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Constitutional and Acquired Autosomal Aneuploidy

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Introduction

The consequences of chromosomal abnormalities have been noted “from the earliest stages of life well through the reproductive years, and even beyond” [1]. These chromosomal imbalances can result from numerical or structural anomalies. The numerical chromosomal abnormalities are often referred to as aneuploid conditions. The Greek translation of the word aneuploidy is “not a good set”. Thus, aneuploidy refers to a chromosomal number that is not an exact multiple of the haploid complement (i. e. in humans 45, 47, 48, etc. chromosomes per cell). Aneuploidy can arise in gametes/embryonic cells (constitutional) or in differentiated somatic cells (acquired) and can involve autosomes (chromosomes 1-22), as well as gonosomes (chromosomes X or Y). This chapter will focus on the occurrence of constitutional and acquired **autosomal** aneuploidy in humans.

Constitutional Autosomal Aneuploidy

Frequency of Aneuploidy

The earliest cytogenetic studies, which were completed in liveborns, showed aneuploidy involving only 3 of the 22 autosomes, with only trisomy (no monosomy) conditions being seen [2,3]. While cytogenetic methodology has advanced, the results of these pioneering investigations have remained relatively unchanged. The most frequently occurring autosomal aneuploidy condition noted in newborns is trisomy 21, which is seen in approximately 1 in 830 livebirths [2,3] (Table 1). The other autosomal trisomies that are seen in newborns include trisomy 18 (observed in approximately 1 in 7,500 livebirths), trisomy 13 (approximately 1 in 22,700 livebirths), and very rare cases of trisomy 22 [2-4]. Soon after the discovery of these autosomal aneuploidy conditions, cytogeneticists conjectured that the incidence of aneuploidy in humans was not limited to primarily three chromosomes (13, 18, and 21), but could occur for all autosomes, with the clinical consequences of aneuploidy for the other autosomes being incompatible with life. To test this hypothesis, investigations

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were initiated to determine if autosomal aneuploidy was present in spontaneous abortus tissue [5]. Chromosomal analyses of products of conception (primarily first trimester) showed the presence of trisomies involving nearly all autosomes. Interestingly, trisomy for chromosome 16 accounted for approximately a third of all autosomal trisomic first trimester abortuses [5] (Table 1). Other autosomes that were observed to have increased frequencies of trisomy in first trimester abortus tissue included chromosomes 2, 7, 8, 18 and the acrocentric chromosomes (13, 14, 15, 21, and 22) (Table 1). Explanations for these observed interchromosomal differences included (but were not limited to): (1) a true difference in the propensity for a chromosome to undergo malsegregation; and/or (2) a selection bias that reflected the differential viability of imbalances involving different chromosomes. To distinguish between these plausible explanations, aneuploidy data was collected directly from gametes.

The earliest of the gametic aneuploidy studies directly analyzed metaphase chromosomes from oocytes or sperm (Figure 1). More recently, investigators have completed these investigations using DNA-based methods (primarily fluorescence in situ hybridization (FISH), but also comparative genomic hybridization techniques) [6-8]. Collectively, the results of these gametic studies have shown that humans have a relatively high frequency of gametic aneuploidy when compared to the frequencies seen in other species [9]. Moreover, the frequency of sperm aneuploidy has been shown to differ between chromosomes (Table 1), suggesting that at least a portion of the observed variation in autosome-specific frequencies of aneuploidy is reflective of true differences in autosomal malsegregation, rather than being limited solely to selective growth pressures [6,10]. Gender differences have also been noted in gametic aneuploidy frequencies, with oocytes having higher levels of aneuploidy than sperm [6-8]. However, technical challenges have thwarted investigators' ability to provide unbiased, chromosome-specific estimates of autosomal aneuploidy present in oocytes [11,12]. One factor that is thought to contribute to the observed overall increased frequency of aneuploidy in oocytes compared to spermatocytes in humans is their means of ascertainment. The majority of oocytes available for study are ones found unsuitable for transfer from assisted reproductive procedures (such as *in vitro* fertilization), thus leading to biases associated with maternal age (see below) and/or with the presence of morphologic anomalies [8]. However, studies of non-human mammals, which are not limited by these ascertainment biases, have also shown significant increases in the frequency of aneuploidy in oocytes compared to spermatocytes [13,14]. Etiological factors that have been suggested to contribute to the higher incidence of aneuploidy in oogenesis include (but are not limited to): (1) the disruption of the meiotic division in prophase I (with the division starting prenatally, but not commencing until ovulation, which may occur decades later); (2) differences in meiotic checkpoint permissiveness for errors in males compared to females; (3) differences in the frequency and chromosomal location of meiotic recombinational events (see discussion of etiology below); and (4) epigenetic differences in response to environmental/stressor exposures.

Mosaicism for Autosomal Aneuploidy

Mosaicism for aneuploidy is defined as the presence of two or more distinct cell lines that are derived from a single zygote but differ from one another because of nondisjunction (or mutation) [15]. The use of interphase FISH techniques has allowed for improvements in our ability to detect autosomal mosaicism, since thousands of interphase nuclei from a variety of different tissues can be evaluated (not just limited to viable cells that can be successfully cultured *in vitro* to produce metaphase spreads) [16,17]. Mosaicism for nearly all of the autosomes has been identified in either liveborns (usually ascertained because of health/developmental concerns) and/or in fetuses through prenatal testing (asymptotically or due to ultrasound aberrations)(Table 1) [18-22]. Given that most of the instances of trisomic

mosaicism in liveborns are case reports, unbiased estimates of the frequency of mosaicism for all of the autosomes are not available. However, mosaicism for trisomy 21, which is thought to be one of the most frequent autosomal mosaicism conditions in liveborns, is seen in only 2% to 5% of all people having Down syndrome (or approximately 1 in 16,670 to 41,670 livebirths)^[18]. A caution to be noted when estimating frequencies of mosaic conditions in liveborns is that there is likely to be a bias toward only studying individuals who have clinical consequences resulting from their mosaicism. Thus, the estimates based on case reports/clinical studies are likely to be under estimates of the true frequency of constitutional autosomal mosaicism in humans.

