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Abnormal Folate Metabolism and Maternal Risk for Down Syndrome

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1. Introduction

Down syndrome (DS) or trisomy 21 (MIM 190685) is the most common genetic disorder with a prevalence of 1 in 660 live births (Jones, 2006). DS is the leading cause of genetically-defined intellectual disability (Contestabile et al., 2010) and its phenotype is complex and variable among individuals, who may present with a combination of dysmorphic features (Ahmed et al., 2005; Pavarino-Bertelli et al., 2009), congenital heart disease (Abbag, 2006), neurological abnormalities such as early manifestations of Alzheimer's disease (Lott & Head, 2005), immunological impairments (Ram & Chinen, 2011), elevated risk of specific types of leukemia (Hasle et al., 2000), and other clinical complications (Venail et al., 2004).
Trisomy 21 can be caused by three types of chromosomal abnormalities: free trisomy, translocation, or mosaicism. Mosaicism accounts for the minority of DS cases (about 1%) and is characterized by some cells containing 46 chromosomes and others, 47 chromosomes. Translocations are attributed to 3-4% of the cases, with Robertsonian translocation involving chromosomes 14 and 21 being the most common type. Finally, free trisomy occurs in about 95% of cases (Ahmed et al., 2005; J.M. Biselli et al., 2008b) and is characterized by the presence of three complete copies of chromosome 21.
Free trisomy, the main chromosomal abnormality leading to DS, is caused by the failure of normal chromosome 21 segregation during meiosis (meiotic nondisjunction) (Hassold & Hunt, 2000). The parental origin of the extra chromosome 21 is maternal in about 80% of cases (Jyothy et al., 2001), and most (about 77%) occur during the first maternal meiotic division in the maturing oocyte, before conception (Antonarakis et al., 1992).

2. Meiosis and chromosomal segregation

Faithful transmission of a genome from one generation to another depends on the mechanism of cell division in which each pair of replicated chromosomes is separated and equally distributed to mother and daughter cells. Meiosis generates haploid gametes through a specialized cell division process that consists of one round of DNA replication followed by two cell divisions. The first division, meiosis I (MI), involves the segregation of

homologous chromosomes from each other, whereas meiosis II (MII) involves the segregation of the sister chromatids (Hassold & Hunt, 2000).

Timing of chromosome attachment and loss of cohesion is essential to faithful chromosome segregation. During MI, the cohesion between sister chromatid arms assures physical attachment by the chiasmata of homologous chromosomes, ensuring their alignment on the meiosis-I spindle, and maintains them at the site of recombination. Chiasmata are resolved at anaphase I by the loss of cohesion between the arms of sister chromatids in the homologous chromosomes; the chromosomes then segregate to opposite poles of the cell. Cohesion, however, must be maintained at centromeres between sister chromatids beyond meiosis I to prevent premature chromatid separation (predivision) and ensure proper attachment of the sister chromatids to opposite spindle poles in meiosis II (Barbero, 2011; Sakuno & Watanabe, 2009; Vogt et al., 2008).

The centromeric cohesion during meiosis I results from the attachment of kinetochores of sister chromatids to only one spindle pole (Sakuno & Watanabe, 2009). Kinetochores are situated on opposite sides of the centromeric heterochromatin at the centromeres of each sister chromatid and they capture and stabilize microtubules for the formation of kinetochore fibers, only then they are capable of chromosome bi-orientation during the metaphase and chromosome segregation during the anaphase of meiosis (Vogt et al., 2008).

During cell division, several chromosomal mal-segregation mechanisms can occur. Classical nondisjunction is due to the failure to resolve chiasmata between homologous chromosomes, whereby both homologues segregate together. In addition, premature resolution of chiasmata or the failure to establish a chiasma between a pair of homologues results in the independent segregation of homologues at MI, which leads to an error if both segregate to the same pole of the MI spindle. A MI error can also involve the segregation of sister chromatids, rather than homologous chromosomes, whereby the premature separation of sister chromatids at MI can result in the segregation of a whole chromosome and a single chromatid to one of the poles. At MII, errors result from the failure of sister chromatid separation (Hassold & Hunt, 2000).

3. The origin of maternal chromosome 21 nondisjunction

The molecular mechanisms involved in meiotic nondisjunction leading to trisomy 21 are still poorly understood and the only well-established risk factor for DS is advanced maternal age at conception (35 years or older) (Allen et al., 2009; Jyothy et al., 2001; Lamb et al., 2005). Studies have suggested many explanations for the maternal age-associated increase in aneuploidy. One model attributes the effect of advanced maternal age to the uterine environment, indicating that there might be an age-related decline in the ability to recognize and then abort trisomic fetuses (Aymé & Lippman-Hand, 1982; Stein et al., 1986). However, the observation that the advanced maternal age effect is restricted to chromosome 21 nondisjunction of maternal origin, but not associated with cases resulting from sperm or post-zygotic mitotic errors, suggests that the uterus is the source of the age effect (Allen et al., 2009).

