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Genetics of multiple myeloma, its precursor disease and predisposition to peripheral neuropathy

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In the last years genetic epidemiological studies have increased our understanding of the etiology of many cancer types and GWASs have been a useful tool to identify new loci associated with a disease. Using the existing and the newly created GWAS data, our study identified new risk alleles associated with MM. In particular, current data and findings from our previous GWAS analyses emphasize the role of endoplasmic reticulum-stress related autophagy, cell cycle regulation, chromatic re-modelling and de-regulation of MYC as a consequence of MM predisposition. Moreover, we investigated on its genetic relationship with MGUS, discovering new susceptibility loci contributing to development of the disease.
Our findings provide additional support for a polygenic model of the disease and insight into the biological basis of tumor development. We made use of several genomic tools to understand the biology behind the identified genetic variations and to investigate on their functional role. Our results are consistent with the discovered risk SNPs mapping within regions of active chromatin state within B cells and having a role in the B-cell cis-regulatory network. Moreover, further studies are necessary to functionally validate our *in silico* predictions and to detect further biomarkers of outcome. Elucidating the mechanisms underlying these associations will contribute to the development of the strategies for the prevention of MM and its clinical phases.
Although considerable progress has been made in the development of novel treatments for this heterogeneous disease, novel targeted therapies with innovative mechanisms are urgently needed. Indeed, therapy limiting side-effects are frequently induced and 40% of patients treated with novel agents develop a neuropathy. In this study we recognized new genetic markers for bortezomib-induced PNP, as serious side-effect in treated myeloma patients. The identified genetic variants map to genes involved in specific pathways like the development and function of the nervous system. Our findings support the hypothesis that germline variations influence outcome following treatment of MM. This is one of the first steps that might allow for the identification of patients at increased risk of severe PNP and help clinicians in developing new therapeutic approaches for the prevention of this serious side-effect.