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ASSOCIATION OF METHYLENETETRAHYDROFOLAT REDUCTASE C677T/A1298C POLIMORPHYSMS WITH THE SUSCEPTIBILITY TO CHIDHOOD OF NONSYNDROMIC CLEFT LIPS WITH OR WITHOUT CLEFT PALATES IN NORTHERN SULAWESI POPULATION

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ABSTRACT

Background

Cleft Lip / Cleft Palate are the most common congenital abnormality found in this world.

Patient and Methode

21 children non sindromic Cleft lips with or without cleft palates and 21 children control was performed in 2012. This research is study distriktiv. A case control study. With Real-Time PCR technology has enabled the detection and amplification polymorphism A1298C and C677T MTHFR clearer.

Results

There is a significant association relationship C677T and A1298C genotypes between case and control groups.

Conclusions

In the C677T and A1298C polymorphism there is a relationship with the possibility of nonsyndromic children cleft lip with or without cleft palate in northern Sulawesi.

KEYWORDS: Cleft Lips / Cleft Palates, Polimorphysms, Genetics

INTRODUCTION

BACKGROUND

Nonsyndromic cleft lip with or without cleft palate (CL/P-NS) is the most common congenital abnormality. Approximately 22 % of the Clefts has a Genetic origin and the other are produced by Environmental result.

Although it is not fatal, but it can have an impact on the process of eating, talking and being social problems for the patient.

Abnormalities defect of CL/P-NS can occur together with other abnormalities known as syndromic Cleft Lip / Palate (22 %) eg van der Woude syndrome, Pierre Robin syndrome, Apert syndrome, Turner syndrome and Down syndrome Or without the presence of another abnormality known as the nonsyndromic Cleft Lip / Palate.

(78 %), meaning that there is only pure cleft abnormalities in lip / palate alone, without other abnormalities. (Zucchero, et. al, 2004).

Incidence CL/P-NS is one of 600 babies born of live births (Murray, 2002; Jugessur, 2005). It was reported that every 2.4 minutes a baby isborn in this world with CL/P-NS or there are 225,000. Babies born each year with CL/P-NS (Anne V. Hing, 2006).

The incidence of CL/P-NS vary based on geographic location, ethnicity and socioeconomic status. The incidence in the world is 1.7 per 1,000 of live births, in Indonesia: 1.47 per 1000 Live births (Winata, 1981).

Cleft lip is more often found in men with a ratio of male: female 2: 1. Cleft palate is more frequently found in women with a ratio of female: male 2.4: 1 (Murray, 2002).

GENETICS

Genetic component CL/P-NS for the first time introduced by Fogh Andersen in his thesis (1942). Ardinger et al, (1960) first reported the genes that play a role in the CL/P-NS there are Transforming Growth Factor alpha (TGF α), IRF6 and MTHFR.

Contributors few specific genes couse of CL/P-NS, are variants in IRF6 (Zucchero et al, 2004; Rachimov et al, 2008), MCX1 (Lidral et al, 1977; Jezewski et al, 2007), BMP4 (Suzuki et al, 2009) and a locus on chromosome 8q.

MTHFR enzyme formation begins with Folic Acid. Folic acid is derived from the word meaning leaf (Folium), where leafy vegetables are the main source.

Folate be conjugated initially in the cell wall of the gut into shape monoglutamat then reduced to the enzyme dihydrofolate (DHF) to tetrahydrofolate enzymes (THF), It will form 5.10 - metilenetetrahidroksifolat. (methylene THF) and glycerin. This molecule is important, because being a precursor of 5 - metilentetrahidrofolat are active in metabolic (5 -methyl- THF), which is involved in the metabolism of homocysteine In the process of the formation of MTHFR.

MTHFR

MTHFR is an enzyme made by the MTHFR gene, which will convert into 5.10 –methylenetetrahydrofolat to 5-methylenhydrofolat.

The function of the MTHFR gene provides instructions for making an enzyme called methylenetetrahydrofolatreductase. This reaction is a multistep process that is necessary to change the amino acid homocysteine into methionine amino acids.

MTHFR gene located on the short arm chromosome 1 (1p36.3).