On the other hand, Zheng & Byers (1993) proposed that age-dependent trisomy 21 results primarily from a mechanism that favors maturation and utilization of euploid oocytes over the pre-existing aneuploid products of mitotic (premeiotic) nondisjunction at an early stage of the reproductive lifespan. In addition, decreased expression of checkpoint proteins in aging oocytes (Vogt et al., 2008) and failure to effectively replace cohesion proteins that are lost from chromosomes during aging (Chiang et al., 2010) also are pointed out as risk factors for predisposing oocytes to errors in chromosome segregation.

A link between altered recombination and maternal age-related nondisjunction has been described. It was observed that recombination is reduced among nondisjoined chromosomes 21 at MI, and this reduction seems to be age-related (Sherman et al., 1994). Lamb et al. (1996) proposed that at least two "hits" are required for chromosome 21 nondisjuntion: (1) the establishment in the fetal ovary of a susceptible pattern of meiotic recombination, and (2) the abnormal processing of susceptible chromosomes in the adult ovary. The second "hit" would involve degradation of a meiotic process (e.g., a spindle component, a sister chromatid cohesion protein, a meiotic motor protein, a checkpoint control protein) that increases the risk of improper segregation for these susceptible bivalents (Hassold & Sherman, 2000). Further studies have shown susceptible patterns of chromosome 21 meiotic recombination, including pericentromeric and telomeric exchanges, described as maternal risk factors for DS even in young DS mothers (Gosh et al., 2009; Lamb et al., 2005).

Besides advanced maternal age, the age of the maternal grandmother at the time of birth of the mother has also been pointed out as a risk factor for the occurrence of DS. At an advanced age, the grandmother's reproductive system may fail to make the essential proteins needed for proper meiotic segregation in the germ cells of her daughter, leading to nondisjunction of chromosome 21 during the embryogenesis of DS child's mother when she was in the grandmother's womb (Malini & Ramachandra, 2006). However, more recent studies failed to support the suggestion that advanced age of the DS grandmother is responsible for meiotic disturbances in her daughter (Allen et al., 2009; Kovaleva et al., 2010).

Although the risk of bearing a child with DS increases substantially with increasing maternal age, many DS children are born to mothers aged less than 35 years-old, suggesting other risk factors influencing DS etiology. In 1999, James et al. produced the first evidence that the occurrence of DS independent of maternal age is associated with DNA hypomethylation due to impairments in folate metabolism.

4. Folate metabolism

Folate represents an essential nutrition component in the human diet, and is involved in many metabolic pathways, mainly the folate metabolism, i.e., a single-carbon transfer from one molecule to another through a series of interconnected biochemical reactions. Folate is a generic term for a family of compounds present in most foods, e.g., legumes, leafy greens, some fruits, vegetables (e.g., spinach, broccoli, asparagus, and lettuce), liver, milk, and dairy products (Lin & Young, 2000). Humans, as all mammals, are unable to synthesize folate, thus its ingestion, either from normal diet or nutritional supplements, is very important. After intestinal absorption, natural folate, known as polyglutamate, requires reduction into monoglutamate by conjugases in the small intestine before it can be absorbed. On the other hand, in its synthetic form, folic acid exists as monoglutamate and does not need to be reduced for release into the blood and cellular uptake (Bailey & Gregory, 1999; Hall & Solehdin, 1998). Another disadvantage of natural food folate is its poor stability especially under typical cooking conditions, which can substantially reduce the vitamin content before it is even ingested, a significant additional factor limiting the ability of natural food folates to enhance folate status (McNulty & Pentieva, 2004; McNulty & Scott, 2008).

Folate metabolism is a complex metabolic pathway that involves multiple enzymes and water-soluble B vitamins such as folate, vitamin B_6 and vitamin B_{12}, that play key roles

as enzyme cofactors or substrates in this metabolism. It includes two main cycles: purine and pyrimidine synthesis, necessary for synthesis and repair of DNA, and DNA methylation, an epigenetic process that acts on the control associated with gene expression and genomic stability essential for normal cellular methylation reactions (Figure 1).

