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Review Article

Genetics of non-syndromic hearing loss in the Middle East

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ABSTRACT

Hearing impairment is the most common sensory disorder, present 1 in every 500 newborns. About 80% of genetic HL is classified as non-syndromic deafness. To date, over 115 non-syndromic loci have been identified of which fifty associated with autosomal recessive non-syndromic hearing loss (ARNSHL). In this review article, we represent the 40 genes function and contribution to genetic deafness in different Middle Eastern populations as well as gene frequencies and mutation spectrum. The wide variety of mutations have so far detected in 19 countries reflects the heterogeneity of the genes involved in HL in this region. The deafness genes can cause dysfunction of cochlear homeostasis, cellular organization, neuronal transmission, cell growth, differentiation, and survival, some coding for tectorial membrane-associated proteins, and the remaining with unknown functions. Non-syndromic deafness is highly heterogeneous and mutations in the *GJB2* are responsible for almost 30–50% in northwest to as low as 0–5% in south and southeast of the Middle East, it remain as major gene in ARNSHL in Middle East. The other genes contributing to AR/ADNSHL in some countries have been determined while for many other countries in the Middle East have not been studied or little study has been done. With the advancement of next generation sequencing one could expect in next coming year many of the remaining genes to be determine and to understand their function in the inner ear.

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1. Introduction

Deafness or hearing loss (HL) can be due to genetic or environmental causes or a combination of both. The genetic HL is classified as syndromic or non-syndromic (NS). Like many disorders in the syndromic HL, the pathology varies widely, however in non-syndromic HL (NSHL), the defect is generally sensorineural. Majority of hereditary HL is classified as non-syndromic [1]. ARNSHL is genetically heterogeneous and is the most common form of inherited HL. Autosomal recessive genes are responsible for about 80% of the cases of hereditary NSHL, with 40 different genes identified to date (http://hereditaryhearingloss.org/), whereas this amount reduced to 27 genes for autosomal dominant NSHL. Of these genes responsible for deafness, many of the encoded proteins have been shown to be expressed within the cochlea and can be grouped into functional categories that affect hair-cell structure, extracellular matrix, ion homeostasis, transcription factors, and miscellaneous. It is believed autosomal recessive disorder are 2–3 times more common in this part of world because of consanguinity marriages compare to European and American population where there is no or little consanguinity exist. In the other hand the number of autosomal dominant genes remain the same. The fact that families in the Middle East are usually large and you can see many affected children in the families, therefore, they are ideal for autozygosity mapping and this is why many of AR genes have been identified in these population. Mutations in many of these genes have also been found in other western countries and have contributed to understand the function of these genes. This extreme genetic heterogeneity suggests that there are many different genes that can malfunction within the inner ear to cause HL. Majority of these genes (40) have been identified in families from the Middle East (supplementary Table 1). The Middle East is a region that comprises 39 countries and encompasses Western Asia and part of Northern Africa, lies at the juncture of Eurasia and Africa and of the Mediterranean Sea and the Indian Ocean. The Middle East and North Africa has a population of about 331 million according to a World Bank report released in 2011, or nearly as many people as the United States. Saudi Arabia is the largest of the core countries of the Middle East in area. Bahrain, an island nation in the Persian Gulf, is the smallest of the Middle Eastern states [2]. The most populous Middle Eastern countries are Turkey, Egypt, Pakistan and Iran, each with more than 60 million people. The Persian Gulf states of Bahrain and Qatar have the smallest populations, about 400,000 each. The Middle East is today home to numerous long established ethnic groups, including Arabs, Turks, Persians, Jews/Israelis, Kurds, Assyrians (Chaldo-Assyrians), Arameans-Syriacs, etc. The most important trouble which Middle East faced is explosive population growth and high consanguineous marriage rate in this region; which increased the risk of recurrence of autosomal recessive forms of genetic disorders such as deafness. With a population projected to grow from 350 million to 1.1 billion by 2050, the greater Middle East is one of the fastest growing regions in the world [3]. The Middle East has uniquely high rates of consanguineous marriage among the world's regions. To determine the incidence of HL among consanguineous marriages in Saudi Arabia, two epidemiological surveys were carried out 10 years apart; 6421 subjects from Riyadh City and 9540 from all other parts of the Kingdom of Saudi Arabia. The survey has conducted among 1st and 2nd cousins and the results showed that about 66% of the 1st cousin offspring had HL and those from a 2nd cousin relationship had an incidence of 37%, concluded that in developing nations, cultural issues affect the incidence of hearing impairment [4]. According to the WHO global estimation on prevalence of HL reported in 2012, there were