

We are IntechOpen, the world's leading publisher of Open Access books Built by scientists, for scientists

6,900

Open access books available

186,000

International authors and editors

200M

Downloads

Our authors are among the

154

Countries delivered to

TOP 1%

most cited scientists

12.2%

Contributors from top 500 universities



WEB OF SCIENCE™

Selection of our books indexed in the Book Citation Index
in Web of Science™ Core Collection (BKCI)

Interested in publishing with us?
Contact book.department@intechopen.com

Numbers displayed above are based on latest data collected.
For more information visit www.intechopen.com



Abnormal Folate Metabolism and Maternal Risk for Down Syndrome

Érika Cristina Pavarino¹, Bruna Lancia Zampieri²,
Joice Matos Biselli² and Eny Maria Goloni Bertollo¹

¹*Faculdade de Medicina de São José do Rio Preto – FAMERP, Unidade de Pesquisa em Genética e Biologia Molecular - UPGEM, Equipe Ding-Down;*

²*Faculdade de Medicina de São José do Rio Preto – FAMERP, Unidade de Pesquisa em Genética e Biologia Molecular - UPGEM, Brazil*

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 nondisjunction: (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 B₆ and vitamin B₁₂, 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).

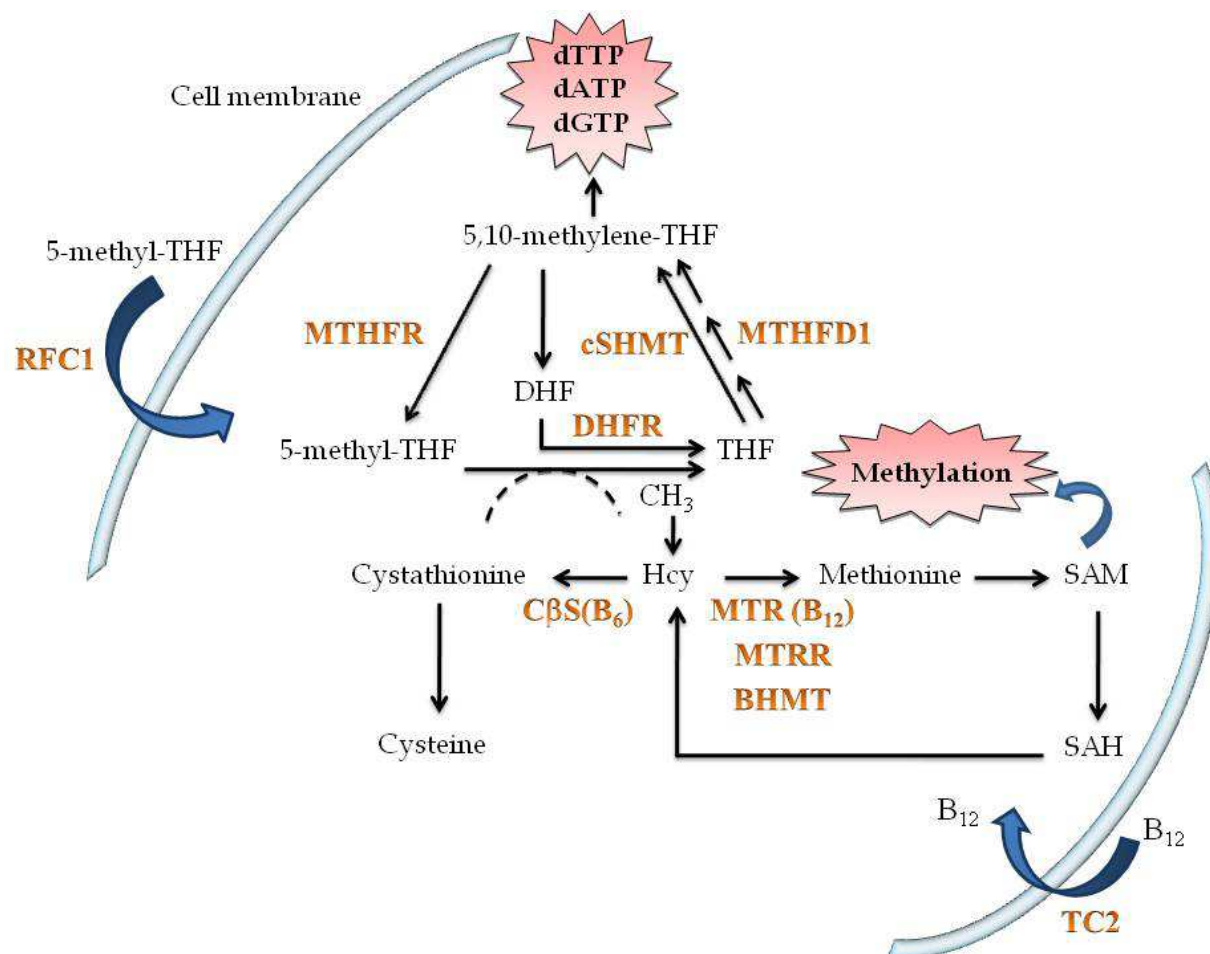


Fig. 1. Folate metabolism. BHMT = Betaine-homocysteine methyltransferase; B₆ = vitamin B₆; B₁₂ = vitamin B₁₂; CβS = Cystathionine β- synthase; CH₃ = Methyl; dATP = Deoxyadenosine 5'-triphosphate; dGTP = Deoxyguanosine 5'-triphosphate; dTTP = Deoxythymidine 5'-triphosphate; DHF = Dihydrofolate; DHFR = Dihydrofolate reductase; Hcy = Homocysteine; MTHFD1 = Methylene-tetrahydrofolate dehydrogenase 1; MTHFR = Methylene-tetrahydrofolate 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 *Dihydrofolate 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 Methylene tetrahydrofolate 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).

Methylene tetrahydrofolate 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 B₁₂ or cobalamin (Cbl) as a cofactor, and results in the formation of S-adenosylmethionine (SAM), the primary methyl (CH₃) 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)alamin acts as a methyl donor. In this reaction, the transfer of a methyl group from methylcob(III)alamin results in the formation of highly reactive cob(I)alamin, which is oxidized into cob(II)alamin, 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)alamin, 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 betaine 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 (C β S), a vitamin B₆-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 allele (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 substrates 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 B₁₂, 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 *MTHFD1* 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 B₁₂ (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 B₁₂ to tissues, resulting in enhanced B₁₂ 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 B₁₂ 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 B₁₂ 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 B₁₂ 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 (Naghbalhossaini 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 B₁₂, B₆, 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

- Abbag, F.I. (2006). Congenital heart diseases and other major anomalies in patients with Down syndrome. *Saudi Medical Journal*, Vol.27, No.2, (February 2006), pp. 219-222, ISSN 0379-5284
- Ahmed, I.; Ghafoor, T.; Samore, N.A. & Chattha, M.N. (2005). Down syndrome: clinical and cytogenetic analysis. *Journal of the College of Physicians and Surgeons – Pakistan: JCPSP*, Vol.15, No.7, (July 2005), pp. 426-429, ISSN 1022-386X
- Allen, E.G.; Freeman, S.B.; Druschel, C.; Hobbs, C.A.; O'Leary, L.A.; Romitti, P.A.; Royle, M.H.; Torfs, C.P. & Sherman, S.L. (2009). Maternal age and risk for trisomy 21 assessed by the origin of chromosome nondisjunction: a report from the Atlanta and National Down Syndrome Projects. *Human Genetics*, Vol.125, No.1, (February 2009), pp. 41-52, ISSN 0340-6717
- Ananth, C.V.; Elsasser D.A.; Kinzler, W.L.; Peltier, M.R.; Getahun, D.; Leclerc, D.; Rozen, R.R. & New Jersey Placental Abruptio Study Investigators. (2007). Polymorphisms in methionine synthase reductase and betaine-homocysteine S-methyltransferase genes: Risk of placental abruptio. *Molecular Genetics and Metabolism*, Vol.91, No.1, (May 2007), pp. 104–110, ISSN 1096-7192
- Andreassi, M.G.; Botto, N.; Cocci, F.; Battaglia, D.; Antonioli, E.; Masetti, S.; Manfredi, S.; Colombo, M.G.; Biagini, A. & Clerico, A. (2003). Methylenetetrahydrofolate reductase gene C677T polymorphism, homocysteine, vitamin B12, and DNA damage in coronary artery disease. *Human Genetics*, Vol.112, No.2, (February 2003), pp. 171-177, ISSN 0340-6717
- Antonarakis, S.E.; Petersen, M.B.; McInnis, M.G.; Adelsberger, P.A.; Schinzel, A.A.; Binkert, F.; Pangalos, C.; Raoul, O.; Slaugenhaupt, S.A.; Hafez, M.; Cohen, M.M.; Roulson, D.; Schwartz, S.; Mikkelsen, M.; Tranebjaerg, L.; Greenberg, F.; Hoar, D.I.; Rudd, N.L.; Warren, A.C.; Metaxotou, C.; Bartsocas, C. & Chakravarti, A. (1992). The meiotic stage of nondisjunction in trisomy 21: determination by using DNA polymorphisms. *American Journal of Human Genetics*, Vol.50, No.3, (March 1992), pp. 544-550, ISSN 0340-6717