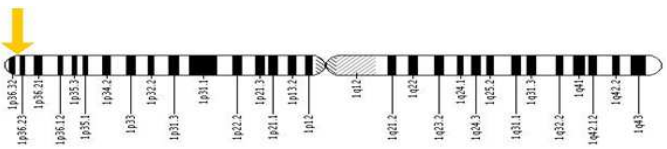

Figure 1: Locations Cytogenetic Gen MTHFR

From The Molecular Biology of the methylenetetrahydrofolate Reductase (MTHFR) and Overview of Mutations / polymorphisms (2000)

MTHFR gene mutations are most commonly found at position 677 or at position 1298 of the MTHFR gene. Mutations at these positions cause changes 677C to T and 1298A to C. Both these polymorphisms were associated with the occurrence of congenital malformation disorders such as neural tube defects, including CB / L – NS (James et al 1999, Hobbs, 2000).

POLYMORPHYSMS

Polymorphism involves morphs of the phenotype. The term is also used somewhat differently by molecular biologists to describe certain point mutations in the genotype, such as SNPs. This usage is not discussed in this article.

C677T gene polymorphism (Alanine → Valine)

677CC genotype (homozygous), is "normal". 677TT genotype (homozygous) is a "mutant", which is thermolabile theenzymaticactivity is less (18-22 %), genotype 677CT (heterozygote) had activity similar to normal (56 %), and 677CC (66-67 %).

677TT geno type have a risk so great to be CB/L-NS (Wilken B. Bamforth)

A1298C gene polymorphism (Alanine →Glutamate)

According to Wilken B. Bamforth F. A1298C genotype have geographic and ethnicity variation. In a study of recombinant human MTHFR, the protein encoded by the 1298C can not be distinguished from the 1298A. In terms of activity, thermolability, FAD release, or a protective effect of 5 - methyl - THF. A1298C polymorphism is a risk factor of: homocysteinuria, Neural Tube defect, Anencephaly, Spina Bifida, Cleft Lip / Palate, Heart Disease, Stroke, Hypertension, Preeclampsia, glaucoma, psychiatric disorders and some types of cancer. (Murray, 2002, Shaw et al, 1998)

Tabel 1: Distribusi Polimorfisme MTHFR C677T Dan A1298C for CLP-NS in Northern Sulawesi

No.	Lab. No	Name	Age	Gender	Polimorfisme MTHFR		Information
					C677T	A1298C	
1.	1203220166	CK.	17 Yr	Male	CC	AA	Control
2.	1203220167	R.S.	26 Yr	Male	CC	AA	Control
3.	1203220170	F.R.	2 Yr	Female	CT	AA	CL
4.	1203220197	V.E.	11 Yr	Female	CC	AA	Control
5.	1203220198	K.S.	12 Yr	Female	CC	AC	Control
6.	1203220199	D.K.	30 Yr	Male	CC	AC	Control
7.	1203220200	S.O	2 Yr	Female	CC	AC	CL
8.	1203220201	R.I.	5 Yr	Male	CC	AC	CP
9.	1203220202	Y.D.	8 Yr	Female	CC	AC	Control
10.	03270029	A.A.	9 Yr	Male	CT	AC	CL
11.	03270032	A.R.	8 Yr	Female	CC	CC	Control
12.	03270034	F.A.	11 Mo	Male	CT	AA	CP
13.	03270036	A.S.	4 Yr	Male	CC	AA	Control
14.	03270038	A.R.	8 Yr	Female	CC	CC	CL
15.	03270039	S.H.	19 Yr	Male	CT	AA	Control
16.	03270041	D.K.	3 Yr	Female	CC	AA	Control
17.	03270043	S.A.	10 Mo	Female	CC	AC	Control
18.	03270028	H.H.	2 Yr	Female	CC	AC	Control
19.	03270031	A.G.	7 Yr	Female	CC	AC	Control
20.	03270033	D.M.S.	9 Yr	Female	CC	AC	Control
21.	03270035	F.N.	7 Yr	Female	CC	AC	Control
22.	03270037	H.M.	4 Yr	Female	CC	AC	CP

