Birth Defects Risk (a multifactorial condition)

Prof Vandana Rai,
Department of Biotechnology
VBS Purvanchal University
Jaunpur-222003 (UP), India

Birth Defects

- The term ‘birth defects/congenital defects’ refers to all abnormalities of structure or function including metabolism, which are present since birth.
- Epidemiological studies showed that the prevalence of different birth defects vary in different populations in the world, pointing to variations in genetic, genomic, environmental, lifestyle, and other factors among them.
- The prevalence rate of congenital malformation in India is 19.4 per 1000 birth.

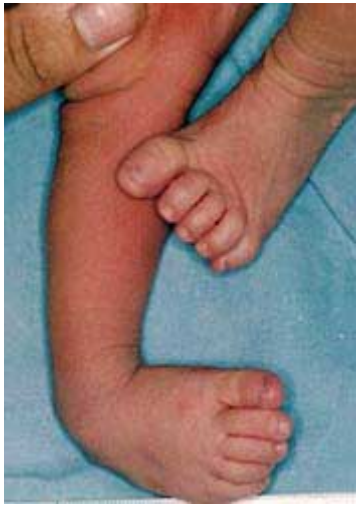
Commonest malformation includes

- neural tube defects (NTD),
- orofacial celfts (OFC)
- talipes (club foot),
- polydactyly,
- hydrocephalus,
- congenital heart defects,
- microcephaly,
- hernia,
- anopthalmia or micropthalmia, and
- Down syndrome (DS).

Craniofacial anomalies=1.1/1000(26,950/year)

Down syndrome =1/1139 (21,510/year)

Mossey and Little, 2009



https://welfarejambo.blogspot.com/2016/11/congenital-malformations.html

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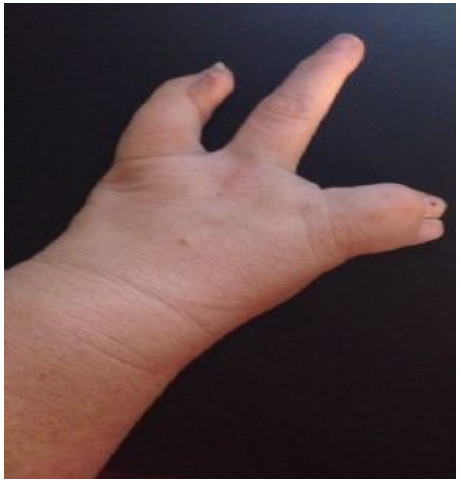
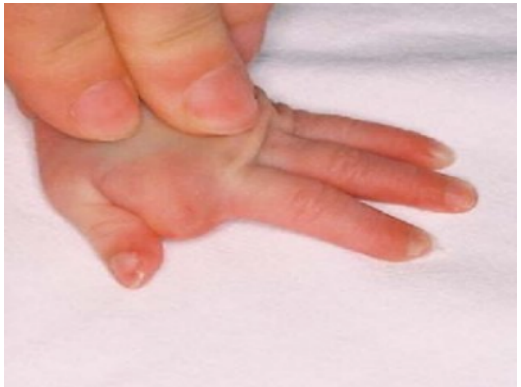
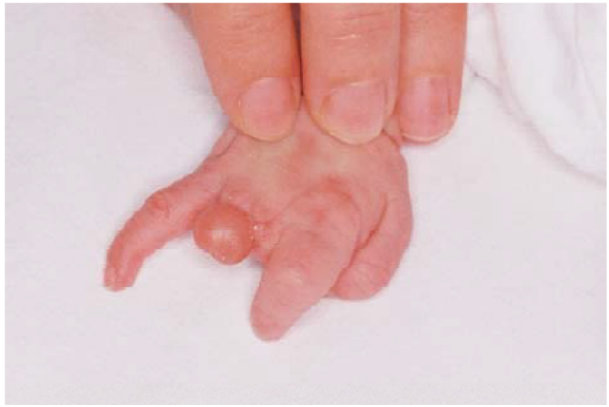
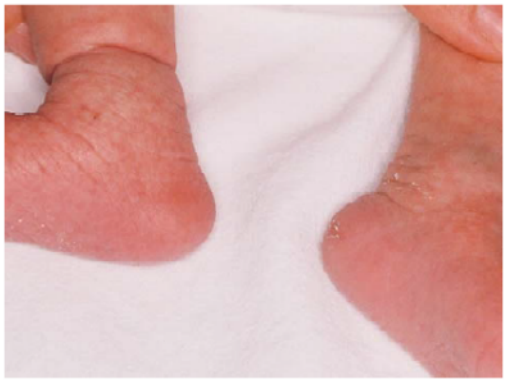


