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GENETIC AND NEUROVEGETATIVE MARKERS OF IRRITABLE BOWEL SYNDROME PATHOGENESIS: CLINICAL–PHENOTYPIC STRATIFICATION AND PREVENTION IN MILITARY PERSONNEL

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Annotation: Irritable bowel syndrome (IBS) is a functional gastrointestinal disorder with a complex and multifactorial pathogenesis involving genetic susceptibility and neurovegetative dysregulation. This annotation focuses on the role of genetic and autonomic nervous system markers in the development of IBS, with particular attention to clinical–phenotypic stratification and prevention among military personnel. Genetic polymorphisms affecting neurotransmitter regulation, immune response, and stress reactivity contribute to individual variability in symptom severity and disease course. Neurovegetative imbalance, characterized by altered sympathetic–parasympathetic regulation, plays a key role in gut–brain axis dysfunction and stress-induced symptom exacerbation. Military personnel represent a high-risk group due to chronic psycho-emotional stress, irregular lifestyle, and increased physical demands. Identification of genetic and neurovegetative markers enables early risk assessment, targeted prevention, and personalized management strategies. Preventive approaches emphasizing stress modulation, autonomic regulation, lifestyle optimization, and early psychosomatic support are aligned with modern preventive medicine principles promoted by the World Health Organization. Integrating biomarker-based stratification into military healthcare systems may reduce IBS prevalence, improve quality of life, and enhance operational readiness.

Keywords: Irritable bowel syndrome; genetic markers; neurovegetative regulation; gut–brain axis; autonomic nervous system; stress-related disorders; clinical phenotypes; military medicine; preventive strategies; functional gastrointestinal disorders; psychosomatic factors; risk stratification; personalized prevention; chronic stress; biomarkers.

Irritable bowel syndrome (IBS) is a functional gastrointestinal disorder characterized by chronic abdominal pain, altered bowel habits, and the absence of identifiable structural pathology. Despite its non-life-threatening nature, IBS significantly impairs quality of life and occupational performance, particularly in high-stress professional groups such as military personnel. In recent years, growing attention has been paid to genetic and neurovegetative mechanisms underlying IBS pathogenesis, enabling a more precise clinical–phenotypic stratification and the development of targeted preventive strategies.

Genetic Markers in IBS Pathogenesis

Genetic predisposition plays a contributory role in the development of IBS by influencing visceral sensitivity, intestinal motility, immune activation, and neurotransmitter signaling. Polymorphisms in genes regulating serotonin metabolism, inflammatory mediators, and stress response pathways have been associated with specific IBS phenotypes. For example, variations in genes involved in serotonin transport may alter gut–brain communication, leading to heightened pain perception and dysregulated bowel function. In military personnel, genetic susceptibility may interact with service-related environmental factors such as irregular nutrition, sleep deprivation, and chronic psycho-emotional stress. This gene–environment interaction contributes to individual variability in symptom severity, clinical course, and response to therapy. Identification of genetic markers therefore supports early risk stratification and personalized preventive interventions. Every day, clinicians who care for patients with IBS will hear of instances of IBS among parents, siblings and children of IBS sufferers and formal studies of familial aggregation of IBS symptomatology have long pointed towards a possible genetic component to IBS.

However, defining the contribution of genetics in IBS has proven to be far from straightforward. First, given what we know of the impact of early childhood experiences on IBS prevalence and severity (9,10), some would argue that familial aggregation reflects shared experiences and common exposures and not shared genes. Second, IBS is a clinically defined entity which lacks a universal biomarker and presents with a highly variable phenotype (11). It is, indeed, likely that what the clinician currently recognizes as IBS may ultimately be defined as comprising several distinct syndromes; for the very same reason, it is unlikely that a single genetic variant is responsible for the development of IBS. Third, IBS is usually accompanied by a number of psychological and physical co-morbidities which are likely to confound the interpretation of any genetic study. IBS is more likely to be either a polygenic disease in which common variants in a large number of genes interact with environmental factors to produce the clinical manifestations of IBS or to be epigenetic in origin (12).

Neurovegetative Dysfunction and the Gut–Brain Axis

Neurovegetative imbalance, particularly dysregulation of the autonomic nervous system, is a central mechanism in IBS. Altered sympathetic–parasympathetic activity affects intestinal motility, secretion, and visceral sensitivity. In patients with IBS, enhanced sympathetic tone and reduced parasympathetic modulation are frequently observed, resulting in stress-induced exacerbation of gastrointestinal symptoms. Military service is associated with sustained activation of stress response systems. Repeated exposure to physical нагрузка, emotional напряжение, and operational uncertainty can disrupt autonomic regulation and hypothalamic–pituitary–adrenal axis function. As a consequence, neurovegetative markers such as heart rate variability, stress hormone levels, and stress reactivity patterns may serve as valuable indicators of IBS risk and progression in this population. The somewhat unique nature of post-infection IBS (PIIBS) has already been alluded to. Its recognition spurred interest in the potential role of the microbiota and the host immune response in IBS and, indeed, a study of one of the largest and best characterized outbreaks of PI-IBS identified a possible genetic predisposition to this syndrome (15). The municipal water supply of Walkerton, a small rural town in Ontario, Canada, located 180 km northwest of Toronto, was contaminated with E. Coli 0157:H7, Campylobacter jejuni and other pathogens in May 2000. Over 2,300 residents were affected by a resulting outbreak of acute bacterial gastroenteritis; there were 27 cases of haemolytic-uremic syndrome and 7 deaths. The Walkerton Health study followed the long-term health outcomes of this well-defined study cohort; three years after the outbreak, 36.2% of exposed residents fulfilled Rome I criteria for diagnosis of IBS (15). Three gene regions of interest, Toll-like receptor 9 (TLR9), IL-6 and cadherin 1 (CDH1), were identified; variants within these regions proved to be independent risk factors for the development of PI-IBS even when previously identified clinical