Table 1: Contd.,

23.	03270040	R.M.	5 Yr	Male	CC	CC	CL
24.	03270042	R.P.	3 Yr	Male	CC	AA	Control
25.	03270044	M.M.	3 Yr	Male	CC	AC	CL
26.	1204090162	M.S.Y.	1 Yr	Male	CT	AA	Control
27.	1204090163	N.M.	4 Yr	Female	CC	AC	CL
28.	1204090164	X.B.	4 Yr	Female	CC	AA	Control
29.	1209180022	I.B.	30 Yr	Male	CC	AC	CL
30.	1209180023	B.Y.	10 Yr	Male	CC	CC	CP
31.	1209180024	J.R.	33 Yr	Female	CC	AA	CL
32.	1209180025	Ng.	65 Yr	Male	CT	CC	CL
33.	1209180026	J.I.	28 Yr	Male	CC	AC	CL
34.	1209180027	T.J.H.	24 Yr	Male	CC	AC	Control
35.	1209180028	B.T.	16 Yr	Male	CC	AC	Control
36.	1209180031	K.	54 Yr	Female	CC	CC	CP
37.	1209180032	U.T.	55 Yr	Male	CC	CC	Control
38.	1209180036	N.S.	29 Yr	Male	TT	AA	Cl
39.	1209180021	R.M.	2 Yr	Male	CC	AA	CP
40.	1209180022	H.B.M	28 Yr	Male	CC	AA	CL
41.	1209190021	R.A.	7 Mo	Male	CT	AC	CL
42.	1209190022	A.S.	35 Yr	Male	CC	AC	CL

Distribution ofMTHFRC677TgenepolymorphismandA1298C

Distribution ofMTHFRC677TgenepolymorphismandA1298Cin the case of CL/P-NS in North Sulawesi consists of:

- 42casestudieswhich consistedof21cases of CLP-NS and21case-control and their genotypes,
  - 21cases ofCB/L-NS consistsof14malecasesand7casesfemale
  - 21controlcasesconsistedof10malecasesand11cases female
  - 21casesof C677Tconsistsgenotype CC: 15 CT: 5. TT: 1
  - 21casesof C677T control consists genotype CC: 19, CT: 2, TT: 0
  - 21cases of A1298C consists genotype AA: 6. AC: 10, CC: 5
  - 21caseof A1298C control consists genotype AA: 9, AC: 10, CC: 2

Distribusi Polimorfisme Gen MTHFR C677T & A1298C

Distribusi polimorfisme gen MTHFR C677T & A1298C pd kasus CB/L-NS di Sulawesi Utara terdiri dari:

- 42 kasus penelitian yg terdiri dari 21 kasus CB/L-NS dan 21 kasus kontrol beserta genotipnya,
  - Dari 21 kasus CB/L-NS Terdiri dari 14 kasusLaki-lakidan 7 kasus Wanita
  - Dari 21 KasusKontrolterdiridari10 kasusLaki-lakidan 11 kasus Wanita
  - Dari 21Kasus CB/L-NS C677T terdiriatasCC: 15. CT: 5. TT: 1.
  - Dari 21 Kasuskontrol C677T terdiriatas CC: 19, CT: 2, TT: 0.
  - Dari 21 CB/L-NS genotip A1298C terdiriatas AA: 6. AC: 10, CC: 5.

- Dari 21 KasusKontrol A1298C terdiriatas AA: 9, AC: 10, CC: 2.

RESULTS

Association between Cleft Lip/PalateandC677T&A1298C polymorphism

Table 2

C677T	C L / P Cleft Lip	-N S Cleft Palate	Controle	$X^2_{Calculated}$	*p*-value
CC	10	5	19		
CT	4	1	2	2,2943	0,411
TT	1	0	0		
A1298C					
AA	4	2	9		
AC	8	2	10	2,3610	0,599
CC	3	2	2		

Chi Square (X^2) MTHFR C677T Genotype

Chi Square = X^2. In C677T Cases was calculated $X^2_{calculated}$= 2.2943

Table $X^2_{0,05\ (1)}$= 3.84. ($X^2_{Calculated} < X^2_{Tabel}$)

H0: Accepted, means that there is a significant difference between the distribution of C677T in Case group and control groups.

***p*-Value:** 0.411 (p > 0.005), no statistically association significant between risk of CL/P-NS with the MTHFR polymorphism C677T genotype. So there is a significant association relationship C677T genotypes between case and control groups.

Chi Square (X^2) MTHFR A1298C Genotype

Chi Square = X^2. In A1298C Cases was Calculate $X^2_{calculated}$= 2.3610.

Table $X^2_{0,05\ (1)}$= 3.84. ($X^2_{calculated} < X^2_{Tabel}$)

H0: Accepted, means that there is a significant difference between the distribution of A1298C in Case group and control groups.

