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1 Article

2 **Dysregulated antibody, natural killer cell and** 3 **immune mediator profiles in autoimmune thyroid** 4 **diseases**

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42 **Abstract:** The pathogenesis of autoimmune thyroid diseases (AITD) is poorly understood and the association
43 between different immune features and the germline variants involved in AITD are yet unclear. We previously
44 observed systemic depletion of IgG core fucosylation and antennary α 1,2 fucosylation in peripheral blood
45 mononuclear cells in AITD, correlated with anti-thyroid peroxidase antibody (TPOAb) levels. Fucose depletion
46 is known to potentiate strong antibody-mediated NK cell activation and enhanced target antigen-expressing cell
47 killing. In autoimmunity, this may translate to autoantibody-mediated immune cell recruitment and attack of

48 self-antigen expressing normal tissues. Hence, we investigated the crosstalk between immune cell traits, secreted
49 proteins, genetic variants and the glycosylation patterns of serum IgG, in a multi-omic and cross-sectional study
50 of 622 individuals from the TwinsUK cohort, 172 of whom were diagnosed with AITD. We observed associations
51 between two genetic variants (rs505922 and rs687621), AITD status, the secretion of Desmoglein-2 protein, and
52 the profile of two IgG N-glycan traits in AITD, but further studies need to be performed to better understand
53 their crosstalk in AITD. On the other side, enhanced afucosylated IgG was positively associated with activatory
54 CD335-CD314+CD158b+ NK cell subsets. Increased levels of the apoptosis and inflammation markers Caspase-
55 2 and Interleukin-1 α positively associated with AITD. Two genetic variants associated with AITD, rs1521 and
56 rs3094228, were also associated with altered expression of the thyrocyte-expressed ligands known to recognize
57 the NK cell immunoreceptors CD314 and CD158b. Our analyses reveal a combination of heightened Fc-active
58 IgG antibodies, effector cells, cytokines and apoptotic signals in AITD, and AITD genetic variants associated
59 with altered expression of thyrocyte-expressed ligands to NK cell immunoreceptors. Together, TPOAb
60 responses, dysregulated immune features, germline variants associated with immunoactivity profiles, are
61 consistent with a positive autoreactive antibody-dependent NK cell-mediated immune response likely drawn to
62 the thyroid gland in AITD.

63 **Keywords:** Multi-omic; autoimmune thyroid diseases (AITD); genetic variants; apoptosis; antibody-
64 dependent cell-mediated cytotoxicity (ADCC); anti-thyroid peroxidase antibody (TPOAb)
65

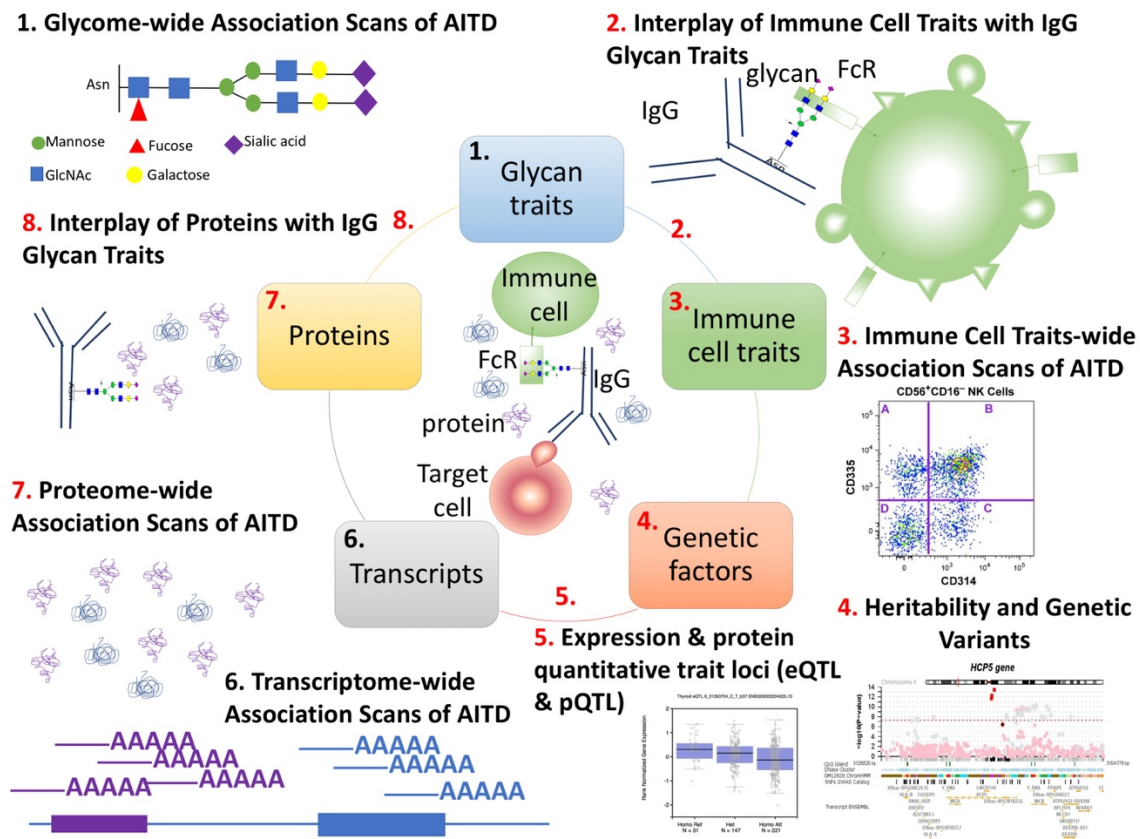
66 1. Introduction

67 Autoimmune thyroid diseases (AITD) are a class of chronic, organ-specific disorders of the
68 thyroid gland with a high genetic heritability (55-75%) [1-4] affecting approximately 5% of the
69 population and with a gender disparity (i.e., women: 5-15%; men: 1-5%) [5-7]. Pathologically, AITD
70 are characterized by autoantibodies against three main thyroid proteins (thyroid peroxidase (TPO),
71 thyroglobulin (Tg), and the thyroid-stimulating hormone (TSH) receptor (TSH-R)), infiltration of the
72 thyroid gland by immune cells (e.g. lymphocytes, NK cells, monocytes, and macrophages), the
73 formation of germinal centers in the thyroid gland [8] and dysregulated TSH levels [9,10]. However,
74 some studies have failed to observe a significant difference in peripheral blood immune cell
75 composition between AITD patients and healthy individuals [11], while others report significant
76 differences in particular cell types or in immune marker expression [12]. Immune cells, thyroid
77 autoantibodies, and secreted proteins including cytokines may play critical roles in AITD
78 development [13] and in immune responses, including in antibody-dependent cell-mediated
79 cytotoxicity (ADCC) pathways [14,15]. However, the underlying autoimmune signatures associated
80 with AITD remain unclear.

81 ADCC is triggered via antigen/antibody/Fc receptor complex formation, bringing the effector
82 cell (macrophages, NK cells) and the target cell (expressing the antigen) in close contact. The
83 formation and function of antigen/antibody complexes are modulated by various factors including
84 post-translational modifications of glycans decorating antibodies [16,17]. One example is lack of
85 fucose on the N-linked core glycan of IgG. Afucosylated antibodies have a higher affinity (~100-fold)
86 for the immunoglobulin Fc receptor Fc γ R3a (CD16a), expressed on NK cells, macrophages and $\gamma\delta$
87 T cells, and are shown to confer enhanced ADCC potential *in vitro* and anti-tumor activity *in vivo* [18-
88 21]. This could result in antibodies with more potent Fc-mediated effector functions able to more
89 effectively recruit and activate immune effector cells such as NK cells to kill target antigen-expressing
90 cells [22,23]. IgG core fucose, observed in approximately 95% of IgG in healthy individuals, is
91 considered a "safe switch" that can attenuate potentially harmful antibody-dependent damage
92 against self-antigen-expressing normal tissues [18-21,24]. However, it is possible that these processes
93 may be altered in autoimmune diseases.

94 We previously studied the glycosylation profiles of total immunoglobulin G (IgG) and of
 95 peripheral blood mononuclear cells (PBMC) in patients with AITD [4], as well as the glycosylation of
 96 IgG-depleted serum proteins in Hashimoto's thyroiditis (HT) patients [25]. In peripheral blood, we
 97 identified both depleted core fucosylation of IgG antibodies and decreased antennary α 1,2
 98 fucosylation of PBMC to be associated with autoantibodies to thyroid peroxidase (TPOAb) and AITD
 99 status [4]. We also identified a network of genes, including *FUT8* and *IKZF1* that regulate
 100 fucosylation, to be implicated in the development of AITD [4,26]. Based on these findings, we
 101 speculated that IgG core fucose deficiencies together with elevated levels of autoantibodies may
 102 participate in autoimmune responses in AITD by enhancing effector cell activation and heightened
 103 immune and inflammatory signals.

104 Therefore, here we investigated immune features that may signify dysregulated, and likely
 105 heightened immune effector cells, antibodies, and immune mediators in AITD. In this *in silico* study
 106 in the blood of 622 subjects from the TwinsUK cohort, of whom 172 have AITD features, we aimed
 107 to investigate: 1) the association of different components of antigen/antibody/Fc receptor complexes
 108 with AITD; 2) the associations between these different immune components in a cohort of samples
 109 from volunteers regardless of disease status, and 3) potential genetic drivers on these components
 110 (study design summarized in Fig. 1). Specifically, we examined the association of total serum IgG
 111 glycosylation, immune traits, such as immune cell subpopulation frequencies (CSFs; i.e. relative
 112 frequencies of circulating immune cell subsets), immune cell surface protein expression levels (SPELs;
 113 i.e. the measurement of the cell-surface expression of critical proteins) and secreted proteins, in the
 114 peripheral blood of patients with AITD compared with those of healthy volunteers (sample sizes of
 115 each study performed are summarized in Table S1).
 116



117 **Figure 1.** Multi-omics computational analyses were used to study the components of
 118 antigen/antibody/effector cell complex structure in AITD. 1) We previously performed glycome-wide
 119 association studies of AITD and TPOAb levels using 3,146 individuals from three European cohorts,
 120 including the TwinsUK cohort. We identified 17 AITD-IgG N-glycan traits in the discovery TwinsUK
 121 cohort, and seven of these 17 have been then replicated in two other cohorts [4]. 2) In the present

122 study, we studied the association of total IgG N-glycan traits with 23,485 immune cell traits in 383
123 individuals from the TwinsUK cohort (regardless of disease status). We showed that 6 out of the 17
124 AITD-IgG glycan traits were correlated with 51 immune cell traits featuring the CD335, CD134, and
125 CD158b receptors. 3) None of these 51 immune cell traits appeared to be associated with AITD in 374
126 individuals (34 with AITD). 4) The heritability of AITD, TPOAb level and several *-omic* features (IgG
127 N-glycan traits and immune cell traits) were performed in previous studies of the TwinsUK cohort
128 [4,27–29]. Here we estimated the heritability of secreted proteins, but we could not determine shared
129 additive genetic variance between different phenotypes studied (AITD status, TPOAb level, level of
130 IgG N-glycan traits, of immune cell traits and of circulating proteins in the bloodstream). 5) We
131 identified genetic variants that alter the expression of genes, proteins and cell-bound immune
132 receptors (highlighted in this study) using the previous GWASs performed in the TwinsUK cohort or
133 from GWAS catalog, eQTLs from GTEx project and pQTLs from INTERVAL project [27,28,30–35]. 6)
134 We previously performed transcriptome-wide association studies of AITD, TPOAb level, and N-
135 glycan structures in the whole blood of approximately 300 individuals and we found no significant
136 associations [4]. 7) We observed 3 out of 1,113 circulating proteins tested in plasma of almost 300
137 individuals shown to be associated with AITD status (TSH, Caspase-2, and Interleukin-1 α). 8) Several
138 secreted proteins were correlated with the level of plasma IgG glycan traits in 164 individuals, but
139 none of them were also associated with AITD. The sample sizes of these different studies are described
140 in **Table S1**. GlcNAc = N-acetylglucosamine. The numbers in black depict analyses performed
141 previously [4,27–29] while the numbers in red depict analyses presented for the first time in the
142 present study.

143 2. Materials and Methods

144 2.1. Study Sample

145 The study was conducted using immune cell traits, glycosylation, proteomics, genotyping,
146 and phenotypes in samples from research volunteers from the UK Adult Twin Registry (TwinsUK
147 cohort). The TwinsUK cohort is comprised of approximately 14,000 monozygotic and dizygotic same-
148 sex adult twins from the UK, unselected for any particular disease or trait (**Table S1**). The cohort is
149 of Northern European/UK ancestry and has been shown to be representative of singleton populations
150 and the UK population in general [36,37]. Ethical approval was granted by the National Research
151 Ethics Service London-Westminster, the St Thomas' Hospital Research Ethics Committee (EC04/015
152 and 07/H0802/84). Informed consent was obtained from all study participants.

153 2.2. Data Statement

154 Multi-omic data were derived from samples in the TwinsUK cohort. Individual-level
155 TwinsUK data, including phenotypes and genotypes, are not permitted to be shared or deposited
156 due to the original consent given at the time of data collection. Access data can be applied for through
157 the TwinsUK data access committee ([http://twinsuk.ac.uk/resources-for-researchers/access-our-
158 data/](http://twinsuk.ac.uk/resources-for-researchers/access-our-data/)).

159 2.3. Definition of AITD and detection of TSH and TPOAb

160 The study was performed using a clinical AITD definition and TPOAb as a threshold trait; it
161 was not possible for AITD (Hashimoto's disease and Graves' disease) clinical diagnosis to be
162 confirmed by a clinician. However, approximately 90% of individuals with Hashimoto's disease,
163 about 75% with Graves' disease, <20% with other thyroid diseases, and <10% of normal individuals
164 are known to have TPOAb-positivity [38–40]. Therefore, individuals were considered to have AITD
165 if they either showed significantly higher than normal TPOAb serum titers (set at 3-fold higher than
166 the threshold set by the manufacturer [18 IU/mL for the Abbott assay and 100 IU/mL for the Roche
167 assay]) or had TSH serum levels >10 mIU/L. We considered individuals as controls if they had normal
168 levels of TSH and a negative TPOAb titer, with no previous clinical diagnosis of thyroid disease and
169 who were not treated with thyroid medications or steroids. Individuals with a history of thyroid
170 cancer or thyroid surgery were excluded. Among the 622 individuals studied, 172 (27.65%) were

171 identified with AITD, 236 (37.94%) considered normal controls, and 214 (34.41%) have TPOAb or
172 TSH serum levels outside the normal range, but do not reach the 3-fold cutoff for inclusion in the
173 AITD cohort. Evaluations of sera to measure TPOAb and TSH levels are described in **Appendix A**.

174 2.4. Detection of IgG glycosylation profiling for discovery

175 Plasma specimens for analysis of IgG glycosylation was collected between 1997 and 2013 in
176 2,279 individuals from the TwinsUK cohort. IgG glycosylation profiling was performed on total
177 plasma IgGs glycome (combined Fc and Fab glycans and all IgG subclasses) in Genos Glycoscience
178 Research Laboratory, Croatia using UPLC analysis of 2AB-labelled glycans. Protocol, data pre-
179 processing and normalization in the TwinsUK cohort were previously described [4] (**Appendix A**).

180 2.5. Detection of immune cell traits

181 Plasma samples for assessment of 78,000 immune traits were collected between 2010 and 2012
182 in 669 female participants from the TwinsUK cohort using high-resolution deep
183 immunophenotyping flow cytometry analysis as previously described [28]. 78,000 different cell
184 surface marker combinations captured by 7 distinct 14-color immunophenotyping panels were
185 detected and described immune cell subset frequencies (CSF) and immune cell-surface protein
186 expression levels (SPELs). After quality control to remove immune cell traits that appeared as poor
187 reproducibility or out of range, 23,485 immune cell traits from 497 individuals of the TwinsUK cohort
188 were analyzed. For this analysis, only 374 twins had immune cell traits data and TPOAb level
189 detected by Roche immunoassay and 245 individuals in a case-control study by combining Roche
190 and Abbott assays (204 controls and 41 AITD). Immune traits were quantile normalized residuals of
191 a linear mixed effect model where age was included as fixed effects, and the batches were considered
192 as random effects.

193 2.6. Detection of protein profiling in plasma

194 With an aptamer-based multiplex protein assay (SOMAscan v2, SomaLogic Inc, Boulder, CO)
195 [41,42], 1,129 proteins were measured (2013) on plasma samples collected between 2004 and 2011
196 from 211 female twins of the TwinsUK cohort (**Appendix A**).

197 2.7. Statistical analyses

198 All statistical analyses were run using R version 3.2.3. Linear mixed effect models were
199 conducted using the R lme of package lme4 [43], and linear models were done in using R function lm
200 of package stat. Custom R scripts developed for this study are available at this URL:
201 https://github.com/TiphaineCMartin/multiomic_AITD.git.

202 For determination of effective number of independent tests for different *-omic* data, association
203 studies between *-omics* features and thyroid phenotypes and heritability analysis for proteins
204 (**Appendix A**).

205 2.8. Genome-wide Association Analysis on IgG N-glycan traits

206 To define genetic variants (i.e., single nucleotide polymorphisms (SNP), short insertions and
207 deletions (indels)) associated with glycosylation profiles regardless of specific phenotypes in the
208 TwinsUK cohort, we ran analyses with the GenABEL software package [44] designed for genome-
209 wide association study (GWAS) analysis of family-based data by incorporating pairwise kinship
210 matrix calculated using genotyping data in the polygenic model to correct relatedness and hidden
211 population stratification. Data were recently published with other datasets [26,45]. We selected
212 genetic variants for each IgG N-glycan traits with a P-value under the GWAS threshold (P-value <
213 5×10^{-8}) and added the list of previously-defined genetic variants [29,45] (**Appendix A**).

214 2.9. Determination of shared genetic variants and genes between IgG N-glycan traits, immune cell traits, 215 protein abundance, and thyroid functions and diseases

216 To examine whether IgG N-glycan, immune cell traits, proteins, thyroid functions and
217 diseases shared genetic variants or genes, we compared the genetic variants from GWASs on
218 TwinsUK data (NHGRI GWAS catalog and other projects). As genetic variants detected by GWASs
219 could be lead genetic variants but not necessarily causal genetic variants [46], we extended the list of
220 genetic variants to other variants in linkage disequilibrium (LD) with an r^2 threshold of 0.8 from
221 1000G Phase 1 European population. Using HaploReg V4.1 [47] and GTEx data [32,33], we extracted
222 tissue-specific expression quantitative traits (eQTLs) associated with these genetic variants.

223 2.10. Visualization

224 Heatmaps were created in using R package ComplexHeatmap. Correlation plots were
225 created with R package corrplot. Boxplots and scatter plot were created in using R package ggplot2.

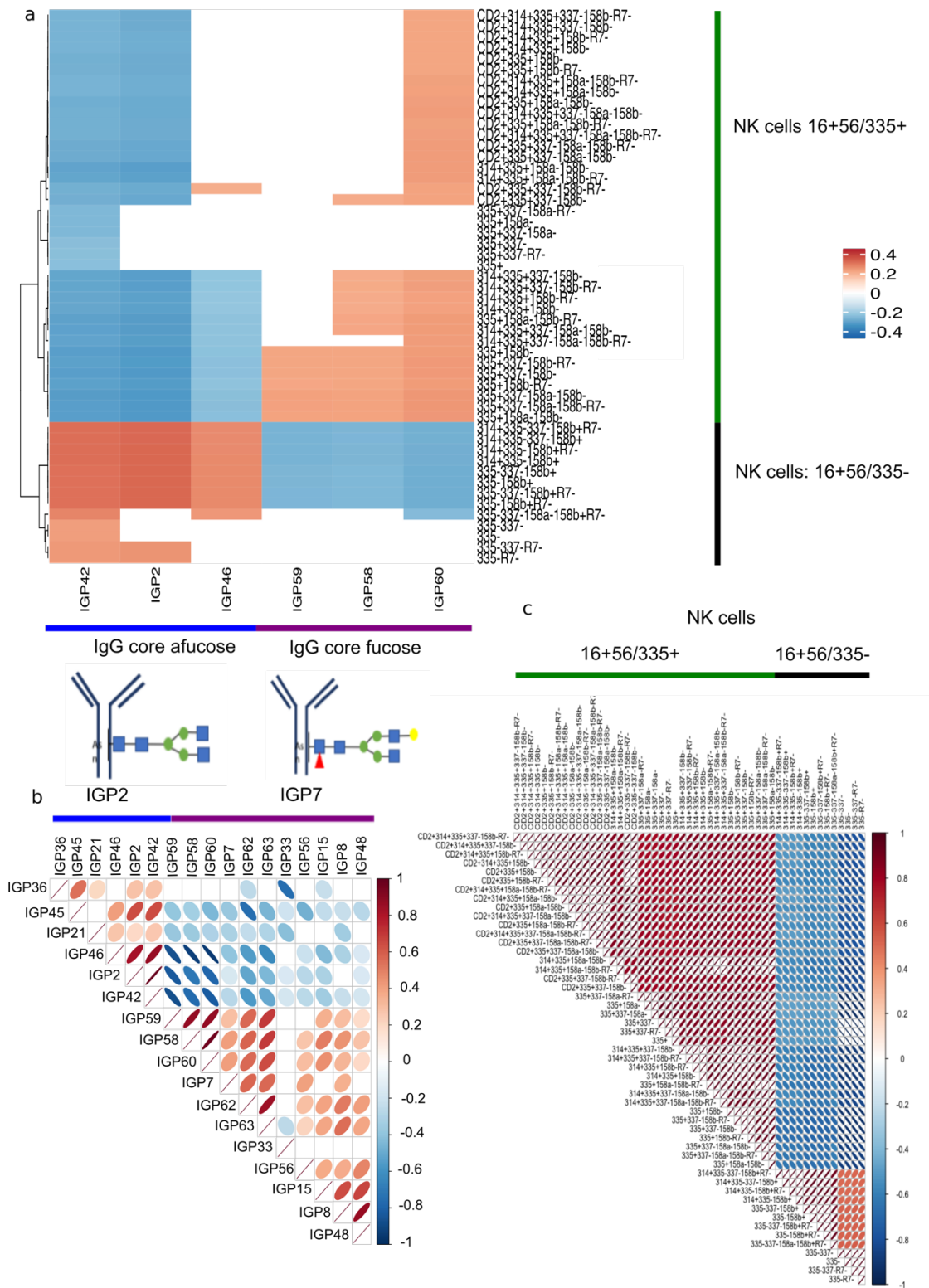
226 3. Results

227 3.1. Depletion of IgG core fucose is positively associated with increased CD158b+CD314+CD335- NK cell 228 subset counts

229 IgG N-glycosylation is considered indispensable for the effector functions of IgG and
230 inflammation control [48–52] and plays an essential role in the recognition and binding to Fc receptors
231 of immune cells [51]. Using high-resolution deep immunophenotyping flow cytometry analysis in
232 669 twins from the TwinsUK cohort and IgG N-Glycan traits in 2,297 twins from the same cohort
233 [4,27,28], we identified 383 samples with measurements of 23,485 immune cell and 17 AITD-IgG N-
234 glycan traits (IGP2, IGP7, IGP8, IGP15, IGP21, IGP33, IGP36, IGP42, IGP45, IGP46, IGP48, IGP56,
235 IGP58, IGP59, IGP60, IGP62 and IGP63) and searched for any associations between them (**Table S1**).

236 In our cohort, we identified 1,357 independent immune cell traits among 23,485 potential
237 tested immune cell traits, where the partial correlation between immune cell traits is highlighted in
238 **Fig. S1a**, 20 independent IgG N-glycan traits among 75 potential tested IgG N-glycan traits, and 6
239 independent AITD-IgG N-glycan traits among 17 potential tested AITD-IgG N-glycan traits [53].
240 Association studies of total IgG N-glycan traits with immune cell traits showed that 6 of the 17
241 identified significant IgG N-glycan traits (IGP2, IGP42, IGP46, IGP58, IGP59, IGP60) previously
242 associated with TPOAb level and AITD status in the TwinsUK cohort, were also associated with 51
243 immune cell traits, which are all NK cells (CD16+CD56) featuring different combinations of 6
244 immunoreceptors (CD2, CD158a, CD158b, CD314, CD335, R7) (**Table S2, Fig. 2**). Three IgG N-glycan
245 traits without core fucose (IGP2, IGP42, IGP46) were negatively associated with the level of the
246 activating subpopulation of CD16+CD56+CD158b-CD335+ NK cells and positively associated with the
247 level of the CD16+CD56+CD335- effector NK cell subpopulation and with the activating subpopulation
248 CD16+CD56+CD158b+CD314+CD335- NK cells [54–59]. In contrast, three other significant IgG N-
249 glycan traits with core fucose (IGP58, IGP59, and IGP60) had the opposite effect associations with the
250 same subpopulations of NK cells (**Fig. 2a**). In agreement with our previous report, there are therefore
251 negative correlations between the set of IgG N-glycan traits without core fucose (IGP2, IGP42, IGP46)
252 and the set of IgG N-glycan traits describing IgG core fucose (IGP58, IGP59, and IGP60) [4]
253 (highlighted in **Fig. 2b**). Moreover, we observed strong correlations between these 51 immune cell
254 traits (**Fig. 2c**). The presence of correlation patterns between the 17 AITD-IgG N-glycan traits (**Fig.**
255 **2b**) as well as between the 51 immune cell traits (**Fig. 2c**) is consistent with our observation of
256 correlations between the 6 AITD-IgG N-glycan traits and the 51 immune cell traits (**Fig. 2a**). When
257 we extended our analysis to the 58 remaining IgG N-glycan traits also identified in our samples, but
258 not associated with AITD, we observed no significant association between them and the 23,485
259 immune cell traits. Moreover, for 23,485 peripheral blood immune cell traits (**Table S1**), no significant
260 association with AITD or TPOAb level could be identified (**Fig. S1b**).

