\subsection{Prioritisation and interpretation of PsA GWAS SNPs}

~~The generation of epigenetic and expression data from different cell types isolated from SF and PB aims to contribute to the general understanding of disease pathophysiology and differences between affected and non-affected tissue. Furthermore, overlapping this data derived from clinical samples with fine-mapped credible sets of SNPs may be more informative for refining the number of putative functional causal variants in non-coding or intergenic GWAS associations, compared to integration of epigenetic data from cell lines or healthy controls.~~

~~\subsubsection{Bayesian fine-mapping using genotype data}~~

~~In order to further refine the PsA Immunochip GWAS signals identified by Bowes and colleagues, Bayesian fine-mapping was conducted using genotype data from 1,103 patients and 8,900 controls (PsA Immunochip UK cohort from Bowes \textit{et al.}, 2015). Bowes and colleagues performed fine-mapping for some of the loci, and the number of independent signals for each locus as well as the number of SNPs in each 90\% credible se were provided in the supplementary material \parencite{Bowes2015}. Nevertheless \textit{de novo} fine-mapping was performed here to obtain the identity of the SNPs in the credible set and conduct further integration with my chromatin accessibility data. Compared to the fine-mapping performed in Bowes \textit{et al.}, 2015, the power of the analysis presented here was limited by a smaller sample size (only UK cohort as previously mentioned) and could be improved by incorporation of additional samples.~~

~~Fine-mapping was performed in thirty-six loci reported in Bowes \textit{et al.}, all showing at least nominal significance in their GWAS study. As expected, the GWAS signals with the lowest significance for the lead SNP (pval$<10^{-4}$) also showed -log$^{\_10}ABF$ under 3 (cut-off used in \parencite{Bunt2015}) for the lead SNP in the fine-mapping association analysis and were not taken forward for the calculation of PP and credible set of SNPs.~~

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\caption[Summary table of the PsA GWAS loci presenting -log$\_{10}ABF>3$ for the fine-mapping lead SNP.]{\textbf{Summary table of the PsA GWAS loci presenting -log$\_{10}$ABF$>$3 for the fine-mapping lead SNP.} For twelve PsA loci -log${\_10}ABF$ of the fine-mapping lead SNP was 3 or greater. In four of those loci ($^{\ast}$) the fine-mapping lead SNP was in low LD (r${^2}<0.5$) with the PsA GWAS SNP, indicating spurious signals identified by the association analysis. MAD= minor allele frequency; OR=odds ratio; ABF=approximate Bayes factor; PP=posterior probability; FM=fine-mapping.}

\label{tab:PsA\_fine\_mapping\_summary} \\

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\textbf{chr} & \textbf{Gene} & \textbf{GWAS} & \textbf{MAF} & \textbf{OR} & \textbf{-log${\_10}ABF$} & \textbf{PP} & \textbf{90\% credible} &\textbf{Bowes FM} & \textbf{Bowes 90\%}\\

& & \textbf{lead SNP} & & & \textbf{FM lead SNP} & & \textbf{set} &\textbf{lead SNP} & \textbf{credible set} \\

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2 &\textit{IFIH1} & rs13406089 &0.33 &0.78 &4.58 &0.48 &2 &rs35667974 &4 \\

5 &\textit{IL12B/ADRA1B} & rs2546890 &0.48 &0.76 &6.53 &0.6 &23 &rs4921482 &3 \\

5 &\textit{IL13} &rs2069616$^{\ast}$ &0.44 &1.25 &5.16 &0.05 &55 &NA &NA \\

1 &\textit{IL23R} &rs12044149 &0.25 &1.41 &9.83 &0.14 &29 &rs12044149 &34 \\

1 &\textit{IL28RA/GRHL3} &rs2135755$^{\ast}$ &0.50 &1.20 &3.06 &0.03 &49 &NA &NA \\