***p*-Value:** 0.599 (p > 0.005), no statistically association significant between risk of CL/P-NS with the MTHFR polymorphism A1298C genotype. So there is a significant association relationship A1298C genotypes between case and control groups.

Odds Ratio

Table 3: Odds Ratio MTHFRC 677T, the TT Genotype against CC Genotype

Cases Controle	Odds Ratio	(95% CI)	*p*-Value		
Genotype TT	1	0	0	1,553-3,309	0,269
Genotype CC	15	19			

Table 4: Odds Ratio MTHFR, the CT+TT Genotype against CC Genotype

Cases Controle	Odds Ratio	(95% CI)	*p*-Value		
GenotypeCT + TT	6	2	3,8	0,669-21,589	0,116
Genotype CC	15	19			

Odds Ratio MTHFR C677T polymorphism TT genotype against CC genotype was = 0. Because the TT genotype control was no value (0)

p-Value of TT genotype against CC genotype was 0,269 (p> 0.005) there was no statistically significant association between cases of CL/P-NS polymorphism TT genotype against CC genotype.

Odds Ratio MTHFR C677T polymorphism CT + TT genotype combination against CC genotype was 3.8. So that the CT + TT genotype combination is to have a chance to occur CL/P-NS as much as 3.8 times more than CC genotype. due to genotype T (mutant)

p-value of CT + TT genotype combination against CC genotype was 0.116(p> 0.005) there was no statistically significant association between the CT + TT genotype combination against CC genotype.

Table 5: Odds Ratio MTHFR the a 1298C CC Genotip against AA Genotype

Cases Controle	Odds Ratio	(95% CI)	*p*-Value
Genotype CC 52	3,75	0,540-26,045	0,170
Genotype AA69			

Table 6: Odds Ratio MTHFR the a 1298c AC+CC Genotip against AA Genotype

Cases Controle	Odds Ratio	(95% CI)	*p*-Value		
Genotype AC+CC15	12	1,9	0,520-6,757	0,334	0,116
Genotype AA6	9				

Odds Ratio A1298 CMTHFRCC genotype against AA genotype was 3.75 so that CC genotype is to have a chance to occur CL/P-NS as much as3.75times more than AA genotype. Due to the mutant genotype C.

p-value of CC genotype against AA genotype was0.170(p>0.005) there was statistically significant association between CC genotype against AA genotype.

Odds Ratio A1298CMTHFRAC+ CC genotype combination against AA genotype, where the odds ratio: 1.9. So that the AC+CC genotype have a risk of getting for CL/P-NS as much as 1.9 times greater AA genotype, due to the mutant genotype C.

The *p*-value of CT+TT genotype combination against CC genotype was0.334 (p>0.005) mean there was no statistically significant association between the cases of CL/P-NS AC+CC genotype against AA genotype So there is a significant association relationship C677T genotype and A1298C genotype between case and control groups.

Allele

An allele is an alternative form of a gene (one member of a pair) that is located at a specific position on a specific chromosome. These DNA codings determine distinct traits that can be passed on from parents to offspring. The process by which alleles are transmitted was discovered by Gregor Mendel and formulated in what is known as Mendel's law of segregation.

Table 7: Allele C677T

C677T	CC	CT	TT	Allele C	Allele T	OR
Cases	15	5	1	35 (83,3%)	7 (16,7%)	4
Controle	19	2	0	40 (95,2%)	2 (4,8%)	

Table 8: Allele A1298C

A1298C	AA	AC	CC	Allele A	Allele C	OR
Cases	6	10	5	22 (52,4%)	20 (47,6%)	1,82
Controle	9	10	2	28 (66,7%)	14 (33,3%)	

Within study cases we found that a significantly higher proportion of cases C677T with the Tallele (16, 7%) which is more than 4 times higher in value when compared with controls (4, 8%). While the case with A1298C Callele (47, 6%) which is almost 2 times higher in value when compared with controls. (33, 3%). Although not reaching statistical significance, we observed a tendency among all cases of mutation carriers T and C, will be much more common CL/P-NS from control.

