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Gene Polymorphisms That Predispose Women for Down Syndrome Child Birth

Sujay Ghosh and Papiya Ghosh

Abstract

Down syndrome caused by presence of extra chromosome 21 originates from nondisjunction during parental gametogenesis. For overwhelming cases, the error occurs in oocyte and all the nondisjunction events are not stochastic. With increasing number of research efforts, it has come to know that maternal genetic architecture may be considered as risk factors for chromosomal errors. Polymorphisms of the genes involved in chromosome segregation, recombination and folic acid metabolisms have been investigated for their association with Down syndrome child birth. But the results are conflicting owing to ethnic and sociocultural differences. Here, we have discussed and summarized the outcome of the studies conducted on different population sample from different parts of world and tried to figure out the common polymorphisms, which could be used as makers for preconceptional screening of Down syndrome child birth risk among the women.

Keywords: down syndrome, maternal genotype, polymorphism, meiotic nondisjunction

1. Introduction

Down syndrome (DS), the most common form of live born intellectual disability in human is caused by trisomy condition of chromosome 21 (Ch21). The trisomy 21 condition arise from nonseparation or nondisjunction (NDJ) of Ch21 in germinal cells that leads to production of disomic gamete which upon fertilization with gamete with correct chromosome count from opposite sex produces trisomic zygote. For overwhelming majority of cases, the error arises in oocyte and this may be due to protracted phase of oocyte development. The lengthy process of oocyte maturation that includes two halts, one at meiotic I diplotene and another before the entry in second meiotic division, provides opportunity to environmental insults to accumulate in ovarian microenvironment that may perturb the process of chromosome segregation.

The first identified risk factor for Down syndrome birth is advanced maternal age of conception. It was identified that [1], women of age 32 years and above have higher risk of having Down syndrome baby. Subsequently, with the help of polymorphic variants of short tandem repeat (STR) makers on Ch21 scientists have characterized that recombination error may be the molecular risk factors for Ch21 NDJ. With elaborate analyses, considering both the maternal age and pattern

of recombination, the US researcher group [2] and Indian researcher group [3] have characterized the interaction between maternal age and erroneous pattern of recombination on non-disjoined chromosome. No chiasma formation or single telomeric chiasma have been proved as risk of Ch21NDJ at MI among the younger mothers (age < 29 years). On contrary, single centromeric chiasma has been identified as risk factors for MII errors among the older women (age > 34 years).

With subsequent analyses of maternal molecular age, it has been proved that mothers of Down syndrome baby have shorter average telomere length than do the mothers of same chronological age and have euploid healthy baby [4, 5]. The authors proposed that a group of women may suffer from advanced molecular and genetic aging and intuitively carry predisposition for NDJ. It is really difficult to interpret whether NDJ is the result of rapid shortening of telomere or telomere shortening and NDJ are linked by some common risk factors, instead it can be said pleiotrophic effects of some genes may relate maternal aging with risk of NDJ. Moreover, frequent occurrence Ch21 NDJ among younger women reinforces the intuitive idea of genetic predisposition for Ch21 NDJ where advancing maternal age is not an issue.

As far as published literatures are concerned studies for identifying the genetic predisposition for DS child birth among the women are not sufficient. Very few initiatives in this regard have been recorded. Of them the recombination regulator genes and folate metabolism regulator genes are major. So, this chapter presents recent updates on finding of the gene polymorphisms that exhibited significant association with Down syndrome birth.

2. PR/SET domain 9 (PRDM9)

The gene is located on chromosome 5 (5p14.2). The protein coded by this gene is a zinc finger protein with histone methyltransferase activity that catalyzes trimethylation of histone H3 lysine 4 (H3K4me3) during meiotic prophase. This protein contains multiple domains, including a Kruppel-associated box (KRAB) domain, an SSX repression domain (SSXRD), a PRD1-BF1 and RIZ homologous region, a subclass of SET (PR/SET) domain, and a tandem array of C2H2 zinc fingers. The zinc finger array recognizes a short sequence motif of histone, leading to local H3K4me3, and meiotic recombination hotspot activity.

Experimental deletion of the gene in mice leads to the production of gametes blocked at pachytene of meiosis I that show a reduced number of Dmc1 loci, a protein that indicates the sites of meiotic crossovers [6]. The major allele A of PRDM9 binds a 13 bp DNA motif enriched at recombination hot spot, namely, CNCCNTNNCCNC [7]. Further, allelic variation in the zinc finger motif of PRDM9 exhibited association with differential hotspot usage in human recombination [8]. Carriers of PRDM9 minor alleles display reduced recombination at meiotic hotspots [8]. All these preceding observation led to the study [9] to inquire whether PRDM9 variants exhibit association with the recombination variation that underlies the NDJ events.