19 &\textit{ILF3} &rs11085727$^{\ast}$ &0.30 &0.79 &3.83 &0.22 &35 &NA &NA \\

17 &\textit{PTRF} &rs730086$^{\ast}$ &0.34 &0.81 &3.39 &0.39 &400 &NA &NA \\

1 & \textit{RUNX3} & rs6600250 &0.50 &1.20 &3.07 &0.03 &48 &rs7523412 &52 \\

12 &\textit{STAT2/IL23A} &rs12368739 &0.06 &1.70 &4.04 &0.02 &110 & rs2020854 &121 \\

6 & \textit{TRAF3IP2} &rs33980500 &0.07 &1.71 &8.26 &0.87 &2 &rs33980500 &7 \\

19 & \textit{TYK2} &rs11085727 &0.30 &0.79 &3.83 &0.21 &32 &rs34725611 &5 \\

5 & \textit{CSF2/P4HA2} &rs11242104 &0.48 &1.24 &5.31 &0.07 &58 &rs715285 &35 \\

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In this analysis, fine-mapping was unsuccessful (-log$\_{10}ABF<3$) in four loci previously fine-mapped by Bowes \textit{et al.} (\textit{B3GNT2}, \textit{NOS2A}, \textit{REL} and \textit{TNIP1}) highlighting the already acknowledged reduced power of the analysis performed here. Of the twelve loci passing the -log${\_10}ABF\geq3$ cut-off, eight had been successfully fine-mapped by Bowes and colleagues (Table \ref{tab:PsA\_fine\_mapping\_summary}). For two loci, \textit{IL23R} and \textit{TRAF3IP2}, the same fine-mapping lead SNPs were reported by the two analyses. For the \textit{IL12B} locus, the second signal reported by Bowes and colleagues was also identified here by step-wise conditional analysis. For the four fine-mapped loci reported here but not by Bowes \textit{et al.}, the fine-mapping lead SNPs were in very low LD (r${^2}<0.5$) with the PsA GWAS lead SNP, suggesting identification of spurious signals or signals from other loci nearby in the association analysis (Table \ref{tab:PsA\_fine\_mapping\_summary} labelled with $\ast$). For example, the association analysis performed for the fine-mapping of \textit{IL13} was confounded by the \textit{TYK2} signal, with no LD found between the fine-mapping and the GWAS index SNPs in the \textit{IL13} locus. Therefore, these four signals were also removed from downstream integration analysis.

\subsubsection{Integrating fine-mapped SNPs and chromatin accessibility from PsA samples}

The union of the 90\% credible sets for the eight successfully fine-mapped loci comprised a total of 294 unique SNPs. These SNPs were used to perform overlap with the significant (FDR$<$0.01 and abs(FC)$>$1.5) DARs identified between SF and PB in CD14$^+$ monocytes, mCD4$^+$, mCD8$^+$ and NK cells. Unfortunately, none of the 294 SNPs were contained by a DAR in any of these cell types. Additional overlap was performed between these SNPs and the accessible chromatin regions (consensus peaks without filtering based on the differential analysis) in each of the four cell types assayed by ATAC. The largest number of SNPs (17) was found to overlap accessible chromatin in CD14$^+$ monocytes, followed by mCD8$^+$, mCD4$^+$ and NK cells (Table \ref{tab:PSA\_fine\_mapping\_ATAC\_overlap}). The 43 unique SNPs from the 90\% credible set overlapping ATAC accessible chromatin were distributed across the \textit{CSF2} (8), \textit{IL12B} (3), \textit{IL23R} (4), \textit{RUNX3} (6), \textit{STAT2} (14), \textit{TRAF3IP2} (1) and \textit{TYK2} (7) loci. A number of these SNPs were found to only overlap accessible chromatin in one particular cell type.

