GGA Genetic Counseling Newsletter

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SNP Array for Prenatal Test and The Importance of Parental Follow-up SNP Array Tests

【Abstract】

In this volume we will share the internal **GGA data on SNP Array for Prenatal Test with focuses on comparisons of fetal and parental results, the importance of parental follow-up testing and how it may change provider-patient genetic counseling discussion as well as risk assessment for the fetus.**

In this current analysis:

- Nearly **7,000 results from SNP Array for Prenatal Test** were analyzed
- The **rate of abnormality within this population was 4.9%**
- About **two-thirds of the abnormal results were genetic changes that cannot be detected by routine chromosome analysis** (karyotype)

The importance of parental follow-up SNP array testing can be clearly seen when a fetus is found to carry a genetic change of unclear clinical significance. **Determination of whether a genetic change in the fetus is inherited or not can help delineate the clinical significance of this change and help reduce parental anxiety. This helps to provide more information for discussion between the providers and the patients, and prevent potential irreversible action on the pregnancy due to insufficient information.**

In this current analysis:

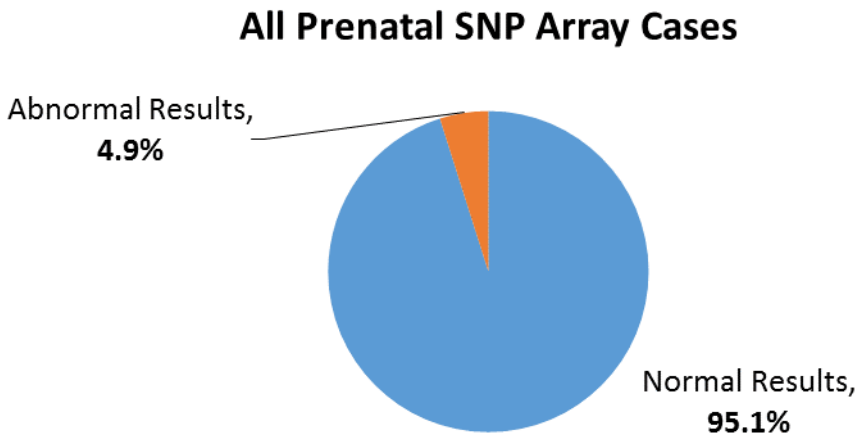
- **Parental follow-up SNP array testing was recommended for 180 fetal results**
- **Over 300 parental follow-up SNP array results were analyzed**
- In cases with known parental information, **about 80% of the fetal genetic changes identified were familial.**
- Of the hereditary cases, about **half was inherited from the mother and half from the father.**

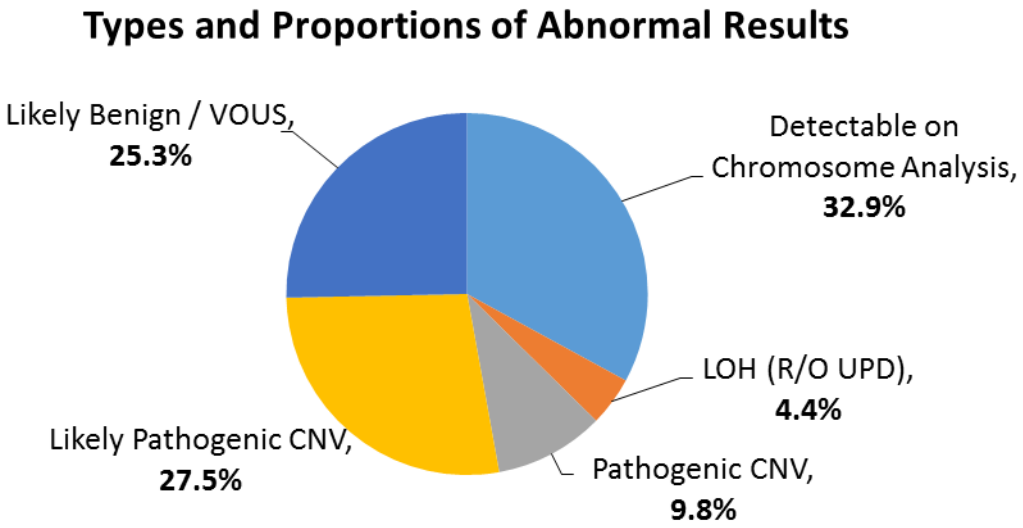
The spectrum of clinical information provided by knowledge of parental status differs based on the type and the pathogenicity nature of the genetic change identified in the fetus.

Here we present our internal findings in regards to a few commonly encountered scenarios in which parental follow-up SNP array test would be recommended. Counseling notes for each scenario are also provided.

