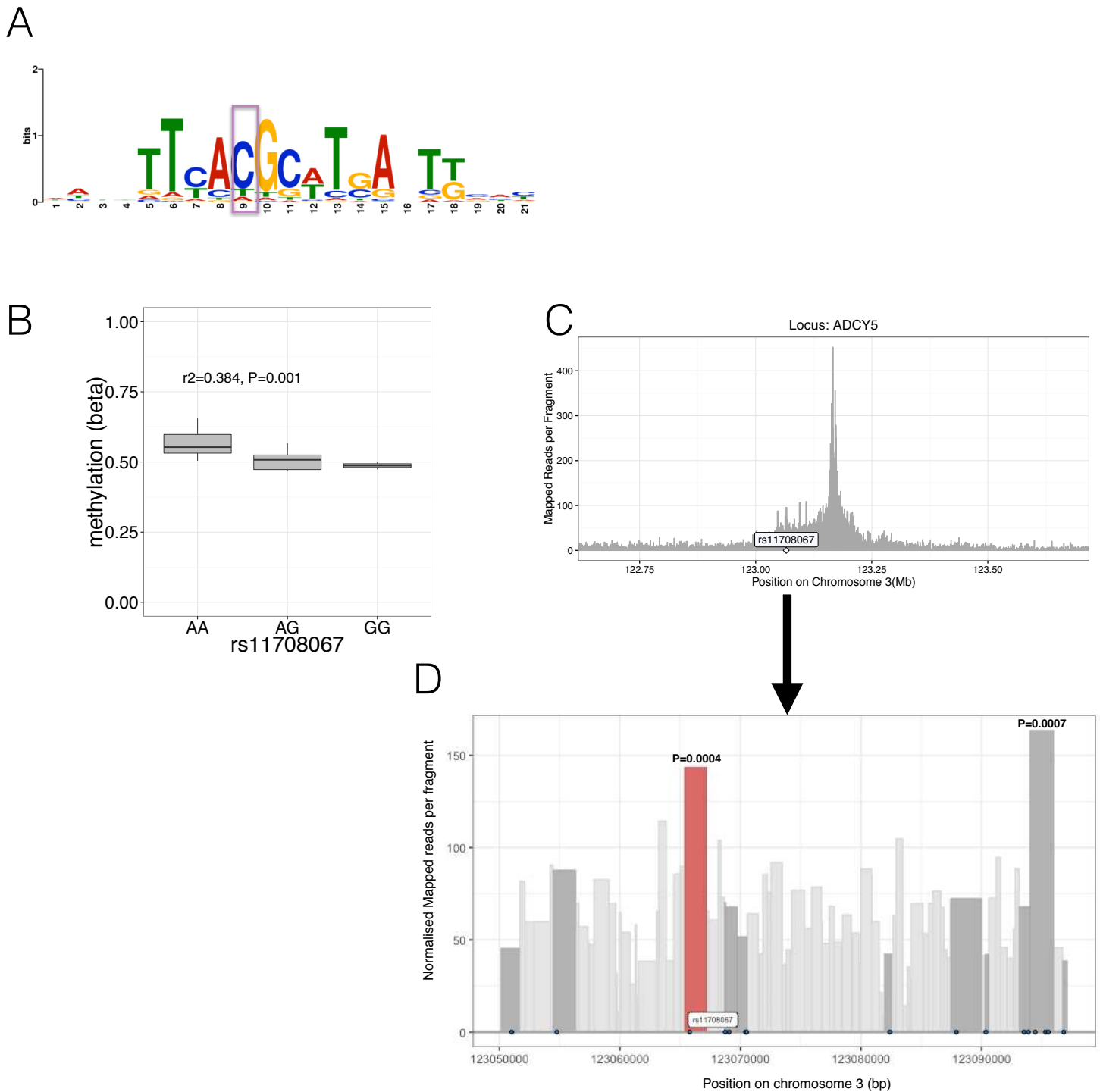
E) Maximum likelihood FGWAS nested model combining ChIP-only, ATAC-peaks and LMR states (y-axis) showing \log_2FE enrichment (x-axis) which was used for the LRT in Figure 3E. For all FGWAS enrichment plots the axis has been truncated at -6 to facilitate visualisation and accurate values are provided in the supplementary tables.



