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Depicting the genetic architecture of AL amyloidosis through genome-wide association studies and data-integration

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Amyloid light-chain (AL) amyloidosis is a rare progressive plasma cell dyscrasia, characterized by a clonal expansion of abnormal bone marrow plasma cells. These cells produce aberrant light chains, which upon accumulation aggregate and misfold in the form of amyloid fibers. These amyloid fibers deposits in many organs such as the heart and/or kidney and/or liver and interfere with their functions. AL amyloidosis and multiple myeloma share comorbidities as both originate from monoclonal gammopathy of undetermined significance (MGUS). This dissertation comes to elucidate the genetic architecture of this poorly understood disease AL amyloidosis. We conducted the first genome-wide association study to characterize germline susceptibility to AL amyloidosis on 1,229 patients with 7,526 matching local healthy controls. Further, we conducted a comparison with a multiple myeloma cohort of 3,790 cases to reveal similarities and differences between those two plasma cell dyscrasias.

We identified four regions genome-wide significant (p-values < 5 x 10−8) and six regions at the suggestive level (p-values < 1 x 10−5). Five loci were previously documented to influence multiple myeloma risk, enforcing the shared susceptibility of the two diseases. The two prominent associations were locus 11q13.3 and locus 7q36.1. Locus 11q13.3 with rs9344 was much stronger in AL amyloidosis compared to multiple myeloma, which is explained by the higher prevalence of t(11;14)-defined cases in AL amyloidosis. Locus 7q36.1 with the sentinel variant rs79419269 maps close to SMARCD3. This gene is involved in chromatin remodeling. This locus has been reported to be involved in the glycosylation of IgGs. Overall, the ten variants described in this AL amyloidosis genome-wide association study provide evidence for a polygenic basis of genetic susceptibility to AL amyloidosis.

Since AL amyloidosis is a heterogeneous disease and its organ tropism and amyloid variability are poorly understood, we took advantage of the full clinical characterization of 1,229 patients to conduct a clinical subtype analysis. We particularly focused on either organ tropism or type of amyloid protein. We characterized five significant regions, which are genome-wide significant in five clinical profiles with homogeneity of results from the three patient cohorts. Among those five regions, three associations were novel. The three novel associations were described in IgG profile, liver profile as well as heart and kidney profile. IgG (rs10507419) at 13q13.2 maps close to the NBEA locus (13q13.3), which is a fragile site causing deletion of the chromosomal end. This deletion is a frequent event in MGUS and multiple myeloma. In 13q13.2, two polymorphisms (rs61947292 and rs9529347 within LINC00457), in complete linkage with the sentinel variant rs10507419, are interacting with NBEA promoter. The liver as well as heart and kidney profile described two associations mapping to FAM150A and LINC01247, respectively.

Finally, this study demonstrated that findings from “hypothesis-free” genome-wide association can implicate genomic loci that were not thought to influence disease

susceptibility. Furthermore, a focus at a well-defined biological and clinical phenotype of the disease (such as amyloid type and organ tropism) has changed this study from “hypothesis-free” to “hypothesis-driven” study, which has led us to considerable success in defining disease sub-categories. Further, functional validation of our results can lead to biomarker discovery for both disease screening and therapy approach.