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Mosaicism for Trisomy 21: A Review

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The clinical and cytogenetic findings associated with mosaicism for trisomy 21/Down syndrome are the focus of this review. The primary topics discussed in this overview of the extant literature include the history of this condition and its diagnosis, the incidence of mosaicism, the meiotic and/or mitotic chromosomal malsegregation events resulting in mosaicism, the observation of mosaicism in the parents of children with the non-mosaic form of Down syndrome, and the variation in phenotypic outcome for both constitutional and acquired traits present in people with mosaicism for trisomy 21/Down syndrome, including cognition, fertility, and overall phenotypic findings. Additional topics reviewed include the social conditions of people with mosaicism, as well as age-related and epigenetic alterations observed in people with mosaicism for trisomy 21/Down syndrome. © 2014 Wiley Periodicals, Inc.

Key words: mosaic Down syndrome; mosaicism for trisomy 21; mosaic; mosaicism; Down syndrome; trisomy 21

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INTRODUCTION AND HISTORY OF DOWN SYNDROME

The earliest documented images of individuals having physical traits consistent with Down syndrome are in artifacts recovered from the Tolteca culture in Mexico (500 AD) and in European Renaissance paintings (dating from the 14–17th centuries) [Berg and Korossy, 2001; Martinez-Frias, 2005]. However, this condition was not described as a clinical entity until 1866, when John Langdon Down noted its association with developmental delay [Down, 1866]. Interestingly, 20 years earlier [1846], Seguin presented a report of a girl with traits typical of those associated with Down syndrome, but failed to describe the condition as a clinical entity that was distinct from cretinism [Tolksdorf and Wiedemann, 1981]. As a result, this condition was named solely for Dr. Down. Nearly 100 years after the first clinical description of Down syndrome, Lejeune et al. [1959] studied the chromosomes of three males with this entity and discovered an extra chromosome 21 in each of these individual's cells. Jacobs et al. [1959] and Böök et al. [1959] soon confirmed the chromosomal etiology of this condition by studying additional individuals with Down syndrome. The identification and confirmation of three chromosomes 21 in individuals with Down syndrome led to this condition also being known as "trisomy 21."

Down syndrome (OMIM 190685) is the most common chromosomal finding seen in liveborns, occurring at a frequency of 1/700–1/800 live births [Sherman et al., 2007]. Early studies to determine the chromosomal complement(s) present in people with Down syndrome showed that the majority of these individuals (90–95%) had trisomy for chromosome 21 in all of their cells, approximately 2–4% of individuals with Down syndrome had translocations involving chromosome 21, and approximately 2–4% of people with Down syndrome had mosaicism [Hamerton et al., 1965; Richards, 1969; Mikkelsen, 1977; Hook, 1981; Devlin and Morrison, 2004a; Shin et al., 2010]. This review will focus on this latter group of people who have mosaicism for trisomy 21/Down syndrome.

DEFINITION AND HISTORY OF MOSAICISM FOR TRISOMY 21/DOWN SYNDROME

Mosaicism is a condition in which an individual has two or more genetically distinct cell lines that originated from a single zygote [Nussbaum et al., 2001]. In the case of mosaicism for trisomy 21, individuals have both trisomic and euploid cell lines. Mosaicism for trisomy 21 was first reported in 1961 by Clarke et al., who described an 11-month-old female who had good muscle tone, no congenital heart defects and a normal development of milestones (Supple-

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mental Table SI in supporting information online). However, several of her facial characteristics, such as upslanting eyes, a flat nasal bridge, and short fingers, could not be attributed to familial resemblance and thus raised the suspicion of Down syndrome. A cytogenetic analysis (pre-banding) of a peripheral blood specimen from this patient revealed a normal female karyotype, but additional studies that were completed on skin cells revealed the presence of mosaicism (47,XX,+G/46,XX) in each of the two independently established cultures.

That same year, Fitzgerald and Lycette [1961] also reported on a 51-year-old male who was clinically diagnosed with Down syndrome at birth, but upon cytogenetic analysis was noted to have three distinct cell lines (Supplemental Table SI), thereby providing evidence that mosaicism in humans was not limited to the existence of only two cell lines, which is an observation that was later confirmed by several other investigators [Gustavson and Ek, 1961; Nichols et al., 1962; Valencia et al., 1963; Lord et al., 1964; Mauer and Noe, 1964; Tonomura and Kurita, 1964; Tsuboi et al., 1968]. After these initial reports, more complex states of mosaicism, including cases of double aneuploidy and structural alterations involving chromosome 21, have been described (Supplemental Table SI) [Edgren et al., 1966; Richards, 1969; Wilson et al., 1974; Mikkelson, 1976; Smith and Berg, 1976; Suleulski et al., 1980; Harada et al., 1998].

FREQUENCY OF MOSAICISM FOR TRISOMY 21/ DOWN SYNDROME

Based on the results of pioneering and more recent studies, the frequency of mosaicism for trisomy 21/Down syndrome has been estimated to range from 1 in 16,670 to 1 in 41,670 conceptuses/ livebirths (or approximately 1.3–5% of all people having some form of Down syndrome) [Jackson-Cook, 2011 and Table I]. Given that the phenotypic appearance of individuals with low level mosaicism is often subtle, leading to a lack of recognition of the condition based on a physical examination, investigators have completed studies to determine the proportion of individuals with mosaicism who were identified through different means of ascertainment. In their population study, Devlin and Morrison [2004b] noted that only 37.5% of individuals with mosaicism were detected by clinical examination, compared to nearly 100% of people having non-mosaic Down syndrome. Similarly, prenatally ascertained fetuses with mosaicism showed a significantly lower frequency of ultrasound aberrations and screening test anomalies when compared to fetuses with non-mosaic trisomy 21 [Bornstein et al., 2009]. Thus, it is possible that low-level mosaicism may be unrecognized and under diagnosed, resulting in a biased ascertainment of only a subset of individuals having mosaicism for trisomy 21 [Gibson, 1973].