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\textbf{ATAC cell type} & \textbf{90\% credible set} & \textbf{Cell type specific} \\

\textbf{master list} & \textbf{overlapping SNPs} & \textbf{overlap} \\

& \textbf{(number)} & \\

\midrule

\midrule

CD14$^+$ monocytes & 32 & \textit{STAT2} (5), \textit{TYK2}(2)\\

& & \textit{RUNX3}(1),\\

& & \textit{TRAF3IP2}(1) \\

mCD4$^+$ & 29 & \textit{CSF2}(1), \textit{IL23R}(1) \\

mCD8$^+$ & 28 & \textit{RUNX3} (1) \\

NK & 19 & \textit{TYK2} (1) \\

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\caption[PsA fine-mapped SNPs from the 90\% credible sets overlapping accessible chromatin identified by ATAC in four cell types.]{\textbf{PsA fine-mapped SNPs from the 90\% credible sets overlapping accessible chromatin identified by ATAC in four cell types.} The number of SNPs in the 90\% credible set union from the eight fine-mapped loci overlapping each cell type ATAC master list are reported. Furthermore, the number of SNPs only found to overlap open chromatin in one cell type are indicated together with the locus in which the SNP was fine-mapped.}

\label{tab:PSA\_fine\_mapping\_ATAC\_overlap}

\end{table}

SNPs from the fine-mapping credible set were significantly enriched in ATAC peaks when compared to all other GWAS Catalog SNPs and SNPs in LD (r$^2$=8) in all four cell types (Fisher exact test: CD14$^+$ monocytes pval=7.12x$10^{-8}$, mCD4$^+$ pval=1.69x$10^{-10}$, mCD8$^+$ pval=6.40x$10^{-9}$ and NK pval=1.86x$10^{-5}$). Notably, the GWAS Catalog SNPs overlapping ATAC accessible regions were significantly enriched (FDR$<$0.001) for particular terms from the Experimental Factor Ontology (EFO) (Figure \ref{figure:GWAS\_traits\_enriched\_for\_ATAC\_ML}). The EFO is a hierarchical tree-like ontology where each term represents a (disease) trait or group of related (disease) traits with which disease-risk SNPs may be annotated (Figure \ref{figure:GWAS\_traits\_enriched\_for\_ATAC\_ML}). Enrichment for general terms (towards the root of the tree) including autoimmune diseases, rheumatic diseases and skin diseases were found across all four cell types. Disease-specific terms (amongst the branches of the tree) related to these general terms, such as CD and IBD, were also found to be enriched for SNPs overlapping ATAC in all four cell types. Conversely, other "branches" from more general terms, including psoriasis and MS, presented significant enrichment (FDR$<$0.001) only in CD14$^+$ monocytes and mCD4$^+$ cells, respectively. Overall, this reinforced the specificity of the overlap between GWAS Catalog genetic variants not included in the fine-mapping credible set with accessible chromatin across the immune cell types investigated in this chapter.

\begin{figure}[htbp]

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\includegraphics[width=0.75\textwidth]{./Results3/pdfs/Enrichment\_for\_FM\_GWAS\_cat\_SNPs\_overlapping\_ATAC}

\caption[Experimental Factor Ontology terms enriched in GWAS Catalog SNPs overlapping ATAC regions in four cell types.]{\textbf{Experimental Ontology Factor terms enriched for GWAS Catalog SNPs overlapping ATAC regions in four cell types.} Each term annotates a set of risk SNPs associated with a disease trait or a group of related disease traits. Enrichment analysis was performed using as input data the GWAS Catalog SNPs overlapping ATAC accessible chromatin regions. A minimum of ten SNPs overlap and FDR$<$0.001 was required for enrichment to be considered significant.}

\label{figure:GWAS\_traits\_enriched\_for\_ATAC\_ML}

\end{figure}

\subsubsection{Further investigating the PsA-specific 5q31 locus}

Following fine-mapping, integration of in-house ATAC and additional functional data with the 90\% set of SNPs was conducted to further investigate the 5q31 locus, harbouring the only PsA GWAS association not shared with psoriasis. Out of the 58 SNPs in the 90\% credible set, only 8 overlapped ATAC accessible chromatin in at least one of the four cell types included in this study (Figure \ref{figure:5q31\_fine\_mapping\_SNPs\_epigenetic\_track} top panel). Amongst those SNPs were three (rs10065787, rs27437 and rs7721882) of the four variants highlighted by Bowes and colleagues as the most functionally relevant according to ENCODE epigenetics data.

