Biomedical and public health studies on susceptibility to post-traumatic stress disorder

IMPACT PARAGRAPH

PTSD is a complex condition that develops after exposure to trauma. Although evidence-based treatments are successful in lowering symptoms, there is no known cure, and low retention rates present a hurdle. As not all people exposed to trauma develop PTSD, underlying interindividual differences in susceptibility are expected. Therefore, it is crucial to create strategies to lower the risk of acquiring PTSD in addition to looking for novel therapies. The aim of this research were to identify the main factors in determining susceptibility to PTSD, with a focus on epigenetics and the use of novel PTSD biomarkers to aid early detection, which can lead to early recognition of those at risk, aiding the process of prevention and early intervention to reduce the burden of the disease, both medical and economic. Accordingly, a number of biomedical studies included in this thesis were developed for this purpose. The thesis also provides a comprehensive starting point and review of the literature for researchers investigating the field of PTSD susceptibility.

In **Chapter 2**, we give a summary of the various molecular biology, biochemical, and physiological changes in PTSD with a focus on genomic and epigenomic abnormalities, and their role in susceptibility to develop PTSD after exposure to traumatic stress. Additionally, we discuss how modern studies on epigenetics and epigenomics could help us identify PTSD patients earlier and provide them with timely management. These results could accelerate advancements in the discovery of novel therapeutic targets and biomarkers for PTSD in the long term. The discovery of predictive biomarkers that may differentiate between people who are at a high or low risk of developing PTSD after experiencing trauma will enable or support preventive measures and early treatments.

In **Chapter 3**, we performed a transcriptomic analysis for susceptibility to PTSD in the PRISMO cohort. We demonstrated that a transcriptome profile of PTSD vulnerability at a post-traumatic time point may offer new perspectives for additional follow-up research into its pathophysiological processes and candidate genes and their regulatory mechanisms to be investigated with more precision. This study adds to the body of research connecting transcriptomic, genetic, and epigenetic factors to biological processes underpinning vulnerability to PTSD by combining multiple layers of molecular data collected from a PTSD cohort. Such integrated knowledge may support future preventive, diagnostic and therapeutic strategies.

In **Chapter 4**, tissue analysis was used to determine the pattern of the RNF39 expression, which is thought to be regulated by epigenetic mechanisms and involved in the pathogenesis of PTSD, among other neuro-epigenetic changes [1, 2]. Since no investigation has provided an insight into the regular brain expression of RNF39 and its changes in relation to traumatic stress yet, this study provides a valuable basis for future researchers

to compare and build upon. Consequently, a blood based biomarker for RNF39 can be investigated for clinical utility.

In **Chapter 5**, we give a summary of recent research on traumatic stress, focusing on disease burden, causes or triggers of stress, variables influencing stress response, and the use of the social-ecological public health paradigm of disease prevention. We focus on the different means to early detect and prevent the development of PTSD. It is supportive to see the adoption of such preventive measures in accordance with public health models of disease prevention as a way to successfully accomplish these objectives. Additionally, we discuss therapeutic considerations, ethnic variations in traumatic stress, and perspective views, including possible biomarkers, all of which can enhance the patient outcome, as well as decrease the burden of the disorder. Implementation of the measurements by the public health sector can accelerate the efforts of traumatic stress prevention and result in improved outcome and diminished burden.

Additionally, in **Chapter 6** recent discoveries in the area of PTSD are reviewed, including pathophysiology, treatment, and disease biomarkers. More dedicated attention is given to these biomarkers as a way to predict, diagnose, and follow-up treatment of PTSD. Susceptibility biomarkers could be especially of added value from a public health point of view, as they can detect those vulnerable to developing PTSD after current or future exposure to traumatic stress, allowing for earlier intervention and prevention of complications. Diagnostic biomarkers, although still not applicable clinically, show promising perspectives, but more research into more reliable and cost-effective biomarkers or biomarker panels that can aid diagnosis is needed. Therapeutic biomarkers appear to be the least developed, but researchers have been able to draw conclusions about some that can help monitor therapy and response to treatment, which can enhance the patient's quality of life and yield better treatment results. None of the potential PTSD biomarkers is reported as being used in therapeutic settings, highlighting the urgent need for further research on PTSD biomarkers with large sample sizes and for translational research methods aimed at understanding the underlying molecular origins of PTSD. Going forward, such development can greatly enhance the outcome of the disorder, both its impact on the patient's quality of life and its economical and societal impact.

The prevalence of trauma exposure and PTSD development is rising substantially, leading to an increased medical and economic burden, affecting both the patient and the community [3, 4]. This thesis contributes to mitigate this burden by addressing various aspects. Factors known to affect the response to trauma are reviewed and linked to prevention (e.g., emotional care, age, education, and gender). Of pivotal importance, examples of practically implementable methods of trauma prevention on various levels based on public health models of prevention are provided. Moreover, these preventive

measures are defined as either primary, secondary or tertiary for appropriate intervention. Additionally, modalities of intervention, including pharmacological and psychotherapeutic are summarized. As the burden of the disease is substantial, it is necessary to develop strategies through prevention and intervention [5]. Another important player to decrease the burden of PTSD is the development and utilization of biomarker panels that can detect susceptible subjects and enable to offer earlier interventions. To address that, and in addition to reviewing the recent advances in this field, we conducted a blood-based study to examine the presence of susceptibility gene expression markers, that expand on the current state of knowledge. Additionally, we provided a first-time insight into RNF39 protein expression, and concluded a possible involvement in the neurobiology of PTSD, and the possibility to utilize it as a biomarker.

The results provided in this thesis serve both researchers and public health authorities. The major initial contribution of this thesis is to the research field. To researchers, it provides multiple sources to be informed about the current up-to-date knowledge about PTSD susceptibility, while giving templates to compare with future studies, both preclinical and clinical ones. To public health agencies and health authorities, as well as researchers, we provide markers of disease susceptibility for timely intervention. However, more in-depth clinical research is needed to confirm the reliability and cost-effectiveness of such markers. This thesis supports such endeavours by providing a contextual discussion of susceptibility prediction or estimation, connecting biomedical and public health perspectives, and a comprehensive overview of methods and modalities for disease prevention, which when integrated can reduce disease burden.

REFERENCES

1. Kim, G.S., et al., Neuroepigenetics of Post-Traumatic Stress Disorder. Prog Mol Biol Transl Sci, 2018. 158: p. 227-253.
2. Rutten, B.P.F., et al., Longitudinal analyses of the DNA methylome in deployed military servicemen identify susceptibility loci for post-traumatic stress disorder. Mol Psychiatry, 2018. 23(5): p. 1145-1156.
3. Atwoli, L., et al., Epidemiology of posttraumatic stress disorder: prevalence, correlates and consequences. Curr Opin Psychiatry, 2015. 28(4): p. 307-11.
4. Kessler, R.C., Posttraumatic stress disorder: the burden to the individual and to society. J Clin Psychiatry, 2000. 61 Suppl 5: p. 4-12; discussion 13-4.
5. McGowan, I., The economic burden of PTSD. A brief review of salient literature. International Journal of Psychiatry and Mental Health, 2019. 1(1): p. 20-26.