LABORATORY METHODS USED FOR THE DETECTION OF MOSAICISM

In addition to clinical challenges in recognizing individuals having mosaicism, diagnostic testing challenges are also present, with conventional cytogenetic technologies being limited in their ability to detect cases with low percentages of trisomic cells. In a conventional metaphase chromosomal analysis, the presence of two or more cells having the same trisomic imbalance is indicative of mosaicism (this definition of a clone is also often applied as the definition for a mosaic cell line) [ISCN, 2013]. Practice guidelines established by the American College of Medical Genetics [2010] state that a minimum of 30 metaphase spreads should be evaluated to rule out mosaicism involving sex chromosomes unless the mosaicism is detected in the analysis of the initial 20 metaphase spreads (section E5.1.2.2). This same approach is also often applied to the assessment of autosomal aneuploidy, with many centers scoring at least 30 metaphase spreads to evaluate patients suspected to have mosaicism for trisomy 21. However, an evaluation of 30 metaphase spreads will only allow for the exclusion of mosaicism that might be present in 8–15% of cells with 0.90–0.99% confidence, respectively [Hook et al., 1977]. Thus, to enhance their ability to detect mosaicism, many laboratory directors evaluate hundreds of interphase nuclei using fluorescence in situ hybridization (FISH) methodology. The specific number of interphase nuclei scored may vary between laboratories based on their established cut-off levels (which reflect the sensitivity/specificity of the probe(s) used by the laboratory). As a general guide, mosaicism present in as few as 5% of cells can be detected with 99% power by scoring 282 nuclei (if one uses a probe having 99% sensitivity) [Dewald et al., 1998]. In addition to FISH, microarray methodology has also been shown to be useful for detecting mosaicism [Biesecker and Spinner, 2013], with our laboratory (unpublished data) and other investigators [Conlin et al., 2010; Rodriguez-Santiago et al., 2010] detecting cell lines present in less than 5% of cells based on the results of microarray studies.

In addition to using multiple assays for assessing mosaicism, one may also consider evaluating more than one tissue to diagnose mosaicism, with blood and buccal mucosa cells being tissues that are most frequently evaluated as they can be collected in a non-invasive manner [Papavassiliou et al., 2009]. Regardless of the tissue or methodology used, laboratory protocols developed to evaluate mosaicism should include criteria to allow for the detection of a small number of cells having a trisomic imbalance against a predominantly euploid chromosomal complement, as well as the ability to detect a low proportion of euploid cells against a predominantly trisomic complement. In our research studies of people with mosaicism, we quantify the proportion of trisomic cells using an interphase FISH analysis of both peripheral blood (1000 cells scored) and buccal mucosa (500 cells scored) nuclei. Based on a statistical probability cutoff value of 0.05, our evaluation of 500–1000 interphase nuclei (using a probe that demonstrates a 0.99 analytic sensitivity level) allows for the detection of a mosaic cell line that might be present in as low as 1.6–1.8% of cells, respectively [Dewald et al., 1998].

MOSAICISM IN PHENOTYPICALLY NORMAL PARENTS OF CHILDREN WITH NON-MOSAIC TRISOMY 21

It has been postulated that when a large number of cells are studied, using fluorescent in situ hybridization (FISH) methodologies, trisomy 21 mosaicism may be surprisingly more common than anticipated in the general population [Hultén et al., 2010]. Evidence supporting this conjecture comes from observations of parental

TABLE I. Estimates of the Frequency of Mosaicism in People Diagnosed With Down Syndrome

Author	% Mosaic	Population	Total # studied	Diagnosis
Mikkelsen et al. [1976]	2.3	Copenhagen, Denmark	235	Postnatal
Mulcahy [1979]	1.0	Western Australia	235	Postnatal
Koulischer and Gillerot [1980]	0.4	Wallonia, South Belgium	268	Postnatal
Iselius and Lindsten [1986]	1.7	Sweden	1,986	Pre-or-Postnatal
Owens et al. [1983]	1.7	Liverpool, UK	175	Postnatal
Li et al. [1988]	6.4	Taiwan, China	63	Postnatal
English et al. [1989]	1.5	Northumberland, UK	65	Postnatal
Stoll et al. [1990]	2.8	France	137	Pre-or-Postnatal
Verma et al. [1990]	0.7	Libya	150	Postnatal
Niazi et al. [1995]	0.0	Saudi Arabia	37	Postnatal
Christianson [1996]	1.6	Sub-Saharan Africa	448	Postnatal
Hook et al. [1999]	4.0	NY, US	10,718	Pre-or-Postnatal
Modi, et al. [2003]	33.0	India	70	Pre-or-Postnatal
Mokhtar et al. [2003]	0.7	Alexandria, Egypt	673	Postnatal
Devlin and Morrison, [2004a]	3.85	Northern Ireland, UK	208	Postnatal
Ahmed et al. [2005]	0.7	Pakistan	295	Postnatal
Rasmussen et al. [2006]	2.3	Atlanta, GA, US	692	Unspecified
Reimand et al. [2006]	2.9	Estonia	239	Pre-or-Postnatal
Azman et al. [2007]	4.7	Malaysia	149	Postnatal
Murthy et al. [2007]	0.7	Dubai, UAE	141	Postnatal
Sheth et al. [2007]	3.9	Gujarat, India	382	Postnatal
Zheng et al. [2009]	5.4	Nanning, China	130	Postnatal
Jaouad et al. [2010]	0.6	Morocco	852	Postnatal
Mandava et al. [2010]	1.8	Mumbai, India	1,572	Postnatal
Shin et al. [2010]	1.9	US	6,300	Unspecified
Wang et al. [2010]	3.5	Hainan, China	86	Postnatal
El-Gilany et al. [2011]	0.8	Mansoura, Egypt	712	Postnatal
Morris et al. [2012]	1.0	England and Wales, UK	29,256	Pre-or-Postnatal
Rankin et al. [2012]	2.1	North of England, UK	1,115	Pre-or-Postnatal
Zhu et al. [2012]	3.2	Denmark	3,530	Pre-or-Postnatal
Kolgeci et al. [2013]	0.98	Kosovo	305	Postnatal