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\textbf{SNP} & \textbf{Cell type ATAC} & \textbf{Top eGene , cell type } \\

& \textbf{overlap} & \textbf{and condition} \\

\midrule

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rs10065787 & CD14$^+$, mCD4$^+$ & \textit{P4HA2} (monocytes LPS2, LPS24, IFN-$\gamma$) \\

& & \textit{SLC22A5} (monocytes UT) \\

rs11242104 & All & NA \\

rs11242105 & All & NA \\

rs2069803 & All & \textit{SLC22A5} (CD4$^+$$^{(\ast)}$, CD8$^+$) \\

rs27437 & CD14$^+$, mCD4$^+$ & \textit{SLC22A5} (CD4$^+$, CD8$^+$) \\

rs4705908 & All & \textit{SLC22A5} (CD4$^+$$^{(\ast)}$, CD8$^+$) \\

rs2089855 & All & \textit{P4HA2} (monocytes LPS2, LPS24, IFN-$\gamma$,) \\

& & \textit{SLC22A5} (monocytes UT, IFN-$\gamma$,\\

& & CD4$^+$$^{(\ast})$, CD8$^+$$^{(\ast)}$) \\

rs7721882 & mCD4$^+$ & \textit{SLC22A5} (CD4$^+$$^{(\ast)}$, CD8$^+$) \\

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\caption[Publicly available \textit{cis}-eQTL datasets reporting an effect for the PsA 5q31 GWAS locus fine-mapped SNPs (90\% credible set) overlapping ATAC accessible regions.]{\textbf{Publicly available \textit{cis}-eQTL datasets reporting an effect for the PsA 5q31 GWAS locus fine-mapped SNPs (90\% credible set) overlapping ATAC accessible regions.} For each of the SNPs, the cell type for the ATAC overlap, the gene which expression is reported to be regulated by the SNP (eGene) and the cell type where the eQTL study was conducted are specified.The eQTLs datasets included in the analysis were monocytes (UT, LPS 2h, LPS 24h, IFN-$\gamma$) \parencite{Fairfax2014}, B cells \parencite{Fairfax2012}, NK untreated \parencite{Naranbhai2015}, neutrophils untreated (unpublished), tCD4$^+$ and tCD8$^+$ \parencite{Kasela2017} and whole blood \parencite{Jansen2017}. $^{(\ast)}$ for eQTLs extremely significant (FDR$<$2.2x10$^{-308}$).}

\label{tab:5q31\_SNPs\_ATAC\_eQTL}

\end{table}

The SNP rs10065787, highlighted by Bowes \textit{et al.} for overlapping with ENCODE clusters of occupancy for TFs relevant in CD4$^+$ and CD8$^+$ biology, presented accessible chromatin in CD14$^+$ monocytes and mCD4$^+$ cells, showing also moderate enrichment for the the enhancer histone mark H3K4me1 in mCD4$^+$ (Figure \ref{figure:5q31\_fine\_mapping\_SNPs\_epigenetic\_track} right hand side panel red line). Similarly, the nearby SNP rs27437 overlapped an ATAC peak in CD14$^+$ monocytes and mCD4$^+$ and the same TFBS site cluster as rs10065787 (Table \ref{tab:5q31\_SNPs\_ATAC\_eQTL} and Figure \ref{figure:5q31\_fine\_mapping\_SNPs\_epigenetic\_track} right hand side panel green line). rs10065787 appeared to be part of an eQTL signal for \textit{SLC22A5} and \textit{P4HA2} expression in unstimulated and stimulated monocytes (LPS2, LPS24, IFN-$\gamma$), respectively (Table \ref{tab:5q31\_SNPs\_ATAC\_eQTL}). However, no \textit{cis} eQTL for tCD4$^+$ was reported for this SNP in the Kasela and colleagues dataset (Table \ref{tab:5q31\_SNPs\_ATAC\_eQTL}). In contrast, rs27437 was part of a \textit{cis}-eQTL in tCD4$^+$ and tCD8$^+$ for \textit{SLC22A5}, the same eGene reported by Bowes and colleagues in their pilot eQTL study. Chromatin conformation data using promoter capture-HiC \parencite{Javierre2016} in unstimulated monocytes does not clearly reveal interaction for rs10065787 with the promoter of \textit{P4HA2} or \textit{SLC22A5}. Conversely, rs27437 is relatively close to the bait in the \textit{IL3} promoter, which interacts with \textit{SLC22A5}, potentially bringing this SNP in proximity with the promoter of \textit{SLC22A5}.

