GGA Genetic Counseling Newsletter

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Familial Inherited Disease and Pre-Test Counseling -Case in Genetic Testing

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【Case information】

Lucy, a 28-year-old woman, is pregnant. Due to her husband's personal history of DiGeorge Syndrome (also known as 22q11 deletion syndrome), she consulted with her attending physician regarding the possibility of prenatal testing to determine if the fetus has inherited this disorder.

【Genetic Counseling】

Even with the same clinical diagnosis, a genetic condition can be caused by very different underlying genetic changes. Genetic confirmation test reports from affected family members can help not only to confirm the diagnosis in the family, but also to verify the specific disease-causing genetic change running in the family.

In this case, based on Lucy's husband's test report, the diagnosis of DiGeorge Syndrome is confirmed to be related to the common and typical 2.54 Mb chromosomal microdeletion. The fetus has a 50% risk of inheriting the same deletion and developing the condition.

Detail Information for Prenatal Genetic Testing

- **Noninvasive prenatal testing (NIPT)**

  Some NIPT tests may detect 22q11 deletion syndrome (also known as DiGeorge Syndrome) as well as other common microdeletion syndromes. However, **NIPT is primarily a screening test**, which means there is still **possibilities for false-negative and false-positive results**. If the NIPT test shows a high risk for fetal genetic abnormalities, diagnostic testing, such as amniocentesis, is still necessary for confirmation.

- **Chromosomal karyotype analysis**

  The chromosomal karyotype analysis can detect numerical chromosomal variations, such as gain or loss of a whole chromosome (for example, Down syndrome), as well as structural variations, such as gain or loss of a piece of a chromosome. **The resolution of a chromosomal karyotype analysis is approximately 5-10 Mb**. This means microdeletions below 5Mb in size, such as that of DiGeorge syndrome, cannot be detected.

- **Fluorescence *In Situ* Hybridization (FISH)**

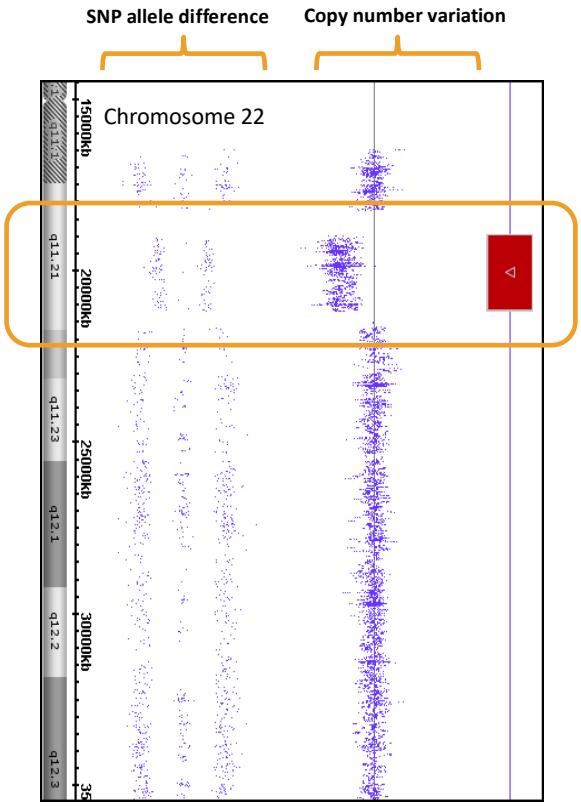
The typical 3 Mb chromosomal deletion associated with DiGeorge Syndrome can be directly screened for by using FISH technology with disease-specific probes (i.e. TUPLE1 or N25). **FISH probes are limited to the analysis of known specific diseases** and cannot simultaneously screen for other untargeted diseases on a large scale.

- **SNP microarray**

SNP microarray allows simultaneous assessment of chromosomal gains and losses of all 23 pairs of chromosomes. This means it can test for the known familial DiGeorge syndrome as well as other small segmental duplications or deletions on all the chromosomes. **A SNP microarray can also detect most abnormalities identifiable through chromosomal karyotype analyses.** Moreover, SNP microarray can further identify absence of homozygosity (AOH), which can be associated with uniparental disomy disease (UPD). UPD disorders are not detectable through karyotype analysis. **Chromosomal karyotype analysis and SNP microarray complement each other, and together reduces fetal risk for chromosomal abnormalities.**

Chromosome analysis (Karyotype)

The 22q11.2 deletion cannot be identified by routine analysis of G-banded chromosomes or other conventional cytogenetic banding techniques.



