Cytogenetics in the Human Genome Era: FISHing for a Diagnosis

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Clinical cytogenetics is the study of the particular processes that may go wrong resulting in clinically significant changes in the number or structure of chromosomes. The general clinical indications for cytogenetics studies can be seen in Figure 1.

Cytogenetic analysis by standard karyotyping has played an important role in the investigation of patients with suspected chromosome anomalies over the past 50 years. Karyotyping is able to detect clinically significant numerical or structural chromosome anomalies without necessarily having a specific diagnosis in mind. However, the test is limited to detecting only microscopically visible and hence genetically large changes in chromosomes.

Meet Stacey

- Stacey is a 26-year-old gravida 1, para 0
- A detailed prenatal ultrasound at 18.5 weeks gestation showed a fetal cardiac defect and suspected cleft palate
- There is no history of drugs, alcohol or maternal illness during this pregnancy
- Stacey's history is significant for a surgically repaired cleft palate and mild learning difficulties as a child
- Amniocentesis is performed for cytogenetic testing and a diagnosis of a chromosome abnormality, 22q11.2 Deletion syndrome, is made

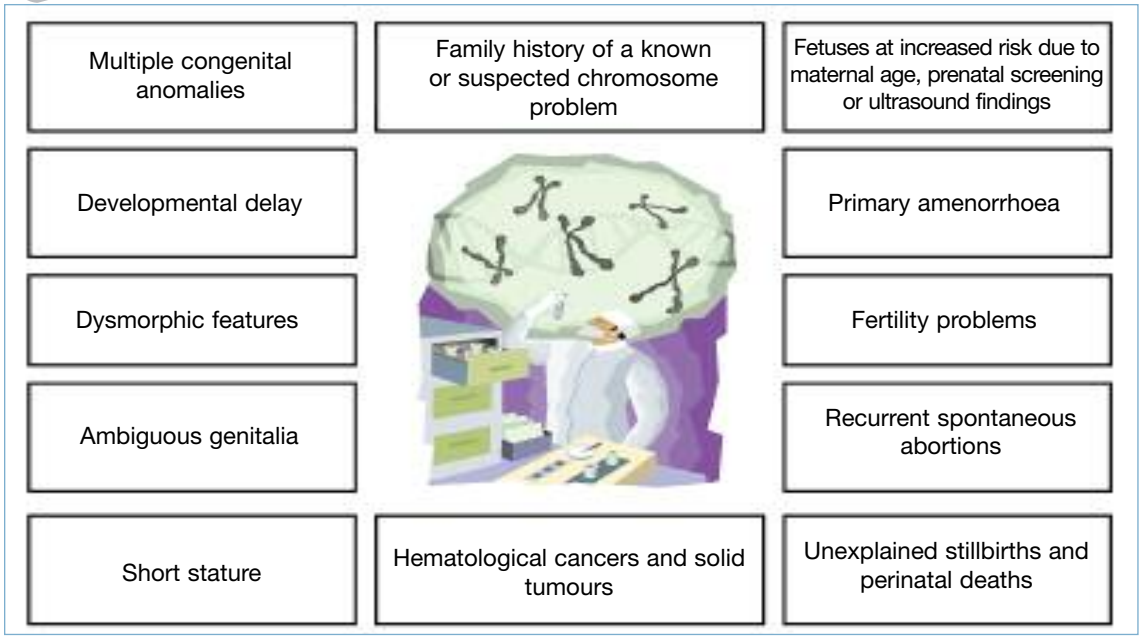

Figure 1. General clinical indications for cytogenetics studies.

Suspecting a chromosome anomaly

As a direct result of the efforts of the Human Genome Project, advances in the understanding of the etiology of genetic disorders, as well as technical developments, have led to improved diagnostic capability. One such powerful genetic diagnostic tool is fluorescent *in situ* hybridization (FISH) which overcomes the limited resolution of karyotyping and extends the ability to diagnose small chromosome imbalances. FISH testing uses small bioengineered segments of DNA (called "probes") tagged with fluorescent dyes to target specific chromosome regions which can be visualized to detect abnormalities. The identification of submicroscopic chromosome imbalances that underlie previously known clinical syndromes has led to the recognition of a new class of cytogenetic anomalies—those due to loss or gain of a set of neighbouring genes—the so-called "contiguous gene" syndromes or "microduplication" (gain)/"microdeletion" (loss) syndromes.

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Stacey's case

A diagnosis of 22q11.2 Deletion syndrome was made on a FISH study despite the fetus having a normal conventional karyotype (Figures 2 and 3). This submicroscopic deletion of the long arm of chromosome 22 (Figure 4) is the most common microdeletion syndrome with an estimated birth prevalence of one in 4,000. Like most genetic disorders, this microdeletion syndrome involves more than one body system and presents with a combination of clinical features (Tables 1 and 2). 22q11.2 Deletion syndrome is associated with a

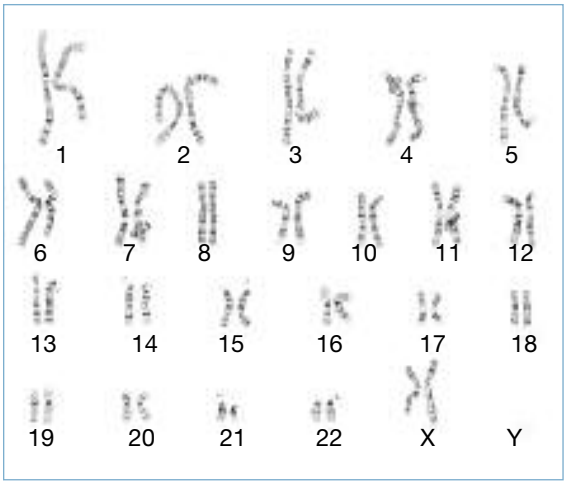

Figure 2. Normal female karyotype.