The overall frequencies of true autosomal mosaicism (not pseudomosaicism) observed through prenatal testing is approximately 0.2% following amniocentesis and 1% to 2% following chorionic villi sampling (CVS) (with this latter figure including both mosaic complements and non-mosaic complements from direct preparations that differed from those of the fetus [indicating confined placental mosaicism])^[22,23]. Chromosome-specific differences in the frequency of prenatally diagnosed autosomal mosaicism have been identified, with trisomies involving chromosomes 13, 18, 20, and 21 being seen most frequently in amniocytes^[24,25].

One means for gaining insight regarding the frequency of mosaicism in humans has been to study early embryos, which were obtained following assisted reproductive procedures. These embryos have shown an unexpectedly high frequency of mosaicism, with the majority (50% to 91%) of early (day 4) embryos having mosaicism involving single or multiple (sometimes referred to as chaotic embryos) chromosomes^[26,27]. Chromosomal mosaicism has also been observed in fetal (30% to 35% of cells) and adult (10%) brains cells^[28,29], liver cells (approximately 3% in adults)^[30], and other tissues^[31], including germline mosaicism, which, if present, could have reproductive consequences^[32]. These observations have led investigators to postulate that mosaicism may occur as a “normal” or global biological process in early human development, with tissue-specific selection leading to loss of most aneuploid cells in the early stages of development, but with some tissues “normally” retaining mosaicism^[31]. Iourov et al^[31] further speculate that mosaicism (often undetected) may contribute to the development of several conditions (including autism, schizophrenia, autoimmune diseases, and Alzheimer disease), with a latent, age-related influence of mosaicism being conjectured for a portion of these conditions.

Phenotypic Findings Associated with Constitutional Mosaicism

As expected, since individuals having trisomy for chromosomes 13, 18, or 21 in every cell can survive to term, fetuses having mosaicism for these conditions can also survive. The phenotype of these individuals ranges from near normal to the demonstration of a subset (or in some cases all) of the phenotypic traits that have been well characterized in people having Patau, Edward, or Down syndrome^[16,33,34]. Individuals with mosaicism for trisomy 21 have phenotypic variation that appears to be influenced by the proportion of cells having a trisomic (compared to a euploid) complement, as well as tissue-specific effects^[16]. However, positive karyotype-phenotype correlations have not consistently been seen in people having mosaicism involving other trisomic conditions^[33,34]. As a result, the percentage of trisomic cells present in an individual having mosaicism cannot be clearly used as a prognostic indicator.

Interestingly, many individuals having mosaicism (regardless of the chromosome involved) have skin pigmentary abnormalities (which may not be present until weeks or years after birth); intrauterine growth compromise; body/facial/limb asymmetry; and developmental delay. As a result of this phenotypic overlap, the term “general chromosomal mosaic syndrome” has been coined^[35]. However, for a subset of these conditions, specific

syndromic patterns have emerged (summarized in Table 2 [4,16,21,23-25,33-75]), thereby facilitating the recognition of the chromosomal basis for these individual's health/developmental problems. The provision of genetic counseling following a prenatal diagnosis of autosomal mosaicism can be especially challenging. Genetic counseling concerns for these patients include: (1) variation in phenotypic consequences ranging from the extremes of a normal outcome to a severely abnormal phenotype; (2) identification/confirmation/quantitation of the trisomic cell line, with fibroblasts (and placenta) tending to show the presence (and/or higher frequencies) of the trisomic line more often than blood; (3) an assessment of the possible presence of uniparental disomy in the euploid line, due to a trisomy (or monosomy) rescue mechanism (particularly in cases where mosaicism was detected through CVS and in cases where the trisomic [monosomic] chromosome is one known to have imprinted regions); (4) recognition that clinical outcome can vary based on the mode of ascertainment (for example, was the mosaicism detected through chorionic villus sampling [if so, is it confined placental mosaicism?] versus amniocentesis, or after birth [due to phenotypic findings]); and (5) the technical criteria that was used to define the mosaicism (true mosaicism versus pseudomosaicism) [22]. For mosaic cases ascertained following prenatal testing, one may wish to recommend a fetal scan to potentially detect phenotypic abnormalities and to advise that follow-up confirmation chromosomal testing be completed (if CVS then confirm through amniocentesis; if amniocentesis then confirm through percutaneous umbilical blood sampling [for cases where the trisomic line can be seen in blood] or at termination/birth) [37].

In addition to mosaicism involving autosomal trisomy, patients having mosaicism for autosomal monosomy have also been described, including mosaic monosomies for chromosomes 13 [62], 21 [70,72], and 22 [4] (Table 2). However, these conditions are too rare to allow for the establishment of a distinct syndromic phenotype. On a cautionary note, when feasible, the presence of an apparent autosomal monosomic cell line should be confirmed using molecular cytogenetic approaches since several patients reported to have monosomic cell lines on the basis of GTG-banding were subsequently determined to have cryptic structural abnormalities (not full monosomy) [72].

Etiology of Constitutional Autosomal Aneuploidy

Having well established that constitutional autosomal aneuploidy was a significant factor leading to morbidity and mortality in humans, investigators initiated studies to understand the underlying causes of aneuploidy and to understand the basis for the observed differences in aneuploidy frequencies between chromosomes. Despite years of study, the etiology of aneuploidy in humans remains largely enigmatic, as does the specific mechanism(s) whereby the observed imbalances (trisomy) result in phenotypic consequences involving multiple organs. Investigators completing epidemiological studies have consistently shown advanced maternal age to be correlated with an increased risk for having a child with trisomy 21 (as well as most other trisomic conditions). This association has been observed in women from all ethnic and geographic backgrounds [76]. Knowledge of other factors (and/or the mechanistic influence of maternal age) contributing to the propensity for human chromosomes to malsegregate in meiosis has come from studies of the parental origin of the extra chromosome in trisomic probands [77]. Investigations of nuclear families (mother, father, and trisomic child) have shown that the majority (93% to 95%) of nondisjunctional events leading to a child having trisomy 21 occurred in oogenesis (primarily meiosis I) [77]. Similar studies of nuclear families in which a child has Edward syndrome or Patau syndrome have also shown that gametic malsegregation occurred more often in oogenesis than spermatogenesis. However, the malsegregational event that occurred in the gametes that resulted in the birth of a child with trisomy 18 occurred more frequently in meiosis II (58.7% of cases) than meiosis I [77]. Studies of abortus tissue (and parental samples) have

revealed variation in the parental and meiotic origin of the malsegregational events for the different autosomes [77].

