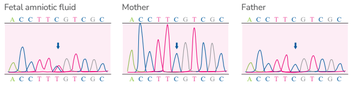
Clinical Cases

- **Ms. Zhang underwent non-invasive prenatal testing for monogenic disease at gestation age of 13 weeks$^{+5\ days}$.**

The test results showed that the SMAD4 gene c.1486C > T pathogenic mutation, which is associated with Myhre syndrome, may cause developmental retardation, intellectual disability, systemic muscle hypertrophy, limited joint motion, peculiar facial features, etc. The verification with amniotic fluid was performed by Sanger sequencing, and the results were consistent and novel mutation was found.

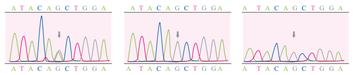
Verification Site	Specimen	Verification Result	Testing Method
SMAD4; NM_005359.5; c.1486C>T; p.Arg496Cys	Fetal amniotic fluid	Heterozygosis	Sanger sequencing
	Mother	N	NSanger sequencing
	Father	N	Sanger sequencing



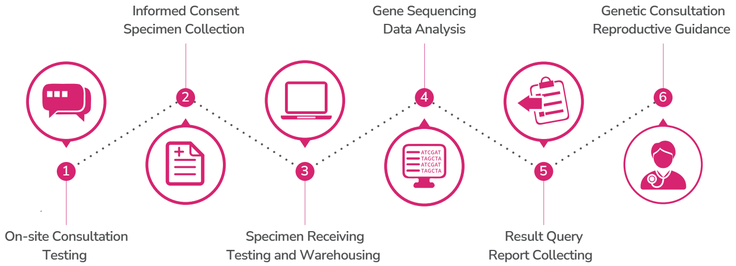
- **Ms. Han underwent non-invasive prenatal testing for monogenic disease at gestational age of 14 weeks$^{+\ 2\ days}$.**

The test results showed that RIT1 gene c.229G > A patho-genic mutation, suggesting that possibility of Noonan syndrome, which may present peculiar facial features, short stature, congenital heart defects and de velopmental retardation. The verification with amniotic fluid was performed by Sanger sequencing at gesta-tional age of 20 weeks$^{+\ 4\ days}$, and the results were consistent and novel mutation was found. Before labor induction, the fetal cardiac ultrasound found ventricular septal defect and overriding aorta.

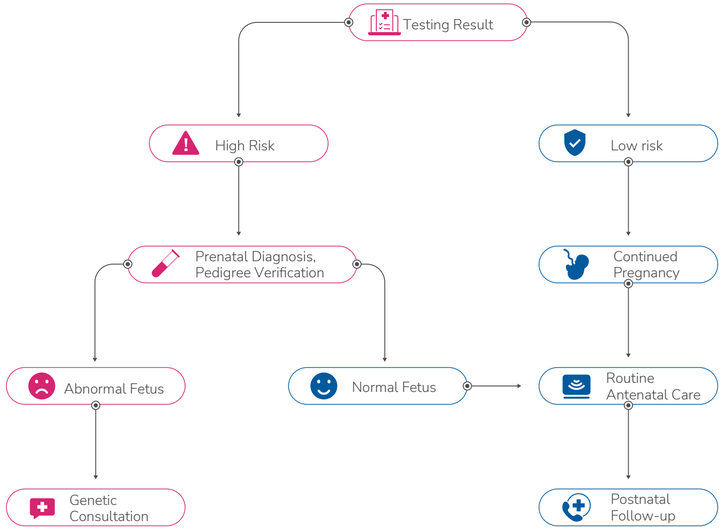
Verification Site	Specimen	Verification Result	Testing Method
RIT1; NM_006912.5; c.229G>A; p.Ala77Thr	Fetal amniotic fluid	Heterozygosis	Sanger sequencing
	Mother	N	NSanger sequencing
	Father	N	Sanger sequencing



Testing Process



Diagnosis and Treatment Recommendation



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[2] https://www.who.int/en/

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@BGI Genomics

NIFTY® mono

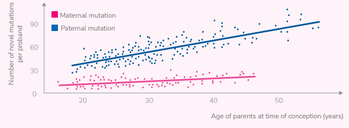
Non-Invasive Prenatal Screening for Monogenic Diseases

High Comprehensive Incidence of Dominant Monogenic Diseases

Monogenic disease refers to genetic disease caused by mutations in a single gene. Over 6,000 distinct monogenic diseases with well-defined molecular mechanisms have been identified, with a comprehensive incidence reaching as high as 1/100[1], among which dominant monogenic diseases account for more than half. A study has shown that 74% of the dominant monogenic diseases are induced by novel mutations. The incidence of monogenic diseases of such origin is about 1/270[2], which is about 3 times that of Down's syndrome.