Figure 3. Fluorescent *in situ* hybridization (FISH) illustrating 22q11.2 Deletion syndrome (only one red signal is seen).

Table 1
When should a diagnosis of 22q11.2 Deletion syndrome be suspected?

Clinical feature	Frequency of 22q11.2 Deletion syndrome
Neonatal hypocalcemia	74%
Velopharyngeal insufficiency	64%
Conotruncal cardiac anomaly	7%-50%
• Interrupted aortic arch	50%-60%
• Tetralogy of fallot	11%-17%
• Any isolated congenital heart lesion	1%
Schizophrenia	0%-6%

Table 2
Clinical findings in patients with 22q11.2 Deletion syndrome

Clinical finding	Frequency of finding
Speech delay	80%
Developmental delay	75%
Immune and hematological abnormalities	75%
Congenital heart defects (typically conotruncal)	74%
Palatal anomalies (including velopharyngeal insufficiency)	69%
Hypocalcemia	50%
Schizophrenia	6%

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clinically heterogeneous group of conditions, including:

- DiGeorge syndrome
- Velocardiofacial syndrome

In light of the genetic anomaly identified in her fetus, Stacey's history of a cleft palate and school difficulties is suspicious for an inherited deletion, with a milder manifestation in Stacey. Therefore, it would be prudent to conduct cytogenetic testing with FISH on Stacey.

Follow-up on Stacey's pregnancy

Following consultation with relevant specialists, including clinical geneticists, Stacey and her partner decided to continue the pregnancy and deliver in a tertiary care facility. Their daughter, Sarah, was delivered at 38 weeks and transferred to the neonatal ICU for assessment and management. A clinical examination confirmed the presence of a cleft palate and a heart murmur. A post-natal ECHO identified a Tetralogy of fallot. Given the known diagnosis of 22q11.2 Deletion syndrome, additional investigations were performed and revealed hypocalcemia and decreased immunoglobulins with absent thymus, suggesting a clinical picture of DiGeorge syndrome. Management included irradiated,

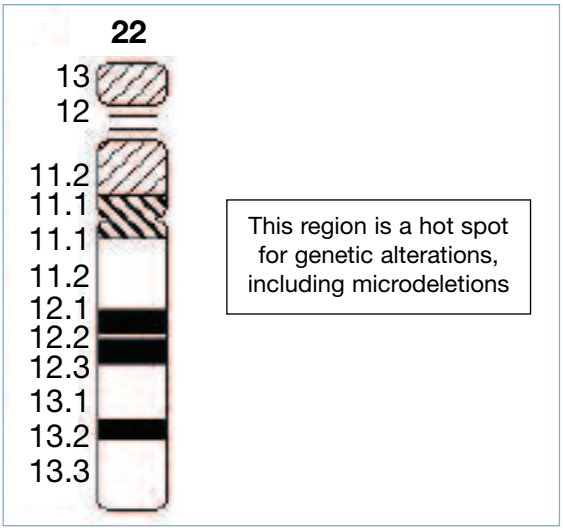

Figure 4. Deletion of chromosome 22.

cytomegalovirus-negative blood products. Referrals to appropriate pediatric sub-specialties were initiated.

This microdeletion syndrome involves more than one body system and presents with a combination of clinical features.

Stacey's test results confirmed that she also has 22q11.2 Deletion syndrome, which would explain her cleft palate and history of learning difficulties. Stacey was referred to a clinical geneticist for a discussion of anticipatory care pertaining to her diagnosis and future reproductive planning. The key issues discussed were:

1. Clinical or phenotypic variability seen in 22q11.2 Deletion syndrome, even within the same family
2. The 50% recurrence risk in Stacey's future offspring since she carries the deletion. If Stacey had not had the deletion, her recurrence risk would have been very low (< 1%)

Take-home message

1. Although chromosome disorders are individually rare, collectively they are a common cause of:
   - mental retardation,
   - birth defects,
   - infertility and
   - cancer
2. Karyotyping and FISH are useful diagnostic tools for suspected cytogenetic conditions
3. If you suspect a genetic condition, consider referral to a clinical geneticist
4. The medical care of patients diagnosed with 22q11.2 Deletion syndrome, like many genetic conditions, requires a multidisciplinary approach with management aimed at treating the clinical features and preventing secondary complications. As a result, establishing a correct diagnosis in a timely fashion is important in the management of the patient

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Resources
1. Donna M McDonald-McGinn, Beverly S Emanuel, Elaine H Zackai. Gene reviews: 22q11.2 Deletion Syndrome. http://geneclinics.org/servlet/access?db=geneclinics&site=gt&id=8888891&key=zvLqNShDjKYCr&gry=&fcn=y&fw=3sD0&filename=/profiles/22q11deletion/index.html. December 2005.
2. Kobrynski LJ, Sullivan KE: Velocardiofacial Syndrome, DiGeorge Syndrome: The Chromosome 22q11.2 Deletion Syndromes. Lancet 2007; 370(9596):1443-52.