Attributes that have been conjectured to influence a chromosome's propensity to malsegregate include the presence of chromosomal heteromorphisms [78,79]. However, since the association of these heteromorphisms with aneuploidy has not been consistently observed, their influence on chromosomal segregation, if any, seems to be either minimal or to act via a mechanism that is not straightforward (for example, increased amounts of heterochromatin may have epigenetic effects that, in turn, influence aneuploidy)[79,80].

Based on information gained from studies of the DNA markers evaluated in parental origin studies, perturbations in recombination have been recognized to occur in gametes that resulted in aneuploidy offspring/conceptuses [80]. For trisomy 21, reductions in the number of chiasmata, as well as changes in their location, have been observed, with the results of more recent studies suggesting that these patterns may be influenced by age, as well as environmental factors [14,81]. One can speculate that a lack of recombination (achiasmate bivalents) could lead to distributive segregation of the chromosomes, which is a phenomenon that has been shown to arise in *Drosophila*, but has not been definitively observed in humans [82]. Simplistically, the hypothesis of distributive pairing can be likened to a "singles' bar" (Figure 2). In distributive pairing, the unpaired chromosome(s) are thought to be more likely to pair with chromosomes having a similar size. By chance, the unpaired homologs could pair with one another, leading to potentially normal segregation at meiosis. Alternatively, the achiasmatic chromosomes could pair with a nonhomologous chromosome. The segregation of these non-homologous chromosomes could result in either a euploid or aneuploidy gamete (Figure 2). Aberrant localization of chiasmata between homologs can also lead to malsegregation, with a location that is too proximal resulting in entanglement while one too distal can result in unorganized, random segregation) [80].

The "trigger(s)" inducing perturbations in recombination, or other mechanisms contributing to the genesis of gametic aneuploidy, have not been clearly recognized, but are likely to include both genetic and environmental influences (Figure 3). While studies of non-human eukaryotic species have allowed for the recognition of many genes that contribute to the proper segregation of chromosomes in meiosis, the *a priori* recognition of genetic changes leading to an increased risk for gametic aneuploidy in humans is still lacking. Genes that have been identified as being likely candidates contributing to gametic aneuploidy include (but are not limited to) those involved in meiotic/spindle checkpoints, centrosome formation/duplication, chromatid cohesion, and chromatin organization [83-89]. A "two-hit" model of aneuploidy has been proposed to integrate the maternal age influence with the effects from genetic and other potential etiological factors that have been associated with aneuploidy in humans [90,91]. This model postulates that the "first hit" is the presence of a primary oocyte(s) having a susceptible meiotic configuration (such as perturbations in recombination). If these susceptible oocytes experience a "second hit", which could occur years later due to compromises in the functioning of key genes (noted above), they could result in an aneuploid conceptus. Alternatively, the "second hit" could be related to environmental exposure(s).

The designation of specific environmental exposures as aneugens in humans has been problematic, with both supportive and non-supportive data being reported for a variety of toxins/lifestyle exposures [92]. In studies that were performed using mice, Hunt et al [93] clearly showed an increase in aneuploidy frequencies in response to Bisphenol A (BPA) exposure. BPA, which is a xenoestrogen that activates estrogen receptors, has been conjectured to elicit its aneugenic effect through perturbations in the function of the tubulin gene, thereby disrupting spindle organization [94]. BPA has also been shown to induce

epigenetic changes in developing mammals that differ between species and vary with dosage [95]. Excitingly, the biological response of mice to BPA can be modulated with diet, suggesting that the impact of this chemical (and possibly the effects of other aneugens) may have biological plasticity/reversibility [95,96].

The field of epigenetics, which investigates heritable alterations in gene expression or phenotype that are caused by mechanisms other than changes in the underlying DNA sequence (such as methylation changes, histone alterations, micro RNA expression, etc.), is an exciting area of study that may allow for improvements in our understanding of etiological factors contributing to aneuploidy [97]. One can conjecture that epigenetic changes may explain, at least in part, the long recognized influence of advanced maternal age on chromosomal aneuploidy in humans. Epigenetic modifications could be acquired (over time) in gametes, leading to changes in the expression of genes that are involved in the resumption of meiosis I segregation or meiosis II segregation (including but not limited to genes involved in chromatid cohesion, meiotic/spindle checkpoints, centrosomes, spindle formation, DNA repair). These epigenetic modifications could result from a wide variety of “environmental” stressors (classical environmental exposures and/or social stresses) that may have occurred over many years, making their detection elusive (Figure 3). Their impact may also be modulated by diet or hormonal influences, thereby mimicking patterns consistent with those noted for complex diseases. While the role of epigenetic changes on the initiation of chromosomal malsegregation is largely speculative, investigators have shown that epigenetic changes arise in response to trisomic imbalances and may also contribute to the variation in phenotypic findings present in people having chromosomal aneuploidy conditions [98].

Studies of individuals having mosaicism may provide valuable insight about the causes of aneuploidy in humans. While all cases of mosaicism require at least one post-zygotic error, we (unpublished data) and other investigators [99,100] have shown that in the majority of individuals having mosaicism for trisomy 21, two chromosome malsegregational events occurred (both a meiotic and a mitotic error), with a “trisomy rescue” scenario giving rise to the normal cell line. Thus, it is feasible that the chromosomes in these individuals (which malsegregated twice) have a biological basis for a predisposition to aneuploidy. From a genetic counseling perspective, this observation is important to recognize since the recurrence risks for couples having a child with mosaicism for trisomy 21 may be comparable to those of couples having a child with “complete” trisomy 21, rather than being negligible, as has been suggested in early literature (probably as a result of the rarity of this condition which prohibited the collection of robust empiric risk data).

Acquired Autosomal Aneuploidy in Healthy Individuals

In addition to constitutional aneuploidy, chromosomal malsegregation can occur in differentiated somatic cells, resulting in acquired aneuploidy. In the first report of acquired chromosomal changes in somatic cells, Jacobs, et al. [101] described an increase in numerical chromosomal abnormalities (primarily losses) in cultured lymphocytes from older, compared to younger, individuals. This observation has since been confirmed for the sex chromosomes by several investigators (with X chromosome loss being seen most often in females and Y chromosome loss being seen most frequently in males) [102-108]. While age-related sex chromosomal aneuploidy has been widely studied, much less is known about the frequency of acquired autosomal aneuploidy.

