Medicine
OPEN

Proceedings of the 27th Annual Meeting of the Portuguese Society of Human Genetics (SPGH – *Sociedade Portuguesa de Genética Humana*) Lisbon, 23 -25 November 2023

Discussion: In our study, the diagnostic rate of aCGH and ES results are slightly higher than in previous studies. ES had a similar detection rate in both groups, isolated and complex, but they are higher when compared with the detection rate of aCGH. The diagnosis rate is even more significant in multisystem cases, achieving 50% with aCGH and 66,7% with ES. In a general way, ES seems to be a potential method to improve the diagnosis, and performed after the aCGH leads to a significant increase in the diagnosis rate, mostly in multisystemic cases. However, we must take note that two years is a short period of evaluation, and our group is also limited. Further research is needed, particularly expanded to other units, for definitive conclusions, standardization of procedures and maximization of benefits and efficiency. Autopsy proved to be an excellent in the diagnostic process.

P52 - LDLR ACTIVITY AND CARDIOVASCULAR BURDEN IN PORTUGUESE FAMILIES WITH FAMILIAL HYPERCHOLESTEROLEMIA

Beatriz R. Miranda[1,2], Ana M. Medeiros[1,2], Ana C. Alves[1,2], Mafalda Bourbon[1,2]

[1] *Grupo de Investigação Cardiovascular, Unidade I&D, Departamento de Promoção da Saúde e Doenças Crónicas, Instituto Nacional de Saúde Doutor Ricardo Jorge, Portugal;* [2] *BioISI– Biosystems & Integrative Sciences Institute, Faculty of Sciences, University of Lisboa, Campo Grande, Lisboa*

Introduction: Familial hypercholesterolemia (FH) is the most common inherited disorder of lipid metabolism and is clinically characterized by elevated plasma cholesterol, which predisposes to cardiovascular disease (CVD). In nearly 90% of the cases, FH is caused by a pathogenic/likely pathogenic variant in the LDLR gene. In this work, we aimed to compare the cardiovascular burden in families from the Portuguese FH Study (PFHS) carrying different LDLR variants functionally studied.
Methodology: The PFHS database (containing clinical and molecular characterization of individuals referred to the PFHS) was consulted. Considering well-documented personal and familial history of CVD, a total of 246 PFHS families carrying LDLR causative variants (previously functionally characterized) were selected for this study.
Results: According to the results of functional assays reported, 47 different pathogenic/likely pathogenic variants (found in 617 subjects) were divided into 3 cut-offs of LDLR activity: <5% (n=15), 5-30% (n=16), and 30-70% (n=16). Within 80 families carrying variants with a LDLR activity of <5% (214 participants), 10% of individuals suffered at least one cardiovascular event (mainly myocardial infarction) at medium age of 44 years, and the majority reported familial history of CVD in more than 2 generations. In 115 families carrying variants with LDLR activity between 5-30% (280 participants), 7% of the subjects had a cardiovascular event at medium age of 41. It is relevant to note that the individuals presenting CVD had, specifically, variants showing less than 15% of activity. Despite comparatively fewer subjects (only 123) in 51 families carrying variants with a LDLR activity of 30-70%, 12% of them reported development of CVD at notably older age (medium of 51).
Discussion: Although the percentage of patients with premature CVD seemed to be very similar in the different groups, the mean age of onset is considerably higher in patients with a higher LDLR activity. To decrease the cardiovascular burden of individuals with FH, the early identification of these individuals and the functional characterization of variants, should be performed for a better and more personalized diagnosis and disease management.

P53 - UNRAVELLING THE GENETIC BASIS OF COMPLEX CLINICAL CASES OF HEMOGLOBINOPATHIES

Eduarda Silva[1], Rita Pena[1], Armandina Miranda[2], Alcina Costa[2], Gisela Gaspar[3], Pedro Lopes[1], Paula Faustino[1,3,4]

[1] *Departamento de Genética Humana, Instituto Nacional de Saúde Doutor Ricardo Jorge, Lisboa;* [2] *Departamento de Promoção da Saúde e Prevenção de Doenças Não Transmissíveis, Instituto Nacional de Saúde Doutor Ricardo Jorge, Lisboa;* [3] *Grupo Ecogenética e Saúde Humana, Instituto de Saúde Ambiental, Faculdade de Medicina, Universidade de Lisboa, Lisboa;* [4] *Laboratório Associado TERRA, Faculdade de Medicina, Universidade de Lisboa, Lisboa*