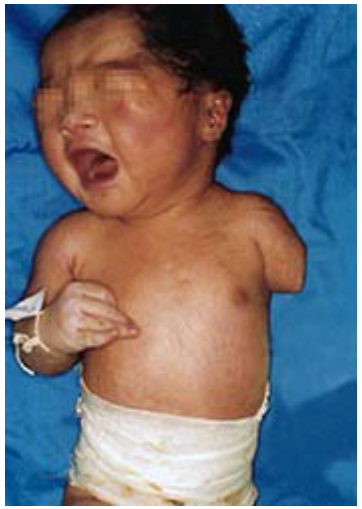
https://www.sparkpeople.com/mypage_public_journal_individual.asp?blog_id=5726353

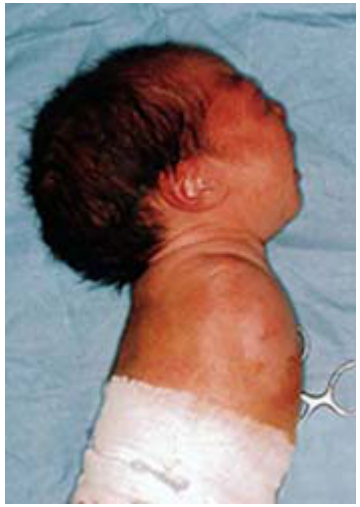


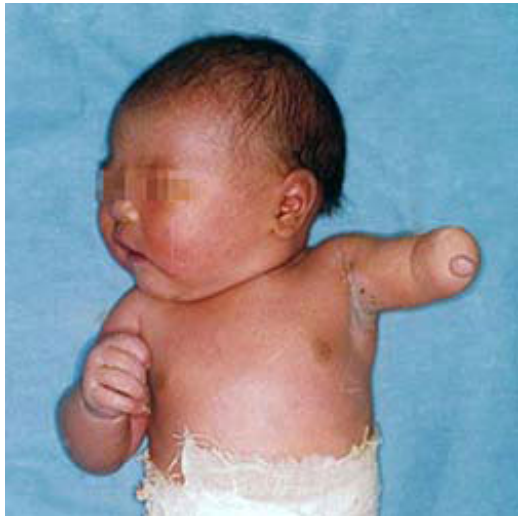


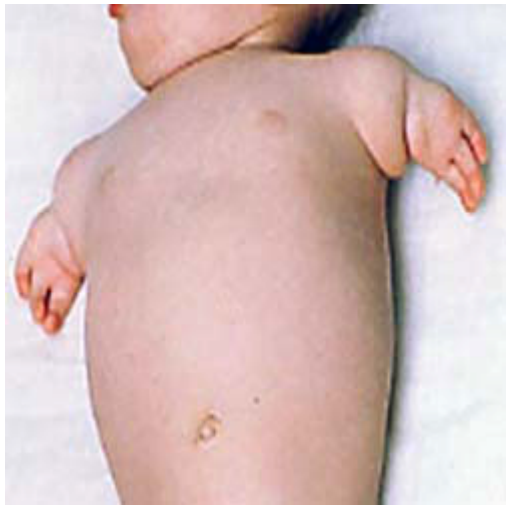


Aleksandra Matić et al., Acta Medica Medianae 2009,48







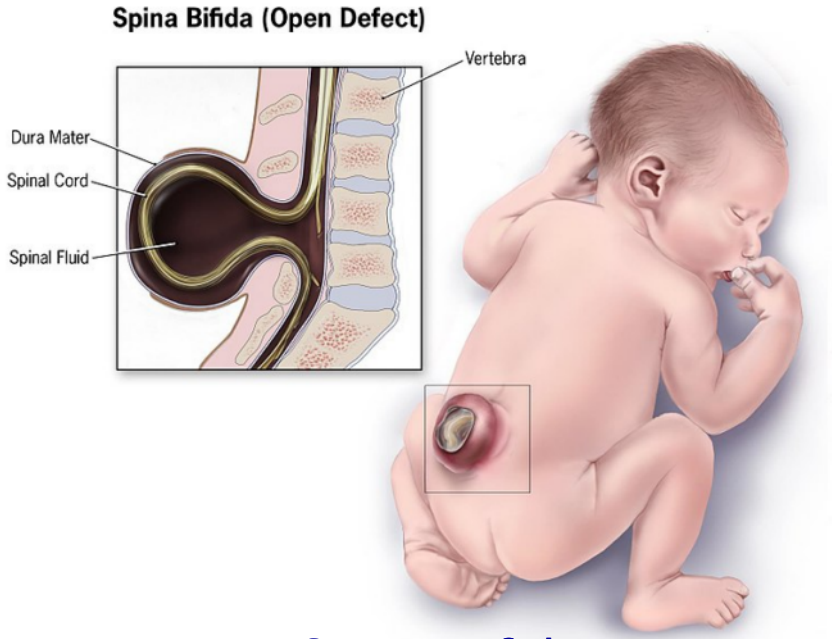


https://welfarejambo.blogspot.com/2016/11/congenital-malformations.html

- In India the incidence rate per 1000 birth of commonest birth defects are NTD (36.3), talipes (14.5), polydactyly (11.6), hydrocephalus (9.5), cleft lip and palate (9.3), congenital heart disease (7.1), hernia (2.6), microcepahly (2.2), intersex and bilateral cryptorchidism (1.6). The estimated number of birth per year of NTD, talipes, hydrocephalus, cleft lip and palate, congenital heart disease, hernia and microcephaly are 88532, 35364, 23169, 22681, 17316, 6341 and 5365 respectively (I C Verma 2000)

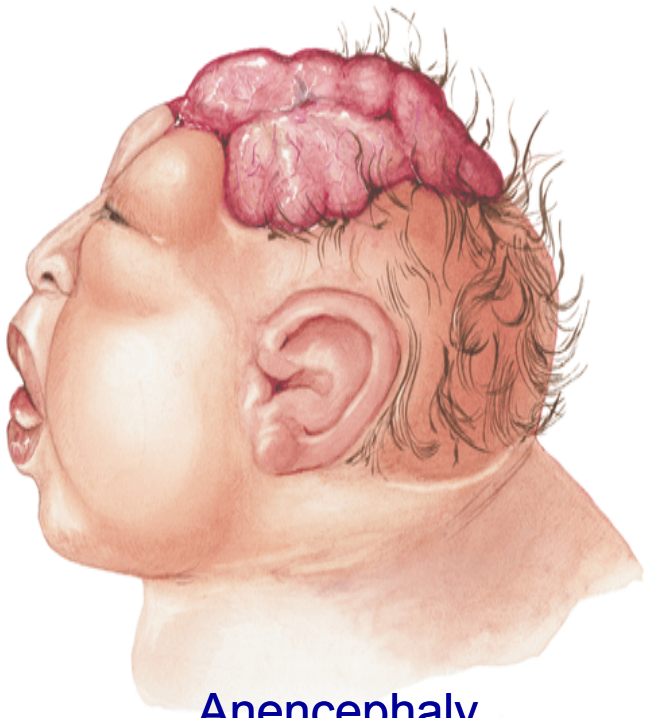
Neural tube defects

- Caused by failure of neural tube to close during neurulation in 21-28 embryonic days.
- Serious birth defects
- Spina Bifida and anencephaly are commonest
- 1 of 1,000 pregnancy
- 300,000 yearly worldwide
- Increased consumption of folic acid can prevent 50%-70%