Frequency of Acquired Autosomal Aneuploidy

In contrast to the sex chromosomes, the potential association between the frequency of acquired autosomal abnormalities and age is **not** clear-cut, with some investigators reporting

an age effect [109,110], and others seeing no such influence [106,111,112]. The earliest studies of acquired autosomal aneuploidy, which were performed by evaluating metaphase spreads, showed an excess of chromosomal losses compared to gains [105,108,112-115]. To avoid potential biases for observing artifactual chromosomal losses that might arise due to cell disruption during harvest/slide making procedures, investigators have used FISH techniques on interphase nuclei to estimate acquired aneuploidy frequencies. While few in number, the results of these interphase FISH studies have also shown losses (monosomy or nullisomy) to occur more often than gains (trisomy, tetrasomy, etc.) [110,111,116]. This consistent observation suggests that age-related, acquired aneuploidy may arise, at least in part, from a loss specific mechanism(s) rather than a mitotic nondisjunctional event(s), the latter of which would be expected to result in equal frequencies of the reciprocal products of monosomy and trisomy.

Akin to the observations of constitutional aneuploidy, the frequencies of acquired somatic cell aneuploidy have been shown to vary among chromosomes. The non-random, chromosome-specific patterns observed by cytogeneticists studying metaphase spreads have shown the smaller chromosomes to have higher frequencies of acquired aneuploidy (primarily loss) than larger chromosomes [117]. However, this size correlation has not been universally observed [118], and has not consistently been seen by investigators studying acquired aneuploidy frequencies in interphase nuclei using FISH methodology [110,111,116,119] (Table 3). The FISH studies of cultured and/or uncultured interphase nuclei have shown **increased** frequencies of loss for autosomes 1, 2, 6, 9, 15, 16, 17, 18, and 21 [110,111,119,120], and **decreased** frequencies of loss for chromosome 3 in both cultured and uncultured cells [110,120] (Table 3). Interestingly, 6 of the 9 autosomes having the highest frequencies of loss are heterochromatin-rich chromosomes [110,121,122].

Etiology of Autosomal Acquired Aneuploidy

The two primary hypotheses that have been proposed to explain chromosome-specific differences in acquired, somatic cell autosomal aneuploidy frequencies are: (1) the selection hypothesis; and (2) the non-random loss/gain hypothesis. The selection hypothesis states that the chromosome-specific differences in the frequency of acquired aneuploidy reflect the differential survival of the resultant imbalanced cells, with the loss (or gain) of a large chromosome that contains many actively transcribed genes having a more deleterious effect on a cell's survival (ultimately being eliminated from the cell population) than the loss of a small chromosome (or a heterochromatin-rich chromosome). Alternatively, the non-random loss hypothesis postulates that different chromosomes have a different propensity for abnormality occurrence and that the genetic make-up or structure of the chromosome, (for example, the heterochromatin content of a chromosome) is the primary determining factor for its acquisition of abnormalities [123].

To test these plausible hypotheses, investigators have studied the frequency of acquired somatic cell chromosomal abnormalities using a cytokinesis-blocked micronucleus assay, which provides information regarding the previous interphase/mitotic division of a somatic cell prior to the presence of selective pressure on the resultant daughter cells. A micronucleus is defined as a small structure that is juxtaposed to the main daughter nuclei and is thought to contain chromatin (from one or more chromosomes) that was not incorporated into the daughter nuclei ("lagging" or "lost") following cell division [124] (Figure 4). Micronuclei frequencies have been shown to be correlated with age and gender, with older subjects (50 years of age or older), showing a higher level than young (less than 30 years old) individuals [109,125-131], and women showing a higher increase with age than men [131]. Through the use of FISH methodology, the chromatin present in spontaneously occurring micronuclei has been inferred and has been observed to have a non-random pattern, with sex chromatin being present most frequently [109,126,127,129,130]. FISH studies

have also shown non-random patterns of autosomal chromatin in micronuclei, but these studies have involved only a targeted subset of autosomes rather than assessing all autosomes in a random manner [132]. Our studies, using spectral karyotyping (SKY) techniques [133], have allowed for the identification of all chromatin that might be present in micronuclei (rather than being limited to a targeted subset of genomic regions as reported in the FISH assays). These SKY analyses have also shown a non-random pattern of autosomal exclusion into micronuclei, with chromatin from chromosomes 4, 8, and 9 being present in the micronuclei most frequently, and chromatin from chromosomes 17 and 22 being present least frequently [data in press].

Thus, the results of the micronuclei studies support the non-random loss hypothesis, with innate differences in acquired aneuploidy frequencies appearing to be present for at least a subset of autosomes. As noted above, one chromosomal attribute that has been suggested to result in an increased tendency for that chromosome to acquire aneuploidy (with age) is its heterochromatin content. However, the molecular basis for this observed correlation is not known (Figure 5). It is feasible that variation in large blocks of heterochromatin between homologs could lead to asynchrony in their replication, which, in turn, may contribute to misalignment and malsegregation. Alternatively, epigenetic changes (primarily hypomethylation) may arise in pericentromeric heterochromatin (especially for autosomes 1, 9, 15, 16, and the acrocentric chromosomes), leading to changes in chromatin conformation that compromises the ability of the chromosomes to align, attach to mitotic spindle fibers, and/or separate [97]. While this latter hypothesis has not yet been fully tested in healthy humans (studies are currently underway in our laboratory), it has been tested through analyses of hypomethylated cells obtained following either: (1) *in vitro* induction (primarily using 5-azacytidine); or (2) as a result of mutation (cells from patients having immunodeficiency, centromeric heterochromatin instability, and facial anomalies [ICF] syndrome, who have a mutation in the DNA methyltransferase 3b gene). Collectively, the results of these studies have shown increases in the frequencies of somatic pairing among chromosomes 1, 9, and 16, with concomitant delays in centromere separation that led to the preferential exclusion of these chromosomes into micronuclei [97,121,134-137]. Given the observation of increased somatic pairing associated with hypomethylation, it is also feasible that the apparent increase of acquired aneuploidy for heterochromatin-rich chromosomes reflects its tendency to coalesce or “merge” in the interphase nuclei (rather than having true loss), with this effect being more pronounced with age [137]. Support for this conjecture comes from studies using multiple probes distributed along the length of heterochromatin-rich chromosomes. While limited in number, investigations of this type have shown the “loss” or observation of single signals to be predominantly localized to the pericentromeric region of chromosomes in the majority of cells evaluated, with two signals (euploid number) being observed for the more distally located probes evaluated in a portion of the same cells [138].

