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A Review of Genetic Diagnosis and Screening of Hereditary Deafness

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Abstract: The incidence of congenital hearing impairment in China is inching ever upwards. Deafness has always been a disabling disease that seriously affects the quality of human life. Molecular diagnostic technology is the main method to detect hereditary deafness. At present, there is no effective treatment for hereditary deafness, so the screening, early intervention and genetic diagnosis of hereditary deafness are particularly important. There are already genetic screening and genetic diagnosis methods for hereditary deafness. Through the analysis of the effectiveness of genetic screening and diagnosis of hereditary deafness, we can find an effective method to prevent hereditary deafness. The purpose of this review article is to explore effective methods to prevent hereditary deafness by analyzing the effectiveness of genetic screening and genetic diagnosis.

Keywords: Hereditary deafness, Non-syndromic deafness, Genetic diagnosis, Genetic screening.

1. Introduction

1.1. An Overview of Hereditary Deafness

Deafness is a genetic disorder that causes problems with language communication. Nonsyndromic deafness in hereditary deafness is one of the common sensory nerve diseases with high clinical and genetic heterogeneity [1]. Research showed that the disabled account for 6.34% of the total population in China, among which 20.4 million individuals with hearing disabilities account for 24.16% [2]. Genetic deafness accounts for a high proportion of hearing disabilities, with at least one in every 1,000 newborns being born with hearing impairment, half of which are due to genetic factors [3].Severe deafness occurs in as many as one 800th to one-thousandth newborns [4]. Deafness has many causes, which genetic factors are the most important. Sixty percent of deafness is caused by genetic defects [5]. Hereditary deafness can be divided into two types based on the presence or absence of other tissue dysfunction: syndromic deafness (SHL) and non-syndromic deafness (NSHL), of which NSHL accounts for about 70% of hereditary deafness.

2. The Pathogenic Gene and Inheritance Mode of Hereditary Deafness

According to the way of heredity, hereditary deafness can be divided into 5 categories: autosomal recessive inheritance, autosomal dominant inheritance, X-linked inheritance, Y-linked inheritance and mitochondrial gene abnormality. The main type of hereditary deafness is non-syndromic deafness (NSHL), 75% ~ 80% of cases of NSHL follow autosomal recessive inheritance, 20% ~ 25% follow autosomal dominant inheritance, with X chromosome inheritance and mitochondrial inheritance relatively rare [2]. Syndromic deafness (SHL) is inherited by autosomal dominant inheritance, recessive inheritance, X-linked inheritance and mitochondrial mutation.

The etiology of deafness is complex and there are many influencing factors, there are more than 200 kinds of known deafness genes [6]. In recent years, with the rapid development of molecular biology technology, a large number of deafness related genes have been identified and cloned. A large number of epidemiological studies have shown that the most common deafness-causing genes in China are GJB2, SLC26A4 and 12SrRNA [7]. Among them, GJB2 is the most common deafness gene in the world as well as in China. The mutation sites of GJB2 have obvious ethnic and regional differences. The majority of GJB2 mutations are 35delG mutations in Europe and America, and 167DELT mutations in Nordic Jews [8].

3. Genetic Screening for Inherited Deafness

3.1. Genetic Screening for Neonatal Deafness

The main mutation sites of deafness gene are GJB2 235del C and SLC26A4 IVS7-2A>G. Genetic screening of hereditary deafness can detect latent and delayed deafness in time, so as to intervene as early as possible. In addition, genetic screening of hereditary deafness is a supplementary screening method in the early screening of newborn deafness, which has important application value [9]. Because the routine physical hearing screening can only detect part of the children with hearing impairment, and for the children with hearing impairment, it will not be shown at birth [10].

In the process of neonatal deafness gene screening, it is necessary to use PCR amplification instrument, nucleic acid molecular hybridization instrument, genetic deafness related gene detection kit and blood genomic DNA extraction kit [9]. First, automated auditory brainstem response screening using otoacoustic emission in order to check the newborn for hearing impairment. Next comes genetic screening for deafness, which first involves extracting DNA from the newborn, blood genomic DNA extraction kit (centrifugal column) was used to extract and purify DNA. The last and most important step is genetic testing for deafness.

