CHROMOSOMAL ABNORMALITIES

Introduction

Visible changes to chromosome structure and morphology have played a very important part as indicators of genetic damage in both clinical and cancer studies.

Most of the changes encountered in clinical studies are "secondary" or "derived" aberrations. This is true also in cancer studies, except that here, there is an ongoing production of aberrations, so that in some cells, a mixture of primary and secondary changes is present, and a continuously changing karyotype (true chromosomal instability).

To appreciate these observed secondary changes we need to understand the primary changes from which they are derived, and it is the purpose of this article to provide a brief introduction to them.

Observation

Primary aberrations are those seen at the first post-induction division, when all the parts are present and there has been no selection by passage through mitosis, nor any modification by subsequent chromosome duplication (Savage, 1976).

Most commonly, observation is made at metaphase, using "solid-staining" with dyes which give high-contrast chromatin staining and negligible cytoplasmic coloration. For more critical work, the chromosomes are banded in various ways, which allows chromosome identification, detection of some forms invisible with solid-staining, and offers more precise positioning of the lesion interaction points (Savage, 1977).

Recently, resolution and classification of transmissible forms has been considerably improved by the introduction of fluoresence *in situ* hybridisation (FISH) chromosome "painting" (Lucas et al., 1992; Savage and Tucker, 1996; Tucker et al., 1995) .

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Classification of Primary changes

For purely pragmatic and diagrammatic purposes, we can regard the chromosomal changes we see down the microscope as being the result of "breaks" followed by "re-joins" of the chromosome thread. However, we must always remember that, in reality, their origin is much more complicated (Savage, 1998; Savage and Harvey, 1994).

RECIPROCAL TRANSLOCATION :

Involves no mechanical separation problems at anaphase, and usually no genetic loss or imbalance. Problems can occur at meiosis because of multivalent formation, and degrees of sterility may arise.

At the molecular level, the re-joining points can disrupt important genetic sequences, leading to inactivation, mutation or position effects .

Derived directly from *chromosome-type* reciprocal translocations or from one segregation sequence of symmetrical *chromatid-type* interchanges. (Note that the alternative interchange segregation leads to imbalance and cell lethality).

PERICENTRIC INVERSION :

Very similar properties to those for reciprocal translocations given above. Large inversions lead to meiotic bridges, sterility and cell death.

Derived directly from *chromosome-type* or *chromatid-type* pericentric inversions.

PARACENTRIC INVERSION :

Very difficult to detect at the chromosome level unless they are very large (many megabases of DNA). Again the re-joining points can disrupt important genetic sequences, and reverse segments of the reading frame. Large inversions will give problems at meiosis.

Derived directly from *chromosome-type* paracentric inversions, or from one form of *chromatid-type* intra-chromatid intra-arm intrachange (Revell-type 3 (Revell, 1959; Savage, 1976; Savage, 1989).

INTERSTITIAL DELETION :

The loss of small segments of a chromosome (usually in only one homologue) is not uncommon. Many mutations that have been genetically sequenced have been shown to be actually small deletions.

Very occasionally, the loss of quite large segments appears to be compatible with cell survival.

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Derived directly from *chromosome-type* interstitial deletions ("double minutes") and from the alternative form of *chromatid-type* intra-chromatid intra-arm intrachange (Revell-type 2 (Revell, 1959; Savage, 1976; Savage, 1989)) to that which produces paracentric inversions. Segregation products from some complex *chromatid-type* interchanges can also carry deletions.

TERMINAL DELETION :

It is now questionable whether true stable terminal deletions actually exist. All those that have been investigated using the new fluorescent telomere probes are found to be "capped" by telomere sequences. This either means that they are disguised interstitial deletions, where one re-join point was almost terminal, or that survival has been rendered possible by *de novo* telomere synthesis. The recent development of end-specific telomere probes should be able to solve this question (Boei and Natarajan, 1998; Boei et al., 1998).

Derivation, if genuine, from various forms of incomplete *chromosome-type* or *chromatid-type* intrachanges and interchanges, followed by telomerase activity to achieve capping.

INTERSTITIAL DUPLICATION :

Segments of a chromosome repeated in tandem, sometimes in reverse sequence. This may not necessarily arise from a pre-existing structural aberration ; segment amplification and re-duplication is a well attested phenomenon under certain conditions (e.g. HSR regions following chronic methotrexate exposure). Nevertheless, there are primary aberrations which can survive as segmental duplication.

Most likely derived from one form *chromatid-type* inter-chromatid intra-arm intrachange (Revell-type 1 (Revell, 1959; Savage, 1976; Savage, 1989)). Some forms of complex *chromatid-type* interchanges can segregate to give surviving chromosomes with duplicated segments.

INTERSTITIAL INSERTION :

Deletion of a segment and its insertion into another chromosome within the same cell is a fairly common transmitted aberration. Much less common is the insertion of a segment additional to the two complete homologues within a cell.