mosaicism (maternal or paternal) as a cause for recurrence of offspring having non-mosaic trisomy 21 in a number of kindreds detected postnatally or prenatally (Table II). As expected, these families having low level parental mosaicism did not show advanced maternal age [Blank et al., 1962; Smith et al., 1962; Blank et al., 1963; Weinstein and Warkany, 1963; Verressen et al., 1964; Warkany et al., 1964; Richards, 1970; Timson et al., 1971; Richards, 1974; Frias et al., 2002].

INFERENCES REGARDING THE MEIOTIC AND/OR MITOTIC NONDISJUNCTIONAL ERROR(S) LEADING TO MOSAICISM FOR TRISOMY 21

One of the first discussions of the meiotic and mitotic origin of the extra chromosome 21 in people with mosaicism was provided by Fitzgerald and Lycette [1961]; who speculated that, for their patient who had multiple cell lines, the zygote was initially trisomic and that a nondisjunctional event in the second or later cleavage divisions resulted in the cell lines having 46 and 48 chromosomes. This theory was later espoused by a number of other investigators attempting to understand the embryonic genesis of mosaic chromosomal patterns [Lindsten et al., 1962; Nichols et al., 1962; Richards and Stewart, 1962]. The development of molecular and cytogenetic methodologies has since provided a means for testing the hypotheses of these early investigators. However, while the parental and meiotic origin of non-mosaic trisomy 21 has been assessed by multiple investigators [reviewed by Sherman et al., 2005; Warren and Gorringe, 2006; Hassold and Hunt, 2012], few scientists have studied the parental origin of the chromosomes 21 in the trisomic and euploid cells from individuals with mosaicism. Niikawa and Kajii [1984] completed the first study of the parental origin of the chromosomes 21 in people with mosaicism. Using morphological chromosomal heteromorphisms localized to the short arms of the chromosomes 21, these investigators found that 4 of the 4 (100%) individuals they studied had initial meiotic errors, followed by a second, mitotic error (i.e., the initially trisomic zygote lost one of its chromosomes 21 during a mitotic cell division ["trisomy rescue"]). Prior to this hallmark study, mosaicism was most often described as arising from a single mitotic nondisjunctional event (Fig. 1). Using microsatellite repeats as a means of evaluating the parental and meiotic origin of the chromosomes 21 in individuals with mosaic

TABLE II. Case Reports of Parental Mosacism*

Report	Affected parent	Age of parent[a] (Years)	Tissues evaluated	Karyotype[b]	% Trisomy for Chr. 21	Total# cells counted
Smith et al. [1962]	Mother	19	Blood Skin	47,XX,+G/46,XX	27, 75	NA, 8
Blank et al. [1962]	Mother	31	Blood	47,XX,+G/46,XX	13[c]	163
Weinstein and Warkany [1963]	Mother	17	Blood Skin	47,XX,+G/46,XX	16[c], 18	105, 50
Verresen et al. [1964]	Mother	32	Blood	47,XX,+G/45,XX,−G/48,XX,+G,+G/46,XX	10/4/3	155
Walker and Ising [1969]	Father	NA	Blood	47,XY,+G/46,XY	22[c]	32
Taylor [1970]	Mother	NA	Blood Skin Ovaries	47,XX,+G/46,XX	6, 6, 90[c]	NA
Hsu et al. [1971]	Father	24	Blood Skin Testicular fibroblast	46,XY 47,XY,+21/46,XY 47,XY,+21/46,XY	0, 8, 4	20, 93, 50
Hsu et al. [1971]	Father	21	Blood	47,XY,+21/46,XY	6	50
Hsu et al. [1971]	Father	30	Blood Skin	47,XY,+21/46,XY	5, 4	43, 50
Krmpotic and Hardin [1971]	Mother	33	Blood	47,XX,+21/46,XX	10	39
Timson et al. [1971]	Mother	26	Blood	47,XX,+21/46,XX	10	NA
Harris et al. [1982]	Mother	NA	Blood Skin	47,XX,+21/46,XX	10, 5	62, 77
Uchida and Freeman [1985]	Mother	31	Blood Skin Ovary	47,XX,+21/46,XX	7.4, 2, 23	150, 200, 94
Nielsen et al. [1988]	Mother	23	Blood Skin Ovary	46,XX 46,XX 47,XX,+21/46,XX	0[c], 0, 12	260, 21, 79
Tseng et al. [1994]	Mother	22	Blood Ovary	46,XX 47,XX,+21/46,XX	0, 40	NA, 20
Street et al. [2007]	Mother	34	Blood AF (Maternal Cells)	47,XX,+21/46,XX 47,XX,+21/46,XY/46,XX	1.5, 15	200, 40