【GGA Experience】

Of the close to 7,000 SNP Array for Prenatal Test results, the proportions of abnormal results are as follows:





About 3.3% of these prenatal samples showed copy number variations (CNV)-microduplications/microdeletions, or loss of heterozygosity (LOH)-risk for uniparental disomy (UPD) disorders. These are genetic changes not typically detectable with routine chromosome analysis. In other words, **for these patients, if SNP Array was not prenatally pursued, it is very likely that the child would not been found to have a severe genetic condition until concerning symptoms develop monthly or years after birth.** This illustrates the importance and the benefit of prenatal testing with SNP array.

Subsequent comparison with parental follow-up SNP array was recommended for 180 fetal results to better delineate the clinical significance of the fetal genetic change discovered. This can help reduce potential uncertainties regarding the fetus. This piece of knowledge also provides

medical staff and the family additional information for discussion in regards to pregnancy plans.

With the SNP array platform and GGA internal analytical standard and reporting criteria for prenatal arrays, some commonly encountered scenarios in which parental follow-up testing is recommended are as follows:

A. **Likely benign or Variant of uncertain clinical significance (VOUS) CNV:**
   - A chromosomal change in which the clinical significance is currently uncertain
   - Available literature support and evidence is limited
   - Can potentially be benign in nature

B. **Likely pathogenic CNV:**
   - A chromosomal change in which there are scientific literature and database to suggest association with abnormal clinical presentations.
   - The change has also been reported in clinically normal individuals.

C. **Loss of heterozygosity / Increased risk for uniparental disomy:**
   - A chromosomal change in which allelic genotypes reveals LOH in large chromosomal segments.
   - This can be non-pathogenic or may be related to UPD disorders with risk for clinical abnormality.

The following are individual discussions of each type of the genetic changes:

A. Likely Benign and Variant of Uncertain Clinical Significance (VOUS) CNV

In this statistical analysis, **about 1.2% of the prenatal samples underwent SNP array test showed CNV (microdeletions or microduplications) of uncertain clinical significance.** There is currently no strong scientific evidence to suggest these CNVs are associated with clinical pathogenicity. These CNVs can be likely benign in nature.

The role of parental follow-up testing:

- If **a healthy parent also carries the same genetic change as the fetus**, this would suggest the CNV may more likely be a benign **familial variation and the clinical risk to the fetus is likely lower.** This CNV can be considered as a **likely benign** change**.**
- If the **fetal genetic change is *de novo*** (not inherited from parents; a new change in the fetus), the **clinical significance of this CNV is uncertain, the clinical risk to the fetus is higher, and its impact on the future growth and development of the fetus would be difficult to predict.** This variation can be considered as a **VOUS** change**.** Genetic counseling for VOUS can be challenging given the lack of information available and the degree of unknowns. The family may need to consider their personal values and acceptance levels for risk and uncertainties.

In our data, **about 71% of these types of CNVs are inherited. Half of the cases was maternally inherited.**

This also means, **fetal *de novo* genetic changes that are of uncertain clinical significance (VOUS) only account for less than 0.5% of all prenatal samples that underwent SNP Array test.**

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Counseling Notes:

1. There is currently limited knowledge about this type of chromosomal changes. Available scientific literature and related information are limited.

2. It is important to collect blood samples for parental follow-up testing to compare with the fetal results for further risk assessment:
   - If the fetal genetic change is inherited from a healthy parent, the CNV may more likely be a benign familial variation and the risk to the fetus is likely lower. There is a 50% recurrence risk for each of the future pregnancies of that parent.
   - If the fetal genetic change is *de novo* (non-familial), the clinical significance is uncertain and the risk to the fetus is likely higher in contrast. Fetal health outcome is difficult to predict. The recurrence risk for the couple's future pregnancies is much lower.

3. Detailed prenatal ultrasound surveys can be considered to assess major structural anomalies in the fetus.

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B. Likely Pathogenic CNV

A likely pathogenic CNV means that the clinical pathogenicity of the chromosomal change is unclear. There are scientific literature and databases to suggest association with abnormal clinical presentations; however, the CNV has also been reported in clinically normal individuals.

Generally speaking, this type of genetic changes also occur in the clinically normal (healthy) population, but the rate of incidence is higher in patient populations with abnormal clinical symptoms. These **CNVs usually are associated with less than 100% clinical expression rate (incomplete penetrance), and variable expression in terms of clinical presentation and severity.** This means carriers of this type of CNV do not always manifest clinical symptoms, while the symptoms in those who do may present in different organ systems and may range from mild to severe.