261 We conclude that a subpopulation of NK cells (CD16+CD56) and specifically the activating
262 subpopulation CD16+CD56+CD158b+CD314+CD335- NK cells is associated with fucose-depleted IgG
263 in individuals with AITD.



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Figure 2. AITD-IgG N-glycan traits associated with a subpopulation of NK cells. (a) Heatmap of immune cell traits associated with AITD-IgG N-glycan traits. The 51 NK cell types were significantly associated with 6 out of 17 AITD-IgG N-glycan traits previously identified [4]. Below the heatmap, there are one representative of IgG core afucose (IGP2) and one representative of IgG core fucose (IGP7), that were both associated with AITD and TPOAb levels [4]. (b) Co-expressions between only 17 IgG N-glycan traits previously associated significantly with AITD status and TPOAb level [4]. (c)

270 Correlations between the profile of 51 immune cell traits that were associated significantly with at
271 least one of 17 AITD-IgG N-glycan traits. The order of immune cell traits is the same as that in Fig 2a.

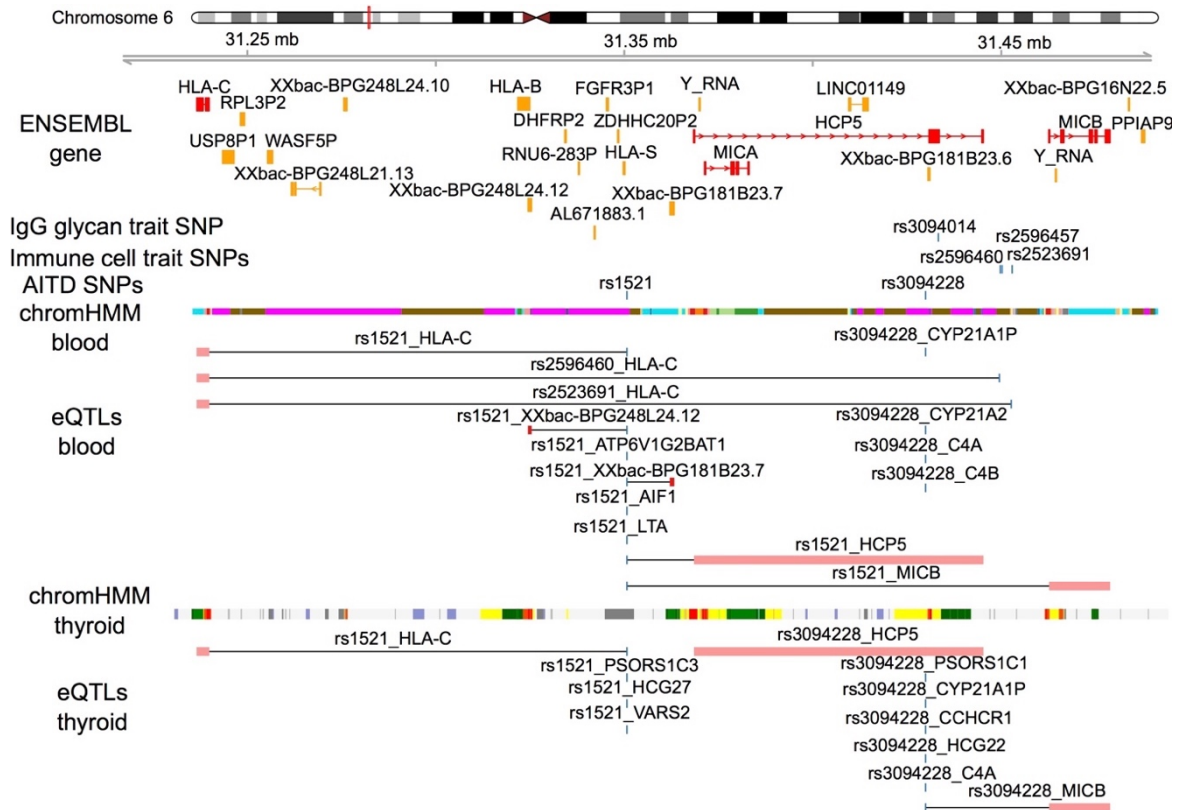
272 3.2. The AITD-associated genetic variants, rs1521 and rs3094228, alter thyroid cell expression of ligands for
273 CD314 and CD158b immunoreceptors

274 The NK cell receptors, CD335 (NKp46), CD314 (NKG2D) and the killer cell immunoglobulin-
275 like receptors (KIRs) including CD158b, are normally associated with activated NK cell states, T cell
276 co-stimulation, and mediating tumor cell lysis [55,57]. To determine whether genetic factors could
277 contribute to AITD, related immune features, or their pathways, we inspected genetic variants
278 associated with AITD, TPOAb levels, and immune cell traits from previous GWAS [27,28,30]. We
279 then compared these with recent large-scale studies on tissue-specific expression quantitative traits
280 (eQTLs) [35], mainly from the GTEx project [32–34] in blood and thyroid tissue.

281 No genetic variants previously associated with AITD or other thyroid phenotypes appeared
282 to be associated with the expression of CD335 or its known ligands in blood and thyroid cells.
283 However, we observed that two genetic variants, rs1521 and rs3094228, associated with Graves'
284 disease and TPOAb-positivity, respectively, fall in the gene regulatory regions of *MIC-A* and *MIC-B*
285 genes, two ligands of CD314 (NKG2D), and alter their gene expressions in thyroid cells [32–34,60–62]
286 (Fig. 3, Table S4, Fig. S2). These two AITD-genetic variants, rs1521 and rs3094228, also alter the
287 expression of the *HLA-C* gene, ligand of CD158b, in thyroid cells. The Graves' disease (GD) risk allele
288 of rs1521 variant is primary associated with a reduced expression of *HLA-C* gene, ligand of CD158b,
289 in thyroid cells. Furthermore, the TPOAb-positivity risk allele of rs3094228 variant is primary
290 associated with an increased expression of *MIC-B* gene, ligand of CD314 (NKG2D), in thyroid cells.
291 As about 75% of patients with Graves' disease have TPOAb-positivity and rs3094228 that has been
292 associated with TPOAb-positivity and Graves' disease [61,63], it is possible that the association of
293 rs1521 with Graves' disease could be also driven by TPOAb-positivity and, so, associated with its
294 phenotypes. Downregulation of *HLA-C* gene expression and upregulation of *MIC-A* and *MIC-B* gene
295 expression in thyrocytes could activate NK cell functions and the cytokine production against
296 thyrocytes when NK cells and thyrocytes are in contact.

297 Furthermore, three genetic variants, rs2596460, rs2596457 and rs2523691, previously
298 associated with higher levels of the subpopulation of NK cells featuring CD16⁺CD56/CD2-
299 CD314⁺CD335⁺CD337⁺CD158a⁺CD158b⁺ [28], are in the same haplotype as the rs3094228 genetic
300 variant, but with a low linkage disequilibrium (LD, $r^2 < 0.8$) (Table S5). Potentially, one of the genetic
301 variants in this locus are the causal genetic variant of higher abundance of CD158b⁺CD314⁺CD335-
302 NK cells. All of the three genetic variants could also alter the expression of the *HLA-C* gene, ligand
303 of CD158b, and *MIC-A*, ligand of CD314 (NKG2D), in immune cells [32–34,64] (Fig. 3, Table S4).

304 Overall, two genetic variants, rs1521 and rs3094228, associated with, respectively, Graves'
305 disease and TPOAb-positivity, appear to alter thyrocyte expression of ligands of two
306 immunoreceptors of NK cells, CD314 and CD158b; both of which have the capacity to enhance
307 cytotoxicity of NK cells after binding with target cells. Additionally, three genetic variants in the same
308 haplotype than rs3094228 could increase the abundance of the immune active CD158b⁺CD314⁺CD335-
309 NK cell subpopulation.



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Figure 3. Association of immune cell traits with AITD status. Annotation tracks around *MIC-A*, *MIC-B* and *HLA-C* genes visualize significant GWAS hits for immune cell traits, the ligands of certain immunoreceptors (such as NK), and thyroid phenotypes previously identified in the TwinsUK cohort as well as chromatin states identified using chromHMM from whole blood from ENCODE [65] and thyroid cells from CEMT [66] and eQTLs from GTEx project [32,33]. The plot was produced using functions from R packages Gviz and coMET [67].

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3.3. AITD is associated with increased serum Caspase-2 and IL-1 α

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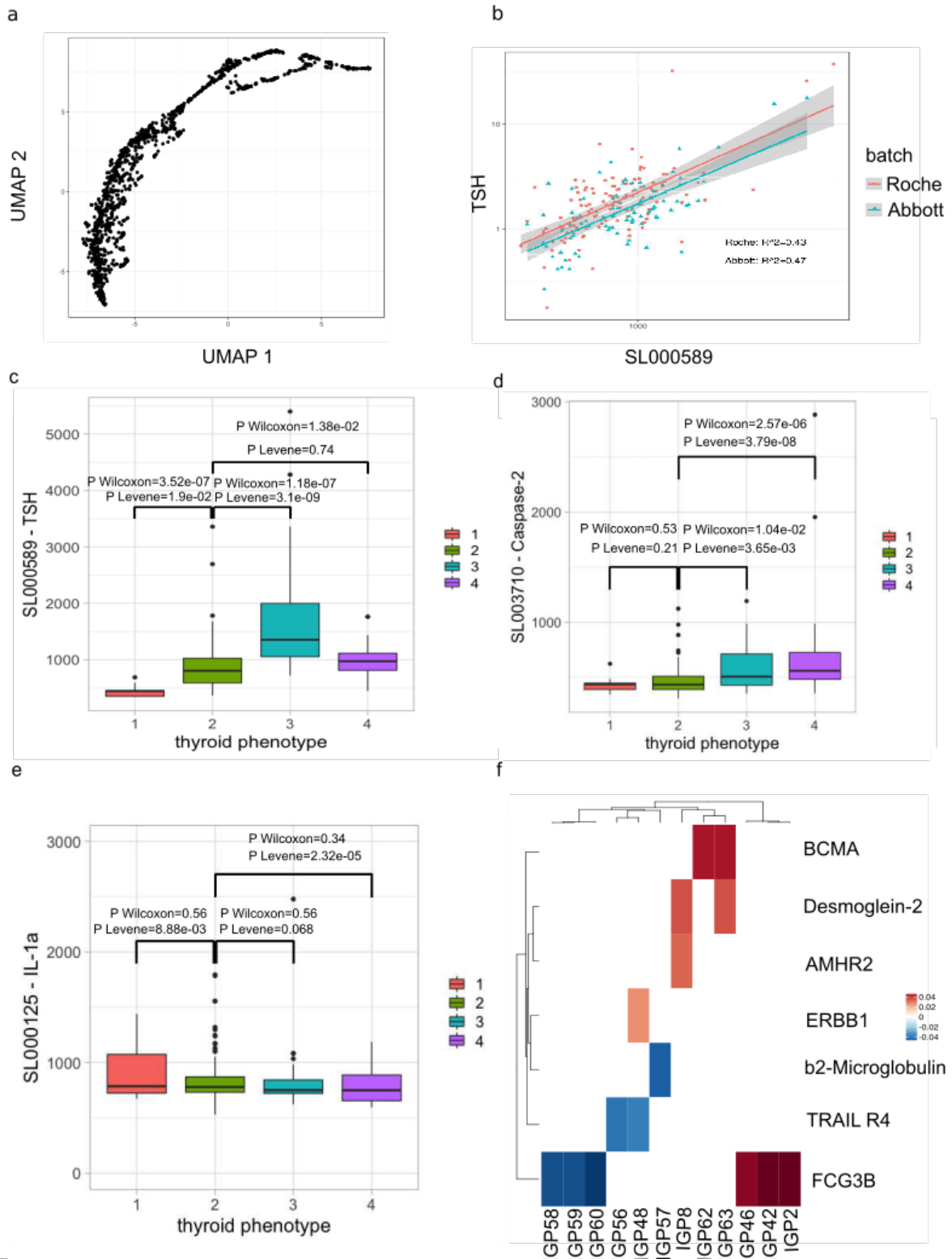
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We next evaluated whether the abundance of 1,113 free soluble proteins, which are partially correlated between each other (**Fig. 4a**), in peripheral blood may be associated with AITD status (27 AITD patients versus 130 healthy controls) and TPOAb levels (155 individuals of whom 25 have AITD) in the TwinsUK cohort (**Table S1**) using aptamer-based multiplex protein assay (SOMAscan) [68]. Firstly, we observed significant moderate correlations of the TSH levels measured by two clinical-certificated assays (Abbott and Roche) with the TSH levels measured by the SOMAscan assay (**Fig. 4b**). This indicated that the SOMAscan assay could reproduce with good accuracy the estimation of TSH levels and probably also for other proteins. Levels of three proteins were positively associated with AITD status (Bonferroni multiple testing correction, P -value $<1.9 \times 10^{-4}$): TSH (P -value $=8.67 \times 10^{-5}$; Beta=0.67; SE=0.16), Caspase-2 (CASP-2; P -value $=2.72 \times 10^{-7}$; Beta=1.10; SE=0.20) and Interleukin-1 α (IL-1 α ; P -value $=7.46 \times 10^{-5}$; Beta=0.41; SE=0.09). We also observed higher mean levels of TSH in patients with AITD (mean_{SOMAscan}=1443.9, sd_{SOMAscan}=1238.5; mean_{clinical}=7.1 IU/mL, sd_{clinical}=10.47) or TPOAb-positivity (mean_{SOMAscan}=1389.9, sd_{SOMAscan}=1018.3; mean_{clinical}=5.7 IU/mL, sd_{clinical}=7.55) compared with controls (euthyroidism with TPOAb-negative) (mean_{SOMAscan}=851.1, sd_{SOMAscan}=368.6; mean_{clinical}=1.64 IU/mL, sd_{clinical}=0.79). Although Caspase-2 and IL-1 α levels were associated with AITD status, Caspase-2 and IL-1 α levels were not associated with TPOAb or TSH levels as continuous variables (P -value $>1.9 \times 10^{-4}$). However, when participants were divided into 4 categories according to TSH and TPOAb levels (**Fig. 4c**), reflecting different clinical categories (hyperthyroidism, euthyroidism/TPOAb-negative, hypothyroidism and euthyroidism/TPOAb-positive), Caspase-2 showed significantly higher mean and variance in two groups: hypothyroidism and euthyroidism/TPOAb-positive (**Fig. 4d**). The hypothyroidism and euthyroidism/TPOAb-positivity in

339 this cohort potentially indicate underlying Hashimoto's thyroiditis (HT). This is because HT is the
340 most common cause of hypothyroidism, spontaneous hypothyroidism (i.e. no previous history of
341 thyroid ablation) is almost always caused by HT, and euthyroid individuals with TPOAb-positivity
342 almost always have HT when studied by cytology and histopathology [69–71]. On the other hand,
343 the variance of IL-1 α was significantly larger in groups with euthyroidism/TPOAb-positive and
344 hyperthyroidism (**Fig. 4e**), but there was no significant difference for their mean values. Hence,
345 individuals from 4 categories have the same levels of IL-1 α , but there are more inter-individual
346 variabilities in euthyroidism/TPOAb-positive and hyperthyroidism than euthyroidism/TPOAb-
347 negative and hypothyroidism.

348 In summary, we confirmed the association of the plasma TSH levels with AITD status, and
349 we found two novel associations of plasma Caspase-2 and IL-1 α with AITD status, but their secretion
350 (mean and variance) seems to also depend on other factors associated with thyroid diseases such as
351 the levels of TSH and TPOAb.



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Figure 4. Association of circulating protein abundances with thyroid diseases and with AITD-IgG N-glycan structures. (a) 1,113 circulating proteins were arranged in two dimensions based on the similarity of their secretion profiles in the serum by the dimensionality reduction technique UMAP [72] using R package umapr [73]. (b) Correlation of log₁₀-transformed TSH measurements between two clinical FDA approved clinical immunoassays (Roche and Abbott) and SOMAscan assay in 217 individuals (122 using Roche immunoassay and 95 using Abbott immunoassay). (c) Box plot of the level of circulating TSH measured by SOMAscan assay in the serum according to the group of thyroid status. (d) Box plot of the level of circulating Caspase-2 measured by SOMAscan assay in the serum according to the group of TSH. (e) Box plot of the level of circulating IL-1 α measured by SOMAscan

362 assay. An extreme outlier sample in the group 4 with an IL-1 α of 250,000mg/ml was discarded for
363 the analysis. (f) Heatmap of circulating protein abundances associated with AITD-IgG N-glycan
364 structures. In fig.2c-e, participants were assigned to 4 categories according to TSH level and TPOAb
365 status: 1=hyperthyroidism (TSH \leq 0.1 mIU/L; 13 individuals), 2=euthyroidism/TPOAb-negative
366 (0.4<TSH>4 mIU/L & TPOAb < 6 IU/mL (Abbott) or TPOAb < 34 IU/mL (Roche); 196 healthy
367 individuals), 3=hypothyroidism (TSH \geq 4 mIU/L; 21 individuals), and 4=euthyroidism/TPOAb-
368 positive (0.4<TSH>4 mIU/L & TPOAb \geq 6 IU/mL (Abbott) or TPOAb \geq 34 IU/mL (Roche); 28
369 individuals). Wilcoxon-Mann-Whitney's test has been performed between groups to estimate
370 whether there are mean differences whereas Levene's test has been performed between groups to
371 estimate whether there are variance differences.

372 3.4. Afucosylated IgG is associated with serum levels of several circulating proteins

373 When we studied the correlation between the level of secreted TSH, Caspase-2 and IL-1 α
374 proteins and IgG N-glycan trait levels in 164 individuals of whom 27 have AITD, we found no
375 significant associations (P-value $>$ 8.3 \times 10⁻⁴, Bonferroni test considering 3 independent proteins and 20
376 independent IgG N-glycan traits) (Table S6, Fig. 4f). However, several AITD-IgG N-glycan traits
377 appeared to be associated with 7 other circulating proteins (AMHR2, BCMA, β 2-microglobulin,
378 ERBB1, Desmoglein-2, TRAILR4, and FCGR3B) (P-value $<$ 3.67 \times 10⁻⁵, Bonferroni test in considering
379 only 227 independent proteins and 6 independent IgG N-glycan traits) (Table S6, Fig. 4f). For
380 example, three AITD-IgG N-glycan traits (IGP2, IGP42, and IGP46) were positively associated with
381 circulating FCGR3B (Fc γ RIIIb or CD16b), an Fc receptor expressed by polymorphonuclear
382 neutrophils (PMN), whereas three AITD-IgG N-glycan traits (IGP58, IGP59, and IGP60) were
383 negatively associated with the antibody Fc receptor FCGR3B. Also, IGP56 and IGP48 were negatively
384 associated with β 2-microglobulin, involved in the presentation of intracellular antigens through the
385 MHC class I complex; and IGP48 was positively associated with ERBB1, the epidermal growth factor
386 receptor (EGFR), a checkpoint molecule associated with cellular proliferation and differentiation.

387 Overall, 12 AITD-IgG N-glycan traits (IGP2, IGP8, IGP42, IGP46, IGP48, IGP56, IGP57, IGP58,
388 IGP59, IGP60, IGP62, and IGP63) were associated with serum levels of 7 circulating proteins
389 (AMHR2, BCMA, β 2-microglobulin, ERBB1, Desmoglein-2, TRAILR4, and FCGR3B) in the TwinsUK
390 cohort.

391 3.5. Free-soluble plasma Desmoglein-2 protein is associated with AITD genetic variants and two AITD-IgG 392 N-glycan traits

393 We evaluated several GWAS on secreted proteins (protein quantification locus traits, pQTL)
394 [31], to determine whether the secretion of proteins associated with AITD or with AITD-IgG N-glycan
395 traits are driven by AITD genetic variants. We found no genetic variants associated with any of 17
396 AITD-IgG N-glycan structures that are also pQTL. However, four genetic variants associated with
397 thyroid phenotypes published in the GWAS catalog (rs3761959, rs7528684, rs505922, and rs3184504)
398 were also associated in *cis* and *trans* with nine circulating protein abundances (BGAT, CHSTB, DC-
399 SIGN, Desmoglein-2, DYR, FCRL3, GP1BA, MBL, and VCAM-1) (Table S7). None of these proteins
400 were associated directly with AITD or TPOAb levels in our study. However, we found that
401 Desmoglein-2 was associated with two AITD-IgG N-glycan traits, IGP8, and IGP63 [4] (Fig. S3).
402 Desmoglein-2 is highly expressed in epithelial cells including thyrocytes and cardiomyocytes and
403 plays a role in the cell-cell junctions between epithelial, myocardial, and certain other cell types and
404 is thought to be a regulator of apoptosis [74].

405 Therefore, four genetic variants associated with thyroid phenotypes are also associated with nine
406 secreted protein abundances, including the apoptosis regulator Desmoglein-2 in blood. Desmoglein-
407 2 was also associated with two AITD-IgG N-glycan traits.

408 4. Discussion

409 The dysregulation of the immune system may affect several biological structures and
410 processes in AITD, such as antigen/antibody/Fc receptor complex formation, possibly driven by

411 genetic and environmental factors [75]. Little is known about the key players and the genetic variants
412 identified in previous GWASs of patients with AITD. Targeting of self-antigen expressing tissues by
413 immune cells may depend on the formation of antigen/antibody/Fc receptor complexes featuring
414 substantial affinity or avidity properties. In the peripheral blood of individuals with AITD, we
415 previously detected depletion in IgG core fucose that is known to enhance such interactions and may
416 influence immune effector cell engagement of target cells by antibodies. We proposed that this
417 signature is associated with TPOAb levels and with immune effector cell activation in patients with
418 AITD [4]. Here, we reveal immune and genetic features pointing to activated NK cell subsets, thyroid
419 cell-derived ligands for immunoreceptors on NK cells, alongside secreted mediators of apoptosis and
420 immune activation, all signals of heightened antibody and innate effector cell responses in AITD.

421 We applied an *in silico* multi-omic approach on peripheral blood specimens from individuals
422 from the TwinsUK cohort to investigate any association between immune features and genetic
423 variants in AITD. In AITD patient samples, we observed increased levels of three circulating proteins
424 (TSH, Caspase-2, and Interleukin-1 α) and a decreased level of IgG core fucosylation associated with
425 an activated subpopulation of NK cells defined primarily by the expression of CD335, CD134, and
426 CD158b receptors. Our data confirms the previously reported association of plasma TSH level with
427 AITD status and also reveals previously unknown potential biomarkers for AITD, which are highly
428 associated with immunological activation functions, such as ADCC, apoptosis and pro-inflammatory
429 pathways. Furthermore, several genetic variants previously associated with AITD appear to alter
430 thyrocyte gene expression of several ligands of NK immunoreceptors and abundance of plasma
431 circulating proteins. This suggest that the genetic background may also play potential roles in NK
432 cell activation likely focused on thyroid cells in individuals with AITD.

433 To our knowledge, no other cohorts have large datasets that are available to interrogate and
434 feature the same diversity of *-omics* data with AITD phenotype or TPOAb levels. In our studies, we
435 note an imbalance in the sample sizes between control individual groups and AITD groups. This is
436 because the dataset comes from unselected twins and reflects the general European population [37],
437 where approximately 5% of the population, but 5-15% for women, present individuals with AITD [5–
438 7]. To overcome such imbalances in our sample sizes and low samples sizes with large *-omics* data,
439 we applied machine learning and non-parametric methods with correction for multiple testing.
440 Another limitation in our present study is the absence of AITD clinical diagnosis confirmed by
441 clinicians for all individuals. We consequently applied more stringent criteria to define patients with
442 AITD versus control individuals, by using TSH and TPOAb levels (see Section 2.3 of our Materials &
443 Methods). We also performed analysis on TPOAb levels, as this is considered the main clinical
444 quantitative biomarker of AITD status [38–40]. Replication and meta-analysis studies on larger *-omic*
445 datasets incorporating clinical features will help to confirm our present findings.