Other SNPs such as rs2089855 also appeared in an eQTL signal for \textit{P4HA2} and \textit{SLC22A5} in untreated and stimulated monocytes, and were associated with \textit{SLC22A5} expression in tCD4$^+$ cells (Table \ref{tab:5q31\_SNPs\_ATAC\_eQTL}). This SNP is proximal to rs11955347, which in Bowes \textit{et al.} presented the most significant correlation with expression of \textit{SLC22A5} in tCD4$^+$ and tCD8$^+$, and has also shown to be within the \textit{cis}-eQTL signal for \textit{SLC22A5} expression in unstimulated and IFN-$\gamma$ stimulated monocytes and for \textit{P4HA2} in monocytes stimulated with LPS (2 and 24h) \parencite{Fairfax2014}. The effect of rs11955347 genotype in modulation of \textit{SLC22A5} expression was also confirmed in the larger data set of Kasela \textit{et al.} in both tCD4$^+$ and tCD8$^+$ cells. These observations suggest a role for the 5q31 PsA-specific GWAS association in regulatingexpression of \textit{P4HA2} and \textit{SLC22A5} not only in T cells but also in monocytes under different conditions.

\begin{figure}[htbp]

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\includegraphics[width=0.7\textwidth]{./Results3/pdfs/UCSC\_chr5q31\_credible\_set\_all\_cell\_types\_multipanel\_final}

\caption[Epigenetic landscape at the genomic location of fine-mapped SNPs for the 5q31 PsA GWAS signal.]{\textbf{Epigenetic landscape at the genomic location of fine-mapped SNPs for the 5q31 PsA GWAS signal.} The top panel shows the genomic location of the six SNPs in the 5q31 fine-mapping 90\% credible set overlapping PsA ATAC accessible regions in at least one of the four cell types (in blue). The schema also includes the location of relevant SNPs for the 5q31 PsA-specific GWAS region from the Bowes \textit{et al.}, study, including the GWAS lead SNP (in red), the eQTL SNP showing the best correlation with the GWAS lead SNP (in green) and one SNPs from the credible set overlapping several ENCODE annotation features with no overlap for my PsA ATAC data (in purple). The left and right hand side panels are the UCSC visualisation of the epigenetic landscape for rs4705908 and rs2069803 (left brown and black lines, respectively) and rs1006587 and rs27437 (right, red and green lines, respectively), which represent four of the most relevant fine-mapped SNPs at the 5q31 in terms of overlap with PsA ATAC data signal for eQTLs. For each panel, all the ATAC tracks from three PsA patients and four cell types isolated from SF and PB are included. ATAC tracks are colour-coded by tissue (SF=purple and PB=turquoise). Additionally, publicly available epigenetic data (H3K4me1, chromatin segmentation maps, digital footprint and ENCODE cluster for TF binding) generated in the same cell types as the in-house ATAC are included. The yellow box highlights a DAR found in CD14$^+$ monocytes near rs2069803 and rs4705908. H3K4me1 relative fold-enrichment signal and ATAC normalised counts within each cell type are shown (y-axis).}