In recent years, due to the improvement of people's living standards, their conception of fertility has also been greatly improved. Therefore, neonatal screening has been widely

carried out in clinical practice, among which neonatal hearing screening is an important screening project. Conventional newborn hearing screening used in the past, the main detection of neonatal ear structure and function is abnormal, so the detection rate of hereditary deafness, drug-induced deafness, delayed deafness is not high, clinical application is limited, that's why genetic deafness genetic screening for neonatal deafness has important clinical significance [11-12]. In addition, this may also give an early warning of the risk of future deafness in their offspring. In other words, genetic screening for neonatal deafness also functions as carrier screening, and brings carrier screening earlier at birth [13].

3.2. Genetic Screening for Deafness in Carriers

Carrier screening is a genetic test that tests each couple for genetic risk. Prior to pregnancy or during pregnancy, understanding the risk of both partners carrying disease-causing mutations can provide couples with reasonable fertility guidance, which is an important measure for the application of genomic technology in the effective prevention or management of birth defects and rare genetic diseases [13].

Peripheral blood was collected from the subjects, and then nine mutated loci in four most common pathogenic genes of deafness (GJB2, GJB3, SLC26A4 and mitochondrial 12SrRNA) were detected by multiallele-specific PCR combined with universal microarray [14].

For the normal young couple before the birth of deafness gene mutation screening, detection of carriers, for their fertility to provide scientific and accurate genetic information and guidance, can be very effective in reducing the occurrence of hereditary deafness. In addition, from the concept of primary prevention of deafness, pregnancy is the best time for screening carriers. Alternatively, for families at high risk of hearing loss identified by pre-pregnancy screening, preimplantation diagnosis or prenatal diagnosis can be used to prevent the birth of deaf children [13].

According to the data, a nationwide screening program could theoretically prevent about 9,000 deaf births a year [15].

4. Genetic Diagnosis of Inherited Deafness

4.1. Current Genetic Diagnosis of Deafness

Early prevention and intervention is the key to reduce hereditary deafness. Using molecular diagnostic technology to detect deafness gene mutation sites can not only provide diagnostic basis for clinical diagnosis but also guide patients and high-risk groups to improve the quality of population [16]. At present, we have the following genetic detection methods:

4.1.1. Denatured High Performance Liquid Chromatography (DHPLC)

Denatured high performance liquid chromatography (DHPLC) is a novel technique for the detection of heterozygous double strand mutations based on single-strand conformation polymorphism analysis and denatured gradient gel electrophoresis [17].

This method not only has high automation and low detection cost, but also can detect multiple mutation sites at the same time. However, special equipment is required for the process, and needs high technical skills. Therefore, the clinical development is limited. Now, it is mostly used for laboratory testing.

4.1.2. Generation Sequencing Technology

Sanger sequencing, as the representative of the first generation of sequencing, began to be applied in the detection of deafness genes in the late 20th century, and GJB2, Pou3f4, myO7a and other deafness-causing genes were successively discovered [18].

Accuracy is the biggest advantage of Sanger sequencing. However, this method is not suitable for clinical detection due to its high cost, time-consuming and high requirements for technicians.

4.1.3. Gene Chip Technology

Gene chip technology first detected the gene for deafness in 2006 [19]. Since then, scholars at home and abroad used this method to carry out large-scale research on deafness gene. In this technology, microarray array method is used to fix the probe probe on the chip through photolithography in-situ synthesis or spot sampling technology. The gene to be tested is amplified, labeled with fluorescence and hybridized with the chip. Finally, the results are interpreted by laser confocal scanning and analysis software [20].

Although this method has high throughput, miniaturization, automation and easy interpretation of results, it cannot be popularized in clinical practice due to its high requirements and high cost.