In this current analysis, **about 1.3% of the samples carried this type of microdeletions/microduplications.** Of those, **74% were inherited from a parent. About 60% of the familial cases were of maternal inheritance.** However, due to the nature of its incomplete penetrance and variable expressivity, **whether the fetus will have abnormal clinical phenotypes is not definitely correlated with the inheritance pattern.**

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Counseling Notes:

1. In general, this type of genetic change:
   - Also occur in the general (clinically normal) populations, but the incidence rate is higher in patient populations (individuals with abnormal clinical phenotypes)
   - Have incomplete penetrance: less than 100% penetrance; This means that CNV carriers do not always manifest clinical symptoms
   - Have variable expressivity: clinical expression varies in affected body systems and severity between individuals, even within the same family.
   - Even if the mutation was inherited from a healthy parent, there is no guarantee that the child will be clinically normal like the parent.

2. If the CNV is inherited:
   - There is a 50% recurrence risk for each of the future pregnancies of that parent.
   - Parents may consider prenatal SNP array test in future pregnancies, or pre-implantation genetic testing with *in vitro* fertilization to assess fetal genetic status.
   - If a related family member has concerning clinical symptoms, then the CNV may be the cause of his/her condition. This gives the family member a direction in which to pursue further investigation into the cause of the symptoms, and may end the diagnostic odyssey.

3. Related family members may also need to concern his/her potential reproductive risks since he/she may also inherited the same CNV.

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C. Loss of Heterozygosity / Uniparental Disomy

Loss of heterozygosity (LOH) is a genetic change that can be detected by SNP-based testing platforms. **LOH neither indicate structural defects in the chromosomes nor any gain/loss of chromosomes or genes**. It only describes that pattern of genotypes observed. **The LOH region indicates that the allelic genotypes of a particular genomic loci of a chromosome pair are identical (homozygous) –AA or BB genotypes. There is no heterozygous genotype – AB.**

There are two mechanisms that can result in LOH:

1) **Biparental inheritance:** the chromosome pair was inherited as expected-one chromosome from the father and one from the mother. The fetus inherited identical genotypes from both parents at the same locus coincidentally. **This generally does not directly lead to clinically abnormal disorders, though the risk for recessive disorders may be increased.**

2) **Uniparental inheritance**: both chromosomes of a pair was inherited from a single parent only (meaning the two chromosomes came from either the father or the mother only), known as uniparental disomy (UPD). **Clinically, this may lead to UPD disorders and abnormal symptoms.**

When the fetal SNP array result reveal LOH of a large chromosomal segment, it is not possible to differentiate the above two mechanisms of LOH based solely on the fetal results. **An LOH result in the fetal sample must be compared with the parental SNP array results to determine whether or not the fetal LOH is associated with UPD disease and clinical abnormality.**

In this analysis, about **15 prenatal samples were found to have LOH on UPD disease-related chromosomes**. To determine if these fetuses truly are affected with UPD disorders, **we conducted comparisons with parental follow-up SNP arrays**. Fortunately, **all of the fetuses were not affected and the families were reassured.**

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Counseling Notes:

1. Loss of heterozygosity (LOH) and uniparental disomy (UPD) are not associated with copy number variations or changes in the total number of genes or chromosome. Therefore, they would not be detected by chromosome analysis or microarrays without SNP probes.

2. SNP probes can detect UPD disorders that lead to clinical abnormality.

3. LOH findings on SNP array analysis are not always associated with UPD disorders and abnormal outcomes. Follow-up comparisons with parental SNP array results are recommended to identify the pathogenic types.

4. LOH and UPD are mostly sporadic events with low recurrence risk for future pregnancies for a couple.

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Note: SNP array can only detect isodisomy UPD, but not heterodisomy UPD.

There are still much to learn in the world of genetics. Not all chromosomal changes have sufficient information to determine their clinical implication with currently available medical and scientific knowledge. **When encountering genetic changes with undetermined clinical significance, parental follow-up SNP array comparisons can help further delineate the clinical significance and the risk to the fetus.** In some cases, the results of the parental analyses not only help further assess the level of risk to the fetus, but also help understand more about individual familial characteristics and potential reproductive risks for other family members. **This information may help lower parental anxiety and concerns, allow providers and patients to have a more comprehensive counseling discussion, and potentially prevent irreversible pregnancy action made because of the lack of information.**

The accumulation of fetal SNP array data and parental results will also allow us to gain knowledge and better understand our own population-specific characteristics for the people in Taiwan. This may serve as a valuable resource for case consultations in the future.

Do you have any questions related to genetic counseling?
What topics would you like the GGA Genetic Counseling Newsletter to discuss?
Your suggestions are greatly appreciated so we can further improve our newsletter!
Email dress of the GGA Genetic Counseling Team:
gcsupport@gga.asia