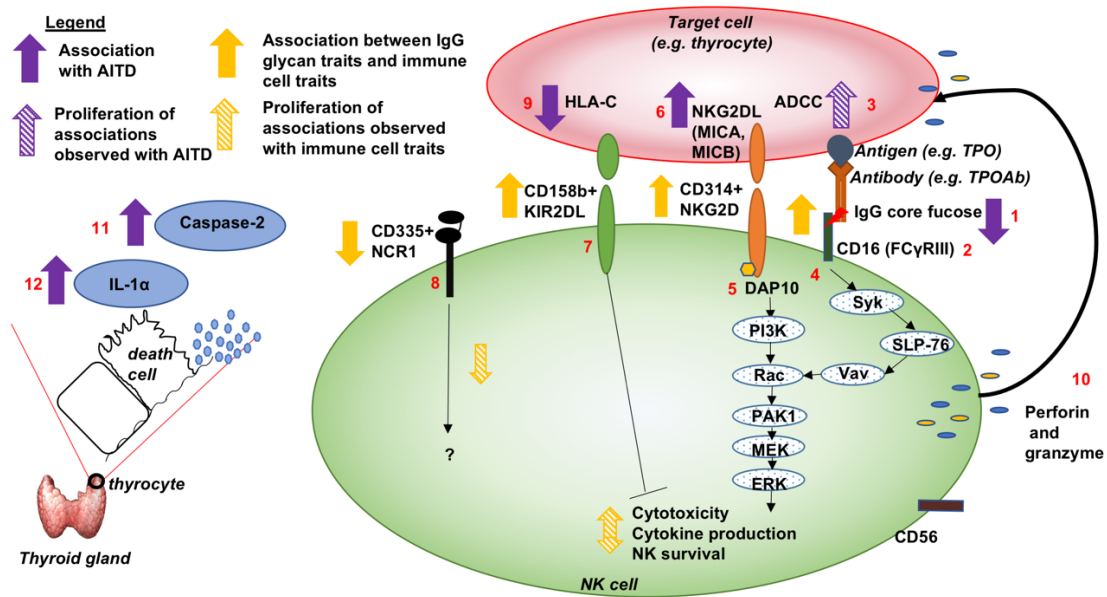
446 Two secreted proteins (Caspase-2 and IL-1 α), which play roles in apoptosis and the
447 inflammatory response, were positively associated with AITD. TPOAb have been proposed to target
448 thyroid cells by engaging effector cells via their Fc receptors [4,14,15,76,77], and the apoptosis protein
449 Caspase-2 may represent a marker potentially signifying antibody-mediated destruction of thyroid
450 cells [78]. In concordance, IL-1 α , produced by activated immune, epithelial and endothelial cells in
451 response to cell injury and apoptosis, is considered an apoptosis index of the target cell [79] and
452 proportional to the degree of lymphoid infiltration in thyroid disorders [80]. IL-1 α seems to reduce
453 the thyroid epithelial barrier, even in the absence of any other signs of cytotoxicity [81]. In
454 concordance, in our study we found higher levels of secreted IL-1 α in AITD blood compared with
455 levels in healthy individuals, and its variance was greater in euthyroidism/TPOAb-positive blood
456 and in hyperthyroidism. This may signify dysregulation in cellular structures in the thyroid gland.
457 Overall, Caspase-2 and IL-1 α may reflect the degree of thyroid cell death or apoptosis and of
458 lymphoid infiltration towards the thyroid gland.

459 A subpopulation of NK cells expressing combinations of immunoreceptors (CD2, CD158a,
460 CD158b, CD314, CD335, R7) was associated with the depletion of IgG core fucose in individuals with
461 AITD. These included an activating NK receptor (CD314) and a differentiation receptor (CD335);
462 whilst, fucose-depleted IgG was also positively associated with a subpopulation of NK cells with an

463 inhibitory NK receptor (CD158b) [54–59,82]. The combination of potentially autoreactive antibodies
464 with enhanced Fc domains and activated effector cells such as NK cells may signal increased
465 inflammation and susceptibility to autoimmune disease [83]. Previous studies showed that
466 afucosylated antibodies have a much higher affinity (100-fold) for Fc γ R3a (CD16a) and may thus
467 have enhanced ADCC [84]. Moreover, ADCC via Fc γ R3a may require NK cells, but not monocytes
468 or polymorphonuclear cells, and activity levels of the antigen/antibody/effector cell complexes have
469 been correlated only with the NK cell numbers present in the PBMC [20]. Our associations between
470 the levels of IgG core fucose and of a subpopulation of NK cells reinforce the notion that there is a
471 complementarity between IgG core fucose levels and NK cells, that could influence effector cell
472 potency, potentially against a range of antigens including self-antigens.

473 It has been previously estimated that AITD are highly heritable (55-75%) and that most of
474 IgG N-glycan traits and the immune cell traits associated with AITD are moderately heritable (**Table**
475 **S8**) [4,27]. By estimating the proportion of genetic and environmental variance of 1,129 proteins in
476 our study using the Structural Equation Modeling and twin structures present in the TwinsUK cohort
477 (**Table S9**), we found a small proportion of proteins having additive genetic variances in their
478 heritability, in concordance with previous findings on a smaller dataset [85]. As the best model of
479 heritability in AITD is only with dominant genetic variance, the shared genetic variance between
480 AITD and proteins as well as with IgG N-glycan traits and immune cell traits could not be estimated
481 with accuracy. However, in our study, we identified several genetic variants previously associated
482 with thyroid phenotypes to be also associated with the secretion of proteins and gene expression of
483 ligands of two NK cell immunoreceptors. Specifically, genetic variants, rs1521 and rs3094228,
484 associated with Graves' disease and TPOAb-positivity, alter the expression of thyroid cell-expressed
485 ligands, *MIC-A*, *MIC-B*, and *HLA-C*, known to recognize CD314 and CD158b immunoreceptors
486 expressed on NK cells. Moreover, rs3094228 falls in the same European haplotype as three genetic
487 variants associated with higher abundance of the activated CD158b⁺CD314⁺CD335⁻ NK cell subset.
488 Thus, individuals having the AITD-risk allele of rs1521 variant have reduced expression of *HLA-C*
489 gene and, at a lesser extent, expression of *MIC-A* in thyrocytes, whereas the carriers of AITD-risk
490 allele of rs3094228 genetic variant associated with TPOAb-positivity showed increased expression of
491 *MIC-B* gene in thyrocytes and potentially higher abundance of the highly active
492 CD158b⁺CD314⁺CD335⁻ NK cells. Consequently, if the thyrocytes in carriers of AITD-risk alleles for
493 CD158b and CD314 ligands crosstalk with the subpopulation of NK cells with CD158b and CD314
494 immunoreceptors with the help of the antibodies, they could trigger the production of cytokines and
495 cytotoxicity against thyrocytes by these NK cells.

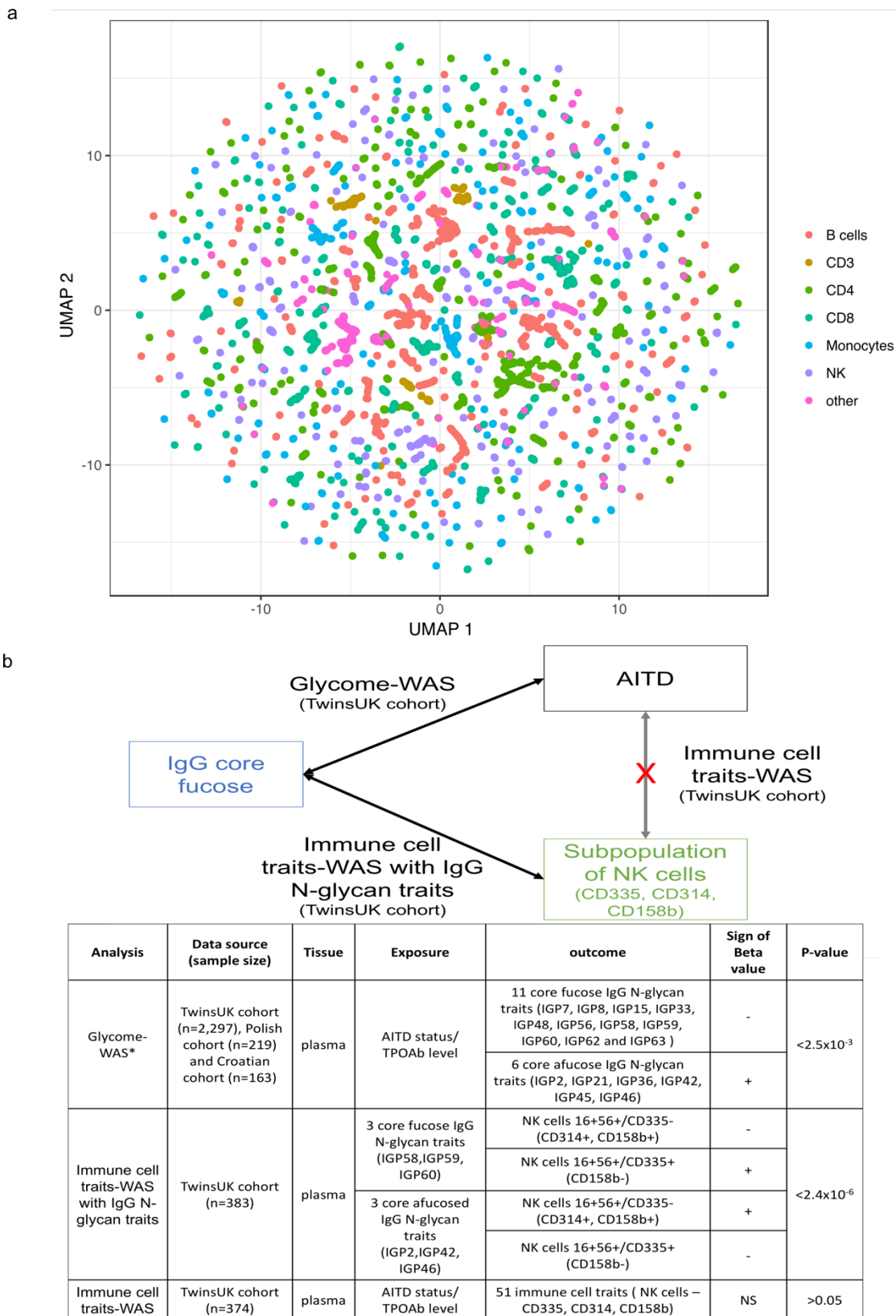
496 Our findings thus highlight different immune features (glycan structures on antibodies, a
497 subpopulation of immunoactive NK cells, the secretion of Caspase-2 and IL-1 α) as potential signals
498 of AITD status detectable in the bloodstream in addition to TSH and TPOAb levels. Moreover, if one
499 speculates that active antibodies with low core-fucose might be thyroid autoantibodies (e.g., TPOAb)
500 [86] and target cells are thyroid cells, it is conceivable (**Fig. 5**) that that immune cell-antibody-target
501 cell interactions may lead to cytotoxicity functions targeting thyroid tissues [76,86,87]. Together, these
502 may form part of a dysregulated autoimmune response in AITD. Further replication studies and
503 validation studies of real-time functional evaluations associated with these immune features and
504 genetic analyses are needed to confirm this model. These features could also be tested in the context
505 of thyroid cancer immunotherapy [77] in future studies.



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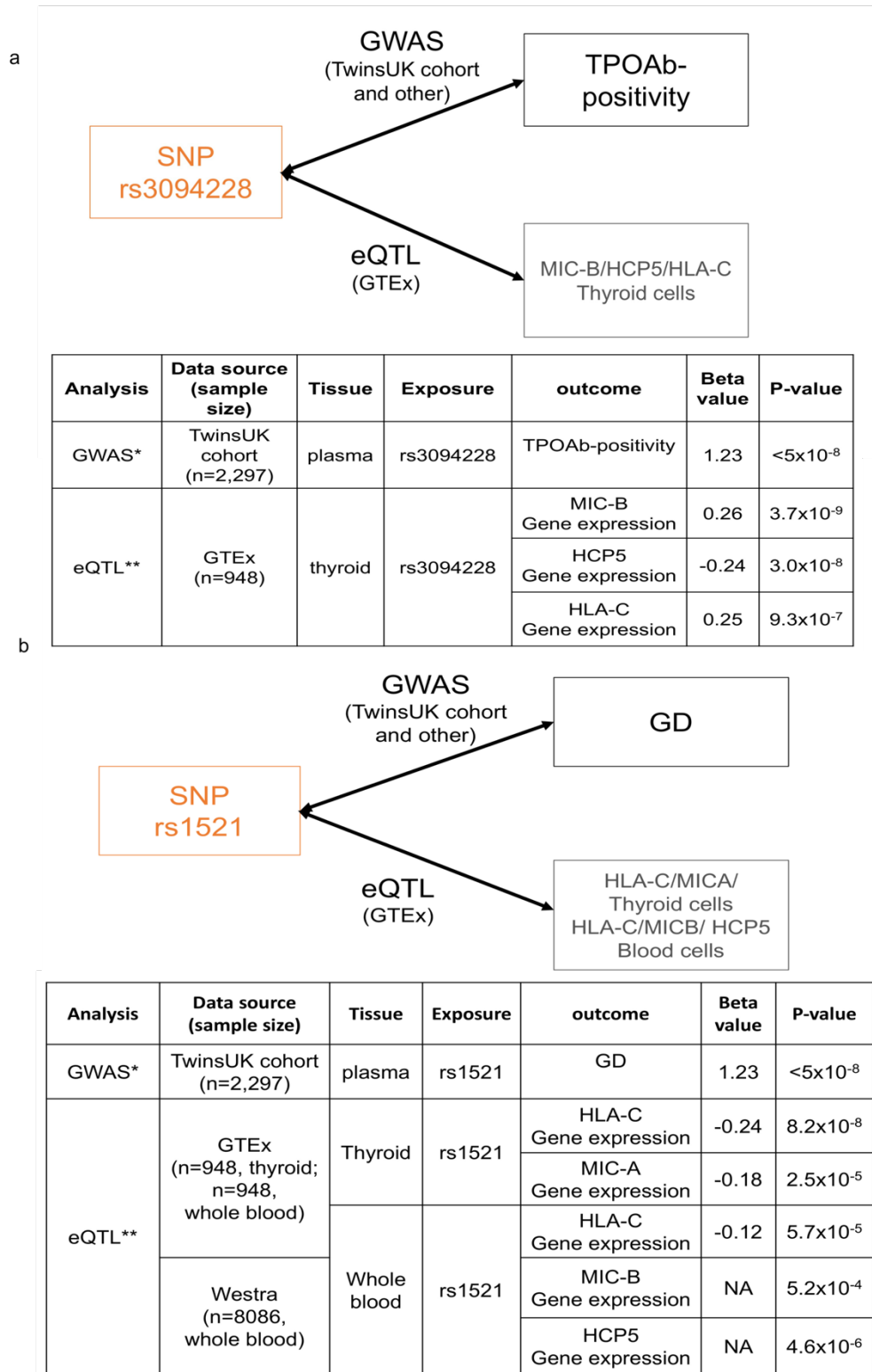
Figure 5. Model of different potential contributing players and their pathways activated in proposed antibody-dependent NK cell-mediated cytotoxicity in the thyroid gland of AITD patients. 1) The depletion of IgG core fucose was associated with TPOAb level and AITD status [4]. 2) The IgG N-glycan traits associated with AITD were also associated with a subpopulation of NK cells in our current study; for example, the depletion of IgG core fucose is associated positively with NK cells with the patterns of co-receptors CD335- or CD335-CD158b+CD314+. 3) Previous studies showed that afucosylated antibodies had increased affinity for binding to CD16 (FcγRIIIa), cell receptors of NK cells, and to enhance ADCC [18–21] via 4) protein tyrosine kinase-dependent pathways, through crosstalk with 5) NKG2D receptor (CD314) [88,89]. 6) Two SNPs, rs3094228 and rs1521, were associated with GD and TPOAb-positivity [60–62] and fall in gene regulatory regions of the *MIC-A* and *MIC-B* genes and increase their expression in thyroid cells [32]. These two genes encode heavily glycosylated proteins that are ligands for the NKG2D type II receptor (CD314). 7) The KIR2DL (CD158b) receptor is known to regulate the cytotoxicity of NK cells by unknown pathways, whereas 8) the NCR1 (CD335) receptor can contribute to the increased potency of activated NK cells to mediate cell lysis by unknown pathway [54,55]. 9) The SNP, rs1521 associated with GD[60], is also shown to reduce the expression of HLA-C gene, producing the ligand of CD158b, in thyroid cells [32,33,58,59]. 10) All together (the binding of NK cells with target cells through antibodies and their ligands), these lead to the activation of NK cells, which release cytotoxic granules containing perforin and granzymes. This release mediates ADCC of target cells (3), which are thyrocytes in AITD. Also, 11) a positive association between the circulation abundance of Caspase-2 protein and AITD were found in this study that could be associated with the destruction of thyrocytes. 12) A positive correlation of circulating abundance of IL-1α with AITD was also found in the bloodstream that could be a marker of lymphocyte infiltration in the thyroid gland of individuals with AITD, and thus of inflammation [80,81].

531 **Supplementary Materials:** The following are available online at www.mdpi.com/xxx/s1,



532

533 Figure S1: Immune cell traits and AITD status. (a) Immune cell traits were arranged in two dimensions based on
 534 the similarity of their quantification profiles by the dimensionality reduction technique UMAP [72] using R
 535 package umapr [73]. Some clusters that emerge spontaneously can be associated with specific immune cell types
 536 (colors). (b) Overview of associations observed between IgG core-fucose, a subpopulation of NK cells and AITD
 537 status in the TwinsUK cohort. *Glycome-wide association studies of AITD and TPOAb levels were previously
 538 performed [4].



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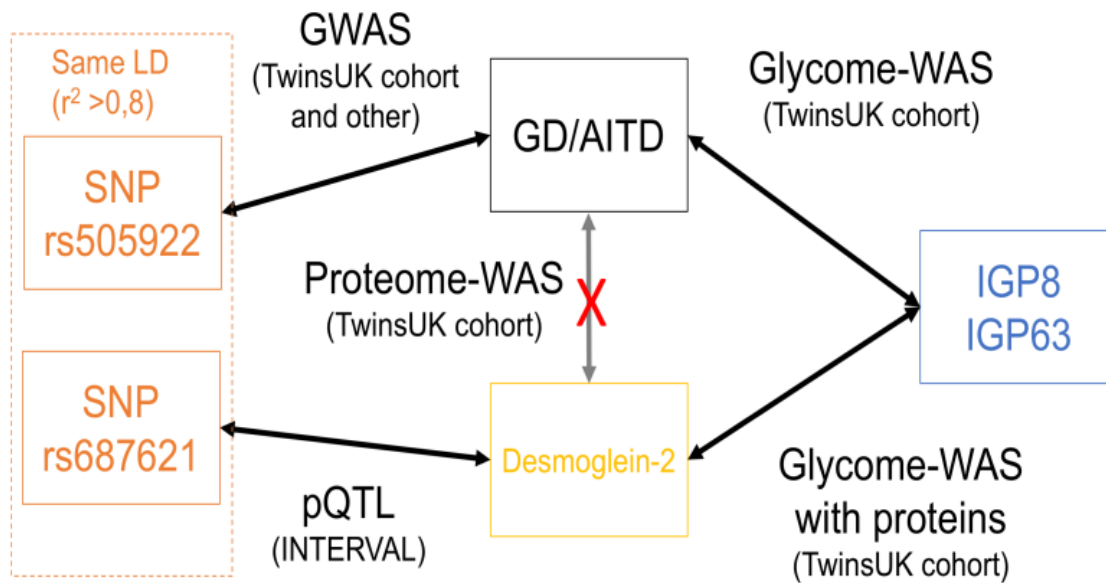
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Figure S2. Overview of associations between AITD-SNP and eQTL in thyroid and blood cells. *Genome-wide association studies of AITD and TPOAb-positivity were previously performed, and the findings are available via GWAS catalog [30] whereas **eQTLs come from GTEx project [34] and Westra and al. [35]. (a) Associations between AITD-SNP and eQTL in thyroid and blood cells for the genetic variant rs3094228. (b) Associations between AITD-SNP and eQTL in thyroid and blood cells for the genetic variant rs1521.



Analysis	Data source (sample size)	Tissue	Exposure	outcome	Beta value/ OR	P-value
GWAS*	TwinsUK cohort (n=2,297)	plasma	rs505922	GD	1.13	<2.5x10 ⁻³
Protein-quantitative trait loci**	INTERVAL (n=3,301)	plasma	rs687621	Desmoglein-2	0.20	1.9x10 ⁻¹¹
Protein-WAS	TwinsUK cohort (n= up to 348)	plasma	AITD status/ TPOAb level	Desmoglein-2	NS	>1.9x10 ⁻⁴
Glycome-WAS***	TwinsUK cohort (n=2,297), Polish cohort (n=219) and Croatian cohort (n=163)	plasma	AITD status/ TPOAb level	IGP8	-6.93	2.1x10 ⁻³
				IGP63	-7.23	1.2x10 ⁻³
Protein-WAS	TwinsUK cohort (n= 164)	plasma	IGP8	Desmoglein-2	0.032	2.2x10 ⁻⁶
			IGP63	Desmoglein-2	0.032	8.0x10 ⁻⁶

545

546 Figure S3. Overview of multi-omic findings associated with Desmoglein-2 in individuals with AITD status and
 547 general population. We highlighted a locus with high LD having SNPs and two IgG glycan traits that are both
 548 associated with GD and the abundance of secreted plasma Desmoglein-2 in plasma. However, no direct
 549 association of AITD status with the abundance of secreted plasma Desmoglein-2. We previously performed
 550 glycome-wide association studies of AITD and TPOAb levels [4]. Genome-wide association studies of AITD and
 551 TPOAb-positivity were previously performed, and the findings are available via GWAS catalog [30] whereas
 552 pQTLs come from INTERVAL project[31]. IGP8 = the percentage of FA2[3]G1 glycan in total IgG glycans. IGP63
 553 = The percentage of fucosylation (without bisecting GlcNAc) of agalactosylated structures.

554 Table S1: Description of TwinsUK cohort used for different analysis performed here

555 Table S2: Significant glycome associations with immune cell traits in the TwinsUK cohort

556 Table S3: Associations of 51 immune cell traits with AITD and TPOAb level in the TwinsUK cohort

557 Table S4: Hits from selected eQTL studies for two SNPs, rs1521 and rs3094228 in the thyroid cells and whole
 558 blood

559 Table S5: Genes reported for genetic variants associated with thyroid phenotypes and immune cell traits

560 Table S6: Glycome-wide associations studies of 17 AITD-IgG N-glycan traits with 1,113 circulating proteins.
561 Only significant ones were put here.

562 Table S7: Genetic variants associated with thyroid phenotypes and AITD-IgG N-glycan traits overlapping pQTL
563 identified in INTERVAL project (LD $r^2 > 0.8$)

564 Table S8: Heritability of AITD, 17 IgG N-glycan traits and 51 immune cell traits in the TwinsUK cohort

565 Table S9: Heritability of 1,113 proteins in the TwinsUK cohort

566 **Abbreviations.** ADCC (Antibody-Dependent Cell-mediated Cytotoxicity), AITD (AutoImmune Thyroid
567 Diseases), CDC (Complement-Dependent Cytotoxicity), CD158b (KIR2DL2/L3 - Killer Cell Immunoglobulin
568 Like Receptor, Two Ig Domains And Long Cytoplasmic Tail 2 or 3 - or NKAT6 - Natural Killer-Associated
569 Transcript 6), CD314 (NKG2D or KLRK1 - Killer Cell Lectin Like Receptor K1), eQTL (gene Expression
570 Quantitative Trait Loci), Fc γ R (Fc gamma Receptor), GD (Graves' Diseases), GlcNAc (N-acetylglucosamine),
571 GWAS (Genome-wide Association Study), HT (Hashimoto's thyroiditis), IgG (Immunoglobulin G), MIC-A
572 (MHC Class I Polypeptide-Related Sequence A), MIC-B (MHC Class I Polypeptide-Related Sequence B), NK
573 (Natural Killer cell), PBMC (Peripheral Blood Mononuclear Cells), pQTL (Protein expression Quantitative Trait
574 Loci), Tg (Thyroglobulin), TSH (Thyroid-Stimulating Hormone), TSH-R (Thyroid-Stimulating Hormone
575 Receptor), TPO (Thyroid Peroxidase), TPOAb (TPO Antibody).

576 **Author Contributions:** Conceptualization, T.C.M.; methodology, T.C.M.; software, T.C.M.; formal analysis,
577 T.C.M.; investigation, T.C.M.; resources, M.R., G.L., S.J.K, R.J.B.D, C.S, E.M.L., J.P.W., and S.G.W.; data curation,
578 T.C.M., A.V., and M.M.; project administration, T.C.M. and T.D.S.; writing—original draft preparation, T.C.M.;
579 writing—review and editing, T.C.M., S.N.K., T.D.S., J.P.W., K.I., M.B., M.P., and J.T.B.; validation, T.C.M. and
580 T.D.S.; visualization, T.C.M.; supervision, S.N.K. and T.D.S.; funding acquisition, T.D.S., S.G.W., G.L., and
581 S.N.K.. All authors have read and agreed to the published version of the manuscript.