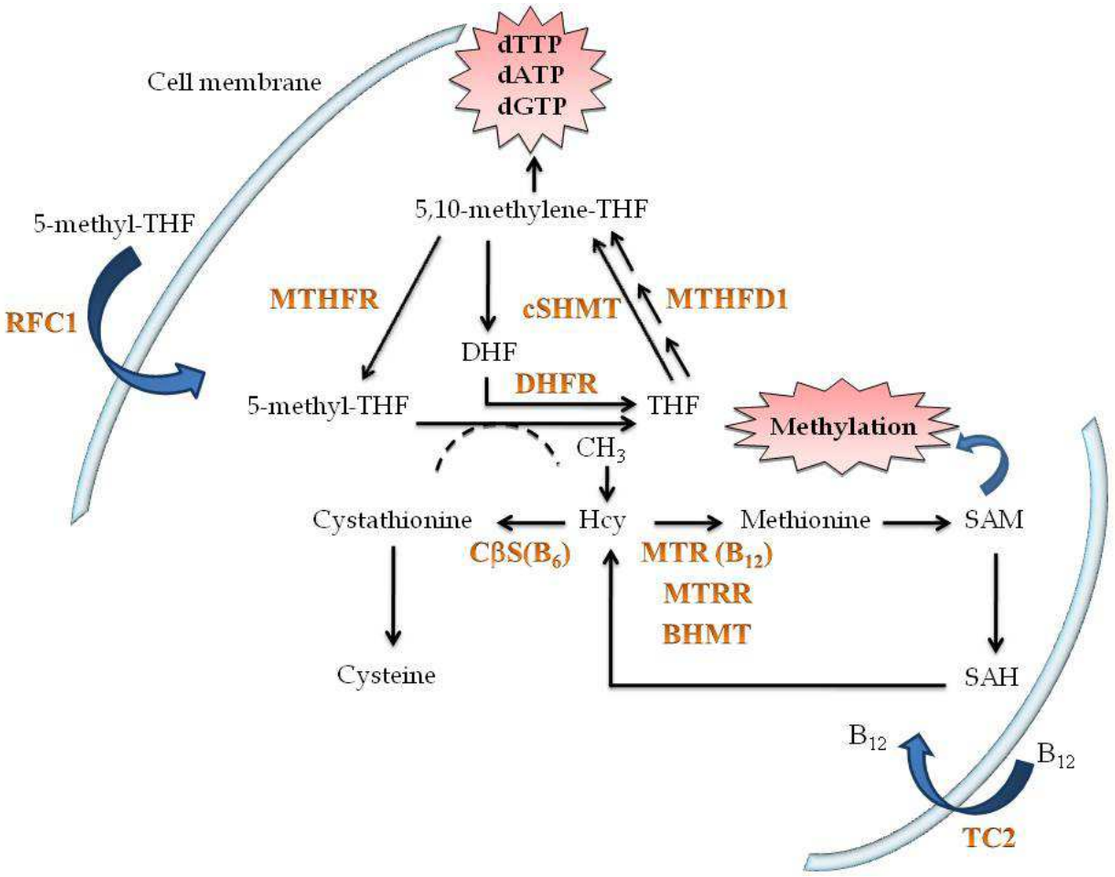

Fig. 1. Folate metabolism. BHMT = Betaine-homocysteine methyltransferase; B_6 = vitamin B6; B_{12} = vitamin B12; CβS = Cystathionine β- synthase; CH_3 = Methyl; dATP = Deoxyadenosine 5′-triphosphate; dGTP = Deoxyguanosine 5′-triphosphate; dTTP = Deoxythymidine 5′-triphosphate; DHF = Dihydrofolate; DHFR = Dihydrofolate reductase; Hcy = Homocysteine; MTHFD1 = Methylenetetrahydrofolate dehydrogenase 1; MTHFR = Methylenetetrahydrofolate reductase; MTR = Methionine synthase; MTRR = Methionine synthase reductase; RFC1 = Reduced folate carrier 1; SAH = S-adenosylhomocysteine; SAM = S- adenosylmethionine; cSHMT= Serine hydroxymethyltransferase; TC2 = Transcobalamin 2; THF = Tetrahydrofolate.

Folate requires several transport systems to enter the cells and the one best characterized is the reduced folate carrier (RFC1), an enzyme located on intestinal cell membranes that carries out the transport of 5-methyltetrahydrofolate (5-methyl-THF) to the interior of a variety of cells, representing an important determinant of folate concentration in the interior of cells (Nguyen et al., 1997). In addition to the folate transport system, several genes and their respective enzymes play important roles in folate metabolism. The D*ihydrofolate reductase* (*DHFR*) gene encodes an enzyme that catalyzes the conversion of dihydrofolate

(DHF) into tetrahydrofolate (THF) (Stanisiawska-Sachadyn et al., 2008), which is then converted into the corresponding 10-formyl, 5,10-methenyl, and 5,10-methylene derivatives by Methylenetetrahydrofolate dehydrogenase 1 (MTHFD1), a trifunctional nicotinamide adenine dinucleotide phosphate-dependent cytoplasmic enzyme. The donor cofactors for *de novo* purine and pyrimidine biosynthesis and, thus, the biosynthesis of DNA (Hum, 1988) are 10-formyl-THF and 5,10-methylene-THF. By an alternative route, THF is converted into 5,10-methylene-THF and glycine by the cytosolic form of the enzyme Serine hydroxymethyltransferase (cSHMT) (Steck et al., 2008).