- Aymé, S. & Lippman-Hand, A. (1982). Maternal-age effect in aneuploidy: does altered embryonic selection play a role? *American Journal of Human Genetics*, Vol.34, No.4, (July 1982), pp. 558-565, ISSN 0002-9297
- Bailey, L.B. & Gregory, J.F. (1999). Folate metabolism and requirements. *The Journal of Nutrition*, Vol.129, No.4, (April 1999), pp. 779-782, ISSN 0022-3166
- Barbero, J.L. (2011). Chromatid Cohesion Control and Aneuploidy. *Cytogenetic and Genome Research*, (January 2011), Epub ahead of print, ISSN 1424-8581
- Barbosa, P.R.; Stabler, S.P.; Trentin, R.; Carvalho, F.R.; Luchessi, A.D.; Hirata, R.D.; Hirata, M.H.; Allen, R.H. & Guerra-Shinohara, E.M. (2008). Evaluation of nutritional and genetic determinants of total homocysteine, methylmalonic acid and S-adenosylmethionine/S-adenosylhomocysteine values in Brazilian childbearing-age women. *Clinica Chimica Acta; International Journal of Clinical Chemistry*, Vol.388, No.1-2, (February 2008), pp. 139-147, ISSN 0009-8981
- Barkai, G.; Arbuzova, S.; Berkenstadt, M.; Heifetz, S. & Cuckle H. (2003). Frequency of Down's syndrome and neural-tube defects in the same family. *Lancet*, Vol.361, No.9366, (April 2003), pp. 1331-1335, ISSN 0140-6736
- Beetstra, S.; Thomas, P.; Salisbury, C.; Turner, J. & Fenech, M. (2005). Folic acid deficiency increases chromosomal instability, chromosome 21 aneuploidy and sensitivity to radiation-induced micronuclei. *Mutation Research*, Vol.578, No.1-2, (October 2005), pp. 317-326, ISSN 0027-5107
- Bestor, T.H. (2000). The DNA methyltransferases of mammals. *Human Molecular Genetics*, Vol.9, No.16, (October 2000), pp. 2395-2402, ISSN 0964-6906
- Biselli, P.M.; Sanches de Alvarenga, M.P.; Abbud-Filho, M.; Ferreira-Baptista, M.A.; Galbiatti, A.L.; Goto, M.T.; Cardoso, M.A.; Eberlin, M.N.; Haddad, R.; Goloni-Bertollo, E.M. & Pavarino-Bertelli E.C. (2007). Effect of folate, vitamin B6, and vitamin B12 intake and MTHFR C677T polymorphism on homocysteine concentrations of renal transplant recipients. *Transplantation proceedings*, Vol.39, No.10, (December 2007), pp. 3163-3165, ISSN 0041-1345
- Biselli, J.M.; Goloni-Bertollo, E.M.; Zampieri, B.L.; Haddad, R.; Eberlin, M.N. & Pavarino-Bertelli E.C. (2008a). Genetic polymorphisms involved in folate metabolism and elevated concentrations of plasma homocysteine: maternal risk factors for Down syndrome in Brazil. *Genetics and Molecular Research*, Vol. 7, No.1, (January 2008), pp. 33-42, ISSN 1676-5680
- Biselli, J.M.; Goloni-Bertollo, E. M.; Ruiz, M.T.; & Pavarino-Bertelli, E.C. (2008b). Cytogenetic profile of Down syndrome cases seen by a general genetics outpatient service in Brazil. *Down's syndrome, research and practice*, Vol.12, No.3, (February 2008), ISSN 0968-7912
- Biselli, J.M.; Brumati, D.; Frigeri, V.F.; Zampieri, B.L.; Goloni-Bertollo, E.M. & Pavarino-Bertelli, E.C. (2008c). A80G polymorphism of reduced folate carrier 1 (RFC1) and C776G polymorphism of transcobalamin 2 (TC2) genes in Down's syndrome etiology. *Sao Paulo Medical Journal*, Vol.126, No.6, (November 2008), pp. 329-332, ISSN 1516-3180
- Bosco, P.; Guéant-Rodriguez, R.M.; Anello, G.; Barone, C.; Namour, F.; Caraci, F.; Romano, A.; Romano, C. & Guéant, J.L. (2003). Methionine synthase (MTR) 2756 (A→G) polymorphism, double heterozygosity Methionine synthase 2756AG / Methionine synthase reductase (MTRR 66AG) and elevated homocysteinemia are three risk

- factors for having a child with Down syndrome. *American Journal of Medical Genetics Part A*, Vol.121, No.3, (September 2003), pp. 219-224, ISSN 1552-4825
- Botto, N.; Andreassi, M.G.; Manfredi, S.; Masetti, S.; Cocci, F.; Colombo, M.G.; Storti, S.; Rizza, A. & Biagini, A. (2003). Genetic polymorphisms in folate and homocysteine metabolism as risk factors for DNA damage. *European Journal of Human Genetics*, Vol.11, No.9, (September 2003), pp. 671-678, ISSN 1018-4813
- Bowron, A.; Scott, J. & Stansbie, D. (2005). The influence of genetic and environmental factors on plasma homocysteine concentrations in a population at high risk for coronary artery disease. *Annals of Clinical Biochemistry*, Vol.42, No.Pt6, (November 2005), pp. 459-462, ISSN 0004-5632
- Brandalize, A.P.; Bandinelli, E.; dos Santos, P.A. & Schüler-Faccini, L. (2010). Maternal gene polymorphisms involved in folate metabolism as risk factors for Down syndrome offspring in Southern Brazil. *Disease Markers*, Vol.29, No.2, pp. 95-101, ISSN 0278-0240
- Brunaud, L.; Alberto, J.M.; Ayav, A.; Gérard, P.; Namour, F.; Antunes, L.; Braun, M.; Bronowicki, J.P.; Bresler, L. & Guéant, J.L. (2003). Vitamin B12 is a strong determinant of low methionine synthase activity and DNA hypomethylation in gastrectomized rats. *Digestion*, Vol.68, No.2-3, (November 2003), pp. 133-40, ISSN 0012-2823
- Bull, C. & Fenech, M. (2008). Genome-health nutrigenomics and nutrigenetics: nutritional requirements or 'nutriomes' for chromosomal stability and telomere maintenance at the individual level. *The Proceedings of Nutrition Society*, Vol.67, No.2, (May 2008), pp. 146-156, ISSN 0029-6651
- Centers for Disease Control. (1992). Recommendations for the use of folic acid to reduce the number of cases of spina bifida and other neural tube defects. *MMWR. Recommendations and reports: Morbidity and mortality weekly report. Recommendations and reports / Centers for Disease Control*, Vol.41, No. RR-14, (September 1992), pp. 1-7, ISSN 1057-5987
- Chang, H.; Zhang, T.; Zhang, Z.; Bao, R.; Fu, C.; Wang, Z.; Bao, Y.; Li, Y.; Wu, L.; Zheng, X. & Wu, J. (2011). Tissue-specific distribution of aberrant DNA methylation associated with maternal low-folate status in human neural tube defects. *The Journal of Nutritional Biochemistry*, (February 2011), Epub ahead of print, ISSN 0955-2863
- Chango, A.; Fillon-Emery, N.; de Courcy, G.P.; Lambert, D.; Pfister, M.; Rosenblatt, D.S. & Nicolas, J.P. (2000). A polymorphism (80G->A) in the Reduced folate carrier gene and its associations with folate status and homocysteinemia. *Molecular Genetics and Metabolism*, Vol.70, No.4, (August 2000), pp. 310-315, ISSN 1096-7192
- Chango, A.; Fillon-Emery, N.; Mircher, C.; Bléhaut, H.; Lambert, D.; Herbeth, B.; James, S.J.; Réthoré, M.O. & Nicolas, J.P. (2005). No association between common polymorphisms in genes of folate/homocysteine metabolism and the risk of Down syndrome among French mothers. *The British Journal of Nutrition*, Vol.95, No.2, (August 2005), pp. 166-169, ISSN 0007-1145
- Chen, X.; Guo, J.; Lei, Y.; Zou, J.; Lu, X.; Bao, Y.; Wu, L.; Wu, J.; Zheng, X.; Shen, Y.; Wu, B.L. & Zhang, T. (2010). Global DNA hypomethylation is associated with NTD-affected pregnancy: A case-control study. *Birth Defects Research. Part A, Clinical and Molecular Teratology*, Vol.88, No.7, (July 2010), pp. 575-581, ISSN 1542-0760