Spina Bifida

https://en.wikipedia.org/wiki/Neural_tube_defect



Anencephaly

https://factdr.com/health-conditions/neural-tube-defects/

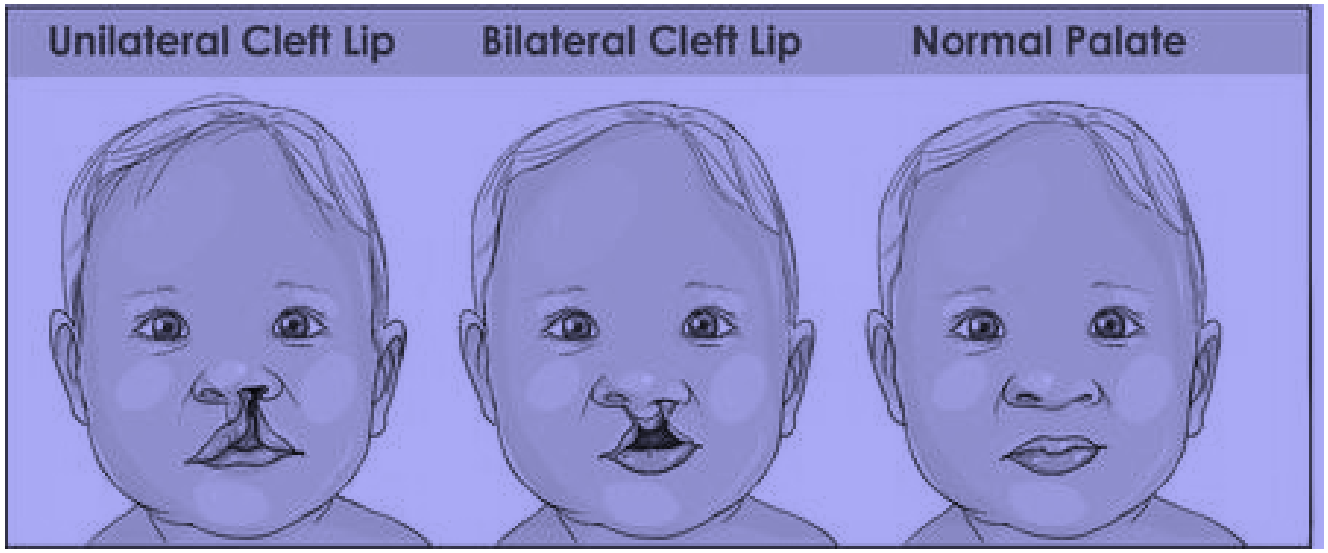
Orofacial Clefts (OFC)
(Cleft Lip and Palate)

Cleft lip (*cheiloschisis*) and **cleft palate** (*palatoschisis*), which can also occur together as **cleft lip and palate**, are variations of a type of clefting caused by abnormal facial development during gestation.

A cleft is a fissure or opening—a gap. It is the non-fusion of the body's natural structures that form before birth.

Approximately 1 in 700 children born have a cleft lip and/or a cleft palate.

A cleft lip or palate can be successfully treated with surgery, especially so if conducted soon after birth or in early childhood.



https://www.123rf.com/photo_97226373_stock-vector-illustration-of-a-cleft-palate-in-a-child.html

https://en.wikipedia.org/wiki/Cleft_lip_and_cleft_palate

Down Syndrome (DS)

Trisomy 21: 3 copies of chromosome 21

male or female

Mental retardation

Narrow eye openings

Up-slanting eyes

Arched eyebrows

Arched palate (cleft)

Flat nose bridge

Bow shaped mouth

low set ears

Short neck

Sloping shoulders

https://www.123rf.com/photo_87964905_stock-vector-down-syndrome-physical-characteristics-infographic-diagram-showing-affected-kid-born-with-this-disab.html

https://depositphotos.com/stock-photos/down-syndrome-adult.html

https://www.istockphoto.com/photos/down sydrome?mediatype=photography&phrase=down%20syndrome&sort=mostpopular

Congenital Heart Defects (CHD)

•A congenital heart defect is a problem with the structure of the heart. It is present at birth.

•Congenital heart defects are the most common type of birth defect.

•The defects can involve the walls of the heart, the valves of the heart, and the arteries and veins near the heart.

•They can disrupt the normal flow of blood through the heart.

