Causal variants in autoimmune disease: a commentary on a recent published fine-mapping algorithm analysis in genome-wide association studies study

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Provenance: This is a Guest Editorial commissioned by Section Editor Mingzhu Gao, MD (Department of Laboratory Medicine, Wuxi Second Hospital, Nanjing Medical University, Wuxi, China).

Comment on: Farh KK, Marson A, Zhu J, *et al*. Genetic and epigenetic fine mapping of causal autoimmune disease variants. Nature 2015;518:337-43.

Submitted Dec 02, 2016. Accepted for publication Jan 04, 2017.

doi: 10.21037/atm.2017.02.26

View this article at: http://dx.doi.org/10.21037/atm.2017.02.26

Genome-wide association studies (GWAS), have become the most powerful tool to search the numerous potential risk genetic loci for the susceptibility of many complicated diseases in recent years. However, despite of the more comprehensive analysis of GWAS, there are some limitations for the method. First, it is difficult to identify true causal variants due to the haplotype construction based on the linkage disequilibrium. Besides, most causal variants identified by GWAS were non-coding variants. Although it has been suggested non-coding causal variants may contribute to epigenetic regulation, such as histone acetylation, methylation or DNA methylation, mRNA splicing and the regulation of RNA transcription. The mechanisms of action, and the cellular states and processes in which they function were largely unknown. In a recent study, Farh *et al.* developed a fine-mapping algorithm to identify candidate causal genetic variants in 21 autoimmune diseases from 39 GWAS studies (1). Through integrated predictions with transcription and cis-regulatory map for several kinds of immune and non-immune cell types, including resting and stimulated CD4+ T cell, regulatory cell, B cell and monocytes, etc., they had provided the unique information about the distributions and features of causal variants in the susceptibility of autoimmune diseases. Accordingly, more than 90% susceptible variants are reside in non-coding and around 60% variants were located in immune-cell transcription factor binding sites (enhancer), which contribute to activating or modulating T or B cell immune response. However, only 10–20% risk variants appear to act directly classical recognizable transcription factor binding sites to regulate gene expression while the 80–90% of non-coding genetic variants functions directly by modifying the non-classical regulatory sequence. In addition, most non-coding risk variants, including those that alter gene expression, affect non-canonical sequence determinants not well-explained by current gene regulatory models.

It has been well established that principle pathogenesis of autoimmune diseases is majorly attributed to predisposing genetic background and environmental factors (2). Numerous genetic studies in the past have been utilized to look for the candidate genetic variants or loci for the susceptibility of autoimmune diseases, and found that most of the impact of genetic variants on the disease pathogenesis are very subtle (3). Most autoimmune diseases related studies in the past have centered on genes participated in the process of antigen presenting cell mediated T-cell activation, including human leukocyte antigen-autoantigen-T cell receptor signals, and co-stimulatory factors, including cytotoxic T-lymphocyte associated factor

4 (CTLA-4), protein tyrosine phosphatase 22, CD40, CD28, inducible T-cell co-stimulator, etc. (3). The studies on B-cell triggering or activation in autoimmune diseases are limited. This study had also addressed that the signals of the causal variants were abundant in both stimulated B-cell and T-cell enhancers, which implied the impact of B-cell activation in regulation the susceptibility of autoimmune diseases is higher than we expected.

Recent findings in study the genetic variants of interferon regulatory factor 8 (IRF8) and B-cell activating factor (BAFF) in autoimmune diseases were also supported their observations. IRF8, one kind of specific transcription factors, is well-established to contribute to myeloid cell and B cell differentiation and maturation, antibody production and modulate type 1 interferon (INF) activity (4). The association analysis disclosed that intronic SNP rs17445836 of IRF8 was strongly linked to the development of systemic lupus erythematosus (SLE) (5) and multiple sclerosis (MS) (6). The rs17445836 was associated with anti-double-stranded DNA (dsDNA) autoantibodies in SLE patients and associated with decreased serum type I IFN. Furthermore, rs17445836 was associated with increased IRF8 expression in B cells of SLE patient (5). In autoimmune thyroid diseases (AITD), rs17445836 was associated with the occurrence of Hashimoto's thyroiditis but not Graves' disease. In addition, rs17445836 was associated with the presence and levels of circulating anti-microsomal antibody in AITD (7). The intronic SNP rs17445836 in IRF8 located in the non-coding region may present as a B-cell enhancer contributed the susceptibility and disease phenotypes in autoimmune diseases.

BAFF, belonging to the tumor necrosis factor family, is regulated by type 1 IFN, and is crucial for B-cell differentiation and maturation (8). By binding to the its principle membrane receptor of B-cell, BAFF receptor, the BAFF promotes B cell proliferation and increases survival time (9). Serum BAFF levels were higher in AITD patients and significantly correlated with TSHRAb levels, Anti-TPO Ab levels and ATA titers in women but not in men. In addition, serum BAFF levels were significantly associated with free thyroxine and TSHRAb levels in women with active GD but not in those with inactive GD (10). In the genetic study, the variant of intronic rs2893321 in the intron 2 was associated with the development of GD in female gender (11). A minor splicing variant of the BAFF, ΔBAFF, lacking a 57-bp coding region, was recognized in humans (exon 3) and mice (exon 4), respectively (12). The ΔBAFF protein is known to inhibit BAFF activity, by suppressing its biological function and release of the complete BAFF protein, and by merging with the BAFF protein to form heterotrimers, which restrains the binding ability of the BAFF to BAFF receptor (12,13). Interestingly, rs2893321 is very adjacent to exon 3, though without direct evidences support; it may associate with the splicing process of BAFF mRNA and followed by altering BAFF function.

In conclusion, Farh *et al.* delineated important concepts on the global view and localized pattern of causal genetic variants in autoimmune diseases. Majority localized in the non-coding regions, these causal variants can be mapped to enhancers and frequently coincide with nucleosome-depleted sites bound by immune-related transcription factors. Although validation and interpretation of non-coding causal variants remains challenging, understanding their regulatory mechanisms could provide the potential strategy for therapeutic intervention in autoimmune diseases.

Acknowledgements

None.

Footnote

Conflicts of Interest: The authors have no conflicts of interest to declare.

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Cite this article as: Lin JD, Cheng CW. Causal variants in autoimmune disease: a commentary on a recent published fine-mapping algorithm analysis in genome-wide association studies study. Ann Transl Med 2017;5(6):151. doi: 10.21037/atm.2017.02.26