- Cheng, D.M.; Jiang, Y.G.; Huang, C.Y.; Kong, H.Y.; Pang, W. & Yang, H.P. (2010). Polymorphism of MTHFR C677T, serum vitamin levels and cognition in subjects with hyperhomocysteinemia in China. *Nutritional Neuroscience*, Vol.13, No.4, (August 2010), pp. 175-182, ISSN 1028-415X
- Chiang, T.; Duncan, F.E.; Schindler, K.; Schultz, R.M. & Lampson, M.A. (2010). Evidence that weakened centromere cohesion is a leading cause of age-related aneuploidy in oocytes. *Current Biology: CB*, Vol.20, No.17, (September 2010), pp.1522-1528, ISSN 0960-9822
- Christensen, K.E.; Rohlicek, C.V.; Andelfinger, G.U.; Michaud, J.; Bigras, J.L.; Richter, A.; Mackenzie, R.E. & Rozen, R. (2008). The MTHFD1 p.Arg653Gln variant alters enzyme function and increases risk for congenital heart defects. *Human Mutation*, Vol.30, No.2, (February 2008), pp. 212-220, ISSN 1098-1004
- Contestabile, A.; Benfenati, F. & Gasparini, L. (2010). Communication breaks-Down: from neurodevelopment defects to cognitive disabilities in Down syndrome. *Progress in Neurobiology*, Vol.91, No.1, (May 2010), pp. 1-22, ISSN 0301-0082
- Coppedè, F.; Marini, G.; Bargagna, S.; Stuppia, L.; Minichilli, F.; Fontana, I.; Colognato, R.; Astrea, G.; Palka, G. & Migliore, L. (2006). Folate gene polymorphisms and the risk of Down syndrome pregnancies in young Italian women. *American Journal of Medical Genetics Part A*, Vol.140, No.10, (May 2006), pp. 1083-1091, ISSN 1552-4825
- Coppedè, F.; Colognato, R.; Bonelli, A.; Astrea, G.; Bargagna, S.; Siciliano, G. & Migliore, L. (2007). Polymorphisms in folate and homocysteine metabolizing genes and chromosome damage in mothers of Down syndrome children. *American Journal of Medical Genetics. Part A*, Vol.143A, No.17, (September 2007), pp. 2006-2015, ISSN 1552-4825
- Coppedè, F.; Migheli, F.; Bargagna, S.; Siciliano, G.; Antonucci, I.; Stuppia, L.; Palka, G. & Migliore, L. (2009). Association of maternal polymorphisms in folate metabolizing genes with chromosome damage and risk of Down syndrome offspring. *Neuroscience Letters*, Vol.449, No.1, (January 2009), pp. 15-19, ISSN 0304-3940
- Coppedè, F. (2009). The complex relationship between folate/homocysteine metabolism and risk of Down syndrome. *Mutation Research*, Vol.682, No.1, (July-August 2009), pp. 54-70, ISSN 0027-5107
- Czeizel, A.E. & Puhó, E. (2005). Maternal use of nutritional supplements during the first month of pregnancy and decreased risk of Down's syndrome: case-control study. *Nutrition*, Vol.21, No.6, (June 2005), pp.698-704, ISSN 0899-9007
- da Silva, L.R.; Vergani, N.; Galdieri, Lde.C.; Ribeiro Porto, M.P.; Longhitano, S.B.; Brunoni, D.; D'Almeida, V. & Alvarez Perez AB. (2005). Relationship between polymorphisms in genes involved in homocysteine metabolism and maternal risk for Down syndrome in Brazil. *American Journal of Medical Genetics Part A*, Vol.135, No. 3, (June 2005), pp. 263-267, ISSN 1552-4825
- De Oliveira, K.C.; Bianco, B.B.; Verreschi, I.T.; Guedes, A.D.; Galera, B.B.; Galera, M.F.; Barbosa, C.P. & Lipay, M.V. (2008). Prevalence of the polymorphism MTHFR A1298C and not MTHFR C677T is related to chromosomal aneuploidy in Brazilian Turner Syndrome patients. *Arquivos Brasileiros de Endocrinologia e Metabologia*, Vol.52, No.8, (November 2008), pp. 1374-1381, ISSN 0004-2730