All insertions are derived from complex exchanges, since, by definition, their production requires the interaction of a minimum of 3 lesions. Either *chromosome-type* or *chromatid-type* complex interchanges may be involved, the range of inter-intrachanges in the latter being particularly productive of insertions.

Occasionally, a surviving dicentric may be found, usually without the related acentric fragment. Very often, the two centromeres lie very close together, because, under these circumstances, only one of the centromeres is active, so anaphase bridges do not form. Likewise, an occasional centric-ring may survive, again usually very small so that "fall-free" separation always happens. Larger rings are very unstable with respect to size, and the positive selection pressure towards very small rings soon eliminates the big ones.

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Most of the above comments apply to the situation in normal individuals and cells. When we turn to cancer-derived cells, or to transformed cell lines growing in culture, the situation is somewhat different. These cells are inherently chromosomally unstable. There is a continuous production of structural change so that new primary changes are superimposed on the already existing background of secondary aberrations, and these new ones, in their turn, become secondary.

Moreover, some of the new changes are being produced in already abnormal chromosomes, so the observed aberrations are often very complicated and bizarre.

On top of this, it is clear that most cancer cells are very tolerant of chromosomal loss, or gain, as is evidenced by considerable numerical variations and multiple chromosome copies. These facts make cancer cytogenetics a very difficult and uncertain field for investigation, and considerable credit goes to those workers whose careful and painstaking efforts have produced meaningful advances.

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Risk Factors for Chromosome Abnormalities

Changes in chromosome numbers are random events during cell division, and as a result, most chromosome abnormalities can't be inherited. There are some factors that put a mother at risk for delivering a baby with a chromosome abnormality. Your genetic counselor or healthcare provider will be able to tell you more about your specific risk factors.

In general, older mothers have a higher chance of having a baby with a chromosomal condition. This is because her eggs are the same age as she is, and chromosome errors are more likely to result from the aging process. The risk is greatest for women who are 35 years or older. Mothers who have had previous pregnancies affected by chromosome abnormalities also have a higher chance of having their current or future pregnancy affected.

Family history plays a role in chromosome abnormalities as well. If you, your partner, or someone in either of your families has a chromosome condition, your baby could have a higher chance of developing one as they develop. A genetic counselor is trained in which conditions run in families and can help you understand your risk.

Testing Options

There is no treatment for genetic abnormalities. There is, however, a lot of value in getting testing done to learn about your baby's potential risk for chromosome abnormalities. Knowledge can do a lot for a family, and perinatologists and other high-risk pregnancy experts like the ones at Valley have a variety of ways to keep parents informed about what could lead to health problems.

Genetic Counseling

Counseling is a good first step for a young family to take prior to any further testing. A genetic counselor will help you figure out what anomalies your baby might be at risk for based on factors in your family and will be able to help make information about those anomalies clear to you. They are experts in inheritance patterns and other risk factors that could lead to early detection and even treatment of some problems. When combined with other testing, this counseling could give a mother-to-be peace of mind.

Amniocentesis

If you have a high-risk for genetic disorders, whether because of a family history, a previous child born with a chromosomal anomaly, age, or abnormal ultrasound results, you might opt to get an amniocentesis test. This test takes a small amount of amniotic fluid from the sac surrounding your baby in the womb, and this fluid gets sent to a lab for analysis. The fluid contains fetal cells that can be tested for birth defects connected to chromosomal abnormalities, such as Down syndrome, or neural tube defects.

Chorionic Villus Sampling

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Chorionic Villus Sampling is another test that collects samples of genetic material around your baby for lab testing. The difference is where this material comes from. This test takes cells from the placenta where it's attached to the uterine wall, either through the cervix or abdominal wall. These cells, called chorionic villi, are placental tissue that share the fetus' genetic makeup, which helps to detect chromosome abnormalities.

Genetic Testing and Perinatal Care at Valley

Every mother worries about how healthy her baby will be during her pregnancy and delivery. Mothers in high-risk pregnancy situations are no exception, and it's so important to know as much as possible about your baby's health. For Phoenix-area mothers-to-be and their pregnancy care teams, Valley has the resources and specialized training to provide peace of mind and more information about potential chromosomal abnormalities. Whether a mother is seeking genetic counseling, prenatal screening, or diagnostic tests for chromosome abnormalities, Valley's team can help her care team make informed choices about her baby's health as well as hers. Talk with your Ob/Gyn about co-managing your pregnancy with Valley.

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Types of Chromosome Abnormalities

Abnormalities that affect the number or structure of chromosomes come in many forms. Some abnormalities happen during the combining of sex cells that make up a baby or during the division of cells as they grow.

- **Monosomy:** A chromosome is missing
- **Trisomy:** There is an extra chromosome
- **Deletion:** Part of a chromosome is missing
- **Duplication:** Part of a chromosome was duplicated
- **Translocation:** A portion of one chromosome is transferred to another chromosome
- **Inversion:** Part of a chromosome was broken off, turned around, and reattached
- **Ring:** A chromosome was broken off and formed a circle or ring instead of a strand
- **Mosaicism:** Two or more sets of chromosomes with different genetic material exist

REFERENCES

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