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603 in high-throughput glycomic analysis and has several patents in this field. M.P. is an employee of Genos Ltd.
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606 Appendix A

607 A.1. Detection of TSH and TPOAb in human sera

608 Sera to assess TPOAb and TSH levels were collected by a trained nurse or phlebotomist using
609 venepuncture and a SafetyLok™ Blood Collection Kit (21G3/4 Needles) and plain 10 ml serum-
610 separating tube vacutainer (no additives) between February 1994 and May 2007. After collection from
611 the study subject, whole blood was held at 22°C for 50 min at room temperature for a clot to form
612 and serum separated within 60 minutes of collection. Processing of blood was performed using a
613 refrigerated (4°C) clinical centrifuge at 3000xg for 10 minutes with the serum supernatant
614 subsequently collected, transferred to a 2ml screw capped Nunc Cryotubes and immediately frozen
615 at -80°C and kept frozen in 2ml screw capped Nunc Cryotube at -80°C until use. Quantitative
616 determination of TSH and TPOAb (only IgG class) levels was performed on the sera either by a
617 chemiluminescent microparticle immunoassay (CMIA) [ARCHITECT® Anti-TPO or TSH (ABBOTT
618 Diagnostics Division, Wiesbaden, Germany, 2005)] (TPOAb titer>6 mIU/L considered positive;
619 reference range for TSH level 0.4-4.0 mIU/L) or by an electrochemiluminescence immunoassay
620 "ECLIA" [Elecsys and Cobas e analyzers, (Roche Diagnostics, Indianapolis, IN, USA, 2010)] (TPOAb
621 titer>34 IU/mL considered positive; reference range for TSH 0.4-4.0 mIU/L).

622 *A.2. Detection of IgG glycosylation profiling*

623 For IgG glycosylation analysis, using UPLC analysis of 2AB-labelled glycans,
624 chromatograms were separated in the same manner into 24 peaks, and the amount of glycans in each
625 peak was expressed as a percentage of the total integrated area. One glycan was excluded before any
626 transformation and standardization of data because of its co-elution with a contaminant that
627 significantly affected its values in some samples whereas two glycan peaks (GP) GP20 and GP21
628 (Zagreb code) were combined into a single trait called GP2021 (Zagreb code) because of difficulty in
629 distinguishing between these peaks in some samples. A global normalization and natural logarithm
630 transformation were applied to 22 directly measured glycan structures. As many of these structures
631 share the same structural features (galactose, sialic acid, core-fucose, bisecting N-acetylglucosamine
632 (GlcNAc)), 55 additional derived traits were calculated that average these features across multiple
633 glycans from the 22 normalized and non-transformed directly measured glycans. Technical
634 confounders (batch and run-day effects) were addressed using R package ComBat. The 22 directly
635 measured glycans and 55 derived glycan traits were centered and scaled to have a mean of 0 and
636 standard deviation (SD) of 1. Samples being more than 6 SD from the mean were considered as
637 outliers and excluded from the analysis.

638 *A.3. Detection of protein profiling in plasma*

639 Plasma protein profiling was conducted using SOMAscan v2 (SomaLogic Inc, Boulder, CO)
640 as previously described [29,30]. Briefly, hemolyzed samples were first excluded. Proteins were then
641 measured using a SOMAmer-based capture array called "SOMAscan." Quality control was
642 performed at the sample and SOMAmer level and involves the use of control SOMAmers on the
643 microarray and calibration samples. At the sample level, hybridization controls on the microarray
644 are used to monitor sample-by-sample variability in hybridization, while the median signal over all
645 SOMAmers is used to monitor overall technical variability. The resulting hybridization scale factor
646 and median scale factor are used to normalize data across samples. The acceptance criteria for these
647 values are 0.4–2.5, based on historical trends in these values. Somamer-by-somamer calibration
648 occurs through the repeated measurement of calibration samples; these samples are of the same

649 matrix as the study samples and are used to monitor repeatability and batch to batch variability.
 650 Historical values for these calibrator samples for each SOMAmer are used to generate a calibration
 651 scale factor. The acceptance criteria for calibrator scale factors is that 95% of SOMAmers must have a
 652 calibration scale factor within ± 0.4 of the median. For the current analysis, only 1,113 proteins were
 653 then studied.

654 A.4. Selection of SNPs associated with immune cell traits

655 To define the list of SNPs associated with immune cell traits regardless to any specific phenotypes in
 656 the TwinsUK cohort, we extracted SNPs for each immune cell traits that have a P-value under GWAS
 657 P-value threshold ($P\text{-value} < 5 \times 10^{-8}$) from previous published GWASs on these immune cell traits
 658 [27,28]. To define the list of SNPs associated with protein abundance found in this study, we extracted
 659 the significant SNPs reported in INTERVAL project [31]. To define the list of SNPs associated with
 660 gene expression (eQTL), we extracted the eQTLs reported significant by GTEx and previous papers
 661 present in HaploReg V4.1 [47]. To define the list of SNPs associated with AITD and thyroid functions,
 662 we selected to SNPs listed in the NHGRI GWAS catalog [52] with words “thyroid” or “Graves” or
 663 “Hashimoto.”

664 A.5. Determination of effective number of independent tests for different -omic data

665 Due to high and partial correlations within glycans, proteins and immune cell traits, we
 666 decided to use the equation 5 proposed by Li & Ji ((2005) [45] to define an effective number (M_{eff}) of
 667 independent tests. We then used this number to define the effective Bonferroni P-value threshold
 668 such as $0.05/M_{\text{eff}}$ instead of $0.05/M$, with M the actual number of tests. 20 independent tests were
 669 estimated for 76 glycans. Consequently, to account for multiple testing in the discovery cohort, we
 670 present results surpassing a conservative Bonferroni correction assuming 20 independent tests, thus
 671 giving a significant threshold of ($P\text{-value} < 2.5 \times 10^{-3} = 0.05/20$). 1,357 independent tests were estimated
 672 for 23,485 immune cell traits, thus giving a significant threshold of 3.68×10^{-5} ($0.05/1,357$). 227
 673 independent tests were estimated among 1,113 proteins ($P < 0.05/227 = 1.9 \times 10^{-4}$).

674 A.6. Association studies between -omics features and thyroid phenotypes

675 To examine whether one of the 17 AITD-IgG N-glycan traits was significantly associated with
 676 one of the 23,485 immune cell traits, we compared the fitted model in equation (2) with a model that
 677 did not include the residual of glycan in equation (1):

$$678 \quad \text{Model null: } Y_i \sim a + h \text{ (fixe intercepts)} + g \text{ (random intercepts)} + \varepsilon_{ij} \quad (1)$$

$$679 \quad \text{Model 1: } Y_i \sim a + \mathbf{b}G_{ij} + h \text{ (fixe intercepts)} + g \text{ (random intercepts)} + \varepsilon_{ij} \quad (2)$$

680 Where Y_i represents the quantification of immune cell traits for individual i and G_{ij} is glycan structure
 681 of type j among 75 N-glycans for the same individual i . If biological covariates (age, sex) have not
 682 been adjusted before association analysis, they have been added in the model. A random intercept
 683 was added only in the discovery cohort in order to model the family-relatedness.

684 To examine whether an immune cell trait was significantly associated with TPOAb level and
 685 AITD status, we compared the fitted model in equation (2) with a model that did not include the
 686 immune cell traits in equation (1) where G_{ij} become the immune cell trait of type j among 23,485 in
 687 discovery cohort for the same individual i . For the discovery and replication cohorts in TwinsUK, we
 688 added a random intercept in order to model the family-relatedness.

689 To examine whether one of the 1,113 protein was significantly associated with TPOAb level
690 and AITD status, we compared the fitted model in equation (2) with a model that did not include the
691 protein in equation (1): where G_{ij} become the protein of type j among 1,129 in discovery cohort for
692 the same individual i . We added a random intercept in order to model the family-relatedness. To
693 examine whether one of 1,113 proteins was significantly associated with one of 17 significant glycans,
694 we compared the fitted model in equation (2) with a model that did not include the protein in
695 equation (1): where G_{ij} become the protein of type j among 1,129 in discovery cohort for the same
696 individual i . We added a random intercept in order to model the family-relatedness.

697 11.7. Heritability analysis for proteins

698 Using twin data and ADCE models (additive genetics (A), dominante genetics (D), shared
699 environment (C) and non-shared environment (E)), heritability of glycosylation structures, immune
700 cell traits and AITD were estimated using the R package called mets that allows us to run the analysis
701 with monozygotic and dizygotic twins as well as unrelated individuals. The significance of variance
702 components A, D, and C was assessed by dropping each component sequentially from the full model
703 (ADCE) and comparing the sub-model fit to the full model. Sub-models were compared to full
704 models by hierarchical χ^2 tests. The difference between log-likelihood values between sub-model and
705 full model is asymptotically distributed as χ^2 with degrees of freedom (df) equal to the difference in
706 df of sub-model and the full model. A statistical indicator of goodness-of-fit is the Akaike information
707 criterion (AIC), computed as $\chi^2 - 2df$; sub-models are accepted as the best-fitting model if there is no
708 significant loss of fit when a latent variable (A, C, D, or E) is fixed to equal zero. When two sub-
709 models have the same AIC compared to the full model, we decide to keep the model the most likely
710 (with additive genetic variance) or with the lowest P-value for different components.

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947

Autoimmune Thyroid Diseases

Healthy vs AITD
or
TPOAb level

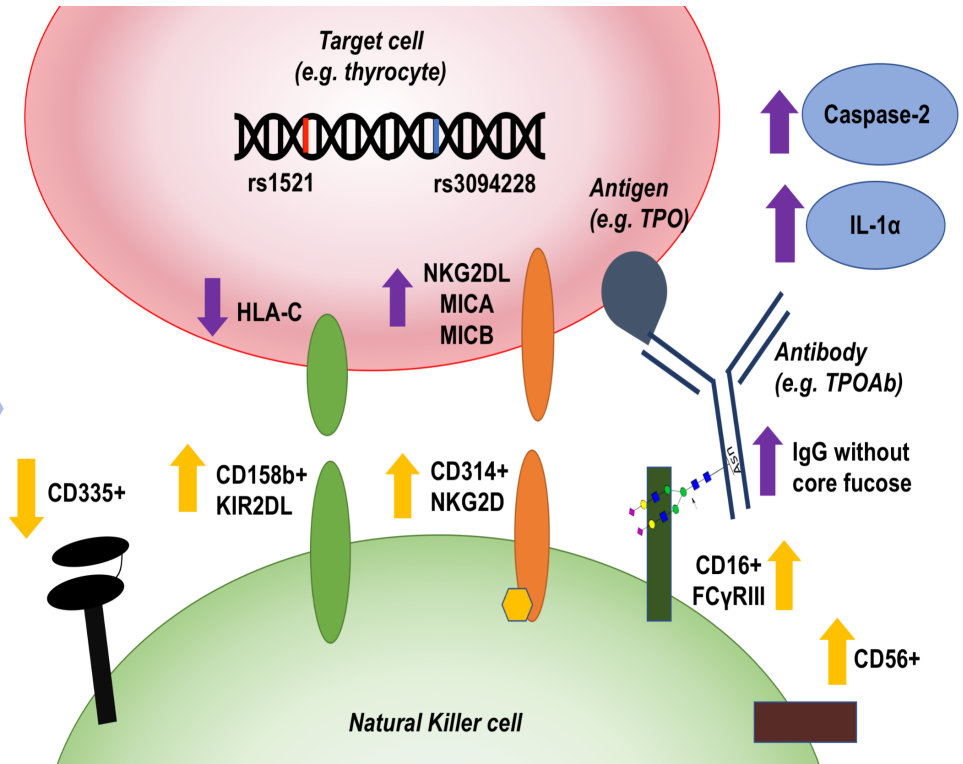
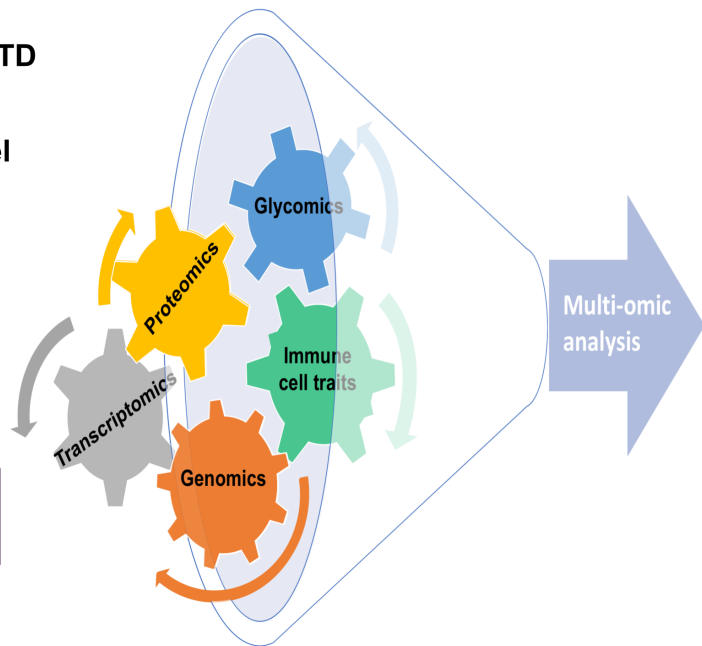


Table S1: Description of TwinsUK cohort used for different analysis performed here

* Roederer, M et al., Cell, 2015, doi: 10.1016/j.cell.2015.02.046 and Mangino et al, Nature Communications, 2017, <https://doi.org/10.1038/ncomms13850>

Analysis	GWAS on immune cell traits*	Immune-wide association studies with thyroid phenotypes				immune cell traits-wide association studies with IgG N-glycan traits	Proteome-wide association studies with thyroid phenotypes				Glycome-wide association studies with proteins		
		TPOAb	AITD				TPOAb	AITD					
Phenotype		continuous	control	case		continuous	control	case					
Group													
TPOAb immunoassay threshold of TPOAb-positivity (UI/mL)	NA	Roche	Abbott	Roche	Abbott	Roche	NA	Roche	Abbott	Roche	Abbott	Roche	NA
	NA	34	6	34	6	34	NA	34	6	34	6	34	NA
Number of individuals	497	374	77	127	19	22	383	155	25	105	9	18	164
Age (mean/sd)	60 (8.2)	55.8 (8.4)	52.59 (7.20)	55.41 (8.4)	51.58 (7.49)	53.40 (8.02)	60 (8.2)	61.19 (6.96)	56.59 (8.10)	61.64 (7.8)	55.20 (4.65)	60.66 (6.73)	64.20 (7.27)
Sex (F/M)	497/0	374/0	77/0	127/0	19/0	22/0	383/0	155/0	25/0	105/0	9/0	18/0	164/0
TPOAb (mean/sd)	NA	50.5 (108.4)	1.42 (8.49)	10.50 (5.37)	463.86 (568.45)	312.68 (146.01)	NA	66.65 (36.19)	0.14 (0.37)	9.33 (5.05)	585.66 (1156.48)	324.81 (147.69)	NA

Table S2: Significant glycome associations with immune cell traits in the TwinsUK cohort
SE=standart error

Glycan ID	Description	immuneTrait ID	Trait ID	Canonical name	Lineage	Subset name	Pvalue	Beta	SE	Zscore
IGP2	The percentage of A2 glycan in total IgG glycans	immuno_64161	P4:2970	NK Activating 1	16+56	16+56/314+335-337-158b+R7-	9.22E-08	0.285	0.052	5.445
IGP42	The percentage of A2 glycan in total neutral IgG glycans (GPn)	immuno_64161	P4:2970	NK Activating 1	16+56	16+56/314+335-337-158b+R7-	5.10E-08	0.277	0.050	5.555
IGP46	The percentage of A2G1 glycan in total Ineutral IgG glycans (GPn)	immuno_64161	P4:2970	NK Activating 1	16+56	16+56/314+335-337-158b+R7-	9.29E-08	0.237	0.044	5.443
IGP58	The percentage of all fucosylated (+/- bisecting GlcNAc) structures in total neutral IgG glycans	immuno_64161	P4:2970	NK Activating 1	16+56	16+56/314+335-337-158b+R7-	7.88E-08	-0.228	0.042	-5.477
IGP59	The percentage of fucosylation of agalactosylated structures	immuno_64161	P4:2970	NK Activating 1	16+56	16+56/314+335-337-158b+R7-	8.11E-08	-0.234	0.043	-5.468
IGP60	The percentage of fucosylation of monogalactosylated structures	immuno_64161	P4:2970	NK Activating 1	16+56	16+56/314+335-337-158b+R7-	2.14E-08	-0.242	0.042	-5.718
IGP2	The percentage of A2 glycan in total IgG glycans	immuno_64190	P4:2997	NK Activating 1	16+56	16+56/314+335-158b+R7-	8.47E-08	0.286	0.052	5.461
IGP42	The percentage of A2 glycan in total neutral IgG glycans (GPn)	immuno_64190	P4:2997	NK Activating 1	16+56	16+56/314+335-158b+R7-	4.69E-08	0.278	0.050	5.571
IGP46	The percentage of A2G1 glycan in total Ineutral IgG glycans (GPn)	immuno_64190	P4:2997	NK Activating 1	16+56	16+56/314+335-158b+R7-	8.94E-08	0.237	0.044	5.451
IGP58	The percentage of all fucosylated (+/- bisecting GlcNAc) structures in total neutral IgG glycans	immuno_64190	P4:2997	NK Activating 1	16+56	16+56/314+335-158b+R7-	7.49E-08	-0.228	0.042	-5.487
IGP59	The percentage of fucosylation of agalactosylated structures	immuno_64190	P4:2997	NK Activating 1	16+56	16+56/314+335-158b+R7-	7.62E-08	-0.234	0.043	-5.480
IGP60	The percentage of fucosylation of monogalactosylated structures	immuno_64190	P4:2997	NK Activating 1	16+56	16+56/314+335-158b+R7-	2.03E-08	-0.243	0.042	-5.728
IGP2	The percentage of A2 glycan in total IgG glycans	immuno_64953	P4:3683	NK Activating 1	16+56	16+56/314+335-337-158b+	9.58E-08	0.285	0.052	5.437
IGP42	The percentage of A2 glycan in total neutral IgG glycans (GPn)	immuno_64953	P4:3683	NK Activating 1	16+56	16+56/314+335-337-158b+	5.24E-08	0.277	0.050	5.550
IGP46	The percentage of A2G1 glycan in total Ineutral IgG glycans (GPn)	immuno_64953	P4:3683	NK Activating 1	16+56	16+56/314+335-337-158b+	9.70E-08	0.237	0.044	5.435
IGP58	The percentage of all fucosylated (+/- bisecting GlcNAc) structures in total neutral IgG glycans	immuno_64953	P4:3683	NK Activating 1	16+56	16+56/314+335-337-158b+	8.37E-08	-0.227	0.042	-5.466
IGP59	The percentage of fucosylation of agalactosylated structures	immuno_64953	P4:3683	NK Activating 1	16+56	16+56/314+335-337-158b+	8.77E-08	-0.233	0.043	-5.454
IGP60	The percentage of fucosylation of monogalactosylated structures	immuno_64953	P4:3683	NK Activating 1	16+56	16+56/314+335-337-158b+	2.28E-08	-0.242	0.042	-5.706
IGP2	The percentage of A2 glycan in total IgG glycans	immuno_64984	P4:3710	NK Activating 1	16+56	16+56/314+335-158b+	8.51E-08	0.286	0.052	5.460
IGP42	The percentage of A2 glycan in total neutral IgG glycans (GPn)	immuno_64984	P4:3710	NK Activating 1	16+56	16+56/314+335-158b+	4.64E-08	0.278	0.050	5.573
IGP46	The percentage of A2G1 glycan in total Ineutral IgG glycans (GPn)	immuno_64984	P4:3710	NK Activating 1	16+56	16+56/314+335-158b+	8.68E-08	0.238	0.044	5.456
IGP58	The percentage of all fucosylated (+/- bisecting GlcNAc) structures in total neutral IgG glycans	immuno_64984	P4:3710	NK Activating 1	16+56	16+56/314+335-158b+	7.57E-08	-0.228	0.042	-5.485
IGP59	The percentage of fucosylation of agalactosylated structures	immuno_64984	P4:3710	NK Activating 1	16+56	16+56/314+335-158b+	7.85E-08	-0.234	0.043	-5.475
IGP60	The percentage of fucosylation of monogalactosylated structures	immuno_64984	P4:3710	NK Activating 1	16+56	16+56/314+335-158b+	2.06E-08	-0.243	0.042	-5.726
IGP2	The percentage of A2 glycan in total IgG glycans	immuno_62860	P4:18	NK Activating 2	16+56	16+56/CD2+314+335+337-158a-158b-R	8.79E-07	-0.250	0.050	-4.999
IGP42	The percentage of A2 glycan in total neutral IgG glycans (GPn)	immuno_62860	P4:18	NK Activating 2	16+56	16+56/CD2+314+335+337-158a-158b-R	8.06E-07	-0.240	0.048	-5.025
IGP60	The percentage of fucosylation of monogalactosylated structures	immuno_62860	P4:18	NK Activating 2	16+56	16+56/CD2+314+335+337-158a-158b-R	5.26E-07	0.208	0.040	5.154
IGP2	The percentage of A2 glycan in total IgG glycans	immuno_63595	P4:2460	NK Activating 2	16+56	16+56/335+337-158a-158b-R7-	1.77E-08	-0.284	0.049	-5.752
IGP42	The percentage of A2 glycan in total neutral IgG glycans (GPn)	immuno_63595	P4:2460	NK Activating 2	16+56	16+56/335+337-158a-158b-R7-	9.79E-09	-0.275	0.047	-5.863
IGP46	The percentage of A2G1 glycan in total Ineutral IgG glycans (GPn)	immuno_63595	P4:2460	NK Activating 2	16+56	16+56/335+337-158a-158b-R7-	4.86E-07	-0.211	0.041	-5.131
IGP58	The percentage of all fucosylated (+/- bisecting GlcNAc) structures in total neutral IgG glycans	immuno_63595	P4:2460	NK Activating 2	16+56	16+56/335+337-158a-158b-R7-	3.67E-07	0.202	0.039	5.183
IGP59	The percentage of fucosylation of agalactosylated structures	immuno_63595	P4:2460	NK Activating 2	16+56	16+56/335+337-158a-158b-R7-	7.23E-07	0.204	0.040	5.044
IGP60	The percentage of fucosylation of monogalactosylated structures	immuno_63595	P4:2460	NK Activating 2	16+56	16+56/335+337-158a-158b-R7-	6.14E-08	0.221	0.040	5.540
IGP2	The percentage of A2 glycan in total IgG glycans	immuno_63596	P4:2461	NK Activating 2	16+56	16+56/CD2+335+337-158a-158b-R7-	4.61E-07	-0.256	0.050	-5.134
IGP42	The percentage of A2 glycan in total neutral IgG glycans (GPn)	immuno_63596	P4:2461	NK Activating 2	16+56	16+56/CD2+335+337-158a-158b-R7-	3.39E-07	-0.248	0.048	-5.206
IGP60	The percentage of fucosylation of monogalactosylated structures	immuno_63596	P4:2461	NK Activating 2	16+56	16+56/CD2+335+337-158a-158b-R7-	4.44E-07	0.210	0.040	5.189
IGP2	The percentage of A2 glycan in total IgG glycans	immuno_63597	P4:2462	NK Activating 2	16+56	16+56/314+335+337-158a-158b-R7-	5.91E-08	-0.276	0.050	-5.527
IGP42	The percentage of A2 glycan in total neutral IgG glycans (GPn)	immuno_63597	P4:2462	NK Activating 2	16+56	16+56/314+335+337-158a-158b-R7-	4.89E-08	-0.264	0.047	-5.565
IGP46	The percentage of A2G1 glycan in total Ineutral IgG glycans (GPn)	immuno_63597	P4:2462	NK Activating 2	16+56	16+56/314+335+337-158a-158b-R7-	1.61E-06	-0.203	0.042	-4.891
IGP60	The percentage of fucosylation of monogalactosylated structures	immuno_63597	P4:2462	NK Activating 2	16+56	16+56/314+335+337-158a-158b-R7-	2.99E-07	0.212	0.040	5.239
IGP2	The percentage of A2 glycan in total IgG glycans	immuno_63622	P4:2485	NK Activating 2	16+56	16+56/335+158a-158b-R7-	4.19E-08	-0.278	0.050	-5.594
IGP42	The percentage of A2 glycan in total neutral IgG glycans (GPn)	immuno_63622	P4:2485	NK Activating 2	16+56	16+56/335+158a-158b-R7-	2.47E-08	-0.269	0.047	-5.697
IGP46	The percentage of A2G1 glycan in total Ineutral IgG glycans (GPn)	immuno_63622	P4:2485	NK Activating 2	16+56	16+56/335+158a-158b-R7-	1.23E-06	-0.205	0.041	-4.945
IGP58	The percentage of all fucosylated (+/- bisecting GlcNAc) structures in total neutral IgG glycans	immuno_63622	P4:2485	NK Activating 2	16+56	16+56/335+158a-158b-R7-	1.19E-06	0.195	0.039	4.948
IGP60	The percentage of fucosylation of monogalactosylated structures	immuno_63622	P4:2485	NK Activating 2	16+56	16+56/335+158a-158b-R7-	2.07E-07	0.214	0.040	5.312
IGP2	The percentage of A2 glycan in total IgG glycans	immuno_63623	P4:2486	NK Activating 2	16+56	16+56/CD2+335+158a-158b-R7-	8.58E-07	-0.250	0.050	-5.010
IGP42	The percentage of A2 glycan in total neutral IgG glycans (GPn)	immuno_63623	P4:2486	NK Activating 2	16+56	16+56/CD2+335+158a-158b-R7-	6.33E-07	-0.242	0.048	-5.082
IGP60	The percentage of fucosylation of monogalactosylated structures	immuno_63623	P4:2486	NK Activating 2	16+56	16+56/CD2+335+158a-158b-R7-	7.60E-07	0.206	0.040	5.082
IGP2	The percentage of A2 glycan in total IgG glycans	immuno_63625	P4:2488	NK Activating 2	16+56	16+56/314+335+158a-158b-R7-	9.03E-08	-0.272	0.050	-5.447
IGP42	The percentage of A2 glycan in total neutral IgG glycans (GPn)	immuno_63625	P4:2488	NK Activating 2	16+56	16+56/314+335+158a-158b-R7-	7.32E-08	-0.261	0.048	-5.490
IGP46	The percentage of A2G1 glycan in total Ineutral IgG glycans (GPn)	immuno_63625	P4:2488	NK Activating 2	16+56	16+56/314+335+158a-158b-R7-	4.19E-07	0.210	0.041	5.173
IGP2	The percentage of A2 glycan in total IgG glycans	immuno_63626	P4:2489	NK Activating 2	16+56	16+56/CD2+314+335+158a-158b-R7-	1.54E-06	-0.245	0.050	-4.885
IGP42	The percentage of A2 glycan in total neutral IgG glycans (GPn)	immuno_63626	P4:2489	NK Activating 2	16+56	16+56/CD2+314+335+158a-158b-R7-	1.34E-06	-0.236	0.048	-4.921
IGP60	The percentage of fucosylation of monogalactosylated structures	immuno_63626	P4:2489	NK Activating 2	16+56	16+56/CD2+314+335+158a-158b-R7-	8.03E-07	0.206	0.041	5.070
IGP2	The percentage of A2 glycan in total IgG glycans	immuno_63674	P4:2531	NK Activating 2	16+56	16+56/335+337-158b-R7-	4.62E-09	-0.282	0.047	-5.994
IGP42	The percentage of A2 glycan in total neutral IgG glycans (GPn)	immuno_63674	P4:2531	NK Activating 2	16+56	16+56/335+337-158b-R7-	2.85E-09	-0.272	0.045	-6.079
IGP46	The percentage of A2G1 glycan in total Ineutral IgG glycans (GPn)	immuno_63674	P4:2531	NK Activating 2	16+56	16+56/335+337-158b-R7-	2.26E-07	-0.207	0.039	-5.276
IGP58	The percentage of all fucosylated (+/- bisecting GlcNAc) structures in total neutral IgG glycans	immuno_63674	P4:2531	NK Activating 2	16+56	16+56/335+337-158b-R7-	1.79E-07	0.198	0.037	5.319
IGP59	The percentage of fucosylation of agalactosylated structures	immuno_63674	P4:2531	NK Activating 2	16+56	16+56/335+337-158b-R7-	4.57E-07	0.198	0.039	5.131
IGP60	The percentage of fucosylation of monogalactosylated structures	immuno_63674	P4:2531	NK Activating 2	16+56	16+56/335+337-158b-R7-	3.49E-08	0.215	0.038	5.638