- DeAngelis, J.T.; Farrington, W.J. & Tollefsbol, T.O. (2008). An overview of epigenetic assays. *Molecular Biotechnology*, Vol.38, No.2, (February 2008), pp. 179-183, ISSN 1073-6085
- DeVos, L.; Chanson, A.; Liu, Z.; Ciappio, E.D.; Parnell, L.D.; Mason, J.B.; Tucker, K.L. & Crott, J.W. (2008). Associations between single nucleotide polymorphisms in folate uptake and metabolizing genes with blood folate, homocysteine, and DNA uracil concentrations. *American Journal of Clinical Nutrition*, Vol.88, No.4, (October 2008), pp. 1149-1158, ISSN 0002-9165
- Feix, A.; Fritsche-Polanz, R.; Kletzmayer, J.; Vychytil, A.; Horl, W.H.; Sunder-Plassmann, G. & Födinger, M. (2001). Increased prevalence of combined MTR and MTHFR genotypes among individuals with severely elevated total homocysteine plasma levels. *American journal of kidney diseases: the official journal of the National Kidney Foundation*, Vol.38, No.5, (November 2001), pp. 956-964, ISSN 0272-6386
- Fenech, M. (2002). Micronutrients and genomic stability: a new paradigm for recommended dietary allowances (RDAs). *Food and chemical toxicology: an international journal published for the British Industrial Biological Research Association*, Vol.40, No.8, (August 2002), pp. 1113-1117, ISSN 0278-6915
- Fenech, M.; Baghurst, P.; Luderer, W.; Turner, J.; Record, S.; Ceppi, M. & Bonassi, S. (2005). Low intake of calcium, folate, nicotinic acid, vitamin E, retinol, b-carotene and high intake of pantothenic acid, biotin and riboflavin are significantly associated with increased genome instability - results from a dietary intake and micronucleus index survey in South Australia. *Carcinogenesis*, Vol. 26, No.5, (May 2005), pp. 991-999, ISSN 0143-3334
- Fenech, M.; Kirsch-Volders, M.; Natarajan, A.T.; Surrallés, J.; Crott, J.W.; Parry, J.; Norppa, H.; Eastmond, D.A.; Tucker, J.D. & Thomas P. (2011). Molecular mechanisms of micronucleus, nucleoplasmic bridge and nuclear bud formation in mammalian and human cells. *Mutagenesis*, Vol.26, No.1, (January 2011), pp. 125-132, ISSN 0267-8357
- Fillon-Emery, N.; Chango, A.; Mircher, C.; Barbé, F.; Bléhaut, H.; Herbeth, B.; Rosenblatt, D.S.; Réthoré, M.O.; Lambert, D. & Nicolas, J.P. (2004). Homocysteine concentrations in adults with trisomy 21: effect of B vitamins and genetic polymorphisms. *The American Journal of Clinical Nutrition*, Vol.80, No.6, (December 2004), pp. 1551-1557, ISSN 0002-9165
- Finkelstein, J.D. & Martin, J.J. (2000). Homocysteine. *The International Journal of Biochemistry & Cell Biology*, Vol.32, No.4, (April 2000), pp. 385-389, ISSN 1357-2725
- Fintelman-Rodrigues, N.; Corrêa, J.C.; Santos, J.M.; Pimentel, M.M. & Santos-Rebouças, C.B. (2009). Investigation of CBS, MTR, RFC-1 and TC polymorphisms as maternal risk factors for Down syndrome. *Disease Markers*, Vol.26, No.4, pp. 155-161, ISSN 0278-0240
- Fredriksen, A.; Meyer, K.; Ueland, P.M.; Vollset, S.E.; Grotmol, T. & Schneede, J. (2007). Large-scale population-based metabolic phenotyping of thirteen genetic polymorphisms related to one-carbon metabolism. *Human Mutation*, Vol.28, No.9, (September 2007), pp. 856-865, ISSN 1098-1004
- Friso, S.; Choi, S.W.; Girelli, D.; Mason, J.B.; Dolnikowski, G.G.; Bagley, P.J.; Olivieri, O.; Jacques, P.F.; Rosenberg, I.H.; Corrocher, R. & Selhub, J. (2002). A common

- mutation in the 5,10-methylenetetrahydrofolate reductase gene affects genomic DNA methylation through an interaction with folate status. *Proceedings of the National Academy of Sciences of the United States of America*, Vol.99, No.8, (April 2002), pp. 5606-5611, ISSN 0027-8424
- Frosst, P.; Blom, H.J.; Milos, R.; Goyette, P.; Sheppard, C.A.; Matthews, R.G.; Boers, G.J.H.; den Heijer, M.; Kluijtmans, L.A.J.; van den Heuvel, L.P. & Rozen, R. (1995). A candidate genetic risk factor for vascular disease: a common mutation in Methylenetetrahydrofolate reductase. *Nature Genetics*, Vol.10, No.1, (May 1995), pp. 111-113, ISSN 1061-4036
- Gellekink, H.; Blom, H.J.; van der Linden, I.J. & den Heijer, M. (2007). Molecular genetic analysis of the human dihydrofolate reductase gene: relation with plasma total homocysteine, serum and red blood cell folate levels. *European Journal of Human Genetics: EJHG*, Vol.15, No.1, (January 2007), pp. 103-109, ISSN 1018-4813
- Ghosh, S.; Feingold, E. & Dey, S.K. (2009). Etiology of Down syndrome: Evidence for consistent association among altered meiotic recombination, nondisjunction, and maternal age across populations. *American Journal of Medical Genetics Part A*, Vol.149A, No.7, (July 2009), pp. 1415-1420, ISSN 1552-4825
- Guenther, B.D.F.; Sheppard, C.A.; Tran, P.; Rozen, R.; Matthews, R.G. & Ludwig, M.L. (1999). The structure and properties of methylenetetrahydrofolate reductase from *Escherichia coli* suggest how folate ameliorates human hyperhomocysteinemia. *Nature Structural and Molecular Biology*, Vol.6, No.4, (April 1999), pp. 359-365, ISSN 1072-8368
- Hall, J. & Solehdin, F. (1998). Folic acid for the prevention of congenital anomalies. *European Journal of Pediatrics*, Vol.157, No.6, (June 1998), pp. 445-450, ISSN 0340-6199
- Harmon, D.L.; Shields, D.C.; Woodside, J.V.; McMaster, D.; Yarnell, J.W.G.; Young, I.S.; Peng, K.; Shane, B.; Evans, A.E. & Whitehead, A.S. (1999). Methionine synthase D919G polymorphism is a significant but modest determinant of circulating homocysteine concentrations. *Genetic Epidemiology*, Vol.17, No.4, (November 1999), pp. 298-309, ISSN 0741-0395
- Hasle, H.; Clemmensen, I.H. & Mikkelsen, M. (2000). Risks of leukaemia and solid tumours in individuals with Down's syndrome. *Lancet*, Vol.355, No.9199, (January 2000), pp. 165-169, ISSN 0140-6736
- Hassold, T. & Sherman, S. (2000). Down syndrome: genetic recombination and the origin of the extra chromosome 21. *Clinical Genetics*, Vol.57, No.2, (February 2000), pp. 95-100, ISSN 0009-9163
- Hassold, T. & Hunt, P. (2001). To err (meiotically) is human: the genesis of human aneuploidy. *Nature Reviews. Genetics*, Vol.2, No.4, (April 2001), pp. 280-291, ISSN 1471-0056
- Herrera, L.A.; Prada, D.; Andonegui, M.A. & Dueñas-González, A. (2008). The epigenetic origin of aneuploidy. *Current Genomics*, Vol.9, No.1, (March 2008), pp. 43-50, ISSN 1389-2029
- Hobbs, C.A.; Cleves, M.A.; Lauer, R.M.; Burns, T.L. & James, S.J. (2002). Preferential transmission of the MTHFR 677 T allele to infants with Down syndrome: implications for a survival advantage. *American Journal of Medical Genetics*, Vol.113, No.1, (November 2002), pp. 9-14, ISSN 1552-4825