Methylenetetrahydrofolate reductase (MTHFR) is responsible for the conversion of 5,10-methylene-THF to 5-methyl-THF, the main circulating form of folate that donates methyl groups for homocysteine (Hcy) remethylation into methionine. This latter reaction is catalyzed by the enzyme Methionine synthase (MTR), which requires vitamin B_{12} or cobalamin (Cbl) as a cofactor, and results in the formation of S-adenosylmethionine (SAM), the primary methyl (CH_3) donor for DNA methylation reactions (Finkelstein & Martin, 2000). SAM is demethylated to form S-adenosylhomocysteine (SAH) and then hydrolyzed to form adenine and Hcy. The DNA methyltransferase (DNMTs) enzymes catalyze the transfer of the methyl group, obtained from conversion of SAM into SAH, to position 5' of cytosine residues located mainly in dinucleotide cytosine-guanine (CpG) (Bestor, 2000; DeAngelis et al., 2008).

Methionine synthase reductase (MTRR), an enzyme codified by the *MTRR* gene, is responsible for the maintenance of the active form of the enzyme MTR. During remethylation of Hcy to methionine, a reaction catalyzed by MTR, methylcob(III)alamine acts as a methyl donor. In this reaction, the transfer of a methyl group from methylcob(III)alamine results in the formation of highly reactive cob(I)alamine, which is oxidized into cob(II)alamine, resulting in MTR inactivation (Yamada et al., 2006). In this inactivation process, a complex is formed between the enzymes MTR and MTRR, and derivative electrons from the oxidation of nicotinamide adenine dinucleotide phosphate (NADPH), catalyzed by MTR, are transferred to the inactive form of MTR. This process favors the transfer of methyl from the SAM to the MTR enzyme, resulting in methylcob(III)alamine, thus reestablishing MTR activity (Leclerc et al., 1999; Olteanu et al., 2001, 2002).

Betaine-homocysteine methyltransferase (BHMT) catalyses the conversion of Hcy to methionine by an alternative pathway of remethylation using the amino acid bethaine as methyl donor. When the Hcy folate-dependent remethylation catalyzed by the MTR enzyme is impaired by genetics or environmental factors, the BHMT enzyme plays an important role maintaining the homeostasis of Hcy (Pajares & Pérez-Salab, 2006).

In the transsulfuration cycle, Hcy is converted into cystathionine by Cystathionine β-synthase (CβS), a vitamin B_6-dependent enzyme, and then into cysteine (Kraus et al., 1998). Under normal physical conditions, all Hcy is remethylated into methionine or catalyzed into cystathionine. The increase of Hcy concentration represents impairment in folate metabolism and thus in methylation reactions (Fenech, 2002).

Besides the enzymes that act directly on folate metabolism, cobalamin-transporting proteins also play an important role in this metabolic pathway, since the MTR enzyme is cobalamin-dependent. The enzyme Transcobalamin 2 (TC2) is synthesized in the intestinal villi and binds itself to Cbl in the interstitial fluid. This formed complex goes into the intestinal villi microcirculation and then reaches the systemic circulation. This circulation distributes the vitamin to all tissues where specific receptors on cell membranes bind and internalize the TC2-Cbl complex by endocytosis (Quadros et al., 1999; Seetharam & Li, 2000).

5. Folate metabolism, genomic stability, and maternal risk for chromosome 21 nondisjunction

Based on evidence that stable centromeric DNA chromatin may depend on the epigenetic inheritance of specific centromeric methylation patterns and on the binding of specific methyl-sensitive proteins to maintain the higher order DNA architecture necessary for kinetochore assembly (Karpen & Allshire, 1997), James et al. (1999) hypothesized that pericentromeric hypomethylation, resulting from impaired folate metabolism secondary to polymorphism of the *MTHFR* gene, could impair chromosomal segregation and increase the risk for chromosome 21 nondisjunction in young mothers. They observed that the risk of having a child with DS was 2.6-fold higher in mothers with 677 C→T substitution in one or both alleles of the *MTHFR* gene than in mothers without the 677 C→T substitution. In addition, DS mothers displayed a significant increase in plasma Hcy concentrations and lymphocyte methotrexate cytotoxicity, consistent with abnormal folate and methyl metabolism.