\label{figure:STAT2\_fine\_mapping\_SNPs\_epigenetic\_track}

\end{figure}

Another two relevant SNPs from the 90\% credible set reported here were rs2069803 and rs4705908, both overlapping ATAC peaks in all four cell types (Figure \ref{figure:5q31\_fine\_mapping\_SNPs\_epigenetic\_track} left hand side panel black and brown lines, respectively). rs4705908 is located upstream from the promoter of the \textit{ACSL6} gene in a region showing H3K4me1 enrichment, supporting a regulatory role. Notably, rs4705908 maps to a CTCF binding site reported in GM12878 and LCLs cell lines. Likewise, rs2069803 also overlaps moderate H3K4me1 signal in mCD4$^+$, mCD8$^+$ and NK cells (Figure \ref{figure:5q31\_fine\_mapping\_SNPs\_epigenetic\_track} left hand side panel). The region has also been annotated as an enhancer and weakly transcribed in mCD4$^+$, mCD8$^+$ and NK cells by the Epigenome Roadmap chromatin segmentation maps (yellow and light green in \ref{figure:5q31\_fine\_mapping\_SNPs\_epigenetic\_track} left hand side panel). Although accessible chromatin has been identified at rs2069803 and rs4705908 for all cell types, \textit{cis}-eQTL for these two SNPs have only been reported in CD4$^+$ or CD8$^+$, with the genotypes of both SNPs correlating with regulation of \textit{SLC22A5} expression with extremely high significance in tCD4$^+$ cells (Table \ref{tab:5q31\_SNPs\_ATAC\_eQTL}). Promoter capture Hi-C data in na\'{i}ve and total CD4$^+$ CD8$^+$ cells revealed interaction of the \textit{IL3} promoter bait containing rs2069803 with the promoter of \textit{SLC22A5}. Interestingly, rs4705908 also appeared within the bait of the \textit{ACSL6} promoter interacting with the \textit{IL3} promoter bait, which also includes the previously mentioned rs2069803 variant. Overall, promoter-capture HiC data revealed potential physical interactions between rs27437, rs2069803 and rs4705908 in CD4$^+$ and CD8$^+$ cells with potential functional relevance in regulation of \textit{SLC22A5} expression.

Lastly, rs7721882 was the only SNP showing a very significant eQTL effect in tCD4$^+$ for \textit{SLC22A5} expression and overlapping with a putative mCD4$^+$ cell type specific ATAC peak (Table \ref{tab:5q31\_SNPs\_ATAC\_eQTL}). However, additional replicates and greater sequencing depth would be required in order to confirm the robustness of this peak as well as the cell type specificity in mCD4$^+$ cells.

In addition to epigenetic evidence, further investigation of the suitability of \textit{SLC22A5} and \textit{P4HA2}, two of the genes showing eQTLs for some of the SNPs in the 5q31 credible set, as drug targets for PsA was investigated. Dr Hai Fang has developed an algorithm named Priority Index (Pi) based on random forest to levearage genetic information in the prioritisation of putative drug targets for particular complex diseases. Interestingly, \textit{SLC22A5} appeared as the third gene in the psoriasis rank supported as eGene in several immune cell eQTLs studies, annotation by the disease ontology with related inflammatory disease terms (including CD, IBD and RA, amongs others) as well as prediction for high druggability based on protein structure data \url{http://galahad.well.ox.ac.uk:3010/pidb/discovery/PSO/SLC22A5#bookmark\_details\_genomic}. In contrast, \textit{P4HA2} appeared 4,172 in the rank for psoriasis, not being such a suitable putative drug target in this disease.

\subsubsection{Overview of fine-mapping and epigenetic data integration for other loci}

In addition to the 5q31 locus (\textit{CSF2/P4HA2}), another seven loci were successfully fine-mapped in this analysis. As previously mentioned, integration of epigenetic data and fine-mapping credible set of SNPs is particularly relevant when trying to identify putative causal SNPs for GWAS signals lying in non-coding regions. An example amongst the fine-mapped loci is \textit{IL12B}, for which a PsA GWAS lead SNP as well as the fine-mapped lead SNP found in this analysis were located upstream of the gene. Out of the 52 SNPs identified in the 90\% credible set only four appeared to overlap accessible chromatin in at least two of the cell types analysed by ATAC in PsA samples and they were not in LD with common non-synonymous SNPs in \textit{IL12B}. The PsA GWAS SNP rs4921482 (primary signal in Bowes and colleagues) overlapped a strong ATAC peak in all cell types as well as H3K4me1 enhancer marks. However, none of the four SNPs in the credible set overlapping ATAC peaks was found within a \textit{cis}-eQTL signal in any of the explored datasets.