- Hum, D.W.; Bell, A.W.; Rozen, R. & MacKenzie, R.E. (1988). Primary structure of a human trifunctional enzyme. Isolation of a cDNA encoding methylenetetrahydrofolate dehydrogenase-methenyltetrahydrofolate cyclohydrolase-formyltetrahydrofolate synthetase. *The Journal of Biological Chemistry*, Vol.263, No.31, (November 1988), pp. 15946-15950, ISSN 0021-9258
- James, S.J.; Melnyk, S.; Jernigan, S.; Pavliv, O.; Trusty, T.; Lehman, S.; Seidel, L.; Gaylor, D.W. & Cleves, M.A. (2010). A functional polymorphism in the reduced folate carrier gene and DNA hypomethylation in mothers of children with autism. *American Journal of Medical Genetics. Part B, Neuropsychiatric genetics : the official publication of the International Society of Psychiatric Genetics*, Vol. 153B, No. 6, (September 2010), pp. 1209-1220, ISSN 1552-4841
- Johnson, W.G.; Stenroos, E.S.; Spychala, J.R.; Chatkupt, S.; Ming, S.X. & Buyske, S. (2004). New 19 bp deletion polymorphism in intron-1 of dihydrofolate reductase (DHFR): a risk factor for spina bifida acting in mothers during pregnancy? *American Journal of Medical Genetics Part A*, Vol.124, No.4, (February 2004), pp.339-345, ISSN 1552-4825
- Jones, K.L. (2006). *Smith's recognizable patterns of human malformation* (6th edition), Elsevier Saunders, ISBN 0-7216-0615-6, Philadelphia.
- Jyothy, A.; Kumar, K.S.; Mallikarjuna. G.N.; Babu Rao, V.; Uma Devi, B.; Sujatha M. & Reddy, P.P. (2001). Parental age and the origin of extra chromosome 21 in Down syndrome. *Journal of Human Genetics*, Vol.46, No.6, pp. 347-350, ISSN1434-5161
- Karpen, G.H. & Allshire, R.C. (1997). The case for epigenetic effects on centromere identity and function. *Trends in Genetics: TIG*, Vol.13, No.12, (December 1997), pp. 489-496, ISSN 0168-9525
- Kim, S.Y.; Park, S.Y.; Choi, J.W.; Kim, D.J.; Lee, S.Y.; Lim, J.H.; Han, J.Y.; Ryu, H.M. & Kim, M.H. (2011). Association between MTHFR 1298A>C polymorphism and spontaneous abortion with fetal chromosomal aneuploidy. *American Journal of Reproductive Immunology* (New York, N.Y.: 1989), (March 2011), Epub ahead of print, ISSN 1046- 7408
- Kovaleva, N.V.; Tahmasebi-Hesari, M. & Verlinskaia, D.K. (2010). Grandmaternal age in children with Down syndrome in St. Petersburg. *Tsitologiya i Genetika*, Vol.44, No.5, (September-October 2010), pp. 47-53, ISSN 0564-3783
- Kraus, J.P. (1998). Biochemistry and molecular genetics of cystathionine beta-synthase deficiency. *European Journal of Pediatrics*, Vol.157, No.Suppl 2, (April 1998), pp. S50-S53, ISSN 0340-6199
- Kumar, J.; Garg, G.; Karthikeyan, G. & Sengupta, S. (2010). Cystathionine beta-synthase 844Ins68 polymorphism is not associated with the levels of homocysteine and cysteine in an Indian population. *Biomarkers: biochemical indicators of exposure, response, and susceptibility to chemicals*, Vol.15, No.3, (May 2010), pp. 283-287, ISSN 1354-750X
- Lamb, N.E.; Freeman, S.B.; Savage-Austin, A.; Pettay, D.; Taft, L.; Hersey, J.; Gu, Y.; Shen, J.; Saker, D.; May, K.M.; Avramopoulos, D.; Petersen, M.B.; Hallberg, A.; Mikkelsen, M.; Hassold, T.J. & Sherman, S.L. (1996). Susceptible chiasmate configurations of chromosome 21 predispose to non-disjunction in both maternal meiosis I and meiosis II. *Nature Genetics*, Vol.14, No.4, (December 1996), pp. 400-405, ISSN 1061-4036

- Lamb, N.E.; Yu, K.; Shaffer, J.; Feingold, E. & Sherman SL. (2005). Association between maternal age and meiotic recombination for trisomy 21. *American Journal of Human Genetics*, Vol.76, No.1, (January 2005), pp. 91-99, ISSN 0002-9297
- Leclerc, D.; Odièvre, M.; Wu, Q.; Wilson, A.; Huizenga, J.J.; Rozen, R.; Scherer, S.W. & Gravel, R.A. (1999). Molecular cloning, expression and physical mapping of the human methionine synthase reductase gene. *Gene*, Vol.240, No.1, (November 1999), pp. 75-88, ISSN 0378-1119
- Li, G.M.; Presnell SR & Gu L. (2003). Folate deficiency, mismatch repair-dependent apoptosis, and human disease. *The Journal of Nutritional Biochemistry*, Vol.14, No.10, (October 2003), pp. 568-75, ISSN 0955-2863
- Lin, M.Y. & Young, C.M. (2000). Folate levels in cultures of lactic acid bacteria. *International dairy journal / published in association with the International Dairy Federation.*, Vol.10, pp. 409-414, ISSN 0958-6946
- Linhart, H.G.; Troen, A.; Bell, G.W.; Cantu, E.; Chao, W.H.; Moran, E.; Steine, E.; He, T. & Jaenisch, R. (2009). Folate deficiency induces genomic uracil misincorporation and hypomethylation but does not increase DNA point mutations. *Gastroenterology*, Vol.136, No.1, (January 2009), pp. 227-235.e3, ISSN 0016-5085
- Lott, I.T. & Head, E. (2005). Alzheimer disease and Down syndrome: factors in pathogenesis. *Neurobiology of Aging*, Vol.26, No.3, pp. 383-389, ISSN 197-4580
- Malini, S.S. & Ramachandra, N.B. (2006). Influence of advanced age of maternal grandmothers on Down syndrome. *BMC Medical Genetics*, Vol.14, (January 2006), pp. 7-4, ISSN 1471-2350
- Martínez-Frías, M.L.; Pérez, B.; Desviat, L.R.; Castro, M.; Leal, F.; Rodríguez, L.; Mansilla, E.; Martínez-Fernández, M.L.; Bermejo, E.; Rodríguez-Pinilla, E.; Prieto, D.; Ugarte, M & ECEMC Working Group. (2006). Maternal polymorphisms 677C-T and 1298A-C of MTHFR, and 66A-G MTRR genes: is there any relationship between polymorphisms of the folate pathway, maternal homocysteine levels, and the risk for having a child with Down syndrome? *American Journal of Medical Genetics. Part A*, Vol.140, No.9, (May 2006), pp. 987-997, ISSN 1552-4825
- Martínez-Frías, M.L. (2008). The biochemical structure and function of methylenetetrahydrofolate reductase provide the rationale to interpret the epidemiological results on the risk for infants with Down syndrome. *American Journal of Medical Genetics Part A*, Vol.146, No.11, (June 2008), pp.1477-1482, ISSN 1552-4825
- Matsuzaki, K.; Deng, G.; Tanaka, H.; Kakar, S.; Miura, S. & Kim, Y.S. (2005). The relationship between global methylation level, loss of heterozygosity, and microsatellite instability in sporadic colorectal cancer. *Clinical Cancer Research: an official journal of the American Association for Cancer Research*, Vol.15, No.11, (December 2005), pp. 8564-8569, ISSN 1078-0432
- McNulty, H. & Pentieva, K. (2004). Folate bioavailability. *The Proceedings of the Nutritional Society*, Vol.63, No.4, (November 2004), pp. 529-536, ISSN 1475-2719.
- McNulty, H. & Scott, J.M. (2008). Intake and status of folate and related B-vitamins: considerations and challenges in achieving optimal status. *The British Journal of Nutrition*, Vol.99, No.Suppl 3, (June 2008), pp. S48-54, ISSN 0007-1145