As described above, the MTHFR enzyme plays an important role in regulating DNA methylation through the reduction of 5,10-methylene-THF to 5-methyl-THF (Figure 1). The 677 C→T polymorphism is known to decrease the affinity of the enzyme for the flavin-adenine-dinucleotide (FAD) cofactor, decreasing enzyme activity (Guenther et al., 1999; Yamada et al., 2001). The *MTHFR* 677 CT genotype seems to reduce enzyme activity by about 35% and the homozygous TT genotype by 70% (Frosst et al., 1995). Since the study by James et al. (1999), polymorphisms in the *MTHFR* gene are the most frequently investigated in attempt to clarify the role of folate and methyl metabolism in the maternal risk for DS (Martínez-Frías et al., 2008). Several studies have associated the MTHFR 677C→T polymorphism and the risk of bearing a child with DS (da Silva et al., 2005; Meguid et al., 2008; Sadiq et al., 2011; Wang et al., 2008) as well as with increasing plasma Hcy concentration (P.M. Biselli et al., 2007; da Silva et al., 2005; Narayanan et al., 2004; Ulvik et al., 2007).

Another common polymorphism in the *MTHFR* gene, the substitution of alanine for cytosine at the 1298 position, was already associated with DS risk and increased plasma Hcy concentration (Martínez-Frías et al., 2006; Meguid et al., 2008; Narayanan et al., 2004, Rai et al., 2006; Scala et al., 2006; Weisberg et al., 2001). This polymorphism proved to have an impact on enzyme activity resulting in an even more pronounced decrease in its activity in homozygous 1298 CC compared to the heterozygous individuals (van der Putt et al., 1998).

In addition to the *MTHFR* gene, other genetic polymorphisms involved in the folate pathway seem to modulate the maternal risk for bearing a child with DS (Bosco et al., 2003; J.M. Biselli et al., 2008a; Meguid et al., 2008; Pozzi et al., 2009; Sadiq et al., 2011; Scala et al., 2006; Wang et al., 2008) as well as the concentrations of metabolites involved in the folate pathway (Ananth et al. 2007; Barbosa et al., 2008; Cheng et al., 2010; Devos et al., 2008). The *MTR* 2756 A→G polymorphism has been associated with increased maternal risk for DS in the presence of AG or GG genotypes, as well as when combined with polymorphisms *MTRR* 66 A→G (*MTR* 2756AG/*MTRR* 66AG) (Bosco et al., 2003) and *MTHFR* 677 C→T (*MTHFR* 677TT/*MTR* 2756AA). In addition, the allele *MTR* 2756 G proved to be more frequent, both in homozygosis and heterozygosis, in DS mothers as compared to mothers of individuals without the syndrome (Pozzi et al., 2009). Concerning its influence on Hcy concentrations, studies have shown conflicting results, since some have associated the *MTR* 2756 A allele to increased Hcy concentration (Fredriksen et al., 2007; Harmon et al., 1999), while others found the same association, but with the polymorphic 2756 G alelle (Feix et al., 2001; Fillon-Emery et al., 2004).

As to the *MTRR* 66 A→G polymorphism, some studies have supported an independent role for this polymorphism in the maternal risk for DS in the presence of the homozygous *MTRR* 66 GG genotype (Hobbs et al., 2000; Pozzi et al., 2009; Wang et al., 2008). Most of the studies have associated this polymorphism with the risk of DS and increased Hcy concentration when combined to other polymorphisms, such as *MTHFR 677* C→T (Hobbs et al., 2000; Martínez-Frías et al., 2006; O'Leary et al, 2002; Yang et al., 2008). Additionally, a steady state kinetic analysis showed a significantly decreased affinity of *MTRR* for *MTR* accompanying substitution 66 A→G, revealing a significant difference in the relative efficacies of the MTRR enzyme (Olteanu et al., 2002). However, several studies have failed to find association between DS risk and the *MTRR* 66 A→G polymorphism, whether alone or combined with other genetic variants (Coppedè et al., 2009; Chango et al., 2005; Scala et al., 2006).

The *RFC1* gene is polymorphic at nucleotide 80 (A→G), and investigation of the impact of this polymorphism on protein function have demonstrated a difference in its affinity for subtracts and/or efficiency in transport in comparison with the wild type enzyme (Whetstine et al., 2001). Few studies have evaluated the influence of the *RFC1* 80 A→G polymorphism on DS risk (J.M. Biselli, 2008a, 2008c; Chango et al., 2005; Coppedè et al., 2006). Some studies have found no association between this polymorphism and DS (Chango et al. 2005; Fintelman-Rodrigues et al., 2009); however, Coppedè et al. (2006) and J.M. Biselli et al. (2008a) suggest a role for this polymorphism when combined with other polymorphisms in genes involved in folate metabolism. Supporting this hypothesis, the combined *RFC1* 80 GG/*MTHFR 677* TT genotype has been associated with increased Hcy concentration and the *RFC1* 80 AA/*MTHFR 677* CT combined genotype with higher plasma folate concentration (Chango et al., 2000).