HARDY-WEINBERG EQUILIBRIUM

The Hardy-Weinberg formulas allow scientists to determine whether evolution has occurred. Any changes in the gene frequencies in the population over time can be detected. The law essentially states that if no evolution is occurring, then an equilibrium of allele frequencies will remain in effect in each succeeding generation of sexually reproducing individuals. In order for equilibrium to remain in effect (i.e. that no evolution is occurring) then the following five conditions must be met:

Table 9

Cases A1298C	Genotype Observation	Expectation H. W. Equil	$X^2_{Calcuated}$	X^2_{Table}	Result
Cases AA	6	5,766			$X^2_{Calculated} < H^2_{Tabel}$
Cases AC	10	10,476	0,237	3,84.	H_0 : Accepted
Cases CC	5	4,758			
Control A1298C				.	
Controle AA	9	9,343			$X^2_{Calculated} < H^2_{Tabel}$
Controle AC	10	9,329	0,104	3,84.	H_0 : Accepted
Controle CC	2	2,329			
Cases C677T					
Cases CC	15	14,57			$X^2_{Calculated} < H^2_{Tabel}$
Cases CT	5	5,84	0,417	3,84.	H_o : Accepted
Cases TT	1	0,599			
Controle 677T				.	
Controle CC	19	19,03			$X^2_{Calculated} > H^2_{Tabel}$
Controle CT	2	1,919	24,265	3,84.	H_o : Unaccepted
Controle TT	0	0			

Cases A1298C

Chi Square $X^2_{Calculate}$ (0.237) < X^2_{Table} (3.84):

H0 is accepted, meaning the possibility of CL/P-NS in the case with the CC genotype Hardy - Weinberg equilibrium expectations Case CL/P-NS CC genotype, *p*-value = 4.758, while the CC genotype of Case Control *p*-value = 2.329, mean that Case A1298C CC genotype is higher than Case Control genotype CC, allows to risk for getting CL/P-NS occurs more to Case CC genotype (Mutant).

Cases C677T

Chi Square $X^2_{Calculate}$ (0.417) < X^2_{Table} (3.84):

H0 is accepted, meaning the possibility of CL/P-NS in the case with the TT genotype Hardy - Weinberg equilibrium expectations Case CL/P-NS genotype TT of C677T *p*-value = 0.599, while the Case Control TT genotype of C677T value = 0, meaning that C677T TT genotype case is higher than the Case Control C677T genotype CC, allows for risk For getting CL / P - NS occurs pd Case C677T genotype (mutant).

Population thereby A1298C Cases were follow with the Hardy – Weinberg proportions. Conclusion allows for Hardy - Weinberg proportions is in accordance withA1298C Cases likewise with C677T Cases So will not change with the times.

So there is a significant association relationship C677T genotype andA1298C between case and control groups.

DISCUSSIONS

In the discussion of the calculation of the relationship between the incidence Association CL/P-NS with the MTHFR gene polymorphism assay results with Chi Square (X^2) MTHFR C677T polymorphism between cases and controls was obtained $X^2_{Calculated}$ = 2.2943, where X^2_{table} = 3,84, so$X^2_{Calculated}$< X^2_{table} (2.2943 <3,84). These results suggested a significant difference in the distribution between cases of C677T and the control groups. This is consistent with studies in Brazil by Brandalize.

In the discussion of the calculation of the relationship between the incidence Association CL/P-NS with the MTHFR gene polymorphism assay results with Chi Square (X^2) of the MTHFR A1298C polymorphism between cases and controls was obtained $X^2_{Calculated}$= 2.3610, where (X^2_{table} = 3,84), so$X^2_{Calculated}$< X^2_{table} (2.3610 <3,84)

These results suggested a significant difference in the distribution between cases A1298C CL/P-NS and control groups. This is consistent with studies in Brazil by Brandalize.

In the discussion of the calculation of the relationship between the incidence Association CL/P-NS with the MTHFR gene polymorphism odds ratio for cases with the MTHFR C677T polymorphism on the TT genotype against CC genotype. Statistically could not be calculated because there is a value of 0.

In Association relationship between the incidence of CL/P-NS with the MTHFR gene polymorphism at position C677T, the combination CT + TT genotype against CC genotype The Odds ratio is = 3.8. So that the combination of CT and TT genotypes at risk for getting CL/P-NS bigger 3.8 times more than the result of a mutant genotype CC.

In Association relationship between the incidence of CLP-NS with the MTHFR gene polymorphism at position A1298C, conditioned on the CC genotype against AA genotype, the calculation of the odds ratio is = 3,75, means that the bigger the CC genotype 2.5 times more risk to get CL/P-NS of the AA genotype, because of the mutant (C). This is according to research by Gaspar et al, from the calculation of odds ratios.