Another chromosome-specific attribute that has been correlated with acquired aneuploidy frequencies in humans is telomere length [122,139] (Figure 5). The mechanisms whereby alterations in telomere length predispose a chromosome to loss are not known, but have been speculated to involve a compromise in the localization of cohesin proteins in mitotic cells [140-142]; illegitimate somatic recombination and/or rearrangements leading to chromosome entanglement or misalignment [97,143]; differential gene expression (especially genes involved in spindle assembly; mitotic checkpoints/controls; or DNA repair); and/or asynchronous replication timing (which, in turn, could lead to misalignment) [144]. The causes of the observed variation in telomere lengths among chromosomes also are not fully known [145], but are thought to include heritable differences in the initial length of the repeats in the telomeres [146,147]; as well as differences in the rates of telomere attrition due to exposure history (including stress, toxins, oxidative stress, etc.) [148].

In addition to chromosome-specific variation in aneuploidy frequencies, individual-specific variation in acquired aneuploidy and micronuclei frequencies has been reported [35,109,126,128,130,149,150], with both genetic (65% of variance) and environmental (35% of variance) factors being shown to influence these frequencies [92,119,131] (Figure 5). Environmental exposures that have been shown to increase the frequency of micronuclei include, but are not limited to, diet (especially folate deficiency) [131,151-153], hormone levels [131,154], tobacco, alcohol and occupational hazards [119,131].

As with constitutional aneuploidy, in humans, the recognition of specific genes that predispose an individual to acquire aneuploidy in non-cancerous somatic cells is lacking. Nonetheless, several genes have been implicated to play a contributory/causal role and include (but are not limited to) genes involved in: (1) centrosomal structure/duplication [155-157]; (2) DNA repair [158-160]; (3) mitotic checkpoint maintenance [161,162]; (4) chromatid cohesion [163]; (5) chromatin organization [164]; and (6) the formation/function of the spindle and other components of the mitotic machinery [165,166] (Figure 5). Perturbations in genes involved in histone methylation or small interfering RNAs have also been noted to lead to disturbances in chromosomal malsegregation or kinetochore protein organization, respectively [167,168].

Phenotypic Findings Reported in People With Acquired Aneuploidy

The clinical consequence(s) of acquired autosomal aneuploidy in normal somatic cells are not known, but are thought to range from no phenotypic effect to being a potential precursor for the development of a variety of diseases. Woida and Witt [169] noted that several of the autosomes that have been shown to have higher frequencies of acquired aneuploidy are chromosomes that harbor genes that play roles in cellular senescence or premature aging syndromes. Aviv and Aviv [170] have further speculated that the imbalances resulting from the acquired changes could be a prerequisite step for the development of cancer or other age-related conditions such as hypertension, non-insulin dependent-diabetes mellitus, atherosclerosis, and cancer.

Summary

When reviewing our knowledge of autosomal aneuploidy in humans one is reminded of a quote by Noam Chomsky which, paraphrased, asks, “How it is we have so much information, but know so little?” [171]. When comparing constitutional to acquired aneuploidy one can detect both similarities and differences in their frequencies and purported etiological mechanisms. Chromosome-specific differences in the frequencies of aneuploidy are observed in both abortus tissue (constitutional) and lymphocytes (acquired), with consistent increases in frequencies being noted for chromosomes 15, 16, and 18 and consistent decreases in frequencies being observed for chromosomes 3, 5, and 19. While acquired aneuploidy frequencies have been shown to be more heavily influenced by genetic than environmental factors, less is known about the impact of genetic versus environmental effects on gametic aneuploidy. Clear overlap in the genes contributing to somatic and gametic aneuploid are present (i.e. genes involved in chromatid cohesion, meiotic/spindle checkpoints, DNA repair, centrosome formation/duplication). Nonetheless, strong influences that are unique to constitutional (i.e. meiotic recombination) and acquired (i.e. telomere attrition) aneuploidy have also been recognized. Technological advances have allowed for improvements in our understanding of the causes and consequences of aneuploidy, and it is anticipated that future improvements will continue to provide the necessary tools to better tease apart the biological basis of autosomal malsegregation. These anticipated advances (especially in the area of epigenetics, which may allow a means for bridging the knowledge gained from studies of environmental and genetic influences) allow one to be guardedly optimistic that we will expand our knowledge of the causes of aneuploidy in the near future.

Exploitation of the knowledge gained from these future studies might allow for the development of screening tests to identify people who are most “at risk” for having offspring with aneuploid conditions, and/or lead to improvements in our understanding and management of the role that aneuploidy plays in the aging process and acquisition of age-related diseases.

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Figure 1. Methods for evaluating sperm chromosomal complements

Hamster-egg/human sperm *in vitro* culture methodology allows one to directly observe chromosomes, as illustrated in this figure (a) which shows QFQ-banded chromosomes from a sperm having a female haploid complement (23,X). Studies using FISH methodology on sperm nuclei allow for estimation of aneuploidy frequencies based on targeted loci (usually pericentromeric sequences). In panel (b) sperm nuclei are shown following FISH with probes for chromosomes X (DXZ1; green); Y (DYZ3; red); 17 (D17Z1; yellow); and 18 (D18Z1; aqua). This field shows 2 sperm with a female complement, 4 sperm with a male complement; and 1 sperm (arrow) having an extra sex chromosome (inferred to be 24,XY) [panel b figure was prepared by Nurcan Gursoy].

Figure 2. Achiasmate chromosomes may engage in distributive pairing

In *Drosophila*, there is evidence that a lack of meiotic recombination leads to non-exchange pairing, with distributive pairing preferentially occurring between chromosomes that are similar in size. In humans it is not known if distributive pairing occurs, but one could speculate that the observed perturbations in recombination could result in distributive pairing. If this occurs between homologs it could lead to a balanced gamete; if it occurs between nonhomologs it could result in either a balanced, euploid gamete (center); or imbalances. [Adapted from Grell⁸²]

Figure 3. Potential genetic and environmental influences on gametic aneuploidy

Maternal age has consistently been shown to be associated with an increased risk for gametic aneuploidy, with the mechanism for this association appearing to include aberrant recombination, as well as other factors. In humans, it is speculated that genetic and environmental components impact one's risk for producing aneuploid gametes, with epigenetic changes acquired over time potentially serving as a bridge for these influences. Genes that have been implicated to contribute to aneuploidy (either through mutation or epigenetic alterations) include those involved with chromatid cohesion, meiotic and spindle checkpoints; repair; centrosome function/duplication; and/or recombination. Chromatin organization (heterochromatin versus euchromatin) has been conjectured to influence a chromosome's propensity for gametic aneuploidy and may be influenced by epigenetic changes, but could also illicit epigenetic alterations (hence, the two headed arrow). Heterochromatin may directly impact the frequency of aneuploidy (possibly by compromising the fidelity of the spindle attachments and replication/pairing processes), or its purported role may result from perturbations in recombination, which, in turn, could lead to aneuploidy.

