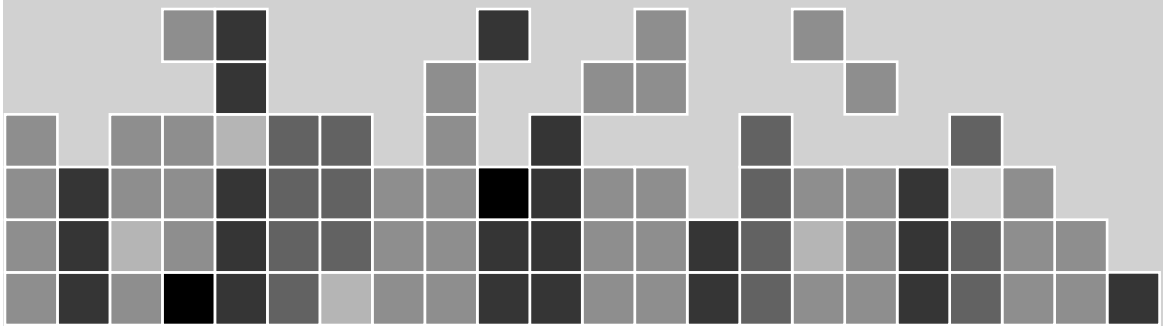
Genetic risk factors in prediction and treatment of chronic post-surgical pain

APPENDIX

Valorisation



Academic research should aim to reach further than solely contributing to scientific knowledge and be beneficial to society as much as possible. For this reason, the current chapter will focus on the societal perspective and valorisation of the research on genetic risk factors in prediction and treatment of Chronic Post-Surgical Pain (CPSP) as presented in this dissertation. Valorisation is defined as follows: *Valorisation is the process of creating value from knowledge by making knowledge suitable and available for societal and/or economic application and by transforming it into products, services, processes and new business.* This definition will be used to address the valorisation of the research in this dissertation specified to the following topics:

- **Impact of research:** What is the social and economic impact of the results of the research as described in this dissertation?
- **Audience of research:** Which stakeholders could benefit from the results of the experiments relevant outside of the academic community?
- **Product of research:** What value (as defined earlier) can be created from the research in this dissertation?

Impact of research

Annually, an estimated 313 million surgeries take place around the globe [1]. Of all patients undergoing surgery, 5-85% develops chronic postsurgical pain (CPSP), varying with the type of surgery and with an average incidence of 18% [2]. CPSP negatively affects the quality of life (QoL) of the patients as well as their relatives. Furthermore, patients with CPSP report higher incidences of sleep disturbances, depressive symptoms and comorbid disorders [3]. CPSP and its comorbid disorders (depression, stress, anxiety) have a large impact on the daily functioning of the patients affected. CPSP patients are less able to participate in private activities and at work, the degree of which is correlated with the pain intensity [3]. Due to the chronic pain and its comorbidities, some patients enter a vicious cycle

wherein the different problems including pain further worsen their quality of life [3]. The QoL can be measured by the use of questionnaires and these have shown QoL to be significantly decreased in patients affected by CPSP [3]. The majority of CPSP patients are prescribed multiple medications against the pain and the comorbidities (including opioids and NSAIDs) and on average visit a medical professional 12 times per year [3]. The economic costs associated with the decreased daily functioning and QoL has been estimated to be $41.463,- per year per patient in the United States of America alone, leading to a huge loss for the world economy [3]. Combining the incidence of CPSP, volume of surgery and estimated cost make clear that CPSP is a major problem with immense societal impact. CPSP has a tremendous impact on the economic status of the patients and their families.

Next to the group of surgical patients who develop CPSP each year, there is also a substantial group of patients exposed to the same surgeries, but who do not develop CPSP. It is important to study these patients as well. Prediction of which patients have a higher risk of developing CPSP is important, as it provides the opportunity to employ preventive strategies (*e.g.* alternative surgical approach, additional counselling) or to personalize the medication regime before, during and after surgery. Research has shown that for a cohort of hysterectomy patients, a combination of demographic and clinical factors explains 78% of the variance in the incidence of CPSP [4]. Nevertheless this implies still 22% of the incidence remains unexplained. Here, genetics might contribute to the solution. Part of the unexplained variance could be related to genetic variations and differential distributions of these variations between the patients with and without CPSP. Data from this dissertation shows that combining genetic data related to multiple surgeries can lead to the identification of genetic risk factors of CPSP and finally may lead to personalized treatment of the patient undergoing surgery. An example of successful personalized medicine has been reported in genetic mutations within

the cytochrome p450 enzyme, which alter the metabolism of opioid medication, thereby leading to a higher or lower dosage requirement for a similar effect [5].