- Meguid, N.A.; Dardir, A.A.; Khass, M.; Hossieny, L.E.; Ezzat, A. & El Awady, M.K. (2008). MTHFR genetic polymorphism as a risk factor in Egyptian mothers with Down syndrome children. *Disease Markers*, Vol. 24, No.1, pp. 19-26, ISSN 0278-0240
- Mendes, C.C.; Biselli, J.M.; Zampieri, B.L.; Goloni-Bertollo, E.M.; Eberlin, M.N.; Haddad, R.; Riccio, M.F.; Vannucchi, H.; Carvalho, V.M. & Pavarino-Bertelli, E.C. (2010). 19-base pair deletion polymorphism of the dihydrofolate reductase (DHFR) gene: maternal risk of Down syndrome and folate metabolism. *Sao Paulo Medical Journal*, Vol.128, No.4, (July 2010), pp. 215-218, ISSN 1516-3180
- Migliore, L.; Boni, G.; Bernardini, R.; Trippi, F.; Colognato, R.; Fontana, I.; Coppedè, F. & Sbrana, I. (2006). Susceptibility to chromosome malsegregation in lymphocytes of women who had a Down syndrome child in young age. *Neurobiology of Aging*, Vol.27, No.5, (May 2006), pp. 710-716, ISSN 197-4580
- Miller, J.W.; Ramos, M.I.; Garrod, M.G.; Flynn, M.A. & Green, R. (2002). Transcobalamin II 775G>C polymorphism and indices of vitamin B12 status in healthy older adults. *Blood*, Vol.100, No.2, pp. 718-720, ISSN 0006-4971
- Mohammad, N.S.; Yedluri, R.; Addepalli, P.; Gottumukkala, S.R.; Digumarti, R.R. & Kutala, V.K. (2011). Aberrations in one-carbon metabolism induce oxidative DNA damage in sporadic breast cancer. *Molecular and Cellular Biochemistry*, Vol.349, No.1-2, (March 2011), pp. 159-167, ISSN 0300-8177
- Naghibalhossaini, F.; Mokarram, P.; Khalili, I.; Vasei, M.; Hosseini, S.V.; Ashktorab, H.; Rasti, M. & Abdollahi, K. (2010). MTHFR C677T and A1298C variant genotypes and the risk of microsatellite instability among Iranian colorectal cancer patients. *Cancer Genetics and Cytogenetics*, Vol.197, No.2, (March 2010), pp. 142-51, ISSN 0165-4608
- Namour, F.; Guy, M.; Aimone-Gastin, I.; de Nonancourt, M.; Mrabet, N. & Guéant, J.L. (1998). Isoelectrofocusing phenotype and relative concentration of transcobalamin II isoproteins related to the codon 259 Arg/Pro polymorphism. *Biochemical and Biophysical Research Communications*, Vol.251, No.3, (October 1999), pp. 769-774, ISSN 0006-291X
- Narayanan, S.; McConnell, J.; Little, J.; Sharp, L.; Piyathilake, C.J.; Powers, H.; Basten, G. & Duthie, S.J. (2004). Associations between two common variants C677T and A1298C in the methylenetetrahydrofolate reductase gene and measures of folate metabolism and DNA stability (strand breaks, misincorporated uracil, and DNA methylation status) in human lymphocytes in vivo. *Cancer epidemiology, biomarkers & prevention : a publication of the American Association for Cancer Research, cosponsored by the American Society of Preventive Oncology*, Vol.13, No.9, (September 2004), pp.1436-1443, ISSN 055-9965
- Nguyen, T.T.; Dyer, D.L.; Dunning, D.D.; Rubin, S.A.; Grant, K.E. & Said, H.M. (1997). Human intestinal folate transport: cloning, expression, and distribution of complementary RNA. *Gastroenterology*, Vol.112, No.3, (March 1997), pp. 783-791, ISSN 0016-5085
- O'Leary, V.B.; Parle-McDermott, A.; Molloy, A.M.; Kirke, P.N.; Johnson, Z.; Conley, M.; Scott, J.M. & Mills, J.L. (2002). MTRR and MTHFR polymorphism: link to Down syndrome? *American Journal of Medical Genetics*, Vol.107, No.2, (January 2002) pp. 151-155, ISSN 0148-7299

- Olteanu, H. & Banerjee, R. (2001). Human methionine synthase reductase, a soluble P-450 reductase-like dual flavoprotein, is sufficient for NADPH-dependent methionine synthase activation. *The Journal of Biological Chemistry*, Vol.276, No.38, (September 2001), pp. 35558-35563, ISSN 21-9258
- Olteanu, H.; Munson, T. & Banerjee, R. (2002). Differences in the efficiency of reductive activation of methionine synthase and exogenous electron acceptors between the common polymorphic variants of human methionine synthase reductase. *Biochemistry*, Vol.41, No.45, (November 2002), pp. 13378–13385, ISSN 0006-2960
- Pajares, M.A. & Pérez-Sala, D. (2006). Betaine homocysteine S-methyltransferase: just a regulator of homocysteine metabolism? *Cellular and molecular life sciences : CMLS*, Vol.63, No.23, (December 2006), pp. 2792-2803, ISSN 1420-682X
- Papoutsakis, C.; Manios, Y.; Magkos, F.; Papaconstantinou, E.; Schulpis, K.H.; Zampelas, A.; Matalas, A.L. & Yiannakouris, N. (2010). Effect of the methylenetetrahydrofolate reductase (MTHFR 677C>T) polymorphism on plasma homocysteine concentrations in healthy children is influenced by consumption of folate-fortified foods. *Nutrition (Burbank, Los Angeles County, Calif.)*, Vol.26, No.10, (October 2010), pp. 969-974, ISSN 0899-9007
- Parle-McDermott, A.; Pangilinan, F.; Mills, J.L.; Kirke, P.N.; Gibney, E.R.; Troendle, J.; O'Leary, V.B.; Molloy, A.M.; Conley, M.; Scott, J.M. & Brody, L.C. (2007). The 19-bp deletion polymorphism in intron-1 of dihydrofolate reductase (DHFR) may decrease rather than increase risk for spina bifida in the Irish population. *American Journal of Medical Genetics. Part A*, Vol.143, No.11, (June 2007), pp. 1174-1180, ISSN 1552-4825
- Pavarino-Bertelli, E.C.; Biselli, J.M.; Bonfim, D. & Goloni-Bertollo, E.M. (2009). Clinical profile of children with Down syndrome treated in a genetics outpatient service in the southeast of Brazil. *Revista da Associação Médica Brasileira* (1992), Vol.55, No.5, (September-October 2009), pp. 547-552, ISSN 0104-4230
- Paz, M.F.; Ávila, S.; Fraga, M.F.; Pollan, M.; Capella, G.; Peinado, M.A.; Sanchez-Cespedes, M.; Herman, J.G. & Esteller, M. (2002). Germ-line variants in methyl-group metabolism genes and susceptibility to DNA methylation in normal tissues and human primary tumors. *Cancer Research*, Vol.62, No.15, (August 2002), pp. 4519-4524, ISSN 0008-5472
- Pepe, G.; Vanegas, O.C.; Rickards, O.; Giusti, B.; Comeglio, P.; Brunelli, T; Marcucci, R.; Prisco, D.; Gensini, G.F. & Abbate, R. (1999). World distribution of the T833C/844INS68 CBS in cis double mutation: a reliable anthropological marker. *Human Genetics*, Vol. 104, No.2, (February 1999), pp. 126-129, ISSN 0340-6717
- Piskac-Collier, A.L.; Monroy, C.; Lopez, M.S.; Cortes, A.; Etzel, C.J.; Greisinger, A.J.; Spitz, M.R. & El-Zein, R.A. (2011). Variants in folate pathway genes as modulators of genetic instability and lung cancer risk. *Genes, Chromosomes & Cancer*, Vol.50, No.1, (January 2011), pp. 1-12, ISSN 1045-2257
- Potter, H. (1991). Review and hypothesis: Alzheimer disease and Down syndrome--chromosome 21 nondisjunction may underlie both disorders. *American Journal of Human Genetics*, Vol.48, No.6, (June 1991), pp. 1192-1200, ISSN 0002-9297
- Pozzi, E.; Vergani, P.; Dalprà, L.; Combi, R.; Silvestri, D.; Crosti, F.; Dell, O. M. & Valsecchi, M.G. (2009). Maternal polymorphisms for methyltetrahydrofolate reductase and methionine synthetase reductase and risk of children with Down syndrome.