Figure 4. Micronuclei as seen following spectral karyotyping (SKY) and FISH using a pantelomeric/pancentromeric probe

The majority of micronuclei contain chromatin from a single chromosome, as shown in the spectral (a) and classified (b) images of a binucleate having 2 micronuclei, one containing chromatin from chromosome 1 (yellow; right) and one containing chromatin from chromosome 13 (red; lower left). The majority of micronuclei also contain telomeric (red) and centromeric (green) signals (c), suggesting that an intact chromosome/chromatid is present in the micronucleus. The micronucleus shown in (c) has 2 telomeric signals (red) and 1 centromeric (green) signal.

Figure 5. Potential genetic and environmental influences on somatic aneuploidy

*Acquired aneuploidy frequencies reflect contributions from both genetic (65% of variance) and environmental (35% of variance) factors [131]. Genes that have been implicated to contribute to acquired aneuploidy (either through mutation or epigenetic alterations) are similar to those associated with constitutional aneuploidy and include genes influencing chromatid cohesion, meiotic and spindle checkpoint function; DNA repair; centrosome function/duplication; histone modification; and microRNAs. Heterochromatin-rich chromosomes have been reported to have increased frequencies of aneuploidy (primarily loss). The presence of heterochromatin in somatic cells has been speculated to be influenced by epigenetic changes, but changes in heterochromatin could also illicit epigenetic alterations (demonstrated with a two-headed arrow). Alterations in heterochromatin may directly impact the frequency of aneuploidy (potentially by compromising the fidelity of the spindle attachments and replication/pairing processes). Telomere attrition has also been suggested to lead to aneuploidy. Telomere shortening would reduce the amount of heterochromatin present in the telomeric region, and could lead to an epigenetic change by altering the chromatin conformation which, in turn, could allow for the expression of a gene(s) that would typically be silenced. Telomeres might also have a direct influence on aneuploidy which may be implemented through perturbations in alignment/somatic pairing/ chromosomal rearrangements, as well as other potential mechanisms. In contrast to constitutional aneuploidy, the role of advancing age on autosomal acquired aneuploidy is uncertain. Age effects have been denoted for a subset of chromosomes, and, when present, may have direct influences on aneuploidy, or indirect influences (for example, increased age leads to telomere shortening, which, in turn, could predispose to aneuploidy).

Table 1
Frequencies of Constitutional Autosomal Aneuploidy at Different Developmental Timepoints

Chromosome	Percent of Trisomy (Disomy in sperm)			
	Liveborn ¹	First trimester spontaneous abortuses ²	Mosaicism	Sperm ³ Disomy
1	-	Case report	-	0.08
2	-	5.6	P/L ⁵	0.09
3	-	0.8	P/L	0.20
4	-	2.5	P/L	0.08
5	-	0.1	p ⁶	-
6	-	0.3	P/L	0.04
7	-	4.5	P/L	0.06
8	-	3.7	P/L	0.03
9	-	2.8	P/L	0.16
10	-	1.9	P/L	-
11	-	0.2	P	-
12	-	0.8	P/L	0.14
13	0.004	5.7	0.0002 ⁷	0.12
14	-	4.2	P/L	-
15	-	7.3	P/L	0.10
16	-	32.4	P/L	0.07
17	-	0.7	P/L	-
18	0.013	5.1	0.00065 ⁸	0.06
19	-	0.1	P/L	-
20	-	2.7	0.009 ⁹	0.12
21	0.120	8.3	0.006 ¹⁰	0.17
22	NA ⁴	10.1	P/L	0.47

¹ Data from Hook [2] and Jacobs, et al [3]

² Data from Bond and Chandley [5]

³ Data from Templado, et al. [10] and presented as disomy frequencies

⁴ Case reports have been described, but the frequency is too rare to be accurately estimated

⁵ Mosaicism for this autosome has been reported through prenatal testing (P) and in liveborns (L), but is too rare for accurate frequencies to be estimated

⁶ Mosaicism for this autosome has been reported through prenatal testing (P), but is too rare for accurate frequencies to be estimated

⁷ Data from Magenis, et al. based on liveborns [19]

⁸ Data from Carey based on liveborns [20]

⁹ Data from Hsu, et al. based on amniotic fluid specimens [22]

¹⁰ Data from Hook based on liveborns [18]