In Association relationship between the incidence of CL/P-NS with the MTHFR gene polymorphism at position A1298C, AA + AC genotype combinations against AA genotype its calculation of odds ratios are = 1.9, so that the AC +CC genotype had a risk to get a CL/P-NS 2.9 times greater than the AA genotypes, due to a mutant (C). This is according to research by Gaspar et al, from the calculation of odds ratios.

So that obviously had some effect on the odds ratio Mutant Genotype of his very influential. In the case of the T allele CL/P-NS C677T that its value 16,7%, while the T allelecase-control value is only 4,8%, meaning the T allele in cases much larger than the T allele of control cases. So the possibility of a risk to get a CL/P-NS is more abundant in the case of CL/P-NS containing mutant C677T Polymorphism (T). This is consistent with studies in Brazil by Brandaize. So that the control group, the group that turned out to be more of a case to get a CLP-NS.

Likewise, the C allele Case CL/P-NS A1298C whose value is 47,6%, while the C allele Case Control only 33,3%, mean allele C Cases were more likely than the C allele Case Control, so the possibility of a risk to get a CL/P-NS is more abundant in CL/P-NS Polymorphism A1298C mutant (C). This is consistent with studies in Brazil by Brandalize

Termolabilitas levels of these enzymes are much smaller in individuals with 677TT genotype (18-22%), when compared with 677CT genotype (56 %) and 677CC (66-67%). Because it is the C677T Polymorphism thermolabile enzyme with less activity (Wilken B. Bamforth)

Actually more A1298C genotype on geographic and ethnic describe an individual (Wilken B. Bamforth) So in this case study CL/P-NS there is a connection / can be caused partly by genetics with C677T and A1298C genotype. Or the contribution of C677T and A1298C polymorphism genotyping in the case of CL/P-NS in North Sulawesi.

In the calculation of the Hardy-Weinberg equilibrium the chi-square (X^2) is obtained for the case of A1298C was 0.237 while the chi-square (X^2) distribution table (Table) = 3.84 ($X^2_{Calculated}<X^2_{table}$) means the balance is accepted and followed the Hardy - Weinberg proportions for Balance Hardy - Weinberg. So it will not change according to Age.

In the calculation of the Hardy-Weinberg equilibrium, the chi-square ($X^2_{Calculated}$) is obtained for the case-control A1298C genotype was 0.107 while the chi-square Table X^2_{Table} = 3.84 ($X^2_{Calculated}< X^2_{Table}$) means the balance is accepted and followed the Hardy - Weinberg proportions for the equilibrium. So it will not change according to Age.

In the calculation of the Hardy-Weinberg equilibrium, the chi-square ($X^2_{Calculated}$) is obtained for the case of C677T genotype was 0.417, while the chi-square Tabel X^2_{Table}= 3, 84 ($X^2_{Calculated} < X^2_{table}$) means the balance is accepted and followed the Hardy - Weinberg proportions for the equilibrium. So it will not change according to Age.

CONCLUSIONS

Final conclusion that an association between the incidence of CL/P-NS with the MTHFR gene polymorphism C677T and A1298C to childhood in North Sulawesi. Association of Methylenetetrahydrofolat Reductase C677T/A1298C Polymorphysme with the suseptibility to Childhood of nonsyndomic Cleft Lips with or without Cleft Palates in northern Sulawesi Population. Two MTHFR gene polymorphisms (C677T and A1298C), has been mired in the etiology of CL/P-NS in populations of children in North Sulawesi. Allows for the possibility of the occurrence of childhood someone who has a polymorphism in the MTHFR gene C677T & A1298C positions to happen the nonsyndromatic Cleft Lip with or without Cleft Palate who in North Sulawersi.

Although this is a small study that relativism, our findings have a higher prevalence of which is significantly TT & CC genotypes (mutant) for the occurrence of CL/P-NS in accordance with the study Martinelli et al.

ADVICE

There needs to be education about the risk of CL/P-NS. Especially antenatal care counseling, with folic acid administration for pregnant woman. Need more extensive studies with samples that much more for knowing the interaction of environmental factors and genetic factors as the cause of the CL/P-NS with genotype polymorphism and sequencing. Genetic counseling needs to be done to all the cases with the risk of CL/P - NS that genetic abnormalities associated with parental. The role of genetic clinics as providers of knowledge and genetic information is expected to help prevent the interchangeable occurrence of congenital anomalies in general and in particular the prevention of disorder.

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