Preliminary Research Study Results on Mosaic Down Syndrome

by

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Down syndrome, which is the most common "chromosomal" finding seen in individuals, occurs at a frequency of about 1 in 800 live births. To briefly review, chromosomes are threadlike packages of heritable material located within the central compartment (nucleus) of an individual's cells. Approximately 90%-95% of individuals with Down syndrome have "trisomy 21", which means they have 3 copies of chromosome 21 in all of their cells. In 2%-4% of individuals having Down syndrome, there is a "translocation" (rearrangement) that involves a third copy of chromosome 21 with another chromosome. Another 2-4% of individuals with Down syndrome have mosaicism. In the case of mosaic Down Syndrome (MDS), most individuals with mosaicism have two types of cells: (1) cells that have 3 copies of chromosome 21 (for a total of 47 chromosomes); and (2) cells that have 2 copies of chromosomes 21 (for a total of 46 chromosomes, which is the typical number seen in humans).

Geneticists in Dr. Jackson-Cook's laboratory in the Department of Human Genetics and Pathology at the Medical College of Virginia Campus of Virginia Commonwealth University have been conducting research on the causes of Down syndrome for over 25 years. Our current studies on Down syndrome are focused on answering the following questions: (1) Does the percentage of trisomic cells vary between different tissues in the body and is one tissue a better predictor of health concerns than another? (2) Does the

chromosomal sorting problem(s) leading to mosaicism arise through mechanisms that are similar to those causing trisomy 21? (3) Is there a difference in the health concerns present in a person with mosaicism as a result of the gene patterns that are present following the chromosomal sorting error? (4) Are there specific patterns of imbalances of gene products that can be recognized in people having mosaicism for Down syndrome and can any of these imbalance patterns be correlated with the presence of specific health/developmental concerns? Through the generosity of many people with mosaicism for Down syndrome (a total of 101 individuals, to date), and their family members, we are beginning to get answers to several of these questions. The preliminary results for some of these studies are summarized below.

Since it has been suggested that the percentage of mosaicism can vary between cells that are located in different parts of an individual's body (question 1 above), in our study we use a technique called fluorescent in situ hybridization (FISH) to estimate the percentage of cells with trisomy 21 in three different types of samples (see figure at end of article). The types of samples we are looking at include:

1. Cultured Blood- This is the standard technique used in diagnostic tests for detecting chromosomal findings.

2. Uncultured Blood- This is a new technique that our laboratory is developing as a potentially improved test for estimating the percentage of mosaicism.

3. Buccal Smear (cheek rubbing)- This is another new test that we developed as a less invasive (compared to a skin biopsy) means for studying skin-type cells and estimating the percentage of mosaicism in those cells.

Based on our current results, there does appear to be a difference in the percentage of cells having trisomy 21 between buccal and blood samples. In particular, there is a trend toward higher levels of trisomy 21 being present in the buccal samples in comparison to the blood samples. Furthermore, it appears that a single sample is not a better predictor for health and developmental progress. Instead, it appears that studying both types of cells provides the best ability to predict the presence of findings that are associated with Down syndrome. For example, during an embryo's development the cells that will ultimately form blood and heart cells originate from a group of cells that is called the mesoderm. Our studies have shown that the presence or absence of heart problems is more closely correlated with the proportion of trisomic cells present in the blood compared to the cheeks (or skin), the latter of which originates from a different type of cell group (called ectoderm) during the embryo's development. We are continuing these types of studies using new statistical methods to determine if there are other traits associated with Down syndrome that might be predicted best from an assessment of blood compared to cheek cells. One problem we have encountered in completing these analyses is a lack of complete health and developmental information that is available for all individuals having mosaicism. Therefore, to gain as much information as possible from this investigation, we may need to contact some of the study participants in the very near future to gather more data. We greatly appreciate your cooperation with this follow-up aspect of our study.

