INTRODUCTION

Since the activity of genes depends upon restrictive epigenetic regulation and the access of transcription factors, it follows that the dynamics of chromatin restructuring plays a pivotal role in the disease process. Consequently the detection of changes in chromosome conformation can be used in disclosing disease-associated changes in gene expression. Spun out from epigenetic research conducted at the University of Oxford, Oxford BioDynamics, created the Episwitch™ technology platform, designed to detect alterations of the systemic epigenetic control of gene expression and develop a diagnostic known as a chromosome conformation signature (CCS). Due to the fact that the immune system may play a role in the complex pathogenesis of several neurodegenerative conditions, OBDb conducted a comparative analysis of epigenetic markers related to CCS detected in whole blood for Alzheimer’s Disease (AD) and Amyotrophic Lateral Sclerosis (ALS) with known autoimmune pathogenesis, including: Relapse-Remitting Multiple Sclerosis (MSRR), Primary Progressive Multiple Sclerosis (MSPP), Rheumatoid Arthritis (RA), Systemic Lupus Erythematosus (SLE), Ulcerative Colitis (UC) and Type 1 Diabetes Mellitus (T1DM). This data was further compared to protein quantitative trait loci (pQTLs) identified to variance in plasma protein abundance in a population of 96 elderly healthy individuals, at risk for age-related chronic disease using Somalogic’s SomaScan® platform.

METHODS

A custom designed Episwitch™ Array was used to screen blood and tissue samples from patients diagnosed with neurodegenerative and autoimmune diseases: AD, ALS, RA, SLE, UC, MS (RR & PP), and T1DM. The array was used to identify epigenetic disease biomarkers based on aberrations in the chromosomal conformations that help to control the epigenetic regulation of gene expression. The analysis encompassed a total of 14,000 epigenomic biomarkers relative to 309 genes, the genetic loci selected for the array involve genes associated with primary immunodeficiency, adaptive and innate immunity, cytokine-signaling and key neurodegenerative genetic loci. The statistically significant chromosomal conformations (CCSs) from each disease condition (p<0.05) relatively to healthy controls were then compared to the significant pQTLs. A total of 776,814 SNPs and 778 proteins were analysed for pQTLs association, 2016 SNPs were found to be significantly (p<0.05) associated to 60 proteins. 1043 Episwitch™ conformations from the 6 studies mapped to within 3kb (BedTools Window function) of the 2016 significant pQTLs. In total there were 124 pQTLs mapping to the 1043 Episwitch™ conformations and the majority of the conformations were shared among the disease conditions.

RESULTS

The significant Episwitch™ conformations mapped to aging linked pQTLs indicated that AD, ALS, RSRR and MSPP share a core of 31 Episwitch™ mapped pQTLs. MSRR and MSPP also share 14 and 15 Episwitch™ pQTLs respectively with ALS (Figure A). ALS does have 35 unique pQTLs but these not unique to other autoimmune conditions, RA & SLE (data not shown). A four-way VENN diagram (Figure B) incorporates AD Episwitch™ mapped pQTLs, this shows that AD has 15 unique biomarkers and these remain unique. Figure C and D compare all the autoimmune conditions including ALS but minus AD and this shows that there is a high level of shared Episwitch™ pQTLs in these conditions but there are differences, with UC having 13 unique Episwitch™ qQTLs. Figure E shows the commonality and difference between the autoimmune conditions (RA, SLE, MSRR, MSPP, T1DM, UC & ALS) and AD. The shared 7 Episwitch™ pQTLs are shown in table 1, these are all located in the CHIT1 locus. Figure F shows the genomic location of the shared 7 Episwitch™ pQTLs, this conformation is deregulated in all 7 disease conditions. Figure G highlights differences between the autoimmune conditions and AD. The 15 unique AD Episwitch™ pQTLs are shown in table 2, these are all located in IT4 loci (SAA1, IL6, IL2, & MAPT). Figure H shows the genomic location of the shared 5 Episwitch™ pQTLs located at the Serum Amyloid A1 (SAA1) locus. This figure (H) shows the genomic location of the significant pQTLs and the chromosomal conformation lost in AD patients.

DISCUSSION

Epigenetics, and more specifically, the delineation of chromosome conformation disease signatures can provide some insights into the links between genotype and phenotype. Comparison of multi autoimmune and neurodegenerative conditions on Episwitch™ Array for >14k Episwitch™ Markers at 309 genetic locations demonstrated a significant level of specificity in epigenetic deregulation for each condition. These deregulated regions were then compared to pQTLs shown to affect protein abundance in patients with risk of age-related chronic disease. The data presented here shows the first layered approach with genetic, epigenetic and proteomics, using multiple disease conditions. The high concordance between the pQTLs and chromosomal conformations strongly suggest that these sites are under shared systemic regulatory controls for ageing conditions and for auto-immune related disease conditions. This is strengthened by the findings at the SAA1 locus. Studies have shown that inflammation plays a crucial role in the development of SAA1 amyloid deposits in the brain3; these studies have also shown that aging plays a role in the incidence and progression of AD4. The combined Episwitch™ and aging pQTLs studies have identified a deregulation at the SAA1, where a chromosomal conformation is lost in AD patients. This gives a strong indication of inflammatory induced epigenetic deregulation which is under pressure in disease and as we age.

CONCLUSIONS

Collectively this study produces a rich pool of knowledge about chronic autoimmune conditions previously not known or exploited. It also shows how chromosomal conformation links genotype to genetic and protein differences in disease. This study demonstrates the utility of using blood based chromatin conformation biomarkers monitored by the Episwitch™ platform for systemic and correlative data analysis.