To further increase understanding of genetic factors involved in CPSP, an increase in sample size is needed. Increasing the sample sizes of genetic studies is expected to lead to the identification of more genetic risk factors of CPSP in general as well as specific genetic risk factors related to specific surgeries. Interestingly, this dissertation has shown that the genetic profile underlying CPSP is not unique, as there is a genetic overlap with multiple chronic peripheral pain syndromes. This suggests that inclusion of other pain syndromes might be very beneficial in the development of new prevention and treatment strategies for chronic pain syndromes. Finally, studying the genetics of CPSP will help to develop personalized medicine and this should increase the responder rate to treatments, thereby lifting a burden from society by decreasing the associated costs and increasing QoL of many patients.

Audience of the research

The main beneficiaries of the research on genetic risk factors of CPSP are the 313 million patients who undergo surgery every year and their families. Studying the genetic factors of CPSP will lead to new developments in individual characterization and possible prediction and prevention of CPSP, but can also lead to personalized treatment after establishment of CPSP. Unravelling the individual genetic risk for each CPSP patient is an initial and important step towards personalized medicine. This will lead to an increase in QoL for the patients and their families. Moreover, research in this dissertation shows that there is genetic overlap across chronic peripheral pain syndromes (*e.g.* chronic widespread pain, sciatic pain) and CPSP, indicating a shared biological mechanism. Therefore, strategies working for one chronic pain disorder might proof beneficial for patients suffering other pain disorders as well. This will be of interest to clinicians treating all kinds of chronic pain patients, and researchers on other chronic pain

disorders. More knowledge on how chronic pain develops will aid the development of novel treatment and prevention strategies, which will ultimately aid the clinician in his or her daily practice. CPSP is an ideal chronic pain disorder to study the chronification of pain, as it involves a clear defined time-point zero.

Finally, Major stakeholders in this research are the health insurance companies and the local and national governments. CPSP has a tremendous effect on the society and the associated costs are very high as explained earlier. Better prediction, prevention and treatment of CPSP will be reflected in a reduction in the associated costs and have major impact for society.

Product of the research

The primary product culminating from the research as described in this dissertation is the deeper understanding of the genetic factors and molecular processes involved in the development of CPSP. Earlier studies have shown that it is possible to integrate genetic risk factors into clinical prediction models [4]. Integrating genome-wide identified risk factors will further optimize the clinical prediction models currently available. Moreover, the identified risk factors could lead to new pharmacological targets for CPSP and other chronic pain disorders. The pharmacological targets of interest need to be tested and verified in preclinical studies before clinical implementation.

The second important product from this research is the establishment of a genetic and pharmacological screening model. Studies performed in zebrafish have shown the possibility of modelling clinical phenotypes and testing the effects on morphology, development and nociception [6]. This provides a novel method to functionally asses the effects of genetic mutation on organisms. Of all the associations between SNPs and phenotypes, roughly 3% has been functionally assessed [7]. Research in this dissertation showed that Dopamine D2 receptor might be a viable candidate in modulating pain and prevention of chronification

of pain but more research is necessary [8]. This screening model can aid in this development.

Preclinical studies in zebrafish has several advantages for animal studies; they provide a fast screening of the targets due to a high replication rate; the genome is fully sequenced and easily manipulated; the associated costs for maintenance are low; and they have less ethical restrictions compared to rodents. Ultimately, research in zebrafish will decrease the numbers of rodents necessary by prioritizing the most likely candidates first.

Next to the pharmacological treatment strategies, non-pharmacological intervention could also aid in the prevention of CPSP. Improving physical health (*e.g.* Better in Better out concept) and/or mental health pre-surgery, focussed on individual risk factors of CPSP, can minimize the risk of developing CPSP.

Finally, through extensive research, the gap between prediction and treatment of CPSP might decrease in the future. Extensive prediction models including genetic information will provide clear indications of the postsurgical recovery trajectory while simultaneously providing options on prevention and treatment of CPSP. The research presented in this dissertation is a first contribution to study genome wide genetic associations in CPSP. The approach presented, combined with further analysis, will be necessary to ensure implementation into the clinical practice to aid a vulnerable population of chronic pain patients.

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