A common polymorphism in the *CβS* gene, 68-base pair (bp) insertion at nucleotide position 844 (844ins68), is also investigated in the risk for DS, but there is no evidence that this variant plays an independent role on this risk (da Silva et al., 2005; Chango et al., 2005; Scala et al., 2006). The *CβS* 844ins68 polymorphism has been associated with reduction of Hcy concentration in the presence of the insertion (Tsai et al., 1996; Tsai et al., 1999; Tsai et al., 2000), and it is believed that this insertion is related to increased enzyme activity (Tsai et al., 1996, Tsai et al., 1999). This variant is always found to be associated in *cis* with an additional polymorphism in the *CβS* gene, a thymine-to-cytosine transition at nucleotide position 833, which causes a threonine-to-isoleucine amino acid substitution, and is reported, together with *CβS* 844ins68, as a 833 T→C/844ins68 *in cis* double mutation (Pepe et al., 1999; Vyletal et al., 2007). Da Silva et al., (2005) observed that the 844ins68 polymorphism, in association with other polymorphisms of the folate pathway, is related to increased risk for DS. Concerning its influence on folate metabolite concentrations, such as folate, Hcy, and vitamin B_{12}, the *CβS* 844ins68 polymorphism showed no significant association with any of the biochemical variables involved in folate metabolism (Bowron et al., 2005; Kumar et al., 2010; Summers et al., 2008).

The *MTHFD1* gene presents a functional polymorphism, a guanine-to-adenine substitution at position 1958 (1958 G→A), that has been shown to reduce the activity and stability of the variant enzyme (Christensen et al., 2008). There are only two studies to date on the influence of this polymorphism on maternal risk for DS. Scala et al. (2006) showed an association of the *MTHFD1* 1958 AA genotype with DS risk, but only when combined with the *RFC1* 80

GG genotype; however, more recently, Neagos et al. (2010) failed to find association. Thus, further investigations are necessary to clarify the role of *MTHFD*1 1958 G→A in the chromosome 21 nondisjunction.

Johnson et al. (2004) described a 19-base pair (bp) deletion polymorphism in intron-1 of the *DHFR* gene and hypothesized that this polymorphism could be functional since the deletion removes a possible transcription factor binding site that affects gene regulation. A study with mothers of individuals with spina bifida showed that the expression of the messenger ribonucleic acid (mRNA) from the *DHFR* gene was 50% higher in the presence of del/del genotype than in the ins/ins genotype (Parle-McDermott et al., 2007). This polymorphism has been associated with the modulation of metabolites' concentrations involved in the folate pathway. Gellekink et al. (2007) reported association between the del/del genotype and reduction of plasma Hcy concentration, but found no association between this genotype and concentrations of serum and erythrocyte folate. Another study found no effect on Hcy concentration, but found increased plasma and erythrocyte folate levels in del/del individuals (Stanislawska-Sachadyn et al., 2008). The results of the only study that investigated the 19-bp deletion polymorphism of *DHFR* gene in DS mothers did not support an association between this variant and the maternal risk for DS. In addition, the polymorphism was not associated with variations in serum folate and plasma Hcy and methylmalonic acid (MMA) concentrations in the study population (Mendes et al., 2010).

The *TC2* gene, which codifies a transporting protein required for the cellular uptake of vitamin B_{12} (Seetharam &Li, 2000), is polymorphic at nucleotide position 776 (C→G). There is evidence that the presence of the *TC2* 776 CC genotype may be more efficient in delivering vitamin B_{12} to tissues, resulting in enhanced B_{12} functional status (Miller et al., 2002; Namour et al., 1998). In other studies, the presence of the *TC2* 776 GG genotype was shown to affect negatively the serum concentration of the TC2 protein-vitamin B_{12} complex (von Castel-Dunwoody et al., 2005) and was associated with low concentrations of SAM in childbearing-age women (Barbosa et al., 2008). Considering that SAM is the major methyl donor for DNA methylation reactions, it was hypothesized that the variant *TC2* 776 C→G could influence the maternal risk for DS by modifying the DNA methylation pattern. This polymorphism has only been investigated in DS risk by two groups to date (J.M. Biselli et al., 2008c; Fintelman-Rodrigues et al., 2009), but no association has been found.

The conflicting results shown by literature have raised the suggestion that the presence of individual polymorphisms in genes involved in folate metabolism might not increase the risk of having a child with DS, although the effect of combined risk genotypes might modify their individual effect and increase DS risk (J.M., Biselli et al., 2008a; Brandalize et al., 2010; Coppedè et al., 2006; Coppedè et al., 2009; da Silva et al., 2005; Martínez-Frías, et al., 2006; Scala et al., 2006; Wang et al., 2008). Moreover, there is evidence that the significance of genetic polymorphisms seems to depend on interactions with nutritional factors (Papoutsakis et al., 2010; Stover & Caudill, 2008).