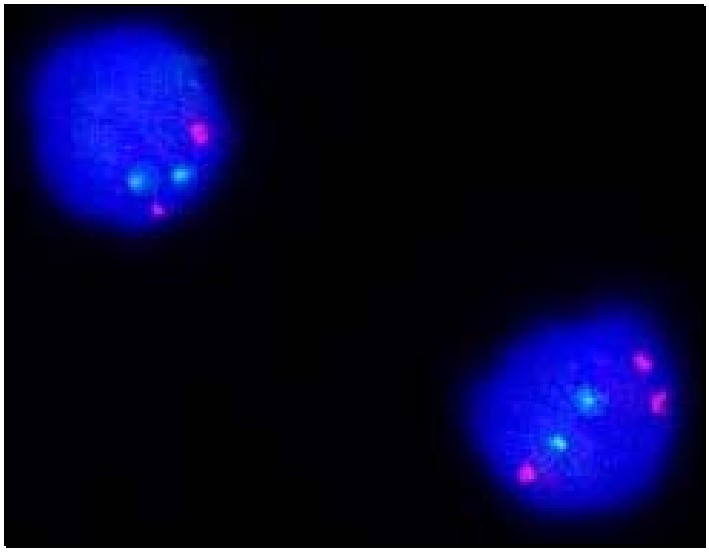
Through our studies assessing the percentage of trisomic cells in tissues, we also noticed a trend toward a decrease in the level of trisomic blood cells noted at the time of diagnosis compared to the time of our research study (which may be months or several years later). Other researchers have reported similar findings in individuals with non-mosaic trisomy 21 as they age. This phenomenon has not yet been shown to be associated with any change in physical or clinical findings. However, in other ongoing studies in our lab (which are funded by the National Institute of Health), we have shown that all people tend to lose chromosomes as they age and that this tendency for loss is related to the length of the structures located at the ends of the chromosomes (the structures are called telomeres). To further investigate the observation of a decrease in trisomic cells with age in people having mosaicism we plan to do additional studies to see if this phenomenon might be associated with the length of their chromosomes' telomeres and if this information can be used to better understand age-related findings (such as Alzheimer-like dementia) in people who have mosaicism. We will study this by determining if there is a difference in the length of the ends of the chromosomes in cells having 2 chromosomes 21 compared to the telomere lengths in cells having three chromosomes 21 and by comparing this information to health-related data.

The data gathered to answer the question regarding the types of chromosomal sorting problems giving rise to an individual with mosaicism suggests that these chromosomal sorting problems are very similar to those that give rise to a person with full trisomy 21. This observation suggests that the recurrence risk for a couple having a child with mosaicism may be very similar to the risks for couples having a child with full trisomy 21

(which is approximately a 1% recurrence risk). We are in the process of evaluating possible correlations between health/developmental outcome and the gene patterns that are present following the chromosomal sorting problems. However, as noted above, we need help in completing our records to enable us to gain as much insight as possible for this portion of the study.

We are also in the process of gathering data to look at the imbalances of gene products that can be recognized in people with Down syndrome and hope to have data completed for this aspect of our study within the next six months.

We anticipate completing several phases of our research study over the next couple of months. As these facets of the project are finished, each participating family will receive a letter describing their specific family's results. We will use the overall information gained from the study of all families to write papers for scientists, physicians, and health care providers of people having mosaic Down syndrome. As those papers are published, we will forward copies to the IMDSA for placement on the website (if desired). Lastly, we sincerely thank all the families who have participated in our study throughout the years.



Cells from an individual with MDS following FISH. This picture shows cells that are evaluated for chromosome 21 (red signals) and for chromosome 13 (green signals). Chromosome 13 is evaluated alongside chromosome 21 as a control measurement for our experiment. The cell on the upper left hand corner has 2 copies of chromosome 21 (2 red signals) and 2 copies of chromosome 13 (2 green signals), while the cell on the lower right hand corner has 3 copies of chromosome 21 (3 red signals) and 2 copies of chromosome 13 (2 green signals).