In this study [9] by US researcher group included 235 mothers having DS child and 85 controls having euploid baby. For characterizing the recombination profile along the 21q, the authors used genotyping with 1536 SNP loci on 21q by the Illumina Golden Gate Assay. The authors scored for 17% of cases of MI error without any recombination events carry homozygosity of minor alleles in contrast to only 2% of MI with single exchange category. The logistic regression analyses revealed women from MI without any exchange category are 2.45 times more likely to have risk of NDJ and Down syndrome birth than do the controls when carry at

least one minor allele in heterozygous condition. The authors found less affinity of minor allele of ZF motif of PRDM9 and they tried to justify this reduced binding of PRDM9 to the recombination hotspot may cause lack of recombination events on 21q and NDJ of Ch21. This notion needs further confirmation by other studies on different DS populations of ethnic variations for considering as acceptable hypothesis.

3. Apolipoprotein E (APOE)

This gene is located on chromosome 19 (19q13.32) and encodes a protein which is essential for normal catabolism of triglyceride-rich lipoprotein. It binds to specific receptor on hepatocytes and peripheral cell receptors. Mutations in this gene leads to familial dysbetalipoproteinemia, or type III hyperlipoproteinemia (HLP III), which is characterized by increased plasma cholesterol and triglycerides due of impaired clearance of chylomicron and VLDL remnants. The gene is expressed specifically in liver, kidney, adipose, adrenal, spleen and neuronal tissues along with some other organs at low level.

Initial study that addressed the maternal APOE genotypes as risk factors of DS birth [10] reported presence of APOE4 allele among women may predispose them for MII NDJ at the younger age, but not at older age. The authors observed in young mothers with a meiosis II error, epsilon4 frequency was 30.0%, which was significantly higher than in older mothers with a meiosis II error (13.0%, $P = 0.03$).

But the study [11] conducted on Spanish population reported some opposite trend. The authors have observed an increased frequency of APOE4 allele among MI mother of age < 28 years as compared to MI mothers of age > 28 years. But this study did not confirm any association of maternal APOE4 genotype with MII error. The study on Colombian population [12] has revealed preferential occurrence of APOE4 allele in DS and their parents (11%) than among the controls (9%) though the difference was found insignificant statistically. More studies are needed to confirm the association between APOE4 allele in maternal genome and Ch21 NDJ.

4. Presenilin I (PSEN1)

This gene is located at the position 14q24.2 and known for its pleiotrophic effects. It has many isoforms that perform variety of functions. The polymorphisms of this gene were first reported for its association with Alzheimer disease. Later, it was tested for risk assessment in women having DS child.

As far as published literatures are concerned, only two studies have been conducted on PSEN 1 polymorphisms as a maternal risk factor for DS birth. The initial study was done on US population [13] where the authors find an association between a polymorphism in intron 8 of maternal genotype with DS birth. This study included 168 probands with free trisomy 21 and recorded an increased frequency of allele 1 in mothers with a meiosis II error (70.8%) than among the mothers of meiosis I error (52.7%, $P < 0.01$), with an excess of the 11 genotype in the meiosis II mothers. Moreover, the author tested polymorphic variants of APOE gene and found the frequency of allele 1 in mothers carrying APOE4 allele (68.0%) was higher than in mothers without APOE4 (52.2%, $P < 0.01$). The author hypothesizes that the PSEN-1 intronic polymorphism might be involved in chromosomal nondisjunction through an influence on the expression level of PS-1 or due to linkage disequilibrium with biologically relevant polymorphisms in or outside the PS-1 gene.

Similar study was conducted on a population samples from India [14]. In this study, 170 Down syndrome patients, grouped according to maternal meiotic stage of NDJ and maternal age at conception, and their parents were genotyped for PSEN-1 intron-8 and APOE polymorphisms. The estimated frequencies of the PSEN-1 T allele and TT genotype, in the presence of the APOE4 allele, were significantly higher among young mothers (< 35 years) with meiosis II NDJ than in young control mothers (96.43 vs. 65.91% $P = 0.0002$ and 92.86 vs. 45.45% $P < 0.0001$, respectively) but not among mothers with meiosis I NDJ. The author hypothesized that the co-occurrence of the PSEN-1 T allele and the APOE 4 allele synergistically increases the risk of meiotic segregation error II among young.

