Centre d'Etudes Doctorales : Sciences et Techniques et Sciences Médicales

Avis de Soutenance

THESE DE DOCTORAT

Présentée par

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Discipline : Biologie
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Sujet de la thèse

Molecular characterization of hereditary hearing loss in a Moroccan population: Exploring GJB2 gene contribution and beyond through whole exome sequencing

Formation Doctorale " Sciences Médicales et Recherche Translationnelle"

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Résumé de la thèse

Hearing loss (HL) is the most common sensory disorders among humans, with a prevalence rate of approximately 1 to 3.47 per 1000 neonates. According to the latest data released by the World Health Organization (WHO), 466 million people worldwide have disabling hearing loss, constituting over 5% of the world's total population. Hereditary hearing loss (HHL) that is attributed to genetic factors accounts for 50-60% of all hearing loss cases. HHL can be categorized into two main groups: non-syndromic HL (NSHL), which comprises 70% of cases and occurs without any accompanying clinical manifestations, and syndromic HL (30%), which presents in conjunction with other medical abnormalities. The landscape of HHL is marked by significant clinical and genetic heterogeneity, with mutations in over 120 genes linked to NSHL and over 400 syndromes presenting with HL have been documented. The aetiological diagnosis of HHL is notably challenging due to this extensive heterogeneity. A delay in establishing a genetic diagnosis in individuals with hearing loss can lead to a range of issues, including incorrect diagnostic procedures, uncertain prognoses, inadequate treatments, delayed referrals to relevant medical specialists, and a lack of preparation for potential additional health complications.

The revelation that mutations in the GJB2 gene are a major cause of autosomal recessive non-syndromic hearing loss (ARNSHL) across various populations was a breakthrough. It underscored the significance of GJB2 gene testing as a valuable initial diagnostic tool in cases of non-syndromic hearing loss. Nevertheless, conventional diagnostic methods, which rely on single gene testing, exhibit limited utility when confronted with monogenic conditions characterized by extensive genetic and phenotypic diversity. Recent advancements in Next-Generation Sequencing (NGS) technologies have emerged as a potent approach for pinpointing patient-specific causes in genetically diverse disorders like hereditary hearing loss (HHL). This advancement has the potential to revolutionize the way patient care is delivered by offering a more comprehensive understanding of the underlying genetic factors involved. However, in the Moroccan context, the mutation profile of GJB2 in cases of non-syndromic hearing loss (NSHL) remains inadequately explored, particularly in simplex cases. Furthermore, our knowledge of the genetics of hearing loss within the Moroccan population is extremely limited, with only a few genes and variants having been characterized, leaving us without a comprehensive understanding of the genetic landscape of hereditary hearing loss (HHL) in the Moroccan population. Given this context, the primary objective of this study was to elucidate the spectrum and prevalence of GJB2 mutations in the Moroccan population, encompassing both simplex and multiplex families affected by NSHL. The secondary objective was to leverage advanced Next-Generation Sequencing (NGS) technologies, specifically whole exome sequencing (WES), to unravel the genetic basis of both non-syndromic and syndromic hearing loss within the Moroccan population. This sheds new light on the genetic diversity of hearing loss in our region.

The second chapter of this study was dedicated to the sequencing of the entire coding region of the genome (exome), achieved through whole exome sequencing (WES) in a cohort of 93 families suspected of having hereditary hearing loss (HHL). The selection of families for inclusion in this study was contingent upon two distinct criteria: firstly, the absence of causative variants in the GJB2 gene in cases of NSHL, and secondly, the presence of hearing loss accompanied with other medical abnormalities, characterizing syndromic cases. Whole exome sequencing analysis revealed known causative variants across 15 different genes in 29% of the families enrolled in the study. Additionally, in approximately 54% of families, potential variants with presumptive implications were uncovered, necessitating further in-depth investigation and validation. This observed high diagnostic yield within our cohort underscores the effectiveness of implementing Next-Generation Sequencing (NGS) technologies in advancing our understanding of the genetic underpinnings of hereditary hearing loss. It holds great promise for both clinical diagnosis and patient care.

The research undertaken in this thesis offers a comprehensive insight into the mutational spectrum of hereditary hearing loss (HHL) and underscores the extreme heterogeneity of genetic variants and genes linked to HHL within the Moroccan population. These findings underscore the imperative need for the adoption of comprehensive genomic sequencing methodologies in the molecular genetic diagnosis of hearing loss within our population. Beyond its clinical significance in enhancing prognostic accuracy and facilitating genetic and reproductive counseling. Interestingly, this approach has also proven invaluable in revealing undiagnosed syndromes with direct clinical relevance. Such revelations possess the power to change the outcome of the disorder, with the potential to ultimately prevent the occurrence of avoidable complications.

Keywords: Hereditary hearing loss; GJB2; Next-Generation Sequencing; Whole exome sequencing