IGP42	The percentage of A2 glycan in total neutral IgG glycans (GPn)	immuno_64980	P4:3707 NK Effector	16+56	16+56/335-158b+	1.54E-07	0.275	0.051	5.345
IGP46	The percentage of A2G1 glycan in total neutral IgG glycans (GPn)	immuno_64980	P4:3707 NK Effector	16+56	16+56/335-158b+	1.42E-07	0.240	0.045	5.362
IGP58	The percentage of all fucosylated (+/- bisecting GlcNAc) structures in total neutral IgG glycans	immuno_64980	P4:3707 NK Effector	16+56	16+56/335-158b+	4.85E-07	-0.226	0.044	-5.122
IGP59	The percentage of fucosylation of agalactosylated structures	immuno_64980	P4:3707 NK Effector	16+56	16+56/335-158b+	4.90E-07	-0.228	0.045	-5.116
IGP60	The percentage of fucosylation of monogalactosylated structures	immuno_64980	P4:3707 NK Effector	16+56	16+56/335-158b+	7.54E-08	-0.244	0.045	-5.483

Table S3: Associations of 51 immune cell traits with AITD and TPOAb level in the TwinsUK cohort

immuneTrait ID	Trait ID	Canonical name	Lineage	Subset name	AITD				TPOAb level			
					Pvalue	Beta	SE	Zscore	Pvalue	Beta	SE	Zscore
immuno_64464	P4:3242	NK Activating 2	16+56	16+56/314+335+158b-	0.043	-0.049	0.024	-2.060	0.768	0.000	0.001	-0.297
immuno_63707	P4:2561	NK Activating 2	16+56	16+56/314+335+158b-R7-	0.045	-0.049	0.024	-2.041	0.769	0.000	0.001	-0.296
immuno_64374	P4:3161	NK Activating 2	16+56	16+56/314+335+158a-158b-	0.049	-0.046	0.023	-1.998	0.709	0.000	0.001	-0.377
immuno_63625	P4:2488	NK Activating 2	16+56	16+56/314+335+158a-158b-R7-	0.050	-0.046	0.023	-1.990	0.723	0.000	0.001	-0.357
immuno_64434	P4:3215	NK Activating 2	16+56	16+56/314+335+337-158b-	0.051	-0.047	0.024	-1.986	0.850	0.000	0.001	-0.191
immuno_63677	P4:2534	NK Activating 2	16+56	16+56/314+335+337-158b-R7-	0.051	-0.047	0.024	-1.985	0.817	0.000	0.001	-0.233
immuno_63703	P4:2558	NK Activating 2	16+56	16+56/335+158b-R7-	0.051	-0.048	0.024	-1.980	0.949	0.000	0.001	-0.065
immuno_64460	P4:3239	NK Activating 2	16+56	16+56/335+158b-	0.052	-0.047	0.024	-1.969	0.951	0.000	0.001	-0.062
immuno_64344	P4:3134	NK Activating 2	16+56	16+56/314+335+337-158a-158b-	0.055	-0.045	0.023	-1.951	0.756	0.000	0.001	-0.314
immuno_63597	P4:2462	NK Activating 2	16+56	16+56/314+335+337-158a-158b-R7-	0.056	-0.045	0.023	-1.945	0.753	0.000	0.001	-0.317
immuno_63674	P4:2531	NK Activating 2	16+56	16+56/335+337-158b-R7-	0.057	-0.047	0.024	-1.930	0.994	0.000	0.001	-0.008
immuno_64431	P4:3212	NK Activating 2	16+56	16+56/335+337-158b-	0.059	-0.046	0.024	-1.914	0.984	0.000	0.001	0.021
immuno_64370	P4:3158	NK Activating 2	16+56	16+56/335+158a-158b-	0.065	-0.044	0.023	-1.870	0.851	0.000	0.001	-0.190
immuno_63595	P4:2460	NK Activating 2	16+56	16+56/335+337-158a-158b-R7-	0.066	-0.044	0.023	-1.867	0.925	0.000	0.001	-0.095
immuno_63622	P4:2485	NK Activating 2	16+56	16+56/335+158a-158b-R7-	0.066	-0.044	0.023	-1.865	0.844	0.000	0.001	-0.198
immuno_64341	P4:3131	NK Activating 2	16+56	16+56/335+337-158a-158b-	0.072	-0.043	0.023	-1.826	0.945	0.000	0.001	-0.070
immuno_64641	P4:3401	NK Activating 2	16+56	16+56/335+158a-	0.086	-0.041	0.024	-1.729	0.750	0.000	0.001	0.324
immuno_63906	P4:2740	NK Effector	16+56	16+56/335-337-R7-	0.086	0.043	0.025	1.726	0.351	0.000	0.001	-0.954
immuno_64680	P4:3437	NK Effector	16+56	16+56/335-337-	0.087	0.043	0.025	1.727	0.365	0.000	0.001	-0.926
immuno_63935	P4:2767	NK Effector	16+56	16+56/335-R7-	0.087	0.043	0.025	1.720	0.335	-0.001	0.001	-0.987
immuno_64730	P4:3482	NK Activating 2	16+56	16+56/335+	0.088	-0.043	0.025	-1.719	0.358	0.000	0.001	0.941
immuno_64710	P4:3464	NK Effector	16+56	16+56/335-	0.088	0.043	0.025	1.718	0.355	0.000	0.001	-0.947
immuno_64610	P4:3374	NK Activating 2	16+56	16+56/335+337-158a-	0.094	-0.040	0.024	-1.688	0.701	0.000	0.001	0.389
immuno_63835	P4:2677	NK Activating 2	16+56	16+56/335+337-158a-R7-	0.096	-0.040	0.024	-1.675	0.710	0.000	0.001	0.378
immuno_64700	P4:3455	NK Activating 2	16+56	16+56/335+337-	0.104	-0.041	0.025	-1.637	0.313	0.001	0.001	1.035
immuno_63925	P4:2758	NK Activating 2	16+56	16+56/335+337-R7-	0.104	-0.041	0.025	-1.636	0.322	0.001	0.001	1.016
immuno_64465	P4:3243	NK Activating 2	16+56	16+56/CD2+314+335+158b-	0.153	-0.033	0.023	-1.443	0.988	0.000	0.001	-0.016
immuno_63708	P4:2562	NK Activating 2	16+56	16+56/CD2+314+335+158b-R7-	0.155	-0.033	0.023	-1.434	0.995	0.000	0.001	0.006
immuno_64375	P4:3162	NK Activating 2	16+56	16+56/CD2+314+335+158a-158b-	0.161	-0.032	0.023	-1.414	0.838	0.000	0.001	-0.211
immuno_63626	P4:2489	NK Activating 2	16+56	16+56/CD2+314+335+158a-158b-R7-	0.162	-0.032	0.023	-1.410	0.855	0.000	0.001	-0.188
immuno_64435	P4:3216	NK Activating 2	16+56	16+56/CD2+314+335+337-158b-	0.164	-0.033	0.023	-1.404	0.916	0.000	0.001	0.109
immuno_63678	P4:2535	NK Activating 2	16+56	16+56/CD2+314+335+337-158b-R7-	0.165	-0.033	0.023	-1.400	0.896	0.000	0.001	0.135
immuno_62860	P4:18	NK Activating 2	16+56	16+56/CD2+314+335+337-158a-158b-R7-	0.175	-0.031	0.023	-1.368	0.963	0.000	0.001	-0.048
immuno_63623	P4:2486	NK Activating 2	16+56	16+56/CD2+335+158a-158b-R7-	0.178	-0.031	0.023	-1.358	0.875	0.000	0.001	-0.162
immuno_63704	P4:2559	NK Activating 2	16+56	16+56/CD2+335+158b-R7-	0.179	-0.032	0.024	-1.354	0.939	0.000	0.001	0.079
immuno_64371	P4:3159	NK Activating 2	16+56	16+56/CD2+335+158a-158b-	0.179	-0.031	0.023	-1.356	0.856	0.000	0.001	-0.187
immuno_64462	P4:3240	NK Activating 2	16+56	16+56/CD2+335+158b-	0.180	-0.032	0.024	-1.354	0.940	0.000	0.001	0.078
immuno_64345	P4:3135	NK Activating 2	16+56	16+56/CD2+314+335+337-158a-158b-	0.180	-0.031	0.023	-1.351	0.923	0.000	0.001	-0.100
immuno_63675	P4:2532	NK Activating 2	16+56	16+56/CD2+335+337-158b-R7-	0.189	-0.031	0.024	-1.323	0.864	0.000	0.001	0.177
immuno_64432	P4:3213	NK Activating 2	16+56	16+56/CD2+335+337-158b-	0.189	-0.031	0.024	-1.326	0.896	0.000	0.001	0.135
immuno_64342	P4:3132	NK Activating 2	16+56	16+56/CD2+335+337-158a-158b-	0.197	-0.030	0.023	-1.300	0.981	0.000	0.001	-0.024
immuno_63596	P4:2461	NK Activating 2	16+56	16+56/CD2+335+337-158a-158b-R7-	0.202	-0.030	0.023	-1.286	0.978	0.000	0.001	-0.028
immuno_64157	P4:2967	NK Effector	16+56	16+56/335-337-158b-R7-	0.805	0.006	0.023	0.248	0.464	-0.001	0.001	-0.758
immuno_64187	P4:2994	NK Effector	16+56	16+56/335-158b+R7-	0.808	0.006	0.023	0.244	0.466	-0.001	0.001	-0.754
immuno_64980	P4:3707	NK Effector	16+56	16+56/335-158b+	0.816	0.005	0.023	0.233	0.459	-0.001	0.001	-0.765
immuno_64950	P4:3680	NK Effector	16+56	16+56/335-337-158b+	0.816	0.005	0.023	0.233	0.457	-0.001	0.001	-0.769
immuno_64161	P4:2970	NK Activating 1	16+56	16+56/314+335-337-158b+R7-	0.893	0.003	0.023	0.135	0.454	-0.001	0.001	-0.778
immuno_64953	P4:3683	NK Activating 1	16+56	16+56/314+335-337-158b+	0.896	0.003	0.023	0.130	0.453	-0.001	0.001	-0.778
immuno_64190	P4:2997	NK Activating 1	16+56	16+56/314+335-158b+R7-	0.904	0.003	0.023	0.121	0.453	-0.001	0.001	-0.780
immuno_64984	P4:3710	NK Activating 1	16+56	16+56/314+335-158b+	0.905	0.003	0.023	0.120	0.453	-0.001	0.001	-0.778
immuno_64084	P4:2900	NK Effector	16+56	16+56/335-337-158a-158b+R7-	0.970	0.001	0.024	0.038	0.528	-0.001	0.001	-0.648

Table S4: Hits from selected eQTL studies for two SNPs, rs1521 and rs3094228 in the thyroid cells and whole blood
 * GWAS catalog for the genetic variants associated with thyroid phenotypes(Data downloaded from GWAS Catalog on 17/06/2015)
 ** eQTLs from Haploreg v4.1 (<https://pubs.broadinstitute.org/mammals/haploreg/haploreg.php>) and GTEx v6,v7, v8 (<https://www.gtexportal.org/home/>)

Lead SNP- risk allele	Thyroid phenotypes (from GWAS catalog)*			Study ID	Paper Title	eQTL** PMID	ref allele	Tissue	Correlated gene	NES	p-value									
	Chromosomestart (hg38)	end (hg38)	Phenotype																	
rs1521-T	6	31382927	31382927	Graves' disease	The GTEx Consortium atlas of genetic regulatory effects across human tissues	Lorgu/10.1101/29022597	C	Thyroid	VARS2	ENSG00000137411.16	0.29	5.00E-12								
								Thyroid	MIR6891	ENSG00000277402.1	0.35	6.20E-11								
								Thyroid	HCG27	ENSG00000206344.7	0.21	1.40E-09								
								Thyroid	HLA-C	ENSG00000204525.16	-0.24	8.20E-08								
								Thyroid	PSORS1C3	ENSG00000204528.3	0.33	7.50E-08								
								Thyroid	XXbac-BPG181B23.7	ENSG00000272221.1	-0.25	1.40E-06								
								Thyroid	MICA	ENSG00000204520.12	-0.18	2.50E-05								
								Thyroid	PRRT1	ENSG00000204314.10	0.12	4.20E-05								
								Thyroid	FLOT1	ENSG00000137312.14	0.11	6.50E-05								
								Whole_Blood	XXbac-BPG181B23.7	ENSG00000272221.1	-0.34	2.20E-17								
								Whole_Blood	PSORS1C3	ENSG00000204528.3	0.28	1.40E-09								
								Whole_Blood	XXbac-BPG299F13.17	ENSG00000272501.1	-0.12	2.20E-07								
								Whole_Blood	HCG27	ENSG00000206344.7	0.088	1.20E-05								
								Whole_Blood	VARS2	ENSG00000137411.16	0.1	2.20E-05								
								Whole_Blood	DDR1	ENSG00000204580.13	0.17	2.80E-05								
								Whole_Blood	ZBTB12	ENSG00000204566.3	0.2	3.20E-05								
								Whole_Blood	HLA-C	ENSG00000204525.16	-0.12	5.70E-05								
								Whole_Blood	C4A	ENSG00000244731.7	-0.2	1.30E-04								
								Whole_Blood	FLOT1	ENSG00000137312.14	0.045	1.70E-04								
								Thyroid	VARS2	ENSG00000137411.12	0.31	3.40E-09								
								Thyroid	HCG27	ENSG00000206344.6	0.23	6.90E-08								
								Thyroid	HLA-C	ENSG00000204525.10	-0.25	8.30E-06								
								Thyroid	PSORS1C3	ENSG00000204528.3	0.31	2.00E-05								
								Whole_Blood	XXbac-BPG181B23.7	ENSG00000272221.1	-0.33	7.90E-08								
Thyroid	HLA-C	ENSG00000204525.10	NA	1.28E-08																
Thyroid	XXbac-BPG248L24.12	ENSG00000204525.10	NA	1.03E-08																
Whole_Blood	HLA-C	ENSG00000204525.10	NA	2.98E-08																
Whole_Blood	XXbac-BPG181B23.7	ENSG00000272221.1	NA	2.86E-07																
Whole_Blood	XXbac-BPG248L24.12	ENSG00000272221.1	NA	8.29E-09																
Whole_Blood	-	-	NA	1.11E-35																
Whole_Blood	-	-	NA	6.64E-38																
Whole_Blood	AIF1	ENSG00000204472	NA	2.51E-06																
Whole_Blood	ATP6V1G2 BAT1	ENSG00000213760	NA	9.31E-16																
Whole_Blood	HCP5	ENSG00000206337.6	NA	4.62E-06																
Whole_Blood	LTA	ENSG00000228979	NA	8.46E-10																
Whole_Blood	MICB	ENSG00000204516.5	NA	5.24E-04																
rs3094228-C	6	31462150	31462150	Thyroid peroxidase antibody positivity (TPOAb-positivity)	The GTEx Consortium atlas of genetic regulatory effects across human tissues	Lorgu/10.1101/29022597	T	Thyroid	C4A	ENSG00000244731.7	-0.39	2.00E-16								
								Thyroid	CYP21A1P	ENSG00000204338.8	-0.37	2.80E-14								
								Thyroid	MICB	ENSG00000204516.9	0.26	3.70E-09								
								Thyroid	HCP5	ENSG00000206337.10	-0.24	3.00E-08								
								Thyroid	FLOT1	ENSG00000137312.14	0.17	5.00E-08								
								Thyroid	PSORS1C1	ENSG00000204540.10	-0.37	7.00E-08								
								Thyroid	CCHCR1	ENSG00000204536.13	0.2	2.00E-07								
								Thyroid	HLA-C	ENSG00000204525.16	0.25	9.30E-07								
								Thyroid	HLA-S	ENSG00000225851.1	-0.31	3.80E-06								
								Thyroid	RNF5	ENSG00000204308.7	-0.14	2.70E-05								
								Whole_Blood	C4A	ENSG00000244731.7	-0.48	1.50E-16								
								Whole_Blood	C4B	ENSG00000223489.8	0.47	2.60E-13								
								Whole_Blood	CYP21A1P	ENSG00000204338.8	-0.4	1.10E-12								
								Whole_Blood	CYP21A2	ENSG00000231852.6	0.4	3.20E-10								
								Whole_Blood	FLOT1	ENSG00000137312.14	0.058	2.20E-05								
								Whole_Blood	HLA-S	ENSG00000225851.1	-0.27	3.70E-05								
								Whole_Blood	CCHCR1	ENSG00000204536.13	0.13	8.10E-05								
								Whole_Blood	XXbac-BPG248L24.12	ENSG00000271581.1	-0.24	1.50E-04								
								Thyroid	C4A	ENSG00000244731.3	-0.4	3.40E-13								
								Thyroid	CYP21A1P	ENSG00000204338.4	-0.37	1.10E-09								
								Thyroid	HCP5	ENSG00000206337.6	-0.32	1.30E-09								
								Thyroid	PSORS1C1	ENSG00000204540.6	-0.4	4.00E-06								
								Thyroid	HCG22	ENSG00000228789.2	-0.35	5.10E-06								
								Thyroid	MICB	ENSG00000204516.5	0.26	5.10E-06								
Thyroid	CCHCR1	ENSG00000204536.9	0.21	1.70E-05																
Whole_Blood	C4A	ENSG00000244731.3	-0.48	4.00E-09																
Whole_Blood	CYP21A1P	ENSG00000204338.4	-0.41	3.80E-07																
Whole_Blood	C4B	ENSG00000223489.4	0.41	9.90E-06																
Whole_Blood	CYP21A2	ENSG00000231852.2	0.38	2.90E-05																
rs2596460	6	31449483	31449483	16+56 CD2-314+335-337-158a+158b+	The GTEx Consortium atlas of genetic regulatory effects across human tissues	https://doi.org/10.1101/787903	A	Thyroid	ATP6V1G2	ENSG00000213760.10	0.28	1.10E-05								
								Thyroid	SKIV2L	ENSG00000204351.11	0.23	2.20E-05								
								Thyroid	CCHCR1	ENSG00000204536.13	-0.22	1.30E-04								
								Thyroid	VARS2	ENSG00000137411.16	-0.27	2.00E-04								
								Whole_Blood	MICA	ENSG00000204520.12	0.22	3.40E-04								
								Whole_Blood	HLA-C	ENSG00000204525.10	-0.3	5.60E-05								
								Thyroid	CCHCR1	ENSG00000204536.9	-0.29	2.40E-05								
								rs2596457	6	31449995	31449995	16+56 CD2-314+335-337-158a+158b+	The GTEx Consortium atlas of genetic regulatory effects across human tissues	https://doi.org/10.1101/787903	A	Thyroid	ATP6V1G2	ENSG00000213760.10	0.3	2.10E-06
																Thyroid	SKIV2L	ENSG00000204351.11	0.24	8.70E-06
																Thyroid	VARS2	ENSG00000137411.16	-0.28	1.70E-04
																Thyroid	CCHCR1	ENSG00000204536.13	-0.21	2.70E-04
																Thyroid	DDR1	ENSG00000204580.13	-0.18	4.60E-04
Whole blood	MICA	ENSG00000204520.12	0.22	2.40E-04																
rs2523691	6	31452660	31452660	16+56 CD2-314+335-337-158a+158b+	The GTEx Consortium atlas of genetic regulatory effects across human tissues	https://doi.org/10.1101/787903	G	Thyroid	ATP6V1G2	ENSG00000213760.10	0.28	1.10E-05								
								Thyroid	SKIV2L	ENSG00000204351.11	0.23	2.20E-05								
								Thyroid	CCHCR1	ENSG00000204536.13	-0.22	1.30E-04								
								Thyroid	VARS2	ENSG00000137411.16	-0.27	2.00E-04								
								Whole_Blood	MICA	ENSG00000204520.12	0.22	3.40E-04								
								Whole_Blood	HLA-C	ENSG00000204525.10	-0.3	5.50E-05								
Thyroid	CCHCR1	ENSG00000204536.9	-0.29	1.90E-05																

Table S5 : Genes reported for genetic variants associated with thyroid phenotypes and immune cell traits

* the closest genes reported in GWAS catalog for the genetic variants associated with thyroid phenotypes and immune cell traits (Data downloaded from GWAS Catalog on 17/06/2015)

** Roederer, M et al., Cell, 2015, doi: 10.1016/j.cell.2015.02.046 and Mangino et al, Nature Communications, 2017, https://doi.org/10.1038/ncomms13850