5. Methylenetetrahydrofolate reductase (MTHFR)

This gene is located at 1p36.22 and the 12 exon long reading frame encodes an enzyme that catalyzes the reduction of 5,10-methylene tetra hydro folate to 5-methyl tetra hydro folate, which is required for the remethylation of homocysteine to methionine. A common MTHFR 677C > T polymorphism (rs1801133) that results in Ala222Val amino acid substitution, is responsible for reduced enzyme activity. The homozygous TT genotype causes dimer destabilization under conditions of reduced folate availability [15, 16]. It was reported initially [17] in the year 1999, that increased plasma hcy level and an increased frequency of both MTHFR 677CT and TT genotypes among the mothers of DS individuals are strongly linked and since then this polymorphism has been tested in more than 30 case-control studies across the globe and confirmed this association with very few exceptions. As far as published literatures are concerned five large meta-analyses have been done till date between the year 2013 and 2014 to address this issue [18–22], with the latest one that includes data from 34 case-control studies for a total of 3,098 women having DS child and 4,852 control mothers [21]. The outcome of all these meta-analyses suggest that the overall risk as represented by odds ratio (OR), for the birth of a child with Trisomy21 to the women who are carriers of the 677 T allele ranges from 1.2 to 1.5 according to the various genetic models under investigation, i.e., allele contrast, dominant, recessive, co-dominant, etc. Subsequent data stratification into ethnic groups revealed that the risk is higher in Asians (OR = 1.5), and lower in Caucasians and/or other groups (OR usually ranging between 1.0 and 1.4) [19, 20, 22]. The meta-analyses performed by Wu et al. [19]; Yang et al. [20]; Rai et al. [21]; Victorino et al. [22] revealed that the frequency of the MTHFR 677 T allele is higher in Caucasian mother of DS child (ranging from 35.6 to 41.5%), followed by Brazilians (ranging from 33.5 to 33.9%), and lower in Asian populations (ranging from 20.0 to 32.3%). When epidemiological data were stratified according to the geographic origin of the mothers and found that the higher risk in Asians (OR = 1.53; 95% CI = 1.29–1.82), followed by Americans (OR = 1.23; 95% CI = 1.07–1.39), and the association remain insignificant for Europeans (OR = 1.04; 95% CI = 0.93–1.16) [21]. When the data was stratified according to latitude, exhibited a significant association of the MTHFR 677C > T polymorphism with DS birth insub-tropical populations (both TT vs. CC and CT vs. CC carriers), followed by tropical regions (only CT vs. CC carriers), but no significant effect was evident in the population from northern temperate region of the globe. These observations suggest complex gene–environment interactions, which might be a product of differences in allele frequencies among different populations in association with different nutritional status and exposure to environmental factors, such as solar radiation, that could interfere with folate

bioavailability [16, 18, 22, 23]. Interestingly, scientists have observed association of the MTHFR 677C > T polymorphism with both chromosome 13 and 21 malsegregation events in lymphocytes from the mothers of DS child [23, 24].

Another common MTHFR polymorphism, the MTHFR 1298A > C one (rs1801131), causes Glu429Ala aminoacidic change. Meta-analysis revealed that the frequency of the MTHFR minor 1298C allele is higher in Asians (~40.0%), with little less frequency among Caucasians (~35.0%) and Brazilians (upto 25.0%) [22]. Interestingly, no studies have demonstrated MTHFR 1298A > C polymorphism is an independent maternal risk factor for the birth of a child with DS. Instead, However, case-control studies demonstrated that genotypes that carry both the MTHFR 677C > T and 1298A > C polymorphisms increase the maternal risk synergistically for a birth of a child with trisomy 21 more than the presence of the single polymorphic site MTHFR 677C > T one alone. These observations suggest intuitive functional interaction of both polymorphisms on protein stability and activity [25–29]. The maternal double homozygous 677TT-1298CC genotype leads to MTHFR protein instability and inactivity, often resulting in prenatal death [16].