Table 2
Phenotypic Consequences of Mosaicism for Autosomal Trisomies

Autosomal Mosaic Condition	Prenatal Ascertainment		Postnatal Ascertainment	
	Consistent Findings at Birth/Termination in Patients with Abnormal Outcome	Possibility of Normal Outcome	References*	Consistent Abnormalities Reported [†]
Mosaicism for Trisomy 2	IUGR ² ; oligohydramnios; CHD ³ ; including aortic; kidney anomalies	Yes (tend to lack confirmation of trisomic line) CVS detection associated with CPM ⁴	Sifakis et al., 2010 [36] Hsu et al., 1997* [24] Sago, et al., 1997* [37]	DD ⁵ ; CHD; small stature; hypertelorism; CFA ⁶ ; radioulnar hypoplasia; microcephaly; Hypomelanosis of Ito; cleft lip and/or cleft palate; small penis; bilateral cryptorchidism, bilateral club foot; body and facial asymmetry, neural tube anomalies; Hirschsprung disease
Mosaicism for Trisomy 3	IUGR; CHD; DD; oligohydramnios; bilateral cleft lip/palate; microphthalmia, vertebral anomalies, ear anomalies	Yes (tend to lack confirmation of trisomic line) CVS ⁴ detection associated with CPM ⁵	Zaslav, et al., 2004* [39] Hsu et al., 1997* [24]	CHD; DD; CFA; short stature; coloboma; and hip dislocation
Mosaicism for Trisomy 4	CFA; CHD; microcephaly; short neck; small stature; pigmentary abnormalities; facial asymmetry; ear anomalies; thumb aplasia & hypoplastic fingers; nail hypoplasia; variable DD	Yes (tend to lack confirmation of trisomic line)	Wieczorek, et al., 2003 [43] Zaslav, et al., 2000* [44] Hsu et al., 1997* [24]	Small stature; pigmentary abnormalities; facial asymmetry; ear anomalies; thumb aplasia & hypoplastic fingers; nail hypoplasia; variable DD
Mosaicism for Trisomy 5	IUGR; CHD; DD; CFA; growth delay	Yes (tend to lack confirmation of trisomic line)	Hsu et al., 1997* [24]	
Mosaicism for Trisomy 6	CHD; DD; growth delay; renal anomalies; cleft hand, syndactylies; overlapping toes; low-set ears; micrognathia	Yes (tend to lack confirmation of trisomic line)	Destree et al., 2005* [45] Hsu et al., 1997* [24]	CHD; DD; growth delay; renal anomalies; cleft hand, syndactylies; overlapping toes; low-set ears; micrognathia
Mosaicism for Trisomy 7	DD; facial asymmetry; Hypomelanosis of Ito; micrognathia; Russell-Silver syndrome and growth abnormalities in cases with uniparental disomy (trisomy rescue)	Yes (tend to lack confirmation of trisomic line)	Chen, et al., 2010* [46] Hsu et al., 1997* [24]	DD; CHD; renal abnormalities; radial hypoplasia; Hypomelanosis of Ito; mental illness
Mosaicism for Trisomy 8	Limited reports	Yes (confirmation of trisomic line in fibroblasts and blood for some cases)	Hsu et al., 1997* [24]	Thick lips; deep-set eyes; prominent ears, deep plantar and palmar creases; CHD; skeletal anomalies; camptodactyly; clinodactyly mild to severe developmental delay (speech most affected); Marfanoid habitus; renal malformations;
				Prontera, et al., 2010* [38] Metaxotou et al., 1981 [40] Kuhn et al., 1987 [41] DeKeyser et al., 1988 [42] Wieczorek, et al., 2003 [43] Destree et al., 2005* [45] Verghese, et al., 1999 [47] Hsu et al., 1997* [24] Hale and Keane, 2010 [48] Wisniewska and Mazurek, 2002 [49] Riccardi 1977 [50]

Autosomal Mosaic Condition	Prenatal Ascertainment		Postnatal Ascertainment	
	Consistent Findings at Birth/Termination in Patients with Abnormal Outcome	Possibility of Normal Outcome	References*	Consistent Abnormalities Reported [†]
Mosaicism for Trisomy 9	IUGR; CHD; CFA; micrognathia, skeletal malformations; low set ears; urogenital anomalies	Yes (confirmation of trisomic line in fibroblasts and blood for some cases)	Chen, et al., 2010[51] Schwendemann et al., 2009[52] Hsu et al., 1997*[24]	Low set ears; microcephaly; CHD; deep set eyes; joint anomalies; small jaw; feeding/respiratory difficulties in infancy; kidney problems; variable DD
Mosaicism for Trisomy 10	CFA; ear abnormalities; cleft lip/palate; rockerbottom feet; hand/finger deformities; cardiac anomalies		Hahnemann et al., 2005*[54]	CHD; CFA; growth retardation; ear anomalies; cleft lip/palate; renal malformations; hand and foot abnormalities; eye anomalies
Mosaicism for Trisomy 11	Acardia; renal anomalies; Potter syndrome facies [‡]	Yes (tend to lack confirmation of trisomic line)	Balasubramanian, et al., 2011*[55] Hsu et al., 1997*[24]	
Mosaicism for Trisomy 12	IUGR; CHD; skeletal anomalies; renal abnormalities	Yes (tend to lack confirmation of trisomic line)	Parasuraman, et al., 2011*[56] Gentilin, et al., 2006[57] Staals, et al., 2003[58] Hsu et al., 1997*[24]	Variable DD; CHD; CFA; microcephaly; scoliosis; short stature; pigmentary findings
Mosaicism for Trisomy 13	IUGR; CHD; DD; low-set ears; syndactyly/polydactyly; scalp defects; cleft lip/palate; small jaw	Yes (liveborns tend to lack confirmation of trisomic line)	Chen, 2010*[60] Wallerstein, et al., 2000*[25]	Mild to typical phenotype seen in trisomy 13, including CHD; ear anomalies; cleft lip/palate; phylloid hypomelanosis; variable DD
Mosaicism for Monosomy 13				Griffith, et al., 2009*[33] Delatycki and Gardner, 1997*[61] Golabi, et al., 2010*[62]
Mosaicism for Trisomy 14	Low set ears; rockerbottom feet; hip anomalies; hydrocephaly;	Yes (tend to lack confirmation of trisomic line)	Merritt and Natarajan 2007[63] Hsu et al., 1997*[24]	IUGR; CFA; CHD; microcephaly; hypertelorism; ptosis; eye anomalies including retinoblastoma; limb/finger abnormalities; renal, and dental anomalies
Mosaicism for Trisomy 15	IUGR; CHD; CFA; renal and gastrointestinal anomalies; skeletal abnormalities; limb anomalies; CPM	Yes (tend to lack confirmation of trisomic line)	Hahnemann, et al., 1999[23] Zaslav, et al., 1998*[65] Hsu et al., 1997*[24]	CFA; variable DD; CHD; Small size; genital anomalies; body/limb asymmetry; pigmentary findings; short neck/redundant neck skin; micro/retrognathia
Mosaicism for Trisomy 16	IUGR; CHD; CFA; DD; renal, skeletal, and gastrointestinal anomalies; skin pigmentary abnormalities; microcephaly	Yes (tend to lack confirmation of trisomic line)	Langlois, et al. 2006[75] Benn, 1998*[66] Hsu et al., 1997*[24]	CHD; IUGR; DD; CFA; skeletal anomalies; hypotonia; hydrosphadius; neck abnormalities; limb anomalies
				Benn, 1998*[66] Hsu et al., 1997*[24]