Hemoglobinopathies encompass all genetic diseases of hemoglobin (Hb), the iron-containing oxygen-transport protein present in red blood cells. They occur due to mutations in globin genes or in their regulatory regions, and are classified as Hb variants and thalassemias. The aim of this work was to identify the molecular lesions in the origin of complex cases of hemoglobinopathies and understand the underlying pathophysiological mechanisms.
We investigated 15 clinical cases suspected of having one or more hemoglobinopathy, presenting with atypical hematological phenotypes. The study included the search for alterations in beta- and alpha-globin gene clusters by PCR, Gap-PCR, Sanger sequencing, and Multiplex Ligation-dependent Probe Amplification. In silico analyses were performed using Polyphen-2, SIFT, and varSeak.
Two beta-thalassemia carriers with abnormally low HbA2 level were found to have double heterozygosity for a mutation in HBB gene (c.92+1G>A, c.92+6T>C) and a delta-chain Hb variant (Hb A2-Yialousa). Another case was justified by a novel large deletion, which removes the entire beta-globin gene cluster as well as the olfactory receptor genes, OR52A1 and OR51V1. Changes in HbA2 values were also justified by a deletion that eliminates the HBD (Corfu deletion) or by the presence of the HbA2′variant. Atypically high levels of fetal Hb were explained by alterations in promoters of HBG genes (HBG1:c.-248C>G, HBG1:c.-228T>C, HBG2:c.-211C>T) or by deletions that remove both HBD and HBB (HPFH-1, HPFH-2). An even more complex case was originated by triple heterozygosity involving the Southeast Asian alpha-thalassemia deletion, the alpha-chain variant Hb Westmead, and the beta-chain variant HbE. As far as we know, this is the first case in which the three alterations were found in the same individual.
Individuals presenting abnormal phenotypes due to more than one hemoglobinopathy may be misdiagnosed if not correctly studied. Unravelling the genetic basis of complex clinical cases allows a better referral to genetic counselling, improves the understanding of the pathophysiology of the disease and its modifying factors, and may reveal new therapeutic targets.

P54 - DEVELOPMENT OF A PIPELINE THAT LINKS GENOMIC DATA WITH CT IMAGES OF HEAD AND NECK CANCER FOR THE IDENTIFICATION OF CLINICAL BIOMARKERS

Alexandre Costa[1], Francisco Caramelo[2,3,4], Francisco Marques[5], Joana Barbosa Melo[1,3,4], Isabel Marques Carreira[1,3,4], Ilda Patrícia Ribeiro[1,3,4]

[1] *Cytogenetics and Genomics Laboratory, Faculty of Medicine, University of Coimbra, Coimbra, Portugal;* [2] *Laboratory of Biostatistics and Medical Informatics, ICBR - Faculty of Medicine, University of Coimbra, Coimbra, Portugal;* [3] *University of Coimbra, Coimbra Institute for Clinical and Biomedical Research (ICBR) and Center of Investigation on Environment Genetics and Oncobiology (CIMAGO), Faculty of Medicine, Coimbra, Portuga;* [4] *CIBB – Centre for Innovative Biomedicine and Biotechnology, University of Coimbra, Coimbra, Portugal;* [5] *Department of Dentistry, Faculty of Medicine, University of Coimbra, Coimbra, Portugal*

Introduction: Head and neck cancer (HNC) is the 7th most common cancer and is also one of the most fatal cancers. Furthermore, as this cancer develops primarily in an area where several important human structures are located, such as the tongue, gums, pharynx, and vocal cords, patients who must undergo more aggressive treatments may lose, partially or totally, their ability to speak, swallow or chew.
This study aimed to develop a pipeline to check for differences in copy number variations between groups of HNC patients with similar radiomic features. An understanding of these differences can be used to develop more personalized treatments to reduce both the mortality and morbidity of this disease.
Methods and Results: For this study, a small dataset of CT images from nine patients with head and neck cancer was used. The pipeline begins with the segmentation phase, using a graphical user interface (GUI) designed for this purpose, of the most visible regions of the tumor in the available images of each patient. Radiomic features are then extracted from the segmented tumor regions that are used, in the next stage, to perform a clustering analysis enabling patients to be grouped into clusters. In the final stage, all the genes identified with copy number alterations, in the DNA extracted from the tumor tissue, using the array Comparative Genomic Hybridization technique are analyzed and it is checked which ones show a significant difference between clusters.
Conclusion: The development of this pipeline has provided a methodology that makes it possible to link copy number alterations to information present in CT images. This form of analyzing data can be applied to other situations provided that clinical images and genomic information is given, which makes it extremely versatile.