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Doctoral Field: MEDICINE

ABSTRACT OF THE HABILITATION THESIS

The view from the clinic genetics to genomic and precision medicine

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ABSTRACT OF THE HABILITATION THESIS

Through its content, the thesis approaches a multidisciplinary, particularly complex scientific field, based on advanced theoretical concepts, principles and models, from the perspective of practical experience and the results of studies and own research carried out over the years since the doctoral thesis was defended and recognized by the main indicators of scientific evaluation (8 Hirsch index and 137 citations).

Human genetics an incredibly exciting and complex field. The images from the microscopic world of DNA, the discoveries about genetic inheritance and the impact on human health and development are fascinating. Genomics has revolutionized our understanding of etiopathogenesis in numerous pathologies and has allowed a better understanding of the genetic causes underlying disease predisposition or development. This has led to significant progress in early diagnosis, prognostication and personalized therapeutic approaches, including the development of targeted therapy which aims specific mutations found in certain pathologies. Personalized medicine, which is based on genomic information, proposes to provide specific treatment and interventions according to its molecular genetic profile, increasing efficiency and reducing possible adverse effects.

The thesis is structured in three main parts, the first being a brief presentation of the professional path and the medical and scientific training; the second part is a synthesis of scientific and academic achievements focused on the most studied research topics, and the third part presents the directions for the development of the professional medical and research career, with the presentation of the main topics of interest for future studies.

The first chapter of the thesis is focused on the presentation, in a concise form, of my entire professional activity that provides a broad context and highlights the progress and experience accumulated in the field of medical genetics, teaching and research career. Focusing on the stages of academic career development, such as education, research, conference attendance, publications and involvement in relevant research projects, highlights my evolution and contributions over time in a dynamic field such as medical genetics, in that there is still much to discover and explore.

The second chapter synthetically describes the main research directions addressed and capitalized on in the form of works published in specialized journals listed in international databases or in monographs. Among the research themes developed throughout my career, I chose to present the most researched pathologies that were the object of my medical and research activity: malformative pathology, neuropsychiatric disorders and oncological diseases.

A common denominator of genetic research in human pathology is the desire to understand the links between genetic information and human disease. Regardless of the specifics of each condition or the various branches of medical genetics, there are certain themes and directions that intersect in genetic research:

Identification of the genes involved: genetic research aims to identify the genes and genetic variants that contribute to the occurrence and development of diseases; this may involve identifying specific mutations, genomic regions associated with a particular disease, or genetic networks involved in pathogenesis.

Studying molecular mechanisms: Once the genes involved are identified, research aims to understand how these genetic variants (polymorphisms) influence the molecular functioning of cells and the body as a whole. This includes understanding changes in gene expression, protein function, or affected biochemical pathways (genomics → transcriptomics → proteomics).

Biomarker validation: genetic research seeks to find and validate biomarkers useful for disease diagnosis, prognosis and monitoring; these biomarkers can be genes, proteins, epigenetic changes, or other molecules that provide specific clues about the presence or progression of a condition.

Development of personalized therapies: another common direction is the development of treatments and therapies that are tailored to the genetic specificity of a person or a condition; this includes targeted therapies that directly aim at the molecular mechanisms affected by genetic mutations.

Population genomics: studies of large samples of populations help to understand genetic variation at the population level and to identify genetic factors that may influence susceptibility to certain diseases in certain ethnic or geographic groups.

These lines of research generate essential information for developing new treatments, improving diagnosis and personalizing the medical approach, thus contributing to the advancement of evidence-based medicine and health care. With the technological advance in genetic sequencing and data analysis, biomarker discovery is becoming more specific and relevant to personalized medicine.

In the third chapter, I describe the directions for academic and professional career development, which will mainly target innovative research in the field of oncogenetics, nutrigenomics and metabolomics, and last but not least, the study of the microbiome in relation to the human genome. These lines of research represent extremely promising areas for the future of medicine and human genetics, and their integrated study can provide a more comprehensive perspective on human health and open doors to new strategies for the prevention and treatment of diseases, including cancer.

Oncogenetics: cancer is an extremely complex disease, with hundreds of different types, each with specific characteristics, and its incidence has increased significantly in recent decades, representing one of the main causes of morbidity and mortality globally. This puts pressure on healthcare systems and requires an integrated approach to diagnosis, treatment and patient care. Oncological research aims to develop more effective and specific therapies, as well as to identify risk factors and methods of prevention. The study of genes involved in cancer development is essential for understanding oncogenetic processes and for developing more precise and personalized therapies. The identification of genetic mutations associated with certain types of cancer offers opportunities for early diagnosis, prognosis and development of targeted therapies.

Nutrigenomics and metabolomics: These fields explore the interaction between the genome and nutrition/metabolism. By studying how certain nutrients or chemical compounds affect gene expression and the metabolome, we can better understand the connection between diet, metabolism and disease predisposition, such as diabetes, obesity or other metabolic conditions, extremely important and current health issues. The resolution and management of these conditions represent one of the great challenges of public health today, and research in these areas is essential for finding effective solutions for prevention and treatment.

Studying the microbiome: Research into the microbiota (or microbiome) and its influence on human health is booming. The microbiome represents all the microorganisms that live in the human body, and the relationship between them and the human genome is particularly interesting. Microbiome research can reveal how bacteria and other microorganisms influence human health, including how they can influence disease susceptibility or response to treatments. Studies suggest that the composition of the microbiota can influence the predisposition to various diseases, including metabolic conditions, allergies, obesity, diabetes and even certain types of cancer. The microbiota has a significant contribution to the development and functioning of the immune system. It can influence the way the immune system reacts to pathogens and can be associated with the development of autoimmune diseases. There is research suggesting that the microbiota can influence mental health and cognitive function. The link between the microbiome and the central nervous system is a growing area of interest in the neurosciences.

These fields are not only booming, but also intersect in a complex and fascinating way. By combining knowledge from these fields, researchers can develop more precise and personalized medical approaches, tailored to each individual's genetic specificity and the complex interactions between genome, environment and lifestyle. Thus, these lines of research promise to bring remarkable

innovations in the medical field and provide new insights into the understanding and treatment of human diseases.

Conclusions: I believe that the extensive research experience and accumulated expertise mean an incredible resource to facilitate the transfer of knowledge to doctoral students and to coordinate doctoral theses according to the scientific standards, helping them navigate the complexities of the research process. My involvement in coordinating and mentoring PhD students can be an excellent opportunity to further my own personal and professional development. Working with a new generation of researchers can give me new perspectives and strengthen my expertise in the field.

This thesis highlights the main directions that support personal development, but also the contributions made for institutional development, which are fundamental and interconnected - by supporting and encouraging high-quality research and innovation, they can contribute to the development of a strong institutional culture that encourages excellence in research and creative thinking.