6. Methionine synthase and methionine synthase reductase (MTR and MTRR)

The gene named as 5-methyltetrahydrofolate-homocysteine methyltransferase (MTR) or methionine synthase in short is located at 1q43 and carries 33 exons. It is a cobalamin-dependent enzyme that catalyzes the transmethylation of homocysteine to methionine and MTRR, which is a NADPH-dependent diflavin enzyme, needed for activation of MTR. On the other hand the gene 5-methyltetrahydrofolate-homocysteine methyltransferase reductase of MTRR is located at 5p15.31 in human genome. This protein functions in the synthesis of methionine by regenerating methionine synthase (MTR) to a functional state.

The second polymorphism of the gene *MTRR* that exhibited association with DS birth among North American women is rs1801394; 66A > G substitution which causes Ile22Met amino acid change [30]. Subsequent studies on different population samples provide conflicting results. Nevertheless, the meta-analysis conducted in 2009 on 623 DS bearing and 936 control mothers [31], confirmed association of this polymorphism in maternal genome with the elevated risk of having DS baby. Further analyses with stratified data, performed in recent time [32, 33], suggest a significant effect in Caucasians under both dominant and recessive genetic models. The estimated score for minor Allele “G” among Caucasian women was 35.8–54.3%, among Brazilian women was from 40.0 to 48.0% and among Asian mothers was from 41.5 to 62.5% [32–34]. Furthermore, when Caucasian samples were stratified by geographic and demographic criteria the estimates revealed that the risk is higher in those of non-residential European descent (OR = 1.47; 95% CI = 1.02–2.11; dominant model) than in residential European Caucasians (OR = 1.31; 95% CI = 1.01–1.70; dominant model). On contrary, when the study was conducted on the Caucasian from Mediterranean regions no significant association was observed (OR = 1.19; 95% CI = 0.91–1.55; dominant model), which suggests that the manifestation of the effect of *MTRR* rs1801394 66A > G is also dependent on geographic and dietary factors [33].

Recently, another *MTRR* polymorphism, namely *MTRR* 524C > T (rs1532268) that causes Ser175Leu replacement in peptide chain, has been identified as related to the maternal risk of birth of a child with DS [35] among Chinese women. This study reported decreased maternal risk for carriers of the 524 T allele that was associated with reduced hcy levels in Chinese women. But the study did not address the issue

of but did not analyze the linkage or interaction of *MTRR* 524C > T (rs1532268) with the *MTRR* 66A > G sites [35].

As far as published literatures on the *MTR* gene polymorphisms are concerned, the *MTR* 2756A > G polymorphism (rs1805087) in maternal genome, leading to the Asp919Gly substitution, was the third variant of the folate pathway to be associated with DS birth [36]. However, subsequent case-control studies failed to confirm this association, and recent meta-analyses confirmed that the *MTR* 2756A > G polymorphism is not an independent maternal risk factor for DS birth [20, 32, 37], rather a strong relation with *MTRR* 66A > G has been evident. The estimated frequency of minor allele 'G' of this polymorphic site in the European and mixed Brazilian populations of women having DS child is 18–21% [37], while the estimate is less than 10% in the Asian women [38]. A large cohort study on Italian population samples [33, 37], revealed the *MTRR* 66A > G polymorphism, but not the *MTR* 2756A > G one, was associated with increased serum folate levels among the GG carriers women. On the other hand study on Brazilian population has [29] reported association of *MTRR* AG and GG genotypes with high methylmalonic acid (MMA) concentrations, an indicator of the vitamin B12 status. However, when both the polymorphisms *MTR* 2756AA/*MTRR* 66GG were present in women having DS child exhibited association with increased serum folate levels, while the carriers of the *MTR* 2756GG/*MTRR* 66AA genotype exhibited reduced folate and hcy levels [33]. Such combined presence of *MTHFR*/*MTRR* or *MTRR*/*MTR* genotypes among the mother of DS, has been many reported by many authors who worked on different ethnic population samples [23, 33, 34, 36, 38, 39].