SNP microarray

The SNP array can detect not only copy number variation and also identifying absence of homozygosity (AOH).

SNP Array Additional Reading：
✓ GGA Genetic Counseling Newsletter Vol.009 Uniparental Disomy

Collection of previous GGA Genetic Counseling Newsletters

【Case Follow-Up】

Lucy eventually decided to proceed with amniocentesis for chromosomal karyotyping and SNP microarray testing. In this way, not only would the fetus be screened for the familial DiGeorge syndrome, other conditions involving large or small chromosomal structural or numerical aberrant that can occur in the absence of a positive family history can also be screened for.

The results of both karyotype and SNP microarray analysis revealed normal male chromosome complement (46,XY) without detectable pathogenic copy number changes.

What is DiGeorge Syndrome

also known as 22q11.2 Deletion Syndrome (22q11.2DS)/CATCH22 Syndrome

- **Clinical Characteristics**

  Highly variable clinical features, even within families, including: congenital heart disease, palatal abnormalities, immune deficiency, characteristic facial features, and learning difficulties…etc.

- **Prevalence**

  Around 1/3800-1/7000, known as the most frequent chromosome microdeletion syndrome. *De novo* event in more than 90% of affected individuals. About 10% of individuals inherited the condition from an affected parent.

- **Inheritance Mode**

  Autosomal dominant manner

- **Genetics**

  Also known as 22q11.2 Deletion Syndrome, characterized by a heterozygous microdeletion on the long arm of chromosome 22. **Approximately 85% of individuals with 22q11.2DS exhibit a heterozygous 3.0 (2.54)-Mb deletion.**

- **Diagnostic Methodology**

  Chromosomal microarray (CMA) or targeted deletion analysis.

- **Treatment & Management**

  Symptomatic treatment and regular follow-ups. There is currently no cure.

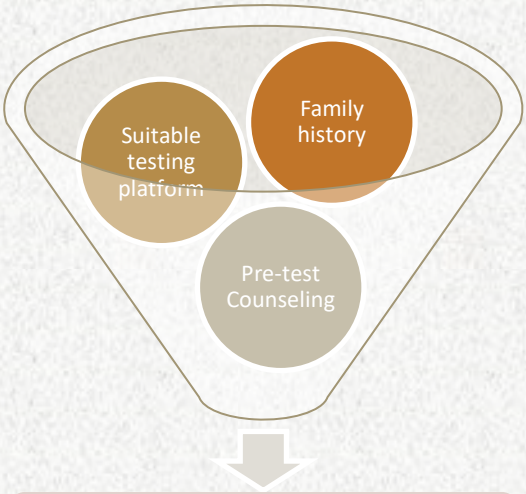
Reference: GeneReview: 22q11.2 Deletion Syndrome [Internet]. Seattle (WA): University of Washington, Seattle; 1993. 1999 Sep 23 [updated 2020 Feb 27].

Counseling Notes

- **Different genetic testing and methodology serve distinct purposes**. Each test has its own set of advantages, disadvantages, and applicable testing scopes. Detection of different pathogenic variations requires the utilization of specific genetic testing techniques.

- **Pre-test counseling is essential to gather information on family history, clarify risk to the pregnancy and formulate appropriate genetic testing strategy.** Choosing a suitable testing methodology to address specific familial variations ensures obtaining clinically relevant results. Additionally, this approach helps prevent unnecessary misdiagnoses, miscarriages, and other associated risks that may arise from inappropriate testing.

- **The genetic diagnosis report of the affected family member is crucial** for review for several reasons:
  - Confirming the diagnosis of familial genetic diseases
  - Determining the inheritance mode and fetal risk
  - Identifying the appropriate genetic testing strategy and methodology for accurate detection of family-specific pathogenic variations



Questions? Thoughts?
Your suggestions are greatly appreciated so we can further improve our newsletter!
Contact GGA Genetic Counseling Team: gcsupport@gga.asia