4.1.4. Matrix-assisted Laser Desorption Ionization Time of Flight Mass Spectrometry

The principle of this method is mainly divided into ionization technology and time of flight quality analysis technology. In 2016, Rogerio Marins Alves et al. [21]used this technique to analyze mitochondrial mutations in patients with sensorineural hearing loss in Brazil, and detected 15 different mtDNA mutations in 152 patients with sensorineural hearing loss and 104 patients with normal hearing control group, which was completely consistent with Sanger sequencing results [16].

Although this method can meet the needs of a large number of samples, the technology requires high purity of samples, expensive equipment and high technical requirements for personnel, so it is not suitable for general medical institutions to carry out.

4.1.5. Next Generation Sequencing (NGS)

Next generation sequencing includes whole genome sequencing (WGS), whole exome sequencing (WES), targeted gene capture (TGC) and so on [22]. NGS uses large-scale parallel DNA sequencing to comprehensively analyze individual coding regions, or entire genomes, opening a new era in the diagnosis of many genetic diseases, including inherited deafness [23].

Compare that to the first generation sequencing, next generation sequencing technology is characterized by its high throughput, high efficiency, advantages such as high accuracy and low cost are increasingly widely applied to different field [24]. However, the detection results still need to be verified by Sanger sequence, and whether the detected mutations are related to deafness requires a large amount of data and bioinformatics analysis [16].

4.1.6. High Resolution Melting (HRM)

The high resolution melting can detect the change of fluorescence intensity in denatured double stranded DNA by increasing the unchain temperature, and then distinguish wild type and mutant type by unchain map, which can be used for the detection of single base sequence variation and unknown mutation [25].

This technology has the advantages of high throughput, high sensitivity, high degree of automation, fully closed tube operation and low cost. However, in recent years, due to the development of technology, HRM is increasingly widely used.

4.1.7. Invader Assay

In 2012, Invader assay screening for 46 mutations in 13 deafness genes became available in Japanese society, In 2016, Kentaro Mori et al. used large-scale parallel DNA sequencing combined with Invader assay and TaqMan genotyping technology to detect 154 mutation sites of 19 deafness genes in 717 Japanese deafness patients. The results showed that the total isometric factor frequency ratio of 154 abrupt changes was 32.64% [26].

This method does not need amplification. Therefore, it has no pollution. It also has high specificity and sensitivity, and is easy to operate, which is the main method for gene detection of deafness in Japan [16].

4.1.8. Multicolor Melting Curve Analysis (MMCA)

This technique is a novel gene mutation detection technique based on real-time PCR developed by Xiamen University in 2011, which is characterized by the detection of multiple mutations in a single reaction [16]. Based on this method, xiamen University developed a screening protocol for 12 common deafness gene mutations in the Chinese population. The method can provide clear genotyping from a wide range of DNA concentrations, and can detect 10% to 20% heterogeneic mutations. A comparative study using 501 clinical samples showed that, MMCA showed 100% consistency with Sanger sequencing [27].

4.2. Expectation

According to the development of genetic diagnosis technology, it can be found that genetic diagnosis technology has been improving with the development of science and technology, and the detection of deafness is more accurate. At present, there is no effective treatment for hereditary deafness, so early diagnosis to reduce the incidence of hereditary deafness is very important.

Unfortunately, at present, there are still some deficiencies in the commonly used deafness gene testing technology, such as low flux, high cost and low diagnosis rate, which limit the popularization of deafness gene testing to a certain extent.

We should combine the advantages and disadvantages of various gene diagnosis technologies to develop more effective gene diagnosis technologies and form a perfect gene detection system, so as to reduce the detection cost and improve the detection accuracy. It is believed that in the near future the genetic detection system of hereditary deafness will be increasingly complete and make clinical contributions to reduce deafness patients.

5. Conclusion

In this review, it describes and compares the genetic screening and diagnosis of hereditary deafness based on the present situation and pathogenic genes of hereditary deafness, and puts forward some ideas on the future treatment of hereditary deafness.

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