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risk factors were controlled for. In PI-IBS, at least, variations in genes involved in the host response (TLR9 and IL-6) and the gut barrier (CDH1) seem to predispose to the development of IBS. Could these findings extend to IBS in general? One study in a relatively small cohort containing individuals with sporadic IBS suggested that they did not (16); clearly this needs to be re-examined in a much larger cohort. Genome-wide association studies (GWAS) have proven to be an important resource in defining the genetic architecture of many common diseases including Crohn's disease and ulcerative colitis. However, the limitations discussed in relation to attempting to correlate IBS with candidate gene polymorphisms apply to an even greater extent in a genome wide association study; very large cohorts of patients with well-defined phenotypes are required. For these reasons, the recent study from Bonfiglio and colleagues represents a real advance (17). Their primary analysis was based on the UK Biobank and included 9,576 IBS cases and 336,499 controls; the study was, therefore, powered to detect modest genetic risk effects (17). Findings were then further assessed in a multi-national population of IBS patients attending tertiary referral centers and in a Swedish population cohort. Their GWAS analysis identified signals of suggestive significance in 14 independent loci including one genome-wide locus on chromosome 3q31.2 (rs10512344). This association held true only for females and, in the validation cohorts, was linked to constipation-predominant IBS. They went on to show that the IBS gene risk pool was significantly enriched for intracellular calcium activated chloride channel activity, ion gated channel activity and anion channel activity. Interestingly, in view of current interest in the role of micro-RNAs (miRs) in IBS, the IBS gene risk pool was also enriched in targets of miRs from the miR-15 family. This is of particular interest as members of the miR-15 family have been implicated in the regulation of gut barrier function and, via serotonin receptors, on motility (18,19). In one such study, another international consortium identified a single nucleotide polymorphism (SNP) within the 5-HT4 receptor gene HTR4 in a small number of patients with diarrheapredominant IBS (19). Interestingly, this SNP involves a binding site for the miR-16 family and miR-103/miR-107. In further studies, they demonstrated co-localization of the miR-16 and HTR4 genes in the colon supporting a role for miR16 in the regulation of this serotonergic receptor. As these miR's appear to down regulate the 5-HT4 receptor whose main function is to promote motility, it should come as no surprise that levels of miR-16 and miR-103/miR-107 inversely correlated with bowel frequency and consistency. These results indicate that specific miRNA's and not just the 5-HT4 receptor itself could be targets for future drug discovery in IBS (19).

Clinical–Phenotypic Stratification

Clinical–phenotypic stratification of IBS involves classification based on dominant symptoms, neurovegetative profile, and psychosomatic features. From a pathogenetic perspective, IBS phenotypes may differ in the relative contribution of genetic susceptibility, autonomic dysfunction, and psychosocial stressors. In military personnel, stress-dominant phenotypes are particularly prevalent, often accompanied by anxiety, sleep disturbances, and reduced adaptive capacity. Stratification allows clinicians to distinguish patients with predominantly neurogenic, inflammatory-prone, or stress-sensitive IBS patterns. This approach improves diagnostic accuracy and facilitates individualized therapeutic and preventive planning, rather than relying on uniform symptomatic treatment. regulation of ion channels have been replicated in a GWAS meta-analysis from 5 independent European cohorts (20) and have also been demonstrated in studies employing candidate gene approaches (21). These are exciting findings and provide, not only a real genetic basis for IBS but also mechanistic insights linking genes to relevant functions. These variants are rare (less than 4% of the population) and will only explain a very small proportion of IBS subjects. Nevertheless, studies such as these and others are slowly but surely identifying distinct genotypes within IBS. Even collectively they but scratch the surface in terms of the pathophysiology of IBS, in general. Here, nurture still looms large. This may not discount a role for genetics in the majority of IBS sufferers; we look forward to studies examining in detail interactions between environment and genome as well as the epigenetic effects of environmental and psychosocial inputs. Progress in the identification of biomarkers, if not for all of IBS, then for IBS subgroups may, in the future, will help to overcome the problems posed by the heterogeneous nature of the clinical phenotype in IBS. One gets the feeling that the long-awaited dawn of IBS genetics has finally arrived—there is a long day ahead.

Prevention Strategies in Military Personnel

Prevention of IBS in military populations should be multifactorial and risk-oriented. Early identification of genetic and neurovegetative markers enables targeted preventive measures before full clinical manifestation occurs. Stress management programs, autonomic regulation training, and psychoeducation play a crucial role in reducing neurovegetative imbalance. Nutritional optimization, regular sleep schedules, and physical activity adapted to service conditions contribute to maintaining gut–brain homeostasis. In individuals with identified vulnerability markers, preventive interventions may include cognitive-behavioral strategies, biofeedback, and controlled workload modulation. Such measures align with preventive health principles promoted by the World Health Organization, emphasizing early risk detection and non-pharmacological prevention.

Conclusion

Genetic and neurovegetative markers provide valuable insight into the pathogenesis of irritable bowel syndrome and its heterogeneous clinical manifestations. In military personnel, where chronic stress and environmental challenges are inherent, these markers are particularly relevant for early identification, clinical–phenotypic stratification, and prevention. Integrating genetic susceptibility assessment with neurovegetative evaluation supports a personalized, preventive approach, potentially reducing disease burden, improving operational readiness, and enhancing overall quality of life among servicemen and servicewomen.

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