Name of gene reported in GWAS catalog* and Roederer's paper **	Thyroid phenotypes (from GWAS catalog)*					A1D status or biomarkers associated with A1D	LD (r2)	distance lead SNP(thyroid)-lead SNP(immune cell traits)	Immune cell traits**					Phenotypes			
	Lead SNP	Chromosome	start (hg38)	end (hg38)	Phenotype				Lead SNP	Chromosome	start (hg38)	end (hg38)	start (hg19)		end (hg19)	Immune Name in TwinsUK	
HCP5	rs3094228	6	31462150	31462150	Thyroid peroxidase antibody positivity	Yes	<0.2	12667	rs2596460	6	31449483	31449483	31449733	31449733	P4:3763	NK Activating 1	16+56/CD2-314+335-337-158a+158b+
								12155	rs2596457	6	31449995	31449995	31450245	31450245	P4:3763	NK Activating 1	16+56/CD2-314+335-337-158a+158b+
								9490	rs2523691	6	31452660	31452660	31452910	31452910	P4:3763	NK Activating 1	16+56/CD2-314+335-337-158a+158b+
MICA	rs1521	6	31382927	31382927	Graves' disease	Yes	<0.2	-66556	rs2596460	6	31449483	31449483	31449733	31449733	P4:3763	NK Activating 1	16+56/CD2-314+335-337-158a+158b+
ACCN1	rs9901756	17	34137135	34137135	Hypothyroidism	No	<0.2	365816	rs12603968	17	33771319	33771319	33771319	33771319	P4:3551	NK Effector	16+56/314-158a+
								366131	rs12602135	17	33771004	33771004	33771004	33771004	P4:3551	NK Effector	16+56/314-158a+
DIRC3	rs6759952	2	217406996	217406996	Thyroid cancer	No	<0.2	-317240	rs744564	2	217724236	217724236	217724236	217724236	P4:3551	NK Effector	16+56/314-158a+
								-278619									
GLIS3	rs1571583	9	4267209	4267209	Thyroid hormone levels	No	<0.2	492850	rs10973456	9	3774359	3774359	3774359	3774359	P7:110	DC mDC imDC	11c+ (nodim)/1c-/16+/32+
HACE1	rs9322817	6	104784358	104784358	Thyroid stimulating hormone level	No	<0.2	378569	rs156205	6	104405789	104405789	104405789	104405789	P4:3763	NK Activating 1	16+56/CD2-314+335-337-158a+158b+
L3MBTL4	rs948426	18	6567183	6567183	Hypothyroidism	No	<0.2	438743	rs17486103	18	6128440	6128440	6128440	6128440	P7:110	DC mDC imDC	11c+ (nodim)/1c-/16+/32+
NFIA	rs334699	1	61154824	61154824	Thyroid hormone levels	No	<0.2	-240528	rs11581697	1	61395352	61395352	61395352	61395352	P4:3551	NK Effector	16+56/314-158a+
NFIB	rs10961534	9	14470835	14470835	Hypothyroidism	No	<0.2	-240632	rs12072379	9	14395456	14395456	14395456	14395456	P4:3551	NK Effector	16+56/314-158a+
NR3C2	rs10028213	4	148731458	148731458	Thyroid stimulating hormone level	No	<0.2	441933	rs3910047	4	148289525	148289525	148289525	148289525	P4:3551	NK Effector	16+56/314-158a+
NRG1	rs7825175	8	32558756	32558756	Thyroid hormone levels	No	<0.2	5271541	rs2479551	8	27287215	27287215	27287215	27287215	P7:110	DC mDC imDC	11c+ (nodim)/1c-/16+/32+
								510838	rs2881470	8	32047918	32047918	32047918	32047918	P7:110	DC mDC imDC	11c+ (nodim)/1c-/16+/32+
								488634	rs1462900	8	32070122	32070122	32070122	32070122	P7:110	DC mDC imDC	11c+ (nodim)/1c-/16+/32+
								480970	rs1381871	8	32077786	32077786	32077786	32077786	P7:110	DC mDC imDC	11c+ (nodim)/1c-/16+/32+
	rs2439302	8	32574851	32574851	Thyroid cancer	No	<0.2	496755	rs1471387	8	32078096	32078096	32078096	32078096	P7:110	DC mDC imDC	11c+ (nodim)/1c-/16+/32+
								494464	rs1947734	8	32080387	32080387	32080387	32080387	P7:110	DC mDC imDC	11c+ (nodim)/1c-/16+/32+
								488995	rs7818326	8	32085856	32085856	32085856	32085856	P7:110	DC mDC imDC	11c+ (nodim)/1c-/16+/32+
								488541	rs16878780	8	32086310	32086310	32086310	32086310	P7:110	DC mDC imDC	11c+ (nodim)/1c-/16+/32+
						<0.2	488339	rs9297185	8	32086512	32086512	32086512	32086512	P7:110	DC mDC imDC	11c+ (nodim)/1c-/16+/32+	
PDE10A	rs753760	6	165632995	165632995	Thyroid hormone levels	No	<0.2	152041	rs551901	6	165480954	165480954	165480954	165480954	P4:3763	NK Activating 1	16+56/CD2-314+335-337-158a+158b+
								151764	rs684847	6	165481231	165481231	165481231	165481231	P4:3763	NK Activating 1	16+56/CD2-314+335-337-158a+158b+
SOX9	rs9915657	17	72131395	72131395	Thyroid hormone levels	No	<0.2	691727	rs9302936	17	71439668	71439668	71439668	71439668	P4:3763	NK Activating 1	16+56/CD2-314+335-337-158a+158b+
								686259	rs1990222	17	71445136	71445136	71445136	71445136	P4:3763	NK Activating 1	16+56/CD2-314+335-337-158a+158b+
VAV3	rs12126655	1	107814198	107814198	Plasma thyroid-stimulating hormone levels	No	<0.2	-121433	rs10494086	1	107935631	107935631	107935631	107935631	P4:3551	NK Effector	16+56/314-158a+
								-127812	rs1020812	1	107942010	107942010	107942010	107942010	P4:3551	NK Effector	16+56/314-158a+
	rs4915077	1	107823394	107823394	Hypothyroidism	No	<0.2	-123692	rs6696531	1	107947086	107947086	107947086	107947086	P4:3551	NK Effector	16+56/314-158a+

Table S6: Glycome-wide associations studies of 17 AITD-IgG N-glycan traits with 1,113 circulating proteins. Only significant ones were put here.

Glycan ID	Description	Soma ID	Target	Uniprot	P-value	Beta	SE
IGP2	The percentage of A2 glycan in total IgG glycans	SL008609	FCG3B	O75015	1.46E-06	0.051	0.010
IGP8	The percentage of FA2[3]G1 glycan in total IgG glycans	SL007464	AMHR2	Q16671	1.50E-07	0.029	0.005
IGP8	The percentage of FA2[3]G1 glycan in total IgG glycans	SL004857	Desmoglein-2	Q14126	2.15E-06	0.032	0.007
IGP42	The percentage of A2 glycan in total neutral IgG glycans (GPn)	SL008609	FCG3B	O75015	2.63E-06	0.050	0.010
IGP46	The percentage of A2G1 glycan in total neutral IgG glycans (GPn)	SL008609	FCG3B	O75015	3.88E-06	0.045	0.009
IGP48	The percentage of FA2[3]G1 glycan in total neutral IgG glycans (GPn)	SL002644	ERBB1	P00533	3.04E-06	0.023	0.005
IGP48	The percentage of FA2[3]G1 glycan in total neutral IgG glycans (GPn)	SL000283	b2-Microglobulin	P61769	4.16E-06	-0.034	0.007
IGP56	The percentage of monogalactosylated structures in total neutral IgG glycans	SL000283	b2-Microglobulin	P61769	5.10E-07	-0.037	0.007
IGP57	The percentage of digalactosylated structures in total neutral IgG glycans	SL004159	TRAIL R4	Q9UBN6	2.95E-06	-0.041	0.008
IGP58	The percentage of all fucosylated (+/- bisecting GlcNAc) structures in total neutral IgG glycans	SL008609	FCG3B	O75015	5.21E-06	-0.044	0.009
IGP59	The percentage of fucosylation of agalactosylated structures	SL008609	FCG3B	O75015	9.33E-06	-0.044	0.010
IGP60	The percentage of fucosylation of monogalactosylated structures	SL008609	FCG3B	O75015	4.06E-07	-0.048	0.009
IGP62	The percentage of fucosylated (without bisecting GlcNAc) structures in total neutral IgG glycans	SL004672	BCMA	Q02223	5.44E-08	0.041	0.007
IGP63	The percentage of fucosylation (without bisecting GlcNAc) of agalactosylated structures	SL004672	BCMA	Q02223	1.47E-07	0.041	0.007
IGP63	The percentage of fucosylation (without bisecting GlcNAc) of agalactosylated structures	SL004857	Desmoglein-2	Q14126	8.02E-06	0.032	0.007

Table S7: Genetic variants associated with thyroid phenotypes and AITD-IgG N-glycan traits overlapping pQTL identified in INTERVAL project (LD r2>0.8)

*Sun et al, Nature, 2018, doi: 10.1038/s41586-018-0175-2

GWAS Catalog (Data downloaded from GWAS Catalog on 17/06/2015)											pQTL*									
chr	Start (hg38)	Stop (hg38)	Strongest SNPs	SNPs	Disease traits	Region	Reported Genes	Mapped Genes	Context	Extra Information about GWAS findings	SOMAmer ID (version 2) used here	SOMAmer ID (version 4)	Target	Target fullname	UniProt	cis/trans	Mapped gene	Sentinel variant	LD with sentinel variant (r2)	
1	157699488	157699488	rs3761959-A, rs3761959-G	rs3761959	Graves disease, Multiple sclerosis	1q23.1	FCRL3	FCRL3	intron											
1	157701026	157701026	rs7528684-T	rs7528684	Type 1 diabetes autoantibodies, Rheumatoid arthritis, Graves disease	1q23.1	FCRL3	FCRL3	nearGene-5	I-A2A	SL014088	FCRL3.4440.15.2	FCRL3	Fc receptor-like protein 3	Q96P31	cis	FCRL3	rs7528684	1	
9	133273813	133273813	rs505922-C, rs505922-T, rs505922-?	rs505922	Protein quantitative trait loci, Venous thromboembolism, End-stage coagulation, Pancreatic cancer, Graves disease, Duodenal ulcer	9q34.2	ABO	ABO	intron	Recessive, TNFA, VWF	No detected SL004516 No detected SL004857 SL005157 No detected	DHFR.9823.2.3 MBL2.3000.66.1 ABO.9253.52.3 DSG2.9484.75.3 CD209.3029.52.2 CHST11.7779.86.3	DYR MBL BGAT Desmoglein-2 DC-SIGN CHSTB	Dihydrofolate reductase Mannose-binding protein C Histo-blood group ABO system transferase Desmoglein-2 CD209 antigen Carbohydrate sulfotransferase 11	P00374 P11226 P16442 Q14126 Q9NNX6 Q9NPF2	trans trans cis trans trans trans	ABO ABO ABO ABO ABO ABO	rs676457 rs139840563 rs505922 rs687621 rs505922 rs687621	0.99 0.98 1 0.97 1 0.97	
12	111446804	111446804	rs3184504-C, rs3184504-?, rs3184504-T	rs3184504	Type 1 diabetes, Platelet counts, Blood metabolite levels, Beta-2 microglobulin plasma levels, Diastolic blood pressure, Coronary artery disease, Eosinophil counts, Systolic blood pressure, Autoimmune hepatitis type-1, Red blood cell traits, Rheumatoid arthritis, Type 1 diabetes autoantibodies, Hypothyroidism, Coronary heart disease	12q24.12	SH2B3, NAA25, C12orf51, ATXN2, BRAP, LOC100101246, PTPN11	SH2B3	missense	T1D, kynurenine, Hgb, EA	SL006460	GP1BA.4990.87.1 VCAM1.2967.8.1	GP1BA VCAM-1	Platelet glycoprotein Ib alpha chain Vascular cell adhesion protein 1	P07359 P19320	trans trans	BRAP SH2B3	rs11065979 rs3184504	0.81 1	

Table S8: Heritability of AITD, 17 IgG N-glycan traits and 51 immune cell traits in the TwinsUK cohort

* Martin et al, 2018

** Mangino et al, Nature Communications, 2017, <https://doi.org/10.1038/ncomms13850>

type	features	general info	best model	H2 [95%CI]	A [95%CI]	D [95%CI]	C [95%CI]	E [95%CI]	
thyroid phenotype*	AITD TPOAb-positivity		DE	0.63 [0.59-0.67]	NS	0.63 [0.59-0.67]	NS	0.36 [0.32-0.40]	
			DE	0.57 [0.50-0.65]	NS	0.57 [0.50-0.65]	NS	0.42 [0.34-0.49]	
IgG N-glycan traits*		The percentage of A2 glycan in total IgG glycans	IGP2	AE	0.731 [0.747,0.716]	0.731 [0.697,0.764]	NS	NS	0.269 [0.236;0.303]
		The percentage of FA2[6]G1 glycan in total IgG glycans	IGP7	AE	0.557 [0.563;0.552]	0.557 [0.509;0.605]	NS	NS	0.443 [0.395;0.491]
		The percentage of FA2[3]G1 glycan in total IgG glycans	IGP8	AE	0.662 [0.676;0.65]	0.662 [0.621;0.702]	NS	NS	0.338 [0.298;0.379]
		The percentage of FA2G1S1 glycan in total IgG glycans	IGP15	AE	0.704 [0.72;0.691]	0.704 [0.669;0.739]	NS	NS	0.296 [0.261;0.331]
		The percentage of A2B[2]S2 glycan in total IgG glycans	IGP21	AE	0.347 [0.327;0.363]	0.347 [0.288;0.406]	NS	NS	0.653 [0.594;0.712]
		Ratio of all fucosylated (+/- bisecting GlyNAc) monosialylated and disialylated structures in total IgG glycans	IGP33	DCE	0.241 [0.183;0.277]	NS	[0.142;0.34]	[0.175;0.316]	0.513 [0.457;0.57]
		Ratio of all fucosylated sialylated structures with and without bisecting GlcNAc	IGP36	AE	0.704 [0.72;0.691]	0.704 [0.669;0.739]	NS	NS	0.296 [0.261;0.331]
		The percentage of A2 glycan in total neutral IgG glycans (GPn)	IGP42	AE	0.739 [0.755;0.724]	0.739 [0.706;0.771]	NS	NS	0.261 [0.229;0.294]
		The percentage of FA2B glycan in total neutral IgG glycans (GP ⁿ)	IGP45	DCE	0.41 [0.407;0.413]	NS	[0.346;0.475]	[0.305;0.416]	0.229 [0.199;0.259]
		The percentage of A2G1 glycan in total neutral IgG glycans (GP ⁿ)	IGP46	AE	0.725 [0.742;0.711]	0.725 [0.691;0.76]	NS	NS	0.275 [0.24;0.309]
		The percentage of FA2[3]G1 glycan in total neutral IgG glycans (GPn)	IGP48	AE	0.776 [0.793;0.761]	0.776 [0.747;0.805]	NS	NS	0.224 [0.195;0.253]
		The percentage of monogalactosylated structures in total neutral IgG glycans	IGP56	ADE	0.678 [0.492;0.749]	0.475 [0.277;0.674]	0.203 [0;0.411]	NS	0.322 [0.281;0.363]
		The percentage of all fucosylated (+/- bisecting GlcNAc) structures in total neutral IgG glycans	IGP58	DCE	0.57 [0.599;0.55]	NS	0.57 [0.494;0.646]	[0.098;0.226]	0.162 [0.268 [0.232;0.303]
		The percentage of fucosylation of agalactosylated structures	IGP59	ADE	0.735 [0.591;0.791]	0.333 [0.136;0.531]	0.441 [0.107;0.803]	NS	0.162 [0.265 [0.231;0.3]
		The percentage of fucosylation of monogalactosylated structures	IGP60	AE	0.714 [0.731;0.7]	0.714 [0.677;0.751]	NS	NS	0.286 [0.249;0.323]
		The percentage of fucosylated (without bisecting GlcNAc) structures in total neutral IgG glycans	IGP62	AE	0.76 [0.777;0.745]	0.76 [0.729;0.79]	NS	NS	0.24 [0.21;0.271]
		The percentage of fucosylation (without bisecting GlcNAc) of agalactosylated structures	IGP63	AE	0.737 [0.754;0.722]	0.737 [0.703;0.771]	NS	NS	0.263 [0.229;0.297]
immune cell traits**		16+56/314+335+158b-	P4:3242	ACE	0.427 [0.20;0.66]	0.427 [0.20;0.66]	NS	0.356 [0.14;0.54]	0.217 [0.16;0.31]
		16+56/314+335+158b-R7-	P4:2561	ACE	0.424 [0.19;0.66]	0.424 [0.19;0.66]	NS	0.358 [0.14;0.54]	0.218 [0.16;0.31]
		16+56/314+335+158a-158b-	P4:3161	AE	0.792 [0.71;0.81]	0.792 [0.71;0.81]	NS	NS	0.208 [0.15;0.29]
		16+56/314+335+158a-158b-R7-	P4:2488	AE	0.792 [0.71;0.81]	0.792 [0.71;0.81]	NS	NS	0.208 [0.15;0.29]
		16+56/314+335+337-158b-	P4:3215	ACE	0.422 [0.19;0.66]	0.422 [0.19;0.66]	NS	0.358 [0.14;0.54]	0.220 [0.16;0.31]
		16+56/314+335+337-158b-R7-	P4:2534	ACE	0.423 [0.19;0.66]	0.423 [0.19;0.66]	NS	0.356 [0.14;0.54]	0.221 [0.16;0.31]
		16+56/335+158b-R7-	P4:2558	ACE	0.439 [0.21;0.68]	0.439 [0.21;0.68]	NS	0.344 [0.12;0.53]	0.217 [0.16;0.31]
		16+56/335+158b-	P4:3239	ACE	0.437 [0.20;0.68]	0.437 [0.20;0.68]	NS	0.344 [0.12;0.53]	0.220 [0.16;0.31]
		16+56/314+335+337-158a-158b-	P4:3134	AE	0.791 [0.71;0.85]	0.792 [0.71;0.85]	NS	NS	0.209 [0.15;0.29]
		16+56/314+335+337-158a-158b-R7-	P4:2462	AE	0.783 [0.70;0.84]	0.783 [0.70;0.84]	NS	NS	0.217 [0.16;0.30]
		16+56/335+337-158b-R7-	P4:2531	ACE	0.433 [0.20;0.67]	0.433 [0.20;0.67]	NS	0.347 [0.13;0.53]	0.217 [0.16;0.31]
		16+56/335+337-158b-	P4:3212	ACE	0.428 [0.19;0.67]	0.428 [0.19;0.67]	NS	0.347 [0.12;0.53]	0.225 [0.16;0.32]
		16+56/335+158a-158b-	P4:3158	AE	0.792 [0.71;0.81]	0.792 [0.71;0.81]	NS	NS	0.208 [0.15;0.29]
		16+56/335+337-158a-158b-R7-	P4:2460	AE	0.782 [0.70;0.84]	0.782 [0.70;0.84]	NS	NS	0.218 [0.16;0.30]
		16+56/335+158a-158b-R7-	P4:2485	AE	0.783 [0.70;0.84]	0.783 [0.70;0.84]	NS	NS	0.217 [0.16;0.30]
		16+56/335+337-158a-158b-	P4:3131	AE	0.781 [0.70;0.84]	0.781 [0.70;0.84]	NS	NS	0.219 [0.16;0.30]
		16+56/335+158a-	P4:3401	ACE	0.475 [0.26;0.70]	0.475 [0.26;0.70]	NS	0.337 [0.12;0.51]	0.188 [0.13;0.27]
		16+56/335-337-R7-	P4:2740	ACE	0.349 [0.15;0.55]	0.349 [0.15;0.55]	NS	0.461 [0.27;0.62]	0.19 [0.14;0.27]
		16+56/335-337-	P4:3437	ACE	0.303 [0.11;0.50]	0.303 [0.11;0.50]	NS	0.509 [0.33;0.66]	0.188 [0.13;0.27]
		16+56/335-R7-	P4:2767	ACE	0.352 [0.15;0.56]	0.352 [0.15;0.56]	NS	0.46 [0.27;0.62]	0.188 [0.13;0.27]
		16+56/335+	P4:3482	ACE	0.303 [0.11;0.50]	0.303 [0.11;0.50]	NS	0.51 [0.33;0.66]	0.187 [0.13;0.27]
		16+56/335-	P4:3464	ACE	0.305 [0.11;0.50]	0.305 [0.11;0.50]	NS	0.508 [0.33;0.66]	0.187 [0.13;0.27]
		16+56/335+337-158a-	P4:3374	ACE	0.475 [0.26;0.70]	0.475 [0.26;0.70]	NS	0.336 [0.12;0.51]	0.188 [0.14;0.27]
		16+56/335+337-158a-R7-	P4:2677	ACE	0.472 [0.26;0.70]	0.472 [0.26;0.70]	NS	0.339 [0.13;0.51]	0.189 [0.14;0.27]
		16+56/335-337-	P4:3455	ACE	0.309 [0.12;0.50]	0.309 [0.12;0.50]	NS	0.505 [0.33;0.65]	0.186 [0.13;0.27]
		16+56/335+337-R7-	P4:2758	ACE	0.306 [0.11;0.50]	0.309 [0.12;0.50]	NS	0.506 [0.33;0.66]	0.187 [0.13;0.27]
		16+56/335+337-R7-	P4:3243	ACE	0.461 [0.23;0.71]	0.461 [0.23;0.71]	NS	0.322 [0.10;0.51]	0.217 [0.16;0.31]
		16+56/CD2+314+335+158b-	P4:2562	ACE	0.465 [0.23;0.71]	0.465 [0.23;0.71]	NS	0.32 [0.09;0.51]	0.215 [0.15;0.30]
		16+56/CD2+314+335+158b-R7-	P4:3162	AE	0.788 [0.71;0.84]	0.788 [0.71;0.84]	NS	NS	0.212 [0.16;0.29]
		16+56/CD2+314+335+158a-158b-R7-	P4:2489	AE	0.79 [0.71;0.85]	0.79 [0.71;0.85]	NS	NS	0.21 [0.15;0.29]
		16+56/CD2+314+335+337-158b-	P4:3216	ACE	0.459 [0.22;0.70]	0.459 [0.22;0.70]	NS	0.323 [0.10;0.51]	0.218 [0.16;0.31]
		16+56/CD2+314+335+337-158b-R7-	P4:2535	ACE	0.46 [0.23;0.70]	0.46 [0.23;0.70]	NS	0.324 [0.10;0.51]	0.216 [0.16;0.31]
		16+56/CD2+314+335+337-158a-158b-R7-	P4:18	AE	0.788 [0.71;0.84]	0.788 [0.71;0.84]	NS	NS	0.212 [0.16;0.29]
		16+56/CD2+335+158a-158b-R7-	P4:2486	AE	0.782 [0.70;0.84]	0.782 [0.70;0.84]	NS	NS	0.218 [0.16;0.30]
		16+56/CD2+335+158b-R7-	P4:2559	ACE	0.471 [0.24;0.72]	0.471 [0.24;0.72]	NS	0.312 [0.08;0.50]	0.217 [0.16;0.31]
		16+56/CD2+335+158a-158b-	P4:3159	AE	0.78 [0.70;0.84]	0.78 [0.70;0.84]	NS	NS	0.22 [0.16;0.30]
		16+56/CD2+335+158b-	P4:3240	ACE	0.466 [0.23;0.71]	0.466 [0.23;0.71]	NS	0.314 [0.09;0.51]	0.219 [0.15;0.30]
		16+56/CD2+314+335+337-158a-158b-	P4:3135	AE	0.786 [0.71;0.84]	0.786 [0.71;0.84]	NS	NS	0.214 [0.16;0.29]
		16+56/CD2+335+337-158b-R7-	P4:2532	ACE	0.47 [0.24;0.72]	0.47 [0.24;0.72]	NS	0.313 [0.08;0.50]	0.217 [0.16;0.31]
		16+56/CD2+335+337-158b-	P4:3213	ACE	0.467 [0.23;0.71]	0.467 [0.23;0.71]	NS	0.314 [0.08;0.51]	0.22 [0.16;0.31]
		16+56/CD2+335+337-158a-158b-	P4:3132	AE	0.78 [0.70;0.84]	0.78 [0.70;0.84]	NS	NS	0.22 [0.16;0.30]
		16+56/CD2+335+337-158a-158b-R7-	P4:2461	AE	0.781 [0.70;0.84]	0.781 [0.70;0.84]	NS	NS	0.219 [0.16;0.30]
		16+56/335-337-158b+R7-	P4:2967	AE	0.772 [0.68;0.84]	0.772 [0.68;0.84]	NS	NS	0.228 [0.16;0.32]
		16+56/335-158b+R7-	P4:2994	AE	0.772 [0.68;0.84]	0.772 [0.68;0.84]	NS	NS	0.228 [0.16;0.32]
		16+56/335-158b+	P4:3707	AE	0.775 [0.68;0.84]	0.775 [0.68;0.84]	NS	NS	0.225 [0.16;0.32]
		16+56/335-337-158b+	P4:3680	AE	0.775 [0.68;0.84]	0.775 [0.68;0.84]	NS	NS	0.225 [0.16;0.32]
		16+56/314+335-337-158b+R7-	P4:2970	AE	0.775 [0.68;0.84]	0.775 [0.68;0.84]	NS	NS	0.225 [0.16;0.32]
16+56/314+335-337-158b+	P4:3683	AE	0.776 [0.68;0.84]	0.776 [0.68;0.84]	NS	NS	0.224 [0.16;0.31]		
16+56/314+335-158b+R7-	P4:2997	AE	0.775 [0.68;0.84]	0.775 [0.68;0.84]	NS	NS	0.225 [0.16;0.32]		
16+56/314+335-158b+	P4:3710	AE	0.777 [0.69;0.84]	0.777 [0.69;0.84]	NS	NS	0.223 [0.16;0.31]		
16+56/335-337-158a-158b+R7-	P4:2900	AE	0.756 [0.66;0.82]	0.756 [0.66;0.82]	NS	NS	0.244 [0.18;0.34]		

