

Stratification and model-based analysis of patients with Irritable Bowel Syndrome using advanced biostatistics and medical data mining techniques

Irritable Bowel Syndrome (IBS) is characterized by symptoms that are dominated by abdominal pain and abnormal bowel habits, as defined by the Rome criteria. The complexity of the disorder is exemplified by the heterogeneity of symptom profiles and the number of putative pathophysiological mechanisms. Currently it is unclear whether IBS is a multifactorial disorder or rather a summary diagnosis for several distinct disease entities displaying similar symptoms.

This thesis aims to identify subgroups of clinical relevance by developing and demonstrating symptom- and mechanism-based stratification approaches, as well as an integrative analysis pipeline aiming to link different pathophysiological mechanisms.

In a clinical sample of IBS patients, as well as in subjects fulfilling IBS in a populationbased sample, symptom-based stratification yielded reproducible subgroups, characterized by combinations of gastrointestinal, extra-intestinal somatic and psychological symptoms. In the population-based sample this subgrouping was associated with differences in healthcare utilization. Mechanism-based stratification, focusing on the function of the autonomic nervous system (ANS), demonstrated altered ANS function in IBS patients compared to healthy controls, and identified a subgroup of IBS patients with aberrant overall ANS function, which was associated with more severe diarrhea. This thesis also introduces a stepwise multilevel integrative analysis pipeline using network theory, which presents associations of host-gene expression with mucosa-adherent gut microbiota as well as key IBS symptoms, revealing distinct IBS-specific associations.

In conclusion, IBS patients show reproducible subgroups with specific profiles of a comprehensive set of IBS related symptoms and differences in healthcare needs based on these subgroups. Further, multivariate comparisons between IBS patients and healthy controls aid in identifying individuals for which specific complex pathophysiological mechanisms may be of relevance, as demonstrated by identifying a subset of IBS patients with aberrant overall ANS function. This stratification approach could be applied to other pathophysiological mechanisms. Our stepwise multilevel integrative analysis pipeline showed differences in variable associations at the gut mucosal level between IBS patients and healthy controls, and is therefore a model for further, comprehensive analysis of the complex pathophysiology of IBS

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