Risk Factors of Dominant Monogenic Disease

Each offspring carries 70.3 novel mutations on average[3]. If a novel mutation occurs in a specific pathogenic domain, it can potentially lead to the development of disease. The number of novel mutations in offspring exhibits a positive correlation with parents' age, particularly the paternal age. Every one-year increase in the mother's age may result in 0.37 new mutation in the offspring, while every one-year increase in the father's age may lead to 1.51 new mutations in the offspring[3].



Necessity to Prevent and Control Dominant Monogenic Diseases through Pregnancy Screening

- Most dominant monogenic diseases are severe and may cause death, teratogenicity and disability, and most lack effective treatments
- Such diseases will place heavy burdens on families and society
- Most dominant monogenic diseases are caused by novel pathogenic mutations. The parents of such cases often have normal phenotypes and do not have familial history. Routine antenatal care may easily miss the testing due to underemphasis.
- The affected fetus does not necessarily have a phenotype in the uterus, and may show ultrasound abnormalities only in the second or the last trimester, thus missing the most effective intervention period.

If pregnant women with no familial history and monogenic phenotype can be routinely screened for common, easily emerging dominant monogenic diseases through non-invasive prenatal testing during pregnancy, the initial occurrences of such dominant monogenic diseases can be effectively reduced.

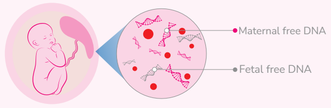
NIFTY® mono

Non-invasive prenatal screening for monogenic diseases

Technical Rationale

Fetal free DNA is present in the maternal peripheral blood, which allows the non-invasive obtaining of genomic information of the fetus by sampling the maternal peripheral blood. Combined with high-throughput sequencing and biochemical analysis, whether the fetus is abnormal can be determined.

When the effective coverage of the testing is increased to a sufficient depth, the pathogenic variants can be tested at the monogenic level.



Testing Range

Based on authoritative databases such as ClinGen, OMIM, and Medlineplus, strict screening on common and frequent dominant monogenic diseases in obstetrics and gynecology, pediatrics, and neurology, and years of clinical experience, NIFTY® Mono has been developed to evaluate the risk of 202 dominant monogenic diseases related to 155 target genes in fetuses.

97	51	36	17	1
Multi-system disorders	Skeletal system disorders	Neuromuscular system disorders	Intellectual disability and related syndromes	Immunodeficiency-associated disorder

Comprehensive incidence of target diseases can reach 1/400, including diseases that are susceptible to missed detection by ultrasound.

Disease	Symptom
Noonan syndrome	Characteristic facial features, short stature, congenital heart defects and varying degrees of developmental retardation
Neurofibroma	Characterized by skin pigmentation (Cafe au lait macules) and tumors in the skin, brain and other parts of the body
Marfan's syndrome	Variable combination of symptoms in various parts of the heart, blood vessels, eyes, and bones, with common symptoms including dislocated lens, aortic dissection, etc.
Rett's syndrome	Failure to thrive (FTT), deterioration of learning ability, loss of language ability at 6-18 months of age, and development of microcephaly, epilepsy,autism, ataxia, mental retardation and stereotyped movements, etc.
Kabuki syndrome	Involving multiple systems throughout the body, with typical features of peculiar facial features, intellectual disability, and developmental retardation,and showing congenital heart defects, genitourinary system abnormalities, etc. in some patients

Technical Advantages

10ng | **Low starting dose requirement for specimen:** Requiring only 10 ng of plasma free DNA

800× | **High sequencing depth:** Average sequencing depth to as high as 800 ×

99% | **Excellent testing performance:** Up to 99% or more in sensitivity and specificity

BGI PHOENIX | **Powerful database support:** BGI Proprietary Phoenix Database *

* Multidimensional population genotype-phenotypic genetic resource database including genetic disease knowledge base, pathogenic gene bank, mutation bank, patient phenotype bank, etc.

Product Characteristics

Early-stage testing

Testing available at 10 weeks of gestation

Safety

Requiring only 10 mL of maternal peripheral blood

Comprehensive

One-time assessment of the risk of 202 dominant monogenic diseases in the fetus

Professional

Profession testing services, databases and interpretation team

Applicable gestational age

10- 24 weeks

Applicable population

All pregnant women with singleton pregnancy who wish to reduce the risk of childbirth in monogenic disease by non-invasive prenatal testing and who do not have a family history of monogenic disease and have a normal phenotype

Contraindicated population

- Gestational age < 10 weeks
- History of transplantation, or stem cell therapy,or allogeneic blood transfusion within 1 year, or cellular immunotherapy with introduction of foreign DNA within 4 weeks, etc.
- Twin or multiple pregnancies, including twins,multiple births with arrested development or fetal reduction
- Monogenic disease patients, or those who have conceived a child with a monogenic disease or had a family history of a monogenic disease
- Other conditions that the physician believes have significant impacts on the accuracy of the results