SL000343	Cathepsin B	P07858	1508	CTSB	RFU	No	No	AE	0.494	0.491	0.496	0.494	0.321	0.668	0	0	0	0	0	0.506	0.332	0.679	
SL000344	Cathepsin D	P07339	1509	CTSD	RFU	No	No	E	0	0	0	0	0	0	0	0	0	0	0	1	1	1	
SL000345	Cathepsin G	P08311	1511	CTSG	RFU	No	No	DE	0.415	0.139	0.452	0	0	0	0.415	0.033	0.797	0	0	0.585	0.203	0.967	
SL000346	Cathepsin H	P09688	1512	CTSH	RFU	No	No	CE	0	0	0	0	0	0	0	0	0	0.557	0.414	0.701	0.443	0.299	0.586
SL000347	CE	P08165	865	CE	RFU	No	No	E	0	0	0	0	0	0	0	0	0	0	0	1	1	1	
SL000357	Coagulation Factor IX	P00740	2158	F9	RFU	No	No	AE	0.515	0.524	0.511	0.515	0.327	0.704	0	0	0	0	0	0.485	0.296	0.673	
SL000358	Coagulation Factor VII	P08709	2155	F7	RFU	No	No	DE	0.730	0.803	0.686	0	0	0	0.730	0.610	0.850	0	0	0.270	0.150	0.390	
SL000360	Coagulation Factor X	P00742	2159	F10	RFU	No	No	CE	0	0	0	0	0	0	0	0	0	0.396	0.218	0.573	0.604	0.427	0.782
SL000377	CK-BB	P12277	1152	CKB	RFU	No	No	E	0	0	0	0	0	0	0	0	0	0	0	1	1	1	
SL000382	CK-MB	P12277	P061152	1158	CKB CKM	RFU	No	AE	0.550	0.577	0.537	0.550	0.376	0.725	0	0	0	0	0.450	0.275	0.624		
SL000383	CK-MM	P06732	1158	CKM	RFU	No	No	AE	0.546	0.573	0.534	0.546	0.364	0.728	0	0	0	0	0.454	0.272	0.636		
SL000384	CTLA-4	P16410	1493	CTLA4	RFU	No	No	DE	0.463	0.377	0.478	0	0	0	0.463	0.114	0.812	0	0	0.537	0.188	0.886	
SL000396	Cytochrome c	P99999	54205	CYCS	RFU	No	No	E	0	0	0	0	0	0	0	0	0	0	0	1	1	1	
SL000398	Cytochrome P450 3A4	P08684	1576	CYP3A4	RFU	No	No	AE	0.721	0.789	0.679	0.721	0.604	0.839	0	0	0	0	0.279	0.161	0.396		
SL000401	Elastase	P08246	1991	ELANE	RFU	No	No	E	0	0	0	0	0	0	0	0	0	0	0	1	1	1	
SL000403	Endostatin	P39060	80781	COL18A1	RFU	No	No	CE	0	0	0	0	0	0	0	0	0	0.687	0.578	0.797	0.313	0.203	0.422
SL000406	Eotaxin	P51671	6356	CCL11	RFU	No	No	CE	0	0	0	0	0	0	0	0	0	0.275	0.085	0.465	0.725	0.535	0.915
SL000408	Epo	P01588	2056	EPO	RFU	No	No	E	0	0	0	0	0	0	0	0	0	0	0	1	1	1	
SL000409	ERK-1	P27361	5595	MAPK3	RFU	No	No	CE	0	0	0	0	0	0	0	0	0	0.513	0.363	0.663	0.487	0.337	0.637
SL000414	Factor B	P00751	629	CFB	RFU	No	No	DE	0.405	0.325	0.435	0	0	0	0.405	0.177	0.633	0	0	0.595	0.367	0.823	
SL000415	Factor H	P08603	3075	CFH	RFU	No	No	DE	0.371	0.252	0.413	0	0	0	0.371	0.131	0.612	0	0	0.629	0.388	0.869	
SL000420	Ferritin	P02794	P022495	2512	FTH1 FTL	RFU	No	AE	0.623	0.673	0.595	0.623	0.479	0.768	0	0	0	0	0.377	0.232	0.521		
SL000424	Fibrinogen	P02671	P022243	2244	FGA FGB FGG	RFU	No	CE	0	0	0	0	0	0	0	0	0	0.226	0.024	0.428	0.774	0.572	0.976
SL000426	Fibronectin	P02751	2335	FN1	RFU	No	No	AE	0.627	0.683	0.598	0.627	0.476	0.779	0	0	0	0	0.373	0.221	0.524		
SL000427	Fractalkine/CX3CL-1	P78423	6376	CX3CL1	RFU	No	No	AE	0.405	0.349	0.430	0.405	0.220	0.589	0	0	0	0	0.595	0.411	0.780		
SL000428	FSH	P01215	P01081	2488	CGA FSHB	RFU	No	DE	0.298	0.157	0.357	0	0	0	0.298	0.157	0.357	0	0	0.702	0.497	0.908	
SL000433	Glucagon	P01275	2641	GCG	RFU	No	No	CE	0	0	0	0	0	0	0	0	0	0.539	0.394	0.683	0.461	0.317	0.606
SL000437	Haptoglobin Mixed Ty	P00738	3240	HP	RFU	No	No	CE	0	0	0	0	0	0	0	0	0	0.370	0.195	0.546	0.630	0.454	0.805
SL000440	Hemopexin	P02790	3263	HPX	RFU	No	No	AE	0.905	0.944	0.872	0.905	0.860	0.949	0	0	0	0	0.095	0.051	0.140		
SL000441	HGF	P14210	3082	HGF	RFU	No	No	E	0	0	0	0	0	0	0	0	0	0	0	1	1	1	
SL000445	HIV-2 Rev	P18093	1724716	Human-virus	RFU	No	No	E	0	0	0	0	0	0	0	0	0	0	0	1	1	1	
SL000449	HSP 40	P25685	3337	DJB1	RFU	No	No	CE	0	0	0	0	0	0	0	0	0	0.211	0.013	0.408	0.789	0.592	0.987
SL000450	HSP 60	P10809	3329	HSPD1	RFU	No	No	CE	0	0	0	0	0	0	0	0	0	0.546	0.403	0.689	0.454	0.311	0.597
SL000451	HSP 70	P08107	3303	HSPA1A	RFU	No	No	CE	0	0	0	0	0	0	0	0	0	0.345	0.163	0.527	0.655	0.473	0.837
SL000456	IC3b	P01024	716	C3	RFU	No	No	CE	0	0	0	0	0	0	0	0	0	0.496	0.339	0.653	0.504	0.347	0.661
SL000458	IFN-g R1	P15260	3459	IFNGR1	RFU	No	No	CE	0	0	0	0	0	0	0	0	0	0	0	1	1	1	
SL000460	IgD	P01880	3495	5080	IGHD	IGK@ IGL@RFU	No	DE	0.454	0.423	0.467	0	0	0	0.454	0.256	0.652	0	0	0.546	0.348	0.744	
SL000461	IgE	P01854	3497	5080	IGHE	IGK@ IGL@RFU	No	AE	0.557	0.586	0.542	0.557	0.384	0.729	0	0	0	0	0.443	0.271	0.616		
SL000462	IGFBP-1	P08833	3484	IGFBP1	RFU	No	No	CE	0	0	0	0	0	0	0	0	0	0.567	0.429	0.705	0.433	0.295	0.571
SL000466	IGFBP-2	P18065	3485	IGFBP2	RFU	No	No	AE	0.527	0.541	0.520	0.527	0.352	0.701	0	0	0	0	0.473	0.299	0.648		
SL000467	IgG	P01857	3500	3501	IGHG1	IGHG2 IGR@RFU	No	DE	0.502	0.503	0.501	0	0	0	0.502	0.316	0.688	0	0	0.498	0.312	0.684	
SL000468	IgM	P01871	3507	3512	IGHM	IGJ IGHG@ IGR@RFU	No	AE	0.432	0.392	0.451	0.432	0.247	0.617	0	0	0	0	0.568	0.383	0.753		
SL000470	IL-11	P20809	3589	IL11	RFU	No	No	DE	0.344	0.196	0.395	0	0	0	0.344	0.101	0.587	0	0	0.656	0.413	0.899	
SL000474	IL-16	Q14005	3603	IL16	RFU	No	No	AE	0.658	0.723	0.622	0.658	0.512	0.804	0	0	0	0	0.342	0.196	0.488		
SL000478	IL-2	P80568	3558	IL2	RFU	No	No	CE	0	0	0	0	0	0	0	0	0	0.584	0.449	0.719	0.416	0.281	0.551
SL000479	IL-3	P80700	3562	IL3	RFU	No	No	E	0	0	0	0	0	0	0	0	0	0	0	1	1	1	
SL000480	IL-4	P05112	3565	IL4	RFU	No	No	E	0	0	0	0	0	0	0	0	0	0	0	1	1	1	
SL000481	IL-5	P05113	3567	IL5	RFU	No	No	CE	0	0	0	0	0	0	0	0	0	0.416	0.245	0.587	0.584	0.413	0.755
SL000483	IL-7	P13232	3574	IL7	RFU	No	No	E	0	0	0	0	0	0	0	0	0	0	0	1	1	1	
SL000493	LDH-H 1	P07195	3945	LDHB	RFU	No	No	AE	0.709	0.772	0.669	0.709	0.593	0.824	0	0	0	0	0.291	0.176	0.407		
SL000496	Lactoferrin	P02788	4057	LTF	RFU	No	No	DE	0.605	0.650	0.581	0	0	0	0.605	0.455	0.755	0	0	0.395	0.245	0.545	
SL000497	Laminin	P25391	P01284217	39	LAMA1 LAMB1	RFU	No	AE	0.616	0.668	0.589	0.616	0.461	0.771	0	0	0	0	0.384	0.229	0.539		
SL000498	Leptin	P41159	3952	LEP	RFU	No	No	AE	0.622	0.680	0.593	0.622	0.462	0.783	0	0	0	0	0.378	0.217	0.538		
SL000506	Luteinizing hormone	P01215	P01081	3972	CGA LHb	RFU	No	CE	0	0	0	0	0	0	0	0	0	0.305	0.119	0.490	0.695	0.510	0.881
SL000507	Lymphotoxin a1b2	P01374	Q04049	4050	LTA LTB	RFU	No	DE	0.538	0.568	0.526	0	0	0	0.538	0.317	0.759	0	0	0.452	0.241	0.583	
SL000508	Lymphotoxin a2b1	P01374	Q04049	4055	LTA LTB	RFU	No	CE	0	0	0	0	0	0	0	0	0	0.296	0.103	0.489	0.704	0.511	0.897
SL000509	Lymphotoxin b R	P36941	4055	LTBR	RFU	No	No	DE	0	0	0	0	0	0	0	0	0	0.274	0.080	0.468	0.726	0.532	0.920
SL000510	Lysozyme	P61626	4069	LYZ	RFU	No	No	CE	0	0	0	0	0	0	0	0	0	0.682	0.570	0.795	0.318	0.205	0.430
SL000515	MCP-2	P80075	6355	CCL8	RFU	No	No	DE	0.388	0.300	0.422	0	0	0	0.388	0.168	0.608	0	0	0.612	0.392	0.832	
SL000516	MCP-3	P80098	6354	CCL7	RFU	No	No	DE	0.760	0.833	0.713	0	0	0	0.760	0.650	0.870	0	0	0.240	0.130	0.350	
SL000517	MCP-4	Q89616	6357	CCL13	RFU	No	No	CE	0	0	0	0	0	0	0	0	0	0.172	-0.027	0.372	0.828	0.628	1.027
SL000519	MIP-1a	P10147	6348	CCL3	RFU	No	No	CE	0	0	0	0	0	0	0	0	0	0.154	-0.045	0.354	0.846	0.646	1.045
SL000521	MMP-1	P03956	4312	MMP1	RFU	No	No	CE	0	0	0	0	0	0	0	0	0	0.367	0.191	0.543	0.633	0.457	0.809
SL000522	MMP-12	P39900	4321	MMP12	RFU	No	No	AE	0.595	0.639	0.572	0.595	0.435	0.755	0	0	0	0	0.405	0.245	0.565		
SL000523	MMP-13	P45452	4322	MMP13	RFU	No	No	E	0	0	0	0	0	0	0	0	0	0	0	1	1	1	
SL000524	MMP-3	P08254	4314	MMP3	RFU	No	No	AE	0.203	-0.032	0.294	0.203	-0.018	0.424	0	0	0	0	0.797	0.576	1.018		
SL000525	MMP-7	P09237	4316	MMP7	RFU	No	No	CE	0	0</													

SL000573	SAP	P02743	325	APCS	RFU	No	No	AE	0.475	0.459	0.482	0.475	0.284	0.666	0	0	0	0	0	0.525	0.334	0.716	
SL000581	SOD	P00441	6647	SOD1	RFU	No	No	CE	0	0	0	0	0	0	0	0	0.249	0.056	0.441	0.751	0.559	0.944	
SL000582	Survivin	O15392	332	BIRC5	RFU	No	No	DE	0.759	0.852	0.705	0	0	0	0.759	0.627	0.891	0	0	0.241	0.109	0.373	
SL000584	TGF-b1	P01137	7040	TGFB1	RFU	No	No	CE	0	0	0	0	0	0	0	0	0	0.227	0.032	0.423	0.773	0.577	0.968
SL000586	Thrombin	P00734	2147	F2	RFU	No	No	CE	0	0	0	0	0	0	0	0	0	0.596	0.465	0.728	0.404	0.272	0.535
SL000587	Thyroglobulin	P01266	7038	TG	RFU	No	No	E	0	0	0	0	0	0	0	0	0	0	0	1	1	1	
SL000588	TMA	P07202	7173	TPO	RFU	No	No	DE	0.513	0.537	0.508	0	0	0	0.513	0.180	0.845	0	0	0.487	0.155	0.820	
SL000590	Thyroxine-Binding Glo	P05543	6906	SERP17	RFU	No	No	DE	0.556	0.585	0.542	0	0	0	0.556	0.388	0.725	0	0	0.444	0.275	0.612	
SL000591	TIMP-1	P01033	7076	TIMP1	RFU	No	No	CE	0	0	0	0	0	0	0	0	0.261	0.065	0.457	0.739	0.543	0.935	
SL000592	TIMP-2	P16035	7077	TIMP2	RFU	No	No	AE	0.472	0.453	0.480	0.472	0.273	0.671	0	0	0	0	0.528	0.329	0.727		
SL000597	TNF-b	P01374	4049	LTA	RFU	No	No	E	0	0	0	0	0	0	0	0	0	0	1	1	1		
SL000601	Transferrin	P02787	7018	TF	RFU	No	No	CE	0	0	0	0	0	0	0	0	0.260	0.062	0.457	0.740	0.543	0.938	
SL000603	Trypsin	P07477	5644	PRSS1	RFU	No	No	AE	0.600	0.649	0.575	0.600	0.434	0.765	0	0	0	0	0.400	0.235	0.566		
SL000605	Ubiquitin+1	P62979	6233	RPS27A	RFU	No	No	CE	0	0	0	0	0	0	0	0	0.449	0.284	0.614	0.551	0.386	0.716	
SL000613	uPA	P00749	5328	PLAU	RFU	No	No	CE	0	0	0	0	0	0	0	0	0.478	0.319	0.637	0.522	0.363	0.681	
SL000615	Vasoaactive Intestil Pep	P01282	7432	VIP	RFU	No	No	DE	0.546	0.575	0.533	0	0	0	0.546	0.349	0.743	0	0	0.454	0.267	0.651	
SL000617	ALT	P24298	2875	GPT	RFU	No	No	CE	0	0	0	0	0	0	0	0	0.340	0.158	0.522	0.660	0.478	0.842	
SL000622	Coagulation Factor V	P12259	2153	F5	RFU	No	No	AE	0.701	0.764	0.662	0.701	0.581	0.821	0	0	0	0	0.299	0.179	0.419		
SL000633	Fas ligand soluble	P48023	356	FASLG	RFU	No	No	DE	0.394	0.320	0.425	0	0	0	0.394	0.189	0.599	0	0	0.606	0.401	0.811	
SL000638	Cadherin-2	P19022	1000	CDH2	RFU	No	No	E	0	0	0	0	0	0	0	0	0	0	1	1	1		
SL000640	Nidogen	P14543	4811	NID1	RFU	No	No	E	0.678	0.755	0.637	0.678	0.528	0.828	0	0	0	0	0.322	0.172	0.472		
SL000645	MMP-10	P09238	4319	MMP10	RFU	No	No	E	0	0	0	0	0	0	0	0	0	0	1	1	1		
SL000655	Keratin 18	P05783	3875	KRT18	RFU	No	No	E	0	0	0	0	0	0	0	0	0	0	1	1	1		
SL000658	GAS1	P54826	2619	GAS1	RFU	No	No	E	0	0	0	0	0	0	0	0	0	0	1	1	1		
SL000668	CD36 ANTIGEN	P16871	848	CD36	RFU	No	No	DE	0.584	0.629	0.582	0	0	0	0.584	0.408	0.759	0	0	0.416	0.241	0.592	
SL000670	GSTA3	Q16772	2940	GSTA3	RFU	No	No	E	0	0	0	0	0	0	0	0	0	0	1	1	1		
SL000674	FST	P19883	10468	FST	RFU	No	No	AE	0.213	-0.141	0.315	0.213	-0.063	0.488	0	0	0	0	0.787	0.512	1.063		
SL000678	Granulysin	P22749	10578	GNLY	RFU	No	No	AE	0.679	0.740	0.643	0.679	0.552	0.806	0	0	0	0	0.321	0.194	0.448		
SL000695	Lipocalin 2	P80188	3934	LCN2	RFU	No	No	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	
SL000836	Hemoglobin	P69905	P613039	3043 HBB	RFU	No	No	CE	0	0	0	0	0	0	0	0	0.397	0.225	0.569	0.603	0.431	0.775	
SL001691	FGF7	P21781	2252	FGF7	RFU	No	No	CE	0	0	0	0	0	0	0	0	0.602	0.470	0.733	0.398	0.267	0.530	
SL001713	IL-17	Q16552	3605	IL17A	RFU	No	No	CE	0	0	0	0	0	0	0	0	0.241	0.044	0.437	0.759	0.563	0.956	
SL001716	IL-12	P29459	P23592	3593 IL12A IL12B	RFU	No	No	E	0	0	0	0	0	0	0	0	0	0	1	1	1		
SL001717	IL-10	P22301	3586	IL10	RFU	No	No	E	0	0	0	0	0	0	0	0	0	0	1	1	1		
SL001718	IL-13	P33225	3596	IL13	RFU	No	No	E	0	0	0	0	0	0	0	0	0	0	1	1	1		
SL001720	VCAM-1	P19320	7412	VCAM1	RFU	No	No	CE	0	0	0	0	0	0	0	0	0.388	0.212	0.564	0.612	0.436	0.788	
SL001721	PECAM-1	P16284	5175	PECAM1	RFU	No	No	E	0	0	0	0	0	0	0	0	0	0	1	1	1		
SL001726	GM-CSF	P04411	1437	CSF2	RFU	No	No	E	0	0	0	0	0	0	0	0	0	0	1	1	1		
SL001729	G-CSF	P09919	1440	CSF3	RFU	No	No	CE	0	0	0	0	0	0	0	0	0.223	0.029	0.416	0.777	0.584	0.971	
SL001737	STRATIFIN	P31947	2810	SFN	RFU	No	No	CE	0	0	0	0	0	0	0	0	0.475	0.317	0.634	0.525	0.366	0.683	
SL001753	Sialoadhesin	Q8B222	6614	SIGLEC1	RFU	No	No	E	0	0	0	0	0	0	0	0	0	0	1	1	1		
SL001766	HCG	P01215	P011081	1082 CGA CGB	RFU	No	No	DE	0.502	0.504	0.502	0	0	0	0.502	0.311	0.694	0	0	0.498	0.306	0.689	
SL001774	FABP	P05413	2170	FABP3	RFU	No	No	CE	0	0	0	0	0	0	0	0	0.422	0.253	0.591	0.578	0.409	0.747	
SL001777	Cystatin C	P01034	1471	CS13	RFU	No	No	DE	0.593	0.635	0.571	0	0	0	0.593	0.439	0.747	0	0	0.407	0.253	0.561	
SL001795	IL-1b	P01584	3553	IL1B	RFU	No	No	CE	0	0	0	0	0	0	0	0	0.169	-0.029	0.367	0.831	0.633	1.039	
SL001796	Myeloperoxidase	P05164	4353	MPO	RFU	No	No	AE	0.600	0.644	0.576	0.600	0.447	0.753	0	0	0	0	0.400	0.247	0.553		
SL001797	Kallikrein 6	Q82876	5653	KLK6	RFU	No	No	CE	0	0	0	0	0	0	0	0	0.202	0.002	0.402	0.798	0.598	0.998	
SL001800	TNF sR-II	P20333	7133	TNFRSF1B	RFU	No	No	CE	0	0	0	0	0	0	0	0	0.493	0.337	0.650	0.507	0.350	0.663	
SL001802	IFN-g	P01579	3458	IFNG	RFU	No	No	CE	0	0	0	0	0	0	0	0	0.697	0.592	0.802	0.303	0.198	0.408	
SL001815	Mn SOD	P04179	6648	SOD2	RFU	No	No	CE	0	0	0	0	0	0	0	0	0.488	0.330	0.646	0.512	0.354	0.670	
SL001868	CASA	P47710	1446	CSN1S1	RFU	No	No	E	0	0	0	0	0	0	0	0	0	0	1	1	1		
SL001888	SLPI	P03973	6590	SLPI	RFU	No	No	AE	0.529	0.543	0.521	0.529	0.362	0.695	0	0	0	0	0.471	0.305	0.638		
SL001890	GA733-1 protein	P09758	4070	TACSTD2	RFU	No	No	E	0	0	0	0	0	0	0	0	0	0	1	1	1		
SL001896	Clusterin	P10909	1191	CLU	RFU	No	No	CE	0	0	0	0	0	0	0	0	0.363	0.184	0.542	0.637	0.458	0.816	
SL001897	SPINT2	Q43291	10653	SPINT2	RFU	No	No	AE	0.685	0.751	0.646	0.685	0.553	0.816	0	0	0	0	0.315	0.184	0.447		
SL001902	BCAM	P50895	4059	BCAM	RFU	No	No	AE	0.523	0.543	0.516	0.523	0.290	0.757	0	0	0	0	0.477	0.243	0.710		
SL001905	Mesothelin	Q13421	10232	MSLN	RFU	No	No	E	0	0	0	0	0	0	0	0	0	0	1	1	1		
SL001938	Activin A	P08476	3624	INHBA	RFU	No	No	CE	0	0	0	0	0	0	0	0	0.318	0.134	0.501	0.682	0.499	0.866	
SL001943	IL-6 sRa	P08887	3570	IL6R	RFU	No	No	AE	0.845	0.899	0.804	0.845	0.777	0.913	0	0	0	0	0.155	0.087	0.223		
SL001945	sE-Selectin	P16581	6401	SELE	RFU	No	No	AE	0.723	0.792	0.680	0.723	0.605	0.841	0	0	0	0	0.277	0.159	0.395		
SL001947	MIA	Q16674	8190	MIA	RFU	No	No	DE	0.669	0.730	0.634	0	0	0	0.669	0.538	0.801	0	0	0.331	0.199	0.462	
SL001973	Mammaglobin 2	O75556	4246	SCGB2A1	RFU	No	No	E	0	0	0	0	0	0	0	0	0	0	1	1	1		
SL001992	TNF sR-I	P19438	7132	TNFRSF1A	RFU	No	No	AE	0.502	0.504	0.502	0.502	0.313	0.692	0	0	0	0	0.498	0.308	0.687		
SL001995	Angiotensin-1	Q15389	284	ANGPT1	RFU	No	No	CE	0	0	0	0	0	0	0	0	0.293	0.107	0.480	0.707	0.520	0.893	
SL001996	Angiotensin-2	Q15123	285	ANGPT2	RFU	No	No	AE	0.666	0.726	0.632	0.666	0.535	0.798	0	0	0	0	0.334	0.202	0.465		
SL001987	IL-1 sRI	P14777	3554	IL1R1	RFU	No	No	AE	0.539	0.560	0.529	0.539	0.362	0.715	0	0	0	0	0.461	0.285	0.638		
SL001998	TFPI	P10646	7035	TFPI	RFU	No	No	CE	0	0	0	0	0	0	0	0	0.540	0.392	0.687	0.460	0.313	0.608	
SL001999	MDM2	Q00987	4193	MDM2	RFU	No	No	CE	0	0	0	0	0	0	0	0	0.220	0.026	0.415	0.780	0.585	0.974	
SL002036	FGFR4	P22455	2264	FGFR4	RFU	No	No	E	0	0	0	0	0	0	0	0	0	0	1	1	1		
SL002075	IFN-a	P01563	3440	IF2																			