SUPPLEMENTARY FIGURE 4. Enrichment of refined islet regulatory states in FG GWAS data A) FGWAS Log₂ Fold Enrichment including 95% CI (log₂FE, x-axis) of all chromatin states (y-axis) in FG GWAS regions. In addition, CDS is shown to also include the effect of protein-coding regions. Significantly enriched annotations are shown in black. B) FG FGWAS maximum likelihood model determined through cross-validation. log₂FE and 95% CI (x-axis) of annotations included in the maximum likelihood model (y-axis) are shown. C) Single feature log₂FE (x-axis) for different enhancer states (grey panels) defined from different combinations of epigenetic marks (y-axis) including ChIP+ATAC+Meth, ChIP+ATAC, ChIP+Meth and ChIP-only. Enhancers are defined as follows: Strong enhancers are marked by both H3K4me1 and H3K27ac, weak Enhancers are defined by H3K4me1 only, gene enhancers are marked by H3K4me1 and H3K36me3, other enhancers are marked by H3K4me1, H3K4me3 and H3K27ac and are often referred to as TSS upstream regions (only included in the FGWAS T2D model for ChIP-only and ChIP+Meth chromatin states). D) Single feature log₂FE including 95% CI (x-axis) results of various annotations derived from ChIP-seq (ChIP-only), ATAC-seq, WGBS methylation status and CDS are shown. E) Maximum likelihood FGWAS nested model combining ChIP-only, ATAC-peaks and LMR states (y-axis) showing log₂FE enrichment (x-axis) which was used for the LRT in Supplementary Figure S3F. F) Chi-square distribution (black curved line) with the indicated results of a maximum likelihood ratio test based on the maximum likelihood difference between a model including LMRs or ATAC-seq peaks compared to the ChIP-only model. The dashed line indicates significance (P-value < 0.05). For all FGWAS enrichment plots the axis has been truncated at -6 to facilitate visualisation and accurate values are provided in the supplementary tables.



Supplementary Figure 5. Evaluating annotation effect on Posterior Probabilities (PPA) derived from the FGWAS maximum likelihood model at significant T2D GWAS loci. (A) Violin plot showing the distribution of 99% credible set variant size (y-axis, log₁₀ scale) of different annotation types used (x-axis, ChIP-only, ChIP+Meth, ChIP+ATAC, ChIP+ATAC+Meth, ATAC-only and LMR-only model). (B) Violin plot showing the distribution in the maximum single variant PPA (y-axis) of different annotation types used (x-axis, ChIP-only, ChIP+Meth, ChIP+ATAC, ChIP+ATAC+Meth, ATAC-only and LMR-only model). Dots indicate mean value. (C) Median 99% credible set variant size (x-axis) and median top variant PPA (y-axis) information for ChIP-only, ChIP+Meth, ChIP+ATAC, ChIP+ATAC+Meth, ATAC-only and LMR-only models.



SUPPLEMENTARY FIGURE 6. A) Predicted *PAX6* Transcription factor binding motif likely affected by allelic imbalance of the variant rs10842991 (highlighted in purple). B) The *ADCY5* rs11708067 risk A allele was associated with increased methylation levels (y-axis, while genotypes are shown on the x-axis). C) Chromatin Capture (Capture C) in the human beta-cell line EndoB1 showed interactions between the *ADCY5* promoter (peak) and the flanking regions of the promoter. The x-axis shows the position on the chromosome in Mb while the y-axis indicates mapped reads per fragment. D) Chromatin Capture (Capture C) in the human beta-cell line EndoB1 focussed at the genomic region (~47kb) near the variant rs11708067 (highlighted) and variants in high LD ($r^2 > 0.8$) with it (variants are depicted as black dots). Fragments containing rs11708067 (red) or other high LD variants (dark grey) are highlighted. The x-axis shows the position on the chromosome in bp while the y-axis indicates normalised mapped reads per fragment. The two fragments with P-values have a significant (FDR < 0.05) number of normalised read counts over background: The fragment with the P-value on the left (in red) contains rs11708067 while the fragment with the P-value on the right harbours rs2877716, rs6798189, rs56371916.