7. Reduced folate carrier (*RFC1* or *SLC19A1*)

The gene is actually named *solute carrier family 19 member 1*, located at 21q22.3 and carries 17 exons. The protein expresses ubiquitously and is the major transport system in mammalian tissues for folate cofactors and regulates intracellular concentration of folate [40]. Though not universal, some workers have reported risk association with polymorphic allele in maternal genome with DS birth. The polymorphic variation *RFC1* 80G > A polymorphism (rs1051266), causes Arg27His replacement in protein chain. This polymorphic sites exhibited association with increased plasma hcy levels in homozygous GG genotype when present together with *MTHFR* 677TT [41] homozygous variants. Similarly study on Italian population [42] observed a borderline significant association of maternal genotype *RFC1* 80GG/*MTHFR* 677TT and DS birth and protective negative association with *RFC1* 80(AA or AG)/*MTHFR* 1298AA genotypes. Two recent meta-analyses [20, 33] suggest that the polymorphism *RFC1* 80G > A is independent maternal risk factor for DS birth with ORs ranging from 1.1 to 1.3. When stratified analyses has been conducted, the *RFC1* 80G allele exhibited higher frequency in Caucasian and Brazilian women having DS child (ranging between 49.0 and 54.0%) than in Asian ones (36.0–36.5%) [33]. Further population based studies are needed to confirm the implication of this polymorphism as a maternal risk factor for DS birth.

8. Cystathionine β -synthase (*CBS*)

The gene is located on chromosome 21 at 21q22.3 and encodes a hemoprotein that catalyzes the condensation of hcy and serine to form cystathionine in the transsulfuration pathway. This enzyme is activated by adenosyl methionine and pyridoxal phosphate acts as co-factor in this reaction. So far published literatures

are concerned two common polymorphisms have been studied as maternal risk factors for DS birth. One of them is an insertion of 68-bp within exon 8 that results in the duplication of a splice site at the intron7/exon 8 junction of the gene [43]. Very recent meta-analyses, performed with 825 mothers of DS child and 1.034 control did not find association of the *CBS* 844ins68 allele and maternal risk of having a DS child [20, 32]. The second polymorphic variants is an 833 T > C substitution (rs5742905) that causes missense mutation Ile278Thr associated with mild hyperhomocysteinemia [44]. Results of association studies related to this site are contradictory and non-conclusive [29, 35], so further study is warrant to reveal its implication in DS birth.

9. Methylenetetrahydrofolate dehydrogenase (*MTHFD1*)

The genetic position of this gene is 14q23.3 and three distinct enzymatic activities, 5,10-methylenetetrahydrofolate-dehydrogenase, 5,10-methenyltetrahydrofolate-cyclohydrolase and 10-formyltetrahydrofolate synthetase. Each of these activities catalyzes one of the three sequential reactions in the interconversion of 1-carbon derivatives of tetrahydrofolate. The *MTHFD1* 1958G > A polymorphism (rs2236225), that causes missense change Arg653Gln which in turn reduces enzyme stability and activity and was first identified maternal genetic risk factor for trisomy 21 in Southern Italian women, exhibited association with DS risk in combination-with-the *RFC1* 80G > A-polymorphism- (the combined *MTHFD1* 1958AA/*RFC1*80GG genotype) [27]. The results of subsequent studies on other population were contradictory [29, 38, 45, 46]. Very recent meta-analysis [32] that included 497 mothers of Ds child and 930 controls, revealed a weak association with maternal heterozygous GA genotype than GG homozygous carriers (OR = 1.33; 95% CI = 1.01–1.75). The result of this single study may not sufficient to draw any inference and more study on other populations is warrant.

10. Transcobalamin (*TCN2*)

The gene is located on chromosome 22 at 22q12.2. This protein can bind cobalamin and helps in its cellular uptake by specific membrane receptors (TCR). The study of this gene for its association with DS birth is limited. A common variant *TCN2* 776C > G (rs1801198), that results in Arg232Pro replacement and impairs cobalamin metabolism [47] exhibited association with maternal risk of DS birth either alone [29], or in combination with *MTR* or *MTHFR* variants. The genotype *TCN2* 776CC/*MTR* 2756AG- [48]-or *TCN2* 776CG/*MTHFR* 677TT [38] have shown association with DS birth. But recent meta-analysis [32] did not confirm this association. The second polymorphism of that gene namely *TCN2* 67A > G (rs9606756) that causes Ile23Val substitution has been studied only in Brazilian population and did not find any association with maternal risk for a DS birth [29].

11. DNA methyltransferase 3B (*DNMT3B*)

This gene is located on chromosome 20 at 20q11.21 and encodes a de novo DNA methyl transferase. The enzyme is located primarily in nucleus and developmentally regulated. Two recent independent studies one on Italian and another on Indian population suggested the polymorphisms of *DNMT3B* might be associated with DS birth as maternal risk factors. In the study on Italian population [37] the

authors genotyped 172 mothers with DS and 157 control mothers and found a decreased risk of birth of a child with DS among the mother who are carrier of *DNMT3B* 579G > T (rs1569686) minor allele T. Further, the author suggested that the combined *DNMT3B*-579GT/-149CC genotype was associated with an even more reduced maternal risk of birth of DS. That means the said genotypes have some protective implication on chromosome 21 NDJ. In Indian study [49] the author tested 150 mothers with Down syndrome and 172 control and found no significant difference in allelic and genotype frequency for individual loci between cases and controls, but found a significant difference in the frequency of haplotype rs1569686-579G: rs2424913-149 T which exhibited preferential occurrence among the DS child bearing mothers. Further study is needed to validate this association.