SL004708	CTAP-III	P02775	5473	PPBP	RFU	No	No	CE	0	0	0	0	0	0	0	0	0	0.367	0.191	0.543	0.633	0.457	0.809
SL004712	SDF-1	P48061	6387	CXCL12	RFU	No	No	CE	0	0	0	0	0	0	0	0	0	0.409	0.233	0.584	0.591	0.416	0.767
SL004714	LIF sR	P42702	3977	LIFR	RFU	No	No	E	0	0	0	0	0	0	0	0	0	0	0	0	1	1	1
SL004716	JNK2	P45984	5601	MAPK9	RFU	No	No	DE	0.696	0.784	0.650	0	0	0	0.696	0.541	0.851	0	0	0	0.304	0.149	0.459
SL004718	Karyopherin- α 2	P52292	3838	KP2	RFU	No	No	AE	0.251	-0.009	0.335	0.251	-0.005	0.506	0	0	0	0	0	0	0.749	0.494	1.005
SL004720	Calcineurin B a	P63098	5534	PPP3R1	RFU	No	No	E	0	0	0	0	0	0	0	0	0	0	0	0	1	1	1
SL004723	HDAC8	Q8Y41	55869	HDAC8	RFU	No	No	AE	0.518	0.530	0.513	0.518	0.323	0.713	0	0	0	0	0	0	0.482	0.287	0.677
SL004724	MOZ	Q92794	7994	KAT6A	RFU	No	No	E	0	0	0	0	0	0	0	0	0	0	0	0	1	1	1
SL004725	Hat1	O14929	8520	HAT1	RFU	No	No	E	0	0	0	0	0	0	0	0	0	0	0	0	1	1	1
SL004726	CD97	P48960	976	CD97	RFU	No	No	DE	0.245	-0.121	0.340	0	0	0	0.245	-0.050	0.540	0	0	0	0.755	0.460	1.050
SL004737	Tropomyosin 1 alpha	P09493	7168	TPM1	RFU	No	No	E	0	0	0	0	0	0	0	0	0	0	0	0	1	1	1
SL004739	ITI heavy chain H4	Q14624	3700	ITI4	RFU	No	No	AE	0.779	0.844	0.735	0.779	0.685	0.873	0	0	0	0	0	0	0.221	0.127	0.315
SL004742	Aflamin	P43652	173	AFM	RFU	No	No	AE	0.463	0.437	0.474	0.463	0.259	0.667	0	0	0	0	0	0	0.537	0.333	0.741
SL004750	DEAD-box protein 19E	Q8UMR2	11269	DDX19B	RFU	No	No	E	0	0	0	0	0	0	0	0	0	0	0	0	1	1	1
SL004751	HO-2	P30519	3163	HMOX2	RFU	No	No	E	0	0	0	0	0	0	0	0	0	0	0	0	1	1	1
SL004752	DRR1	Q95990	11170	FAM107A	RFU	No	No	E	0	0	0	0	0	0	0	0	0	0	0	0	1	1	1
SL004757	DRG-1	Q9NP79	51534	VTA1	RFU	No	No	CE	0	0	0	0	0	0	0	0	0	0.569	0.431	0.707	0.431	0.293	0.569
SL004759	eIF-5	P55010	1983	EIF5	RFU	No	No	DE	0.822	0.894	0.773	0	0	0	0.822	0.731	0.913	0	0	0	0.178	0.087	0.269
SL004760	PAFAH beta subunit	P68402	5049	PAFAH1B2	RFU	No	No	CE	0	0	0	0	0	0	0	0	0	0.642	0.521	0.763	0.358	0.237	0.479
SL004765	MAPKAPK3	Q16644	7867	MAPKAPK3	RFU	No	No	AE	0.734	0.806	0.690	0.734	0.618	0.851	0	0	0	0	0	0	0.266	0.149	0.382
SL004768	AIF1	P55008	199	AIF1	RFU	No	No	AE	0.387	0.301	0.421	0.387	0.172	0.602	0	0	0	0	0	0	0.613	0.398	0.828
SL004771	Aurora kise A	O14965	6790	AURKA	RFU	No	No	DE	0.500	0.500	0.500	0	0	0	0.500	0.260	0.739	0	0	0	0.500	0.261	0.740
SL004781	CSK	P41240	1445	CSK	RFU	No	No	AE	0.753	0.817	0.710	0.753	0.651	0.855	0	0	0	0	0	0	0.247	0.145	0.349
SL004782	TSG-6	P98066	7130	TNFAIP6	RFU	No	No	AE	0.656	0.714	0.623	0.656	0.522	0.791	0	0	0	0	0	0	0.340	0.209	0.478
SL004791	DR3	Q83038	8718	TNFRSF25	RFU	No	No	DE	0.880	0.927	0.843	0	0	0	0.880	0.826	0.935	0	0	0	0.124	0.065	0.174
SL004795	ERAB	Q99714	3028	HSD17B10	RFU	No	No	DCE	0.230	-0.053	0.303	0	0	0	0.230	-0.022	0.481	0.539	0.305	0.772	0.232	0.129	0.335
SL004804	Nectin-like protein 1	Q8N126	57863	CADM3	RFU	No	No	E	0	0	0	0	0	0	0	0	0	0	0	0	1	1	1
SL004805	Nectin-like protein 2	Q98Y67	23705	CADM1	RFU	No	No	DE	0.383	0.278	0.421	0	0	0	0.383	0.146	0.620	0	0	0	0.617	0.380	0.854
SL004812	Triosephosphate isom	P60174	7167	TP1	RFU	No	No	ACE	0.374	-0.437	0.412	0.374	-0.039	0.787	0	0	0	0.371	-0.014	0.756	0.256	0.144	0.368
SL004814	Coactosin-like protein	Q14019	23406	COTL1	RFU	No	No	DE	0.545	0.587	0.530	0	0	0	0.545	0.304	0.787	0	0	0	0.455	0.213	0.696
SL004820	Phosphoglycerate mut	P18669	5223	PGAM1	RFU	No	No	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA
SL004823	Cyclophilin A	P62937	5478	PP1A	RFU	No	No	CE	0	0	0	0	0	0	0	0	0	0.601	0.470	0.732	0.399	0.268	0.530
SL004837	Actinin AB	P08476	P093624	3625	INHBA	INHBB	RFU	No	No	CE	0	0	0	0	0	0	0	0.389	0.215	0.563	0.611	0.437	0.785
SL004844	EphA5	P54756	2044	EPHA5	RFU	No	No	E	0	0	0	0	0	0	0	0	0	0	0	0	1	1	1
SL004845	EphB4	P54760	2050	EPHB4	RFU	No	No	DE	0.289	0.146	0.350	0	0	0	0.289	0.087	0.492	0	0	0	0.711	0.508	0.913
SL004849	IL-1 sR	Q9NP60	26280	IL1RAPL2	RFU	No	No	E	0	0	0	0	0	0	0	0	0	0	0	0	1	1	1
SL004850	IL-17 sR	Q96F46	23765	IL17RA	RFU	No	No	DE	0.936	0.962	0.912	0	0	0	0.936	0.907	0.965	0	0	0	0.064	0.035	0.093
SL004851	ALK-1	P37023	94	ACVRL1	RFU	No	No	DE	0.563	0.668	0.539	0	0	0	0.563	0.252	0.875	0	0	0	0.437	0.125	0.748
SL004852	B7-H1	Q9NZ07	29126	CD274	RFU	No	No	CE	0	0	0	0	0	0	0	0	0	0.152	-0.047	0.351	0.848	0.649	1.047
SL004853	B7-H2	O75144	23308	ICOSLG	RFU	No	No	AE	0.472	0.455	0.480	0.472	0.279	0.665	0	0	0	0	0	0	0.528	0.335	0.721
SL004855	contactin-1	Q12860	1272	CNTN1	RFU	No	No	AE	0.464	0.439	0.475	0.464	0.256	0.672	0	0	0	0	0	0	0.536	0.328	0.744
SL004856	Desmoglein-1	Q02413	1828	DSG1	RFU	No	No	AE	0.262	-0.182	0.356	0.262	-0.064	0.587	0	0	0	0	0	0	0.738	0.413	1.064
SL004857	Desmoglein-2	Q14126	1829	DSG2	RFU	No	No	DE	0.618	0.673	0.590	0	0	0	0.618	0.461	0.776	0	0	0	0.382	0.224	0.539
SL004858	GFR-1	P56159	2674	GFR1	RFU	No	No	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA
SL004859	GTR	Q83056	8784	TNFRSF18	RFU	No	No	CE	0	0	0	0	0	0	0	0	0	0	0	0	1	1	1
SL004860	HTRA2	Q43464	27429	HTRA2	RFU	No	No	E	0	0	0	0	0	0	0	0	0	0.371	0.194	0.548	0.629	0.452	0.806
SL004861	IL-18 Rb	Q95256	8807	IL18RAP	RFU	No	No	DE	0.794	0.880	0.740	0	0	0	0.794	0.680	0.908	0	0	0	0.206	0.092	0.320
SL004862	PD-L2	Q98051	80380	PDCD1LG2	RFU	No	No	DE	0.584	0.639	0.560	0	0	0	0.584	0.385	0.783	0	0	0	0.416	0.217	0.615
SL004863	TAJ	Q9NS68	55504	TNFRSF19	RFU	No	No	E	0	0	0	0	0	0	0	0	0	0	0	0	1	1	1
SL004864	Cadherin-12	P55289	1010	CDH12	RFU	No	No	DE	0.300	-0.176	0.383	0	0	0	0.300	-0.052	0.653	0	0	0	0.700	0.347	1.052
SL004865	Cadherin-6	P55285	1004	CDH6	RFU	No	No	E	0	0	0	0	0	0	0	0	0	0	0	0	1	1	1
SL004866	Carbonic anhydrase I	P00915	759	CA1	RFU	No	No	AE	0.551	0.578	0.538	0.551	0.379	0.723	0	0	0	0	0	0	0.449	0.277	0.621
SL004867	Carbonic anhydrase III	P07451	761	CA3	RFU	No	No	AE	0.591	0.633	0.569	0.591	0.433	0.748	0	0	0	0	0	0	0.409	0.252	0.567
SL004868	Carbonic anhydrase V	P43166	766	CA7	RFU	No	No	DE	0.389	0.111	0.435	0	0	0	0.389	0.032	0.746	0	0	0	0.611	0.254	0.968
SL004869	Carbonic anhydrase X	Q8N101	377677	CA13	RFU	No	No	CE	0	0	0	0	0	0	0.498	0.344	0.651	0.502	0.349	0.656	0.452	0.283	0.628
SL004871	DR6	Q75509	27242	TNFRSF21	RFU	No	No	CE	0	0	0	0	0	0	0	0	0	0.538	0.390	0.686	0.462	0.314	0.610
SL004872	EDAR	Q9JNE0	10913	EDAR	RFU	No	No	AE	0.765	0.829	0.722	0.765	0.668	0.862	0	0	0	0	0	0	0.235	0.138	0.332
SL004875	IL-1Rrp2	Q9HB29	8808	IL1RL2	RFU	No	No	CE	0	0	0	0	0	0	0	0	0	0.286	0.094	0.478	0.714	0.522	0.906
SL004876	Kallistatin	P29622	5267	SERP4	RFU	No	No	CE	0	0	0	0	0	0	0	0	0	0.487	0.325	0.650	0.513	0.350	0.675
SL004891	hnRNP A2/B1	P22626	3181	HNRNPA2B1	RFU	No	No	DE	0.723	0.809	0.674	0	0	0	0.723	0.583	0.862	0	0	0	0.277	0.138	0.417
SL004899	HSP70 protein 8	P11142	3312	HSPA8	RFU	No	No	DE	0.548	0.613	0.530	0	0	0	0.548	0.261	0.835	0	0	0	0.452	0.165	0.739
SL004901	Protein disulfide-isom	P07237	5034	P4HB	RFU	No	No	E	0	0	0	0	0	0	0	0	0	0	0	0	1	1	1
SL004908	Tropomyosin 2	P07951	7169	TPM2	RFU	No	No	E	0	0	0	0	0	0	0	0	0	0	0	0	1	1	1
SL004914	PPase	Q15181	5464	PPA1	RFU	No	No	E	0	0	0	0	0	0	0	0	0	0	0	0	1	1	1
SL004915	CCC27	Q09299	1192	CLIC1	RFU	No	No	AE	0.745	0.809	0.702	0.745	0.640	0.849	0	0	0	0	0</				

SL006119	TFF3	Q07654	7033	TFF3	RFU	No	No	CE	0	0	0	0	0	0	0	0	0	0.184	-0.015	0.383	0.816	0.617	1.015	
SL006132	Lamin-B1	P20700	4001	LMNB1	RFU	No	No	DE	0.546	0.599	0.530	0	0	0	0.546	0.278	0.814	0	0	0	0.454	0.186	0.722	
SL006189	KIF23	Q02241	9493	KIF23	RFU	No	No	DE	0.362	0.171	0.413	0	0	0	0.362	0.071	0.654	0	0	0	0.638	0.346	0.929	
SL006197	DJ homolog	Q86DA6	131118	DJC19	RFU	No	No	E	0	0	0	0	0	0	0	0	0	0	0	0	0	0	1	
SL006268	NSF1C	Q8JUN2	55965	NSFL1C	RFU	No	No	CE	0	0	0	0	0	0	0	0	0	0.479	0.321	0.636	0.521	0.364	0.679	
SL006372	YES	P07947	7525	YES1	RFU	No	No	AE	0.704	0.770	0.664	0.704	0.581	0.826	0	0	0	0	0	0	0	0.296	0.174	0.419
SL006374	BMX	P51813	660	BMX	RFU	No	No	E	0	0	0	0	0	0	0	0	0	0	0	0	1	1	1	
SL006378	Esterase D	P10768	2098	ESD	RFU	No	No	CE	0	0	0	0	0	0	0	0	0	0.337	0.155	0.519	0.663	0.481	0.845	
SL006397	NRP1	Q14786	8829	NRP1	RFU	No	No	AE	0.335	0.217	0.383	0.335	0.127	0.543	0	0	0	0	0	0	0	0.665	0.457	0.873
SL006406	PLXC1	Q06486	10154	PLXNC1	RFU	No	No	AE	0.692	0.759	0.653	0.692	0.564	0.821	0	0	0	0	0	0	0	0.308	0.179	0.436
SL006448	HRG	P04196	3273	HRG	RFU	No	No	CE	0	0	0	0	0	0	0	0	0	0.467	0.306	0.627	0.533	0.373	0.694	
SL006460	GP1BA	P07359	2811	GP1BA	RFU	No	No	E	0	0	0	0	0	0	0	0	0	0	0	0	1	1	1	
SL006476	NMT1	P30419	4836	NMT1	RFU	No	No	CE	0	0	0	0	0	0	0	0	0	0.540	0.396	0.685	0.460	0.315	0.604	
SL006480	TRY3	P35030	5646	PRSS3	RFU	No	No	E	0	0	0	0	0	0	0	0	0	0	0	0	0	0	1	
SL006512	HGF	Q04756	3083	HGFAC	RFU	No	No	AE	0.826	0.881	0.785	0.826	0.755	0.898	0	0	0	0	0	0	0	0.174	0.102	0.245
SL006522	LC3BP	Q08380	3959	LGALS3BP	RFU	No	No	CE	0	0	0	0	0	0	0	0	0	0.739	0.646	0.832	0.261	0.168	0.354	
SL006523	MFGM	Q08431	4240	MFGE8	RFU	No	No	CE	0	0	0	0	0	0	0	0	0	0.494	0.340	0.649	0.506	0.351	0.660	
SL006528	SEPR	Q12884	2191	FAP	RFU	No	No	CE	0	0	0	0	0	0	0	0	0	0.255	0.061	0.450	0.745	0.550	0.939	
SL006542	FCN2	Q15485	2220	FCN2	RFU	No	No	DE	0.707	0.788	0.662	0	0	0	0.707	0.567	0.848	0	0	0	0.293	0.152	0.433	
SL006544	BGH3	Q15582	7045	TGFBI	RFU	No	No	CE	0	0	0	0	0	0	0	0	0	0.385	0.208	0.563	0.615	0.437	0.792	
SL006550	ECM1	Q16610	1893	ECM1	RFU	No	No	AE	0.493	0.487	0.495	0.493	0.285	0.700	0	0	0	0	0	0	0.507	0.300	0.715	
SL006610	ATS13	Q76LX8	11093	ADAMTS13	RFU	No	No	CE	0	0	0	0	0	0	0	0	0	0.600	0.468	0.732	0.400	0.268	0.532	
SL006629	SIRT2	Q8JKJ6	22933	SIRT2	RFU	No	No	CE	0	0	0	0	0	0	0	0	0	0.431	0.265	0.598	0.569	0.402	0.735	
SL006675	CKAP2	Q8WV93	26586	CKAP2	RFU	No	No	AE	0.286	0.110	0.353	0.286	0.060	0.512	0	0	0	0	0	0	0.714	0.488	0.940	
SL006694	CNDP1	Q86KJ2	84735	CNDP1	RFU	No	No	AE	0.670	0.730	0.635	0.670	0.540	0.801	0	0	0	0	0	0	0.330	0.199	0.460	
SL006698	transcription factor MLI	Q8N3X6	254261	LCORL	RFU	No	No	E	0	0	0	0	0	0	0	0	0	0	0	0	1	1	1	
SL006705	PFD5	Q99471	5204	PFDN5	RFU	No	No	CE	0	0	0	0	0	0	0	0	0	0.341	0.154	0.528	0.659	0.472	0.846	
SL006713	Collectin Kidney 1	Q98W98	78989	COLEC11	RFU	No	No	AE	0.621	0.670	0.594	0.621	0.476	0.765	0	0	0	0	0	0	0.379	0.235	0.524	
SL006777	FETUB	Q9UGM5	26998	FETUB	RFU	No	No	AE	0.638	0.690	0.609	0.638	0.502	0.775	0	0	0	0	0	0	0.362	0.225	0.498	
SL006803	ANGL3	Q9Y5C1	27329	ANGPTL3	RFU	No	No	DE	0.919	0.955	0.887	0	0	0	0.919	0.878	0.959	0	0	0	0.081	0.041	0.122	
SL006805	MRCKB	Q9Y552	9578	CDC42BPB	RFU	No	No	E	0	0	0	0	0	0	0	0	0	0	0	0	1	1	1	
SL006830	complement factor H-n	Q98XR6	81494	CFHR5	RFU	No	No	CE	0	0	0	0	0	0	0	0	0	0.385	0.210	0.560	0.615	0.440	0.790	
SL006892	ABL1	P00519	25	ABL1	RFU	No	No	E	0	0	0	0	0	0	0	0	0	0	0	0	0	1	1	
SL006910	Cathepsin V	Q60911	1515	CTSL2	RFU	No	No	AE	0.361	0.269	0.400	0.361	0.162	0.559	0	0	0	0	0	0	0.639	0.441	0.838	
SL006911	CHK1	C14757	1111	CEK1	RFU	No	No	E	0	0	0	0	0	0	0	0	0	0	0	0	1	1	1	
SL006912	FCR	P09769	2288	FCR	RFU	No	No	E	0	0	0	0	0	0	0	0	0	0	0	0	1	1	1	
SL006913	FYN	P06241	2534	FYN	RFU	No	No	AE	0.672	0.729	0.638	0.672	0.548	0.797	0	0	0	0	0	0	0.328	0.203	0.452	
SL006914	Glucocorticoid recepto	P04150	2908	NR3C1	RFU	No	No	CE	0	0	0	0	0	0	0	0	0	0.363	0.185	0.540	0.637	0.460	0.815	
SL006915	IL-27	Q8NEV9	Q1246778	10 IL27 EB3	RFU	No	No	AE	0.264	-0.018	0.347	0.264	-0.008	0.536	0	0	0	0	0	0	0.736	0.464	1.008	
SL006916	LCK	P06239	3932	LCK	RFU	No	No	E	0	0	0	0	0	0	0	0	0	0	0	0	1	1	1	
SL006917	LYN	P07948	4067	LYN	RFU	No	No	CE	0	0	0	0	0	0	0	0	0	0.587	0.454	0.720	0.413	0.280	0.546	
SL006918	MK01	P28482	5594	MAPK1	RFU	No	No	ACE	0.426	0.230	0.440	0.426	0.030	0.821	0	0	0	0.364	-0.016	0.744	0.210	0.118	0.302	
SL006919	RSK-like protein kise	Q75582	9252	RPS6KA5	RFU	No	No	CE	0	0	0	0	0	0	0	0	0	0.543	0.398	0.687	0.457	0.313	0.602	
SL006920	MAPK14	Q16539	1432	MAPK14	RFU	No	No	CE	0	0	0	0	0	0	0	0	0	0.569	0.431	0.707	0.431	0.293	0.569	
SL006921	EPK1	C15118	5163	EPK1	RFU	No	No	AE	0.264	-0.114	0.347	0	0	0	0.264	-0.007	0.534	0	0	0	0.736	0.466	1.027	
SL006922	RAD51	Q08600	5888	RAD51	RFU	No	No	AE	0.438	0.403	0.455	0.438	0.255	0.621	0	0	0	0	0	0	0.562	0.379	0.745	
SL006923	TBP	P20226	6908	TBP	RFU	No	No	E	0	0	0	0	0	0	0	0	0	0	0	0	1	1	1	
SL006924	ART	Q00253	181	AGRP	RFU	No	No	DE	0.505	0.509	0.504	0	0	0	0.505	0.308	0.702	0	0	0	0.495	0.298	0.692	
SL006970	DLL1	Q00548	28514	DLL1	RFU	No	No	AE	0.257	0.054	0.333	0.257	0.030	0.485	0	0	0	0	0	0	0.743	0.515	0.970	
SL006992	MATN3	O15232	4148	MATN3	RFU	No	No	DE	0.553	0.613	0.535	0	0	0	0.553	0.287	0.819	0	0	0	0.447	0.181	0.713	
SL006993	MK13	O15264	5603	MAPK13	RFU	No	No	E	0	0	0	0	0	0	0	0	0	0	0	0	1	1	1	
SL006998	PDPK1	O15530	5170	PDPK1	RFU	No	No	AE	0.730	0.794	0.689	0.730	0.622	0.838	0	0	0	0	0	0	0.270	0.162	0.378	
SL007003	DHH	Q43323	50846	DHH	RFU	No	No	AE	0.604	0.649	0.579	0.604	0.452	0.756	0	0	0	0	0	0	0.396	0.244	0.548	
SL007022	HNRPO	Q60506	10492	SYNCRIP	RFU	No	No	CE	0	0	0	0	0	0	0	0	0	0.259	0.063	0.456	0.741	0.544	0.937	
SL007024	GREM1	Q60565	26595	GREM1	RFU	No	No	AE	0.628	0.700	0.594	0.628	0.448	0.808	0	0	0	0	0	0	0.372	0.192	0.552	
SL007025	JAK2	Q60674	3711	JAK2	RFU	No	No	AE	0.779	0.841	0.736	0.779	0.687	0.870	0	0	0	0	0	0	0.221	0.130	0.313	
SL007049	CYTF	Q78096	8530	CS17	RFU	No	No	DE	0.721	0.784	0.681	0	0	0	0.721	0.610	0.832	0	0	0	0.279	0.168	0.390	
SL007056	BMP10	Q95393	27302	BMP10	RFU	No	No	CE	0	0	0	0	0	0	0	0	0	0.240	0.046	0.434	0.760	0.566	0.954	
SL007059	LY86	Q95711	9450	LY86	RFU	No	No	CE	0	0	0	0	0	0	0	0	0	0.211	0.010	0.411	0.789	0.589	0.990	
SL007100	LKHA4	P09960	4048	LTA4H	RFU	No	No	CE	0	0	0	0	0	0	0	0	0	0.506	0.354	0.658	0.494	0.342	0.646	
SL007121	CATE	P14091	1510	CTSE	RFU	No	No	E	0	0	0	0	0	0	0	0	0	0	0	0	1	1	1	
SL007122	IDE	P14735	3416	IDE	RFU	No	No	CE	0	0	0	0	0	0	0	0	0	0.182	-0.016	0.379	0.818	0.621	1.016	
SL007145	NR1D1	P20393	9572	NR1D1	RFU	No	No	E	0	0	0	0	0	0	0	0	0	0	0	0	1	1	1	
SL007153	PERL	P22079	4025	LPO	RFU	No	No	AE	0.550	0.579	0.537	0.550	0.366	0.734	0	0	0	0	0	0	0.450	0.266	0.634	
SL007173	GRN	P28799	2896	GRN	RFU	No	No	DE	0.707	0.772	0.667	0	0	0	0.707	0.588	0.826	0	0	0	0.293	0.174	0.412	
SL007179																								