6. Folate metabolism, genomic stability, and genetic polymorphisms

Both *in vitro* and *in vivo* studies have shown that DNA methylation is an important mechanism for the maintenance of genomic stability. Literature provides several examples that genome-wide DNA hypomethylation enhances the occurrence of aneuploidy and chromosomal rearrangements (Herrera et al., 2008), loss of heterozygosity (Matsuzaki et al., 2005), and chromosome malsegregation (Fenech et al., 2011). Folate and vitamin B_{12} are

among the most important minerals and vitamins required for DNA maintenance and prevention of DNA damage that could be induced by inadequate intake of these antimutagenic vitamins (Fenech, 2002). In human cells, folate deficiency is associated with DNA hypomethylation (Chang et al., 2011; Linhart et al., 2009), DNA instability (strand breakage, uracil misincorporation) (Linhart et al., 2009; Williams & Jacobson, 2010), aneuploidy of chromosomes 17 and 21 (Beetstra et al., 2005; Wang et al., 2004), apoptosis (Li et al., 2003), and necrosis (Beetstra et al., 2005). Low vitamin B_{12} status is also associated with DNA hypomethylation (Brunaud et al., 2003) and genetic instability (Andreassi et al., 2003; Botto et al., 2003).

There is increasing evidence of association between polymorphisms in folate and Hcy metabolizing genes and levels of chromosome damage. The *MTHFR* 677 C→T polymorphism is associated with diminished levels of 5-methylcytosine and DNA hypomethylation (Chen et al., 2010; Friso et al., 2002; Paz et al., 2002), micronucleus formation (Andreassi et al., 2003; Botto et al., 2003), and microsatellite instability (Naghibalhossaini et al., 2010) in the presence of the variant T allele. The homozygous variant genotype of another polymorphism of the *MTHFR* gene, 1298 A→C, was more frequent in patients with Turner syndrome (de Oliveira et al., 2008), and a higher frequency of the C allele was observed in spontaneous abortions with fetal chromosomal aneuploidy as compared to those with normal fetal karyotypes (Kim et al., 2011), suggesting its involvement in the origin of chromosomal imbalances. The *MTR* 2756 A→G polymorphism was associated with reduced number of hypermethylated CpG islands of suppressor tumor genes and with higher micronucleus rates in the presence of the *MTRR* 66 GG variant genotype (Botto et al., 2003; Paz et al., 2002; Zijno et al., 2003).

The polymorphism *RFC1* 80 A→G has been associated with reduced percentage of 5-methylcytosine in the DNA of mothers of children with autism in the presence of homozygous and heterozygous genotypes for the G allele as compared to AA genotype (James et al., 2010); however, the presence of the A allele was recently associated with increased oxidative DNA damage, while the *cSHMT* 1420 C→T polymorphism was associated with reduced oxidative DNA damage (CC>CT>TT) (Mohammad et al., 2011).

Moreover, Piskac-Collier et al. (2011) recently demonstrated that lymphocytes from lung cancer patients showed a considerably increased frequency of cytogenetic damage in the presence of *MTHFR* 677 C→T, *MTHFR* 1298 A→C, and *cSHMT* 435 C→T allelic variants, suggesting that interactions between genetic polymorphisms may also have a significant impact on genetic instability.

7. Predisposition to chromosome malsegregation in young DS mothers and its association with folate-metabolizing gene polymorphisms

Studies with women who have a DS child at a young age have suggested that they present genetic predispositions to chromosome malsegregation in both somatic and germ line cells. Migliore et al. (2006) observed increased frequency of binucleated-micronucleated lymphocytes in women who had a DS child before 35 years of age, and fluorescence in situ hybridization analysis revealed that micronuclei were mainly originating from chromosomal malsegregation events, including chromosome 21 malsegregation. Further studies from their group confirmed increased chromosome damage in blood cells of young DS mothers and showed a significant correlation between micronucleated cells and both

MTHFR 677C→T and 1298A→C polymorphisms. The mean frequency of binucleated-micronucleated cells increased significantly with the increasing number of *MTHFR* 677 T alleles, and *MTHFR* 1298 AA women have significantly higher binucleated-micronucleated cells frequency than do *MTHFR* 1298 AC + CC carriers (Coppedè et al., 2007; Coppedè, 2009). In addition, mothers who had a DS child at a young age showed increased frequency (of about 5-fold) of Alzheimer's disease (AD) (Schupf, et al., 2001). A unifying hypothesis trying to relate DS, trisomy 21, and AD has proposed that trisomy 21 mosaicism at the germ cell level or in brain cells could account for the familial aggregation of AD and DS (Potter, 1991). Together, these results suggest that young DS mothers are more prone to chromosome malsegregation, which could be true both for somatic (peripheral blood lymphocytes, brain) and for germ cells and, importantly, folate-metabolizing gene polymorphisms seem to play an important role on this susceptibility to aneuploidy.