12. Serine-hydroxymethyltransferase (*SHMT*), thymidylate synthase (*TYMS*), and dihydrofolate reductase (*DHFR*)

The gene *SHMT*, *TYMS* and *DHFR* are located at 17p11.2, 18p11.32 and 5q14.1 respectively. *SHMT* converts tetrahydrofolate (THF) into 5,10-methyleneTHF using serine as the one-carbon donor. This THF is then used for thymidylate synthesis in the reaction catalyzed by *TYMS* that produces dTMP and dihydrofolate (DHF). DHF is then reduced back to THF by *DHFR*. As far published literatures are concerned the polymorphisms of *SHMT*, *TYMS*, and *DHFR* have been analyzed as maternal risk factors for DS birth only in one case-control study each [50–52]. The *SHMT*1420C > T polymorphism (rs1979277), which causes Leu474Phe replacement and defects in nuclear transport of *SHMT*, was investigated [53] in 105 DS bearing and 185 control mothers from Brazil, and both the homozygous and 1420CT heterozygous genotypes exhibited decreased maternal risk of birth of a child with DS in comparison to the 1420TT genotype [52]. A team of Italian researchers [50] investigated two common *TYMS* polymorphisms in 94 DS bearing and 113 control mothers from the population of Italy. These polymorphisms were rs34743033, which is a 28-bp short tandem repeats in the 5'-untranslated region (5'-UTR) that is linked to gene expression levels [54], and rs34489327, which is a 6-bp deletion (1494 ins/del) polymorphism in the 3'-UTR that causes mRNA instability into the cytoplasm [55, 56]. But the result suggested no independent association of these two polymorphic sites with DS birth, but synergistic effect of the combined *MTHFR* 1298 AC/*TYMS* 28-bp 2R/2R genotype resulted in decreased maternal risk. Regarding *DHFR* gene polymorphism, only known study [51], was conducted including 105 DS bearing and 185 control mothers from Brazilian population for rs70991108 which is the presence of a 19-bp ins/del polymorphism, but no association with maternal risk of a DS birth was detected. But the confirmation of these results has not possible due to lack of replication of study in other populations.

13. Discussion and conclusion

Risk factors associated with Down syndrome birth the enigmatic. Both the genetic and environmental and habitual implications are known to be associated with DS birth. Regarding maternal genotypes that may impose risk of chromosome 21 nondisjunction in oocyte is extremely complicated owing to multifactorial nature of chromosome segregation system. It includes genes that are involved directly in chromosome segregation and also, cell cycle regulators, replication and recombination regulators, and metabolism regulators that maintain the optimum nutrient level affecting the genetic and epigenetic environment. In respect to recombination

regulators, only gene that has been investigated in maternal genome is PRDM9. This study [9] is only known analyses on that gene and is needed to be replicated in other populations. Another gene is APOE that exhibited association with DS birth when APOE4 allele is present. Again very limited study has been conducted in this regard. Rest of the genes that have analyses so far in maternal genome for association with DS child are from folate metabolism regulators. Since the initial publication [17] on relation between DS birth risk and folate metabolism regulator polymorphisms in the year 1999, several studies on different ethnic populations have been carried and the results are conflicting. But considering the gene X environment concept, it can be justified. The defects in folate metabolism pathways can only be manifested in term of chromosome segregation errors when genetic background interacts with nutritional status of the women. As the genetic background is different for different ethnic populations and as the nutritional level vary according to social architecture of given population, the association study gives different and contradictory results. Moreover, level of folic acid in grand maternal genome is of scientific concern as the oocytes starts growing in the fetal ovary.

In summary, it can be said that genetic architecture of maternal genome is needed to be explored in relation to prevention of DS child birth. Population specific genetic markers are needed to be developed in order to screen the women prior to their conception to test the genetic susceptibility for DS fetal conception. The biggest break through will come with highest level of application of basic research in biomedical field.

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