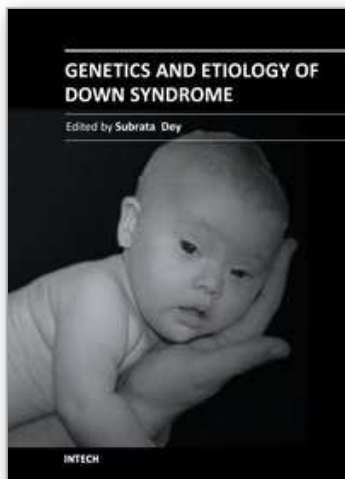
- American Journal of Obstetrics and Gynecology, Vol.200, No.6, (June 2009), pp. 636.e1-6, ISSN 0002-9378
- Quadros, E.V.; Regec, A.L.; Khan, K.M.; Quadros, E. & Rothenberg, S.P. (1999). Transcobalamin II synthesized in the intestinal villi facilitates transfer of cobalamin to the portal blood. *The American Journal of Physiology*, Vol.277, No.1 Pt 1, (July 1999), pp. G161-166, ISSN 0002-9513
- Rai, A.K.; Singh, S.; Mehta, S.; Kumar, A.; Pandey, L.K. & Raman, R. (2006). MTHFR C677T and A1298C polymorphisms are risk factors for Down's syndrome in Indian mothers. *Journal of Human Genetics*, Vol.51, No.4, (February 2006), pp. 278-283, ISSN 4-5161
- Ram, G. & Chinen, J. (2011). Infections and immunodeficiency in Down syndrome. *Clinical and Experimental Immunology*, Vol.164, No.1 (April 2011), pp. 9-16, ISSN 0009-9104
- Ray, J.G.; Meier, C.; Vermeulen, M.J.; Cole, D.E.C. & Wyatt, P.R. (2003). Prevalence of trisomy 21 following folic acid food fortification. *American Journal of Medical Genetics. Part A*, Vol.120, No.3, (July 2003), pp. 309-313, ISSN 1552-4825
- Sadiq, M.F.; Al-Refai, E.A.; Al-Nasser, A.; Khassawneh, M. & Al-Batayneh, Q. (2011). Methylenetetrahydrofolate Reductase Polymorphisms C677T and A1298C as Maternal Risk Factors for Down Syndrome in Jordan. *Genetic Testing and Molecular Biomarkers*, Vol.15, No.1-2, (January-February 2011), pp. 51-57, ISSN 1945-0265
- Sakuno, T. & Watanabe, Y. (2009). Studies of meiosis disclose distinct roles of cohesion in the core centromere and pericentromeric regions. *Chromosome Research: an international journal on the molecular, supramolecular and evolutionary aspects of chromosome biology*, Vol.17, No.2, pp. 239-249, ISSN 0967-3849
- Scala, I.; Granese, B.; Sellitto, M.; Salomè, S.; Sammartino, A.; Pepe, A.; Mastroiacovo, P.; Sebastio, G. & Andria, G. (2006). Analysis of seven maternal polymorphisms of genes involved in homocysteine/folate metabolism and risk of Down syndrome offspring. *Genetics in medicine : official journal of the American College of Medical Genetics*, Vol.8, No.7, (July 2006), pp. 409-416, ISSN 1098-3600
- Schupf, N.; Kapell, D.; Nightingale, B.; Lee, J.H.; Mohlenhoff, J.; Bewley, S.; Ottman, R. & Mayeux, R. (2001). Specificity of the fivefold increase in AD in mothers of adults with Down syndrome. *Neurology*, Vol.57, No.6, (September 2001), pp. 979-984, ISSN 0028-3878
- Seetharam B, & Li N. (2000). Transcobalamin II and its cell surface receptor. *Vitamins and Hormones*, Vol.59, pp. 337-66, ISSN 0083-6729
- Sherman, S.L.; Petersen, M.B.; Freeman, S.B.; Hersey, J.; Pettay, D.; Taft, L.; Frantzen, M.; Mikkelsen, M. & Hassold, T.J. (1994). Non-disjunction of chromosome 21 in maternal meiosis I: evidence for a maternal age-dependent mechanism involving reduced recombination. *Human Molecular Genetics*, Vol.3, No.9, (September 1994), pp. 1529-1535, ISSN 0964-6906
- Stanisiawska-Sachadyn, A.; Brown, K.S.; Mitchell, L.E.; Woodside, J.V.; Young, I.S.; Scott, J.M.; Murray, L.; Boreham, C.A.; McNulty, H.; Strain, J.J. & Whitehead, A.S. (2008). An insertion/deletion polymorphism of the Dihydrofolate reductase (DHFR) gene is associated with serum and red blood cell folate concentrations in women. *Human Genetics*, Vol.123, No.3, (April 2008), pp. 289-295, ISSN 0340-6717

- Steck, S.E.; Keku, T.; Butler, L.M.; Galanko, J.; Massa, B.; Millikan, R.C. & Sandler, R.S. (2008). Polymorphisms in Methionine synthase, Methionine synthase reductase and Serine hydroxymethyltransferase, folate and alcohol intake, and colon cancer risk. *Journal of Nutrigenetics and Nutrigenomics*, 2008, Vol.1, No.4, (June 2008), pp. 196–204, ISSN 1661-6499
- Stein, Z.; Stein, W. & Susser, M. (1986). Attrition of trisomies as a maternal screening device. An explanation of the association of trisomy 21 with maternal age. *Lancet*, Vol.1, No.8487, (April 1986), pp. 944-947, ISSN 0140-6736
- Stover, P.J. & Caudill, M.A. (2008). Genetic and epigenetic contributions to human nutrition and health: managing genome-diet interactions. *Journal of The American Dietetic Association*, Vol.108, No.9, (September 2008), pp. 1480-1487, ISSN 0002-8223
- Stover, P.J. (2004). Physiology of folate and vitamin B12 in health and disease. *Nutrition Reviews*, Vol.62, No.6Pt 2, (June 2004), pp. S3-S12, discussion S13, ISSN 0029-6643
- Summers, C.M.; Hammons, A.L.; Mitchell, L.E.; Woodside, J.V.; Yarnell, J.W.G.; Young, I.S.; Evans, A. & Whitehead, A.S. (2008). Influence of the cystathionine b-synthase 844ins68 and methylenetetrahydrofolate reductase 677C4T polymorphisms on folate and homocysteine concentrations. *European Journal of Human Genetics: EJHG*, Vol.16, No.8, (August 2008), pp.1010-1013, ISSN 1018-4813
- Tsai, M.Y.; Bignell, M.; Schwichtenberg, K. & Hanson, N.Q. (1996). High prevalence of a mutation in the cystathionine-b-synthase gene. *American Journal of Human Genetics*, Vol.59, No.5, (October 1996), pp. 1262–1267, ISSN 0002-9297
- Tsai, M.Y.; Welge, B.C.; Hanson, N.Q.; Bignell, M.K.; Vessey, J.; Schwichtenberg, K.; Yang, F.; Bullemer, F.E.; Rasmussen, R. & Graham, K.J. (1999). Genetic causes of mild hyperhomocysteinemia in patients with premature occlusive coronary artery diseases. *Atherosclerosis*, Vol.143, No.1, (March 1999), pp. 63-170, ISSN 0021-9150
- Tsai, M.Y.; Bignell, M.; Yang, F.; Welge, B.G.; Graham, K.J. & Hanson, N.Q. (2000). Polygenic influence on plasma homocysteine: association of two revalent mutations, the 844ins68 of cystathionine b-synthase and A2756G of methionine synthase, with lowered plasma homocysteine levels. *Atherosclerosis*, Vol.149, No.1, (March 2000), pp. 131–137, ISSN 0021-9150
- Ulvik, A.; Ueland, P.M.; Fredriksen, A.; Meyer, K.; Vollset, S.E.; Hoff, G. & Schneede, J. (2007). Functional inference of the Methylenetetrahydrofolate reductase 677 C > T and 1298A > C polymorphisms from a large-scale epidemiological study. *Human Genetics*, Vol.121, No.1, (March 2007), pp. 57-64, ISSN 0340-6717
- van der Put, N.M.; Gabreëls, F.; Stevens, E.M.; Smeitink, J.A.; Trijbels, F.J.; Eskes, T.K.; van den Heuvel, L.P. & Blom HJ. (1998). A second common mutation in the methylenetetrahydrofolate reductase gene: an additional risk factor for neural-tube defects? *American Journal of Human Genetics*, Vol.62, No.5, (May 1998), pp. 1044–1051, ISSN 0002-9297
- Venail, F.; Gardiner, Q.; & Mondain, M. (2004). ENT and speech disorders in children with Down's syndrome: an overview of pathophysiology, clinical features, treatments, and current management. *Clinical Pediatrics (Phila)*, Vol.43, No.9, (November-December 2004), pp. 783-791, ISSN 0009-9228
- Vogt, E.; Kirsch-Volders, M.; Parry, J.; & Eichenlaub-Ritter, U. (2008). Spindle formation, chromosome segregation and the spindle checkpoint in mammalian oocytes and