Autosomal Mosaic Condition	Prenatal Ascertainment		Postnatal Ascertainment	
	Consistent Findings at Birth/Termination in Patients with Abnormal Outcome	Possibility of Normal Outcome	References*	Consistent Abnormalities Reported ¹
Mosaicism for Trisomy 17	CFA; CPM	Yes (majority have normal phenotype; tend to lack confirmation of trisomic line)	Utermann, et al., 2006* [67] Genuardi, et al., 1999[68] Hsu et al., 1997* [24]	DD; growth delay; microcephaly; cerebellar malformations; limb/body asymmetry Utermann, et al., 2006* [67] Hsu et al., 1997* [24]
Mosaicism for Trisomy 18	IUGR; CFA; CHD	Yes (liveborns tend to lack confirmation of trisomic line)	Wallerstein, et al., 2000* [25]	Mild to typical phenotype seen in trisomy 18, including CHD; variable DD; CFA; microcephaly; delayed bone age; brachydactyly; short stature; premature ovarian delay; ear/respiratory infections; high arched palate Tucker, et al., 2008* [34]
Mosaicism for Trisomy 19		Yes ^c Limited to a single case	Hsu et al., 1997* [24]	CFA; neonatal death [†] Hsu et al., 1997* [24]
Mosaicism for Trisomy 20	IUGR; CFA; hypotonia; variable DD; seizures; renal anomalies	Yes (majority have normal phenotype; tend to lack confirmation of trisomic line)	Wallerstein, et al., 2000* [25] Hsu, et al., 1992[24]	Hypomelanosis of Ito; variable development (normal to delay with learning disabilities in cases having normal intelligence); spinal abnormalities: hypotonia; lifelong constipation; sloped shoulders Willis, et al. 2008[21] Bianca, et al. 2008[69]
Mosaicism for Trisomy 21	IUGR; CHD; Facies consistent with Down syndrome	Yes (tend to lack confirmation of trisomic line)	Wallerstein, et al., 2000* [25]	CHD; CFA including upslanting palpebral fissures and flat nasal bridge; variable DD; simian crease; ear/respiratory infections; eye findings; short hands/fingers; low set ears; hyperextensibility of joints; hypotonia P Papavasiliou, et al., 2009[16] Wallerstein, et al., 2000* [25]
Mosaicism for Monosomy 21	Holoprosencephaly; low-set ears; renal and lung anomalies; thumb abnormalities		Van der Kevie-Kersemaekers, et al., 2010* [70] Cheng, et al., 2006[71]	IUGR; CHD; CFA; DD; microcephaly; seizures; eye and ear anomalies; cleft lip/palate; renal anomalies; low set ears; syndactyly; limited number of cases Nguyen, et al., 2009* [72]
Mosaicism for Trisomy 22	IUGR; CHD; CFA; nuchal thickening; hydrocephaly; cleft lip; microcephaly; skeletal anomalies; facial asymmetry; finger anomalies; neonatal death	Yes (tend to lack confirmation of trisomic line)	Hsu et al., 1997* [24]	CHD; variable DD; CFA; small stature; eye, ear, limb anomalies; facial/body asymmetry; microcephaly; epicanthal folds; hypoplastic nails; clinodactyly; dental anomalies; hearing loss; ovarian failure Leclercq, et al., 2010* [73] Crowe, et al., 1997* [74] Hsu et al., 1997* [24]
Mosaicism for monosomy 22				IUGR; microcephaly; CFA Wang 1999 [4]

* When available, the reference(s) cited are review papers that summarize the findings of multiple investigators. These review papers are denoted by an * in the list of references.

¹ Represents a biased population presenting with phenotypic outcome (does not include people who might have mosaicism with a normal outcome)

² IUGR = Intrauterine growth retardation

³ CHD= Congenital heart defect

⁴ CPM = Confined placental mosaicism

⁵ DD = Developmental delay

⁶ CFA=Craniofacial anomalies

⁷ Based on a small number of cases, so not clear if these findings are indicative of a syndromic pattern or incidental observations

Table 3
Distribution of Acquired Somatic Cell Autosomal Aneuploidy in Lymphocytes from Healthy Subjects

Chromosome	Cultured			Uncultured		
	Loss ^I	Gain ^I	Number Subjects	Loss	Gain	Number Subjects
1	2.7 ²	0.5	68	2.9 ³	0.7 ³	53
2	1.2	0.6	60	2.45 ^{3,4}	0.11 ^{3,4}	75
3	0.8	0.8	62	0.36 ⁴	0.7 ⁴	22
4	1.3	0.1	65	0.93 ⁵	0.03 ⁵	24
5	0.9	0.7	44	1.36 ³	0.41 ³	53
6	2.0	0.3	40	-	-	-
7	1.8	0.2	62	1.9 ^{3,4}	0.16 ^{3,4}	75
8	1.4	0.2	66	0.80 ⁵	0.05 ⁵	24
9	1.8	0.5	36	4.09 ³	0.32 ³	53
10	1.4	0.2	36	-	-	-
11	1.7	0.3	61	1.23 ⁴	0.11 ⁴	22
12	1.2	0.3	59	1.84 ^{3,4}	0.34	75
13	1.4	0.6	58	1.50 ³	0.42 ³	53
14	1.6	0.5	65	0.64 ⁵	0.28 ⁵	24
15	2.5	0.6	33	-	-	-
16	2.9	0.4	43	4.68 ³	0.41 ³	53
17	1.5 ²	0.4	50	4.75 ^{3,6}	0.25 ^{3,4}	96
18	2.7	0.6	67	0.52 ⁵	0.08 ⁵	24
19	1.2	0.8	31	-	-	-
20	0.9	0.6	66	0.53 ⁵	0.04 ⁵	24
21	1.0	0.5	40	3.10 ³	0.60 ⁵	53
22	2.0	0.7	66	0.97 ⁷	0.03 ⁷	31

^I Data from unpublished studies completed in our lab on males and females ages 7-85 years.

- ² Data from unpublished studies completed in our lab and from data published by Guttentbach, et al., 1995 [111], who evaluated males and females ages 1 week to 93 years
- ³ Data from Rehder, et al. [119] on females ages 52-80 years
- ⁴ Data from Aboalela, et al. [120] on males (ages 7-78 years) and females (ages 15-32 years)
- ⁵ Data from Aboalela, et al. [120] on males (ages 9-78) and females (ages 15-25 years)
- ⁶ Data from Aboalela, et al. [120] on males (ages 7-80 years)
- ⁷ Data from Aboalela, et al. [120] on males (ages 9-78 years) and females (ages 15-25 years)