*Reports include those with mosaicism levels greater than 5% in an at least one tissue.
[a]Age at the time of first pregnancy resulting in a child with Down syndrome.
[b]In cases where multiple tissues are examined and found to have the same karyotype, one karytoype is listed.
[c]Percent trisomy 21 represents an average over multiple cultures.

Down syndrome, Pangalos et al. [1994] concluded that 10 of the 17 probands with mosaicism whom they studied (58.8%) resulted from a meiosis I error followed by a mitotic error. For seven probands (41.2%), these investigators concluded that postzygotic, mitotic errors most likely occurred, as three distinct alleles could not be detected in the specimens from the mosaic study participants. However, they further noted that one could not rule out the possibility that these cases might have resulted from either: (A) a mitotic error in gametic cells prior to meiosis, thereby resulting in an aneuploid gamete, with post-zygotic loss of the extra chromosome; or (B) a non-recombinant meiosis in which a meiosis II error occurred followed by a mitotic error. Additionally, using microsatellite markers, Papavassiliou et al. [2009] concluded that 35 of the 37 mosaic probands from informative kindreds that they studied were trisomic at conception, with a second mitotic chromosomal segregation error giving rise to the euploid cell line. Importantly, based on the results of these studies, the recurrence risk for the majority of couples having a child with mosaicism for trisomy 21/Down syndrome may be similar to that of couples having a child with non-mosaic trisomy 21, as the mechanisms underlying the aneuploidy in the mosaic kindreds most frequently reflect the occurrence of meiotic errors.

When considering the phenotypic variability in people with mosaicism for trisomy 21/Down syndrome, the potential effect of the parental and cell division origin of the trisomy should not be ignored. If the chromosomal nondisjunctional error(s) lead to an increase in homozygosity of alleles for recessive traits, then one could speculate that this may negatively impact clinical outcome [Antonarakis et al., 2004]. In particular, in individuals with mosaicism for trisomy 21/Down syndrome, a genetic imbalance characterized by a reduction to homozygosity for alleles on chromosome 21 can arise through either: (1) meiosis II (non-recombinants or limited recombination) errors; (2) mitotic errors; or (3) uniparental disomy in the euploid cells that arise from trisomy rescue. To date, the phenotypic impact, if any, of uniparental disomy for chromosome 21 is not clear [Blouin et al., 1993; Henderson et al., 1994; Rogan et al., 1999; Bruyere et al., 2000], but the recognition of a subset of genes localized to chromosome 21 whose expression is influenced by sequence-related differential methylation or imprinting effects, supports the conjecture that the phenotype in people with mosai-