- susceptibility to meiotic error. *Mutation Research*, Vol. 651, No.1-2, (March 2008), pp. 14-29, ISSN 0027-5107
- von Castel-Dunwoody, K.M.; Kauwell, G.P.; Shelnutt, K.P.; Vaughn, J.D.; Griffin, E.R.; Maneval, D.R.; Theriaque, D.W. & Bailey, L.B. (2005). Transcobalamin 776C->G polymorphism negatively affects vitamin B-12 metabolism. *American Journal of Clinical Nutrition*, Vol.81, No.6, (June 2005), pp. 1436-1441, ISSN 0002-9165
- Vyletal, P.; Sokolová, J.; Cooper, D.N.; Kraus, J.P.; Krawczak, M.; Pepe, G.; Rickards, O.; Koch, H.G.; Linnebank, M.; Kluijtmans, L.A.; Blom, H.J.; Boers, G.H.; Gaustadnes, M.; Skovby, F.; Wilcken, B.; Wilcken, D.E.; Andria, G.; Sebastio, G.; Naughten, E.R.; Yap, S.; Ohura, T.; Pronicka, E.; Laszlo, A. & Kozich, V. (2007). Diversity of cystathionine beta-synthase haplotypes bearing the most common homocystinuria mutation c.833T>C: a possible role for gene conversion. *Human Mutation*, Vol.28, No.3, (March 2007), pp. 255-264, ISSN 1059-7794
- Wang, X.; Thomas, P.; Xue, J. & Fenech, M. (2004). Folate deficiency induces aneuploidy in human lymphocytes in vitro-evidence using cytokinesis-blocked cells and probes specific for chromosomes 17 and 21. *Mutation Research*, Vol.551, No.1-2, (July 2004), pp. 167-180, ISSN 0027-5107
- Wang, S.S.; Qiao, F.Y.; Feng, L. & Lv, J.J. (2008) Polymorphisms in genes involved in folate metabolism as maternal risk factors for Down syndrome in China. *Journal of Zhejiang University. Science. B*, Vol.9, No.2, (February 2008), pp. 93-99, ISSN 1673-1581
- Weisberg, I.S.; Jacques, P.F.; Selhub, J.; Bostom, A.G.; Chen, Z.; Ellison, C.; Eckfeldt, J.H. & Rozen, R. (2001). The 1298A→C polymorphism in methylenetetrahydrofolate reductase (MTHFR): in vitro expression and association with Homocysteine. *Atherosclerosis*, Vol.156, No.2, (June 2001), pp. 409-415, ISSN 0021-9150
- Whetstone, J.R.; Gifford, A.J.; Witt, T.; Liu, X.Y.; Flatley, R.M.; Norris, M.; Haber, M.; Taub, J.W.; Ravindranath, Y. & Matherly, L.H. (2001). Single nucleotide polymorphisms in the human reduced folate carrier: characterization of a high-frequency G/A variant at position 80 and transport properties of the His(27) and Arg(27) carriers. *Clinical cancer research : an official journal of the American Association for Cancer Research*, Vol. 7, No. 11, (November 2001), pp. 3416-3422, ISSN 1078-0432
- Williams, J.D. & Jacobson, M.K. (2010). Photobiological implications of folate depletion and repletion in cultured human keratinocytes. *Journal of photochemistry and photobiology. B, Biology*, Vol.99, No.1, (April 2010), pp. 49-61, ISSN 1011-1344
- Yamada, K.; Chen, Z.; Rozen, R. & Matthews, R.G. (2001). Effects of common polymorphisms on the properties of recombinant human methylenetetrahydrofolate reductase. *Proceedings of the National Academy of Sciences of the United States of America*, Vol.98, No.26, (December 2001), pp. 14853-14858, ISSN 0027-8424
- Yamada, K.; Gravel, R.A.; Toraya, T. & Matthews, R.G. (2006). Human methionine synthase reductase is a molecular chaperone for human methionine synthase. *Proceedings of the National Academy of Science of the United States of America*, Vol.103, No.25, (June 2006), pp. 9476-9481, ISSN 0027-8424
- Yang, Q.H.; Botto, L.D.; Gallagher, M.; Friedman, J.M.; Sanders, C.L.; Koontz, D.; Nikolova, S.; Erickson, J.D. & Steinberg, K. (2008). Prevalence and effects of gene-gene and gene-nutrient interactions on serum folate and serum total homocysteine

- concentrations in the United States: findings from the third National Health and Nutrition Examination Survey DNA Bank. *American Journal of Clinical Nutrition*, Vol.88, No.1, (July 2008), pp. 232–246, ISSN 0002-9165
- Yoon, P.W.; Freeman, S.B.; Sherman, S.L.; Taft, L.F.; Gu, Y.; Pettay, D.; Flanders, W.D.; Khoury, M.J. & Hassold, T.J. (1996). Advanced maternal age and the risk of Down syndrome characterized by the meiotic stage of chromosomal error: A population-based study. *American Journal of Human Genetics*, Vol.58, No.3, (March 1996), pp. 628–633, ISSN 0002-9297
- Zheng, C.J. Byers, B. (1993). Oocyte selection: a new model for the maternal-age dependence of Down syndrome. *Human Genetics*, Vol.90, No.1-2, (September-October 1993), pp. 1-6, ISSN 0340-6717
- Zijno, A.; Andreoli, C.; Leopardi, P.; Marcon, F.; Rossi, S.; Caiola, S.; Verdina, A.; Galati, R.; Cafolla, A. & Crebelli, R. (2003). Folate status, metabolic genotype, and biomarkers of genotoxicity in healthy subjects. *Carcinogenesis*, Vol.24, No.6, (June 2003), pp. 1097-1103, ISSN 0143-3334

IntechOpen



Genetics and Etiology of Down Syndrome

Edited by Prof. Subrata Dey

ISBN 978-953-307-631-7

Hard cover, 328 pages

Publisher InTech

Published online 29, August, 2011

Published in print edition August, 2011

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.

How to reference

In order to correctly reference this scholarly work, feel free to copy and paste the following:

Érika Cristina Pavarino, Bruna Lancia Zampieri, Joice Matos Biselli and Eny Maria Goloni Bertollo (2011). Abnormal Folate Metabolism and Maternal Risk for Down Syndrome, Genetics and Etiology of Down Syndrome, Prof. Subrata Dey (Ed.), ISBN: 978-953-307-631-7, InTech, Available from: <http://www.intechopen.com/books/genetics-and-etiology-of-down-syndrome/abnormal-folate-metabolism-and-maternal-risk-for-down-syndrome>

INTech
open science | open minds

InTech Europe

University Campus STeP Ri
Slavka Krautzeka 83/A
51000 Rijeka, Croatia
Phone: +385 (51) 770 447
Fax: +385 (51) 686 166
www.intechopen.com

InTech China

Unit 405, Office Block, Hotel Equatorial Shanghai
No.65, Yan An Road (West), Shanghai, 200040, China
中国上海市延安西路65号上海国际贵都大饭店办公楼405单元
Phone: +86-21-62489820
Fax: +86-21-62489821

© 2011 The Author(s). Licensee IntechOpen. This chapter is distributed under the terms of the [Creative Commons Attribution-NonCommercial-ShareAlike-3.0 License](https://creativecommons.org/licenses/by-nc-sa/3.0/), which permits use, distribution and reproduction for non-commercial purposes, provided the original is properly cited and derivative works building on this content are distributed under the same license.

IntechOpen

IntechOpen