For another two loci fine-mapped in this analysis, \textit{STAT2/IL23A} and \textit{TRAF3IP2}, previous evidence for high LD between the psoriasis GWAS signal and missense coding variants in \textit{STAT2} and \textit{TRAF3IP2}, respectively, had been reported \parencite{Tsoi2012}. For the psoriasis GWAS \textit{STAT2} signal, Tsoi \textit{et al.}, 2012 highlighted a missense mutation (rs2066807) with a predicted highly damaging effect in this gene that is in very high LD with the GWAS lead SNP (Figure \ref{figure:STAT2\_fine\_mapping\_SNPs\_epigenetic\_track} purple line). This SNP also appeared in the 90\% credible set of SNPs in this analysis. Although rs2066807 did not overlap ATAC accessible chromatin in any of the four cell types, it mapped to a RUNX3 and CTCF binding site in the cell lines GM12878 and K562. SNPs from the credible set located in the vicinity of this missense variant were found within eQTL signals of interest. For example, rs2371494 overlapped an ATAC peak in all four cell types (Figure \ref{figure:STAT2\_fine\_mapping\_SNPs\_epigenetic\_track} black line) and presented a highly significant eQTL effect for \textit{STAT2} expression in unstimulated monocytes (FDR=7.54x10$^{-31}$) and to a lesser significance under IFN-$\gamma$ stimulation (FDR=9.94x10$^{-6}$). Fairfax and colleagues reported a negative effect for the major allele (G) of rs2371494 and also for the PsA GWAS lead SNP rs2020854 (T) (LD r$^2$=0.79) in both conditions, indicating increased expression of \textit{STAT2} for the GWAS risk allele. Interestingly, the nearby SNP rs57870697 which is in very high LD (r${^2}\geq$0.79) with rs2371494, overlapped a CD14$^+$ monocyte specific ATAC peaks in SF and PB (Figure \ref{figure:STAT2\_fine\_mapping\_SNPs\_epigenetic\_track} red line) but no eQTL for any gene has been reported at the location of this SNP.

Lastly, fine-mapping for the \textit{RUNX3/SYF3} locus identified 48 SNPs in the credible set, of which six overlapped ATAC peaks in CD14$^+$ monocytes and mCD8$^+$ cells. One mapped to a discrete mCD8$^+$ specific peak at the edge of a CTCF and RELA binding site in GM12878. Nevertheless, no eQTL has been reported for any of the six SNPs overlapping ATAC in any of the datasets.

\begin{figure}[htbp]

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\includegraphics[width=0.6\textwidth]{./Results3/pdfs/UCSC\_STAT2\_IL23A\_credible\_set\_all\_cell\_types\_all\_epigenetic\_marks}

\caption[Epigenetic landscape at the genomic location of three fine-mapped SNPs from the \textit{STAT2/IL23A} PsA GWAS signal.]{\textbf{Epigenetic landscape at the genomic location of three fine-mapped SNPs from the \textit{STAT2/IL23A} PsA GWAS signal.} UCSC visulisation of the epigenetic landscape for three relevant fine-mapped SNPs at the \textit{STAT2/IL23A} locus (x-axis), including rs2371494 (black line), rs35157967 (red line) and the missense putative damaging mutation reported by Tsoi \textit{et al.}, 2012 rs2066807 (purple line). ATAC tracks from three PsA patients and four cell types isolated from SF (purple) and PB (turquoise) are included. Publicly available epigenetic data (H3Kme1, chromatin segmentation maps, digital footprint and ENCODE cluster for TF binding) generated in the same cell types as the in-house ATAC are also included. H3K4me1 relative fold-enrichment signal and ATAC normalised counts within each cell type are shown (y-axis).}

\label{figure:STAT2\_fine\_mapping\_SNPs\_epigenetic\_track}

\end{figure}