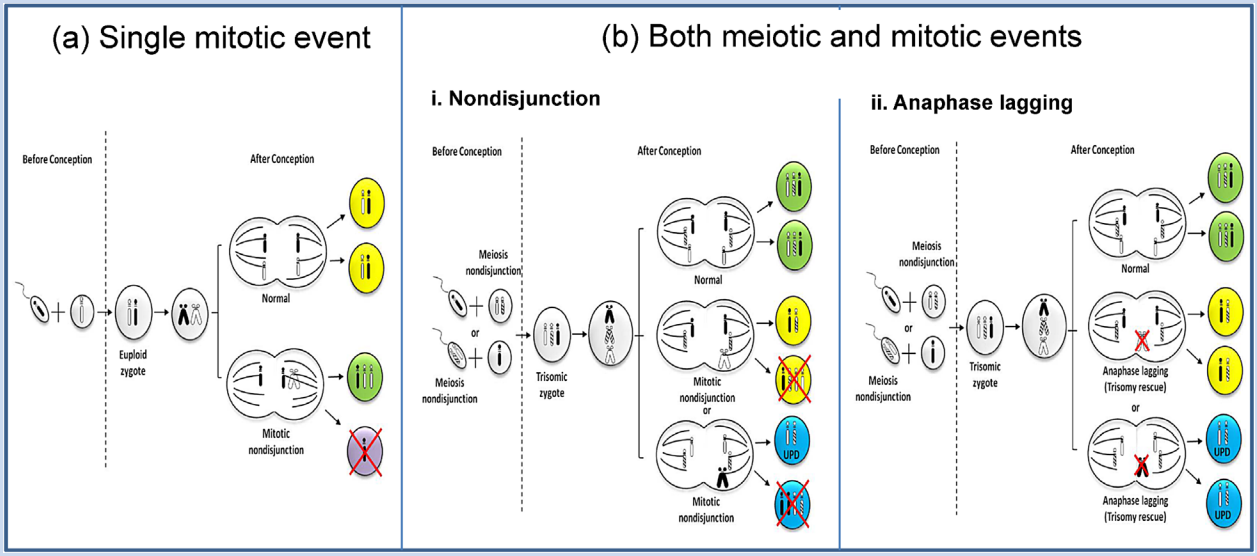

FIG. 1. Cell division and chromosomal malsegregation events leading to trisomy 21 mosaicism. (a) Following fertilization, a euploid (normal) zygote with 46 chromosomes undergoes a mitotic nondisjunctional event, resulting in a cell with three copies of chromosome 21 (green cell) and a cell with a single copy of chromosome 21 (purple cell). It is thought that the cell with one copy of chromosome 21 would not successfully proliferative (selection to remove this cell line), while the cell with three copies of chromosome 21 would continue to proliferate and give rise to a mosaic zygote containing trisomy 21 cells (green) and normal cells (yellow). This mechanism would result in the presence of two identical copies of one homolog in the trisomic cells. (b) A zygote with three copies of chromosome 21 is formed following the merging of a normal gamete and an aneuploidy gamete (meiotic error). If the nondisjunctional event occurred in meiosis I, there would be three different homologs present in the trisomic cells (indicated by black, white, and hatched patterns on three distinct homologs). (i) During embryogenesis, a second, mitotic (somatic) nondisjunction event occurs to give rise to cells having two chromosomes 21 or four chromosomes 21, with the latter cells failing to successfully proliferate (selection to remove this cell line). The cells having two copies of chromosome 21 could include either one homolog from each parent (biparental disomy; middle yellow cell), or two homologs from the same parent (uniparental disomy [UPD]; lower blue cell). (ii) During embryogenesis, a second, mitotic (somatic) chromosome malsegregation event occurs due to anaphase lagging (sometimes referred to as "trisomy rescue"), with the laggard chromosome potentially being excluded into a micronucleus and/or otherwise eliminated from the cell. The resultant euploid cells would either have biparental disomy (yellow cells) or uniparental disomy (blue cells).

cism could reflect influences from both the trisomy and euploid cell lines [Gertz et al., 2011; Docherty et al., 2014].

PHENOTYPIC OUTCOME (CONSTITUTIONAL)

Physical Traits

The clinical manifestations of mosaicism for trisomy 21/Down syndrome are highly variable, ranging from a phenotypic presentation comparable to that of individuals having non-mosaic trisomy 21 to a nearly normal phenotype (Fig. 2). These phenotypic differences are thought to primarily reflect variable numbers of trisomic cells in different people, as well as variation from tissue to tissue within a person [Papavassiliou et al., 2009; Shin et al., 2010], but could also reflect, in part, the chromosomal allele combinations, as noted above. One postulate that emerged from early discussions of varied mechanisms giving rise to mosaicism was that tissue specific differences might occur depending on when the mitotic chromosomal nondisjunctional event(s) were initiated during embryogenesis [Gibson and Gibbins, 1958; Rosencrans, 1968]. Mosaicism originating during early stages of embryogenesis, such as blastulation, may lead to generalized mosaicism in which most tissues are similarly affected. A chromosome segregation error that occurs at a later embryonic stage, such as gastrulation, during which time the three major cell lineages (i.e., ectoderm, mesoderm, and endoderm) are being/have been established, may affect a smaller proportion of the cells or result in mosaicism that is confined to a certain tissue(s). One interesting case report by Yokoyama et al. [1992] confirmed the potential for variation in the percentage of trisomic cells present in different tissues through their cytogenetic studies of a girl with mosaicism and a ventricular septal defect of the heart. Her cultured lymphocytes showed 16% of cells to have trisomy 21. In contrast, cells that were surgically obtained from myocardium, lung and skin biopsies from this patient revealed 90.5%, 72.7%, and 33.3% trisomic levels, respectively. In our studies of paired lymphocyte and buccal mucosa specimens obtained concurrently from individuals with mosaicism, we detected a significant difference between tissues for 71.4% of the propositi studied, with the mean percentage of trisomic cells being higher in buccal mucosa compared to peripheral blood [Papavassiliou et al., 2009].

In general, individuals with mosaicism who have a higher frequency of trisomy 21 cells tend to have more clinical traits associated with Down syndrome than individuals with mosaicism who have lower proportions of trisomic cells [Papavassiliou

FIG. 2. Variability in phenotype of people with mosaicism for trisomy 21. The appearance and health/developmental outcome of people with mosaicism for trisomy 21 varies from person to person, as evidenced from the facial traits of the 11 people with mosaicism for trisomy 21/Down syndrome included in this composite photograph (provided [with permission] by the International Mosaic Down Syndrome Association; www.imdsa.org).

et al., 2009], but this relationship has not been universally observed for all traits. For example, while some investigators have observed a significantly lower prevalence of major congenital heart disease in children with mosaicism (36.4%) compared to children with non-mosaic Down syndrome (49.3%) [Shin et al., 2010], other investigators have not detected a significance difference in the overall frequency of congenital heart disease between mosaic and non-mosaic cohorts [Papavassiliou et al., 2009]. However, the types of congenital heart disease have been reported to differ between individuals with mosaicism and non-mosaic trisomy 21, with atrioventricular canal defects being more common in individuals having non-mosaic trisomy 21, whereas the less severe anomaly, atrial septal defect, appeared to be more prevalent in individuals with mosaicism [Papavassiliou et al., 2009]. The variation in the presence or severity of traits seen in people with mosaicism compared to non-mosaic Down syndrome has also been observed for ophthalmic conditions, [Motley et al., 2011], language impairment [Paoloni-Giacobino et al., 2007], and overall survival [Shin et al., 2010; Zhu et al., 2013], with the results of these studies showing either significant differences or trends indicating a less severe outcome in people with mosaicism. Of particular note is the observation by Zhu et al. [2013] that people with mosaicism for trisomy 21 showed a significant increase in survival compared to people with non-mosaic forms of Down syndrome (50 year survival probability of 0.81 for mosaic cases compared to 0.64 for non-mosaic cases).

Cognitive Performance

An important clinical question that has been studied is whether the proportion of trisomic cells in individuals with mosaicism for trisomy 21/Down syndrome is related to intellectual development. Zellweger and Abbo [1963] were the first to study intellect in people with mosaicism for Down syndrome, but their study was limited to a single case report. Since that pioneering study, several investigators have assessed intellectual function in people with mosaicism for trisomy 21/Down syndrome (Table III). Not surprisingly, given the small sample sizes evaluated by a number of the investigators, the conclusions regarding intellect and the proportion of trisomic cells present have varied, with most, but not all, reporting higher IQ scores for the mosaic probands compared to the non-mosaic individuals. Our studies have also shown that while infants with mosaicism achieve most developmental milestones earlier than infants with non-mosaic Down syndrome, their milestone attainment is delayed when compared to their chromosomally normal siblings [Papavassiliou et al., 2009]. We have also observed a significant negative correlation between IQ scores and the proportion of trisomic buccal cells for people with mosaicism (higher levels of trisomic cells correlate with lower IQ scores) [Papavassiliou et al., 2009], with the same trend being observed (but not reaching significance) for lymphocyte trisomy values and IQ scores. In contrast, the presence of congenital heart disease was significantly correlated to the proportion of trisomic lymphocytes [Papavassiliou et al., 2009], with the same trend being observed (but not reaching significance) for correlations between buccal cell trisomy values and congenital heart conditions. These tissue-related observations may reflect the underlying embryonic origin of the specimens with the phenotypic findings, as both buccal cells and brain cells are ectodermal in origin, while both lymphocytes and cardiac muscle cells are derived from the mesoderm.

The clinical variation noted in people with mosaicism for trisomy 21/Down syndrome has also prompted investigators to examine whether or not there was a relationship between the number/type of physical stigmata and intellectual potential in patients having Down syndrome due to different chromosome 21 aberrations. Shipe et al. [1968] found a subtle inverse relationship between the number of physical stigmata and intelligence. In another report, Johnson and Abelson [1969] observed no difference in the number or types of stigmata between non-mosaic, translocation or mosaic trisomy 21 cases.

Fertility

Most information regarding fertility in people with mosaicism for Down syndrome is anecdotal. However, in their study of adults from a register-based cohort in Denmark, Zhu et al. [2013] reported 7% of adults with mosaic Down syndrome had a child, compared to 1% of non-mosaic trisomic probands. Both males and females with mosaicism have been reported to demonstrate fertility. Estimating the risk for having a child with trisomy 21 for an individual with mosaicism for trisomy 21 is not straightforward due to uncertainty regarding the proportion of germline/gonadal cells having a trisomic imbalance. For example, theoretically (assuming no selection bias) an individual who has a 47, XX,+21 or 47,XY,+21 complement in 50% of their germline cells would have a 25% risk of forming a gamete with a trisomic imbalance (based on a 2:1 segregation pattern for the 3 chromosome 21 homologs at meiosis I). While the most frequently anticipated reproductive outcome for a person with mosaicism for trisomy 21 (constitutional or germline only) would be a conceptus with either a normal or trisomy 21 complement [Delhanty, 2011], in one rare kindred cytogenetic studies showed mosaicism for trisomy 21 in two successive generations [Werner et al., 1982].

Social Conditions

People with mosaicism have been observed to have improved social conditions when compared to individuals with non-mosaic Down syndrome [Zhu et al., 2014]. These improvements, which were observed in a register-based cohort from Denmark, were recognized by observations of a higher proportion of people with mosaicism who attended secondary or post-secondary schools (18% for mosaic vs. 1% for non-mosaic probands); secured a full-time job (28% for mosaic vs. 2% for non-mosaics probands); and were married (15% for mosaic vs. 1% for non-mosaic probands). However, social and workforce integration clearly remains an area of opportunity for improvements for people with mosaic and non-mosaic forms of Down syndrome.

TABLE III. Comparisons of Developmental Delay in People With Mosaicism for Trisomy 21/Down Syndrome Compared to Non-mosaic Down Syndrome

Reference	Study participants[a]	Inverse association between % trisomic cells and developmental delay[b]	Additional findings
Zellweger and Abbo [1963]	8 M	Yes (Significant)	Patients with 50% or more trisomic cells showed developmental delay
Carter [1967]	1 M 1 NM 1T	Yes (Significant)	Less development delay noted in probands with translocation Down syndrome and mosaicism
Shipe et al. [1968]	NA	Yes (Trend)[c]	Suggested individuals with Down syndrome having relatively good intellectual functioning might be mosaic
Tsuboi et al. [1968]	NA	Yes (Trend)	Observed the percent of abnormal cells tended to be negatively associated with the degree of mental impairment
Rosencrans [1968]	20 M	Skin cells: Yes (Significant) Blood cells: No	Suggested differential correlation between tissues reflected shared embryologic origin (brain and skin cells)
Johnson and Abelson [1969]	18 M 254 NM 21 T	No	Individuals with translocation trisomy 21 showed highest intellectual ability
Kohn, et al. [1970]	8M	Yes (Trend)	Described considerable overlap between mosaic and non-mosaic individuals
Fishler et al. [1976]	25 M 25 NM	Yes (Significant)	Suspect mosaicism in children with Down syndrome having IQ of 50 or more and fewer speech problems
Fishler and Koch [1991]	30 M 30 NM	NA	Children with mosaicism were described to follow their own "idiosyncratic pattern of developmental progress"
Papavassiliou et al. [2009]	81 M 50 NM 106 siblings	Buccal cells: Yes (Significant) Blood cells: Yes (Trend)	Children with mosaicism attained developmental milestones earlier than non-mosaic individuals, but later than chromosomally normal siblings

[a]M = person with mosaicism for trisomy 21; NM = person with non-mosaic Down syndrome; T = person with a trisomic imbalance of chromosome 21 due to a translocation; NA = Number of participants not reported.
[b]Inverse association = higher proportion of trisomic cells tended to have lower intellectual ability.
[c]Trend = Trend toward inverse directionality, but did not meet statistical significance.

PHENOTYPIC OUTCOME (ACQUIRED)

Although most of the phenotypic findings associated with mosaic and non-mosaic forms of trisomy 21/Down syndrome are present at birth, there are some aspects of the phenotype that are acquired, such as (but not limited to) developing leukemia, solid tumors, signs of premature aging, and Alzheimer disease.

Risks for Leukemia

In contrast to the above noted observations trending toward a lower risk for clinical consequences in people with mosaicism for trisomy 21 compared to non-mosaic forms of this condition, studies of the chromosomally varied forms of Down syndrome among patients with megakaryoblastic leukemia or transient leukemia have shown significantly higher frequencies of mosaicism and other atypical chromosome 21 rearrangements [Shen et al., 1995]. Investigators have also reported that the presentation of megakaryoblastic leukemia with *GATA1* mutations led to the detection of previously unrecognized constitutional mosaicism for trisomy 21 in their patients, with a portion of these patients having normal phenotypes [Simon et al., 1987; Hu et al., 2005; Sandoval et al., 2005]. Based on these findings, it is suggested that constitutional studies be completed as part of the clinical assessment for patients having transient leukemia/megakaryoblastic leukemia [Hu et al., 2005; Sandoval et al., 2005]. Akin to the prognostic findings in patients with non-mosaic trisomy 21 who develop leukemia, patients with mosaicism who develop megakaryoblastic leukemia have been shown to have a good prognosis, with reductions in the intensity of the administration of chemotherapy also appearing to be effective for this group [Kudo et al., 2010].

Risks for Solid Tumors

Little is known about the propensity for people with mosaicism to develop solid tumors. Interestingly, individuals with non-mosaic forms of Down syndrome have been noted to have a reduced risk for

developing most types of solid tumors, with the exception of tumors derived from germ cells and potentially ovarian cancer, although this latter observation is not certain [Schepis et al., 1994; Hasle, 2001; Nizetic and Groet, 2012]. The biological basis for this solid tumor "protective" effect of a non-mosaic trisomic imbalance is not known, but has been conjectured to reflect: (1) differential expression of genes localized to chromosome 21 (including, but not limited to, *CDKN2A*, *ETS2*, *DYRK1A*, and *RCAN1*) [Adorno et al., 2013]: (2) alterations in stem cell proliferation/senescence rates [Cairney et al., 2009]; and (3) stromal microenvironmental alterations [Benard et al., 2005].

Our review of the literature resulted in the detection of only 3 people with mosaicism for trisomy 21 who were reported to have a solid tumor, including one person with mosaicism who had a ganglioneuroma [Hosoi et al., 1989], one mosaic proband with clear cell sarcoma in the right kidney [Satge et al., 2003], and one patient with mosaicism who had an embryonal carcinoma involving the left testis [Satge et al., 2003]. However, the larger surveys reporting the incidence of solid tumors in people with Down syndrome have tended to not include karyotypic information for all the subjects evaluated, thereby precluding one's ability to draw conclusions regarding the relative risk to acquire solid tumors for individuals with mosaic compared to non-mosaic from of Down syndrome.

In a report by Schepis et al. [1994] a single patient with mosaicism was observed among the 14 subjects they recognized who had palpebral syringomas, which is a rare benign tumoral entity that has been recognized to be more prevalent in people with Down syndrome. The patient with mosaicism described by these investigators was a female, as were the majority of non-mosaic probands they identified who had palpebral syringomas.

Age-related Fluctuations in the Proportion of Cells having a Trisomic Complement

A factor that has hampered previous efforts to draw conclusions regarding karyotype-phenotype correlations for individuals with mosaicism for trisomy 21/Down syndrome is the fluctuation of the percentage of trisomic cells with age. In their seminal paper, Jacobs et al. [1961] observed age-related acquired chromosomal abnormalities in three study populations (chromosomally normal individuals, males with Klinefelter syndrome, and individuals with non-mosaic Down syndrome). These investigators described a higher rate of chromosome loss (rather than gain) with increasing age. In addition, this trend was more apparent in the two groups of individuals with abnormal karyotypes than in the people having a euploid chromosomal complement. Additional support for the notion that the proportion of cells with chromosomal aneuploidy can vary with age for different cell types comes from studies of individuals with mosaicism involving chromosome 21 [Taylor, 1968; Taylor, 1970; Taysi et al., 1970; Wilson et al., 1980; Papavassiliou et al., 2009], as well as mosaicism for a variety of chromosomal imbalances other than chromosome 21 [Böök 1964; LaMarche et al., 1967; Neu et al., 1969; Gravholt et al., 1991]. The causes of acquired changes involving chromosome 21 (and other chromosomes) with advanced aging are not fully known. Mechanisms that have been postulated to account for these alterations include (but are not limited to): (1) an increase in chromosome loss during cell division with increasing age; (2) trisomic cells may be unable to maintain a growth equilibrium with normal cells (selective growth differences); and (3) trisomic cells progress through the cell cycle more rapidly than euploid cells, thereby attaining "aging critical" values associated with age-related increases in aneuploidy at a chronologically earlier age than the euploid cells.

Telomere Attrition with Aging

We and other investigators have shown that age-related acquired chromosomal loss is associated with telomere shortening [reviewed in Jackson-Cook, 2011]. Telomeres are an integral component of chromosome structure because, much like the aglets at the ends of shoelaces that protect against fraying, telomeres cap the ends of chromosomes and prevent chromosomal instability [reviewed by Blackburn, 1990]. Telomeres are thought to also be involved in the: (1) positioning of chromosomes during interphase [Galy et al., 2000]; and (2) segregation of chromatids during mitosis [Kirk et al., 1997; Ye and de Lange, 2004; Dynek and Smith, 2004]. While there have been several studies in which telomere attrition was reported for individuals having non-mosaic trisomy 21 [Wilson et al., 1980; Percy et al., 1993; Vaziri et al., 1993; Jenkins et al., 1997; Borsatto et al., 1998; Maluf and Erdtmann, 2001; Panossian et al., 2003; Jenkins et al., 2006; Jenkins et al., 2008; Jenkins et al., 2010], there is a paucity of information regarding telomere length in individuals with mosaicism. Interestingly, many of the studies of telomere length in non-mosaic individuals with Down syndrome have shown an association between telomere shortening and the presentation of dementia and/or Alzheimer disease [Jenkins et al., 2006; Jenkins et al., 2008; Jenkins et al., 2010; Jenkins et al., 2012]. The biological basis for the role of the telomere in Alzheimer disease development is not known, but has been proposed to reflect increases in sensitivity to DNA-damaging agents, decreased efficiency in DNA repair processes, and/or increases in DNA breakage due to abnormal oxidation and/or free-radical metabolism. Alterations in mitochondrial gene function and superoxide dismutase (a gene localized to chromosome 21) dosage have been suggested to serve as mediators for these telomere and age-related biological changes [Druzhyna et al., 1998; Maluf and Erdtmann, 2001; Morawiec et al., 2008].

Epigenetic Alterations

Investigators have recently studied epigenetic alterations associated with Down syndrome by assessing methylation patterns for genes on chromosome 21 and the other chromosomes in the genome in the hopes of gaining additional insight as to the mechanisms underlying the clinical findings seen in people with Down syndrome [Kerkel et al., 2010; Jin et al., 2013; Jones et al., 2013]. In one of these few epigenetic studies completed to date, Kerkel et al. [2010] evaluated a single person who had mosaicism for trisomy 21 (less than 50% of the patient's cells were trisomic) and found that the mosaic proband had methylation patterns that fell between those of the non-mosaic trisomic subjects and the chromosomally normal controls.

SUMMARY

In summary, the biological basis for how an imbalance of trisomy 21, either with or without mosaicism, leads to clinical consequences in people with Down syndrome is not fully known. This imbalance has been shown to directly impact the function of a subset of genes on chromosome 21 (but not all genes on chromosome 21) [Aït Yahya-Graison et al., 2007]. In addition, the imbalance on chromosome 21 appears to bring about perturbations in the expression of genes localized to other chromosomes through epigenetic alteration(s) and potentially via biological cascades [Kerkel et al., 2010; Jin et al., 2013; Jones et al., 2013; Letourneau et al., 2014]. Historically, scientists have limited their etiological studies on Down syndrome to focus on individuals with non-mosaic forms of trisomy 21 or partial trisomies of chromosome 21 due to: (1) concerns that the variation present in patients with mosaicism might confound their ability to interpret their findings; and (2) difficulties in ascertaining individuals having the relative rare condition of mosaicism. However, based on the adage of genetics where we have learned to "treasure our exceptions", we contend that this mosaic cohort provides a unique opportunity to tease apart the influences of a trisomic imbalance for chromosome 21 from other genetic and environmental influences that are not directly related to this imbalance. This opportunity stems from the fact that the euploid cells and trisomic cells in a person with mosaicism have identical genetic backgrounds (except for the presence or absence of an additional chromosome 21) and also have identical environmental exposure histories (as they are both present in the same person). By comparing the biological patterns (gene expression; methylation, etc.) in the isogenic trisomic compared to euploid cells from a person with mosaicism, one can "subtract" the influences of factors that are not associated with the trisomic imbalance to "unmask" or reveal the biological effects that are specifically attributable to trisomy for chromosome 21, including perturbations in the expression/regulation of genes localized to: (1) chromosome 21; (2) chromosomes other than chromosome 21; and (3) mitochondria. We anticipate that knowledge gained from the study of individuals with mosaicism will complement the recent exciting findings that are emerging from investigations of people with non-mosaic trisomy 21, as well as studies using animal models. It is hoped that these future discoveries will lead to the development of interventions/treatments for people with all forms of Down syndrome.

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