8. Folate supplementation and DS prevention

Two important emerging areas of nutrition science are nutrigenomics, which refers to the effect of diet on DNA stability, and nutrigenetics, which refers to the impact of genetic differences between individuals on their response to a specific dietary pattern, functional food, or supplement for a specific health outcome. On these terms, two premises are important: (a) inappropriate nutrient supply can cause considerable levels of genome mutation and alter the expression of genes required for genome maintenance, and (b) common genetic polymorphisms may alter the activity of genes that affect the bioavailability of micronutrients and/or the affinity for micronutrient cofactors in key enzymes involved in DNA metabolism or repair, resulting in a lower or higher reaction rate (Bull & Fenech, 2008; Fenech, 2005).

As mentioned before, the folate-dependent biosynthesis of nucleotide precursors for DNA synthesis and genome methylation is dependent on the availability of many vitamins, including B_{12}, B_6, niacin, riboflavin, and minerals (zinc, cobalt), and is subject to regulation by other nutrients, such as iron and vitamin A, not directly involved in DNA or SAM biosynthesis (Stover, & Caudill 2008). Therefore, impairments in one-carbon metabolism, and the SAM cycle in particular, induced by nutritional deficiencies and/or genetic polymorphisms that encode folate-dependent enzymes, alter genome methylation patterns and gene expression levels (Stover, 2004; Stover, & Caudill 2008).

Since 1992, supplementation with 0.4 mg/daily of folic acid is recommended for women of childbearing age for the prevention of neural tube defects (Centers for Disease Control, 1992). Barkai et al. (2003) observed that families at risk for neural tube defects present with a higher frequency of DS cases and vice-versa, suggesting that both disorders are influenced by the same folate-related risk factors. However, two issues ought to be considered in the prevention of DS by folic acid: the dose and the timing of folic acid intake (Scala et al., 2006). It has been proposed that genomic instability is reduced at plasma folate concentrations above 34 nmol/L and Hcy concentrations below 7.5 μmol/L; these concentrations can only be reached with the ingestion of more than 0.4 mg/day of folic acid (Fenech, 2002). A report of a decreased occurrence of DS offspring in mothers supplemented with high doses of folic acid (6 mg/day) (Czeizel & Puho, 2005) supports the hypothesis of an involvement of folate in the etiology of DS. Concerning the timing of folate intake, it should be remembered that maternal MI errors in the primary oocyte may occur in a process that begins during fetal life and ends at the time of ovulation, whereas MII errors occur at the time of fertilization (Yoon

et al., 1996). Therefore, it is likely that only MII errors would be immediately affected by folic acid intake in adult women (Ray et al., 2003).

9. Conclusion

Currently available literature suggests that abnormal folate metabolism is associated with increased maternal risk for DS, with a complex interaction between genetic polymorphisms, environmental factors (i.e., nutritional factors), and epigenetic processes. However, given the complexity of the folate pathway, these complex interactions cannot be easily understood and none of the polymorphisms studied so far can be used in genetic counseling to predict the maternal risk for having a DS child (Coppedè et al., 2009). However, nutrigenetics and nutrigenomics are promising areas for evaluating the possibility of DS prevention with folic acid supplementation associated with susceptible genotypes. Thus, further large-scale studies are necessary to better understand the complex association between chromosomal 21 nondisjunction and folate metabolism.

10. References

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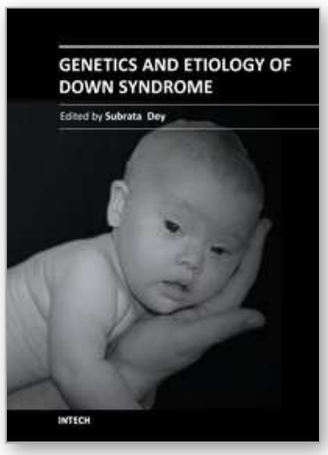

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This book provides a concise yet comprehensive source of current information on Down syndrome. Research workers, scientists, medical graduates and paediatricians will find it an excellent source for reference and review. This book has been divided into four sections, beginning with the Genetics and Etiology and ending with Prenatal Diagnosis and Screening. Inside, you will find state-of-the-art information on: 1. Genetics and Etiology 2. Down syndrome Model 3. Neurologic, Urologic, Dental & Allergic disorders 4. Prenatal Diagnosis and Screening Whilst aimed primarily at research workers on Down syndrome, we hope that the appeal of this book will extend beyond the narrow confines of academic interest and be of interest to a wider audience, especially parents and relatives of Down syndrome patients.

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