•The blood flow can slow down, go in the wrong direction or to the wrong place, or be blocked completely.

•Congenital heart defects (CHD) are among the most common congenital anomalies worldwide, occurring in approximately one in hundred living newborns.

• Heart defects at birth occur as an isolated malformation, but are also associated with other anomalies or occur as part of a syndrome.

•The aetiology of CHD is only partly illuminated.

https://medlineplus.gov/congenitalheartdefects.html#:~:text=A%20congenital%20heart

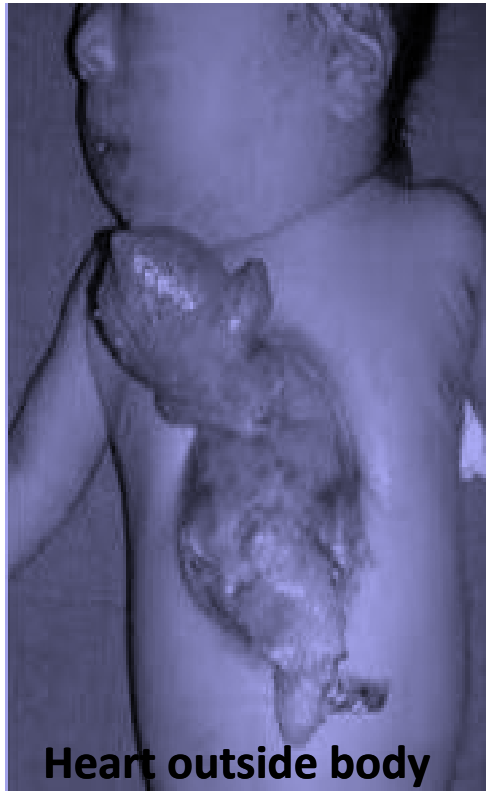
Congenital Heart Defects (CHD)

•Several studies have proposed that maternal periconceptional use of folic acid protects against the occurrence of congenital anomalies, including CHD.

CHDs mainly result from incomplete development of the heart during the first 6 weeks of pregnancy.

In <20% of the cases, a cause can be found, including 22 q11 deletion, trisomy 21, and established environmental risk factors as maternal diabetes, exposure to certain drugs and infectious agents, but the cause is unknown for the vast majority.

Most CHDs are thought to be of complex multifactorial origin, with one or more alleles at a number of loci interacting with environmental



Heart outside body

Types of congenital heart defects:

Aortic valve stenosis (5% of cases of congenital heart disease), c

oarctation of the aorta,

Ebstein's anomaly (less than 1% of congenital heart disease cases),

patent ductus arteriosus (5/1,00,000 birth),

pulmonary valve stenosis (10% of cases of congenital heart disease),

septal defects (atrial septal defects (2/1000 birth),

ventricular septal defects (2/1000 birth)),

single ventricle defects (tricuspid atresia (10/1,00,000 birth)

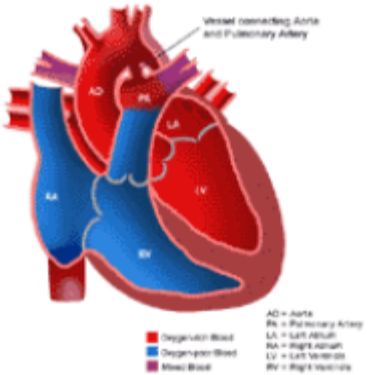
hypoplastic left heart syndrome),

tetralogy of Fallot (3/10,000 birth),

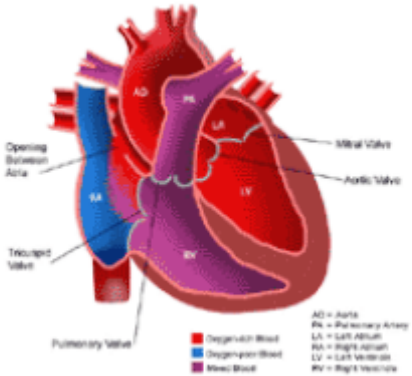
total anomalous pulmonary venous connection,

transposition of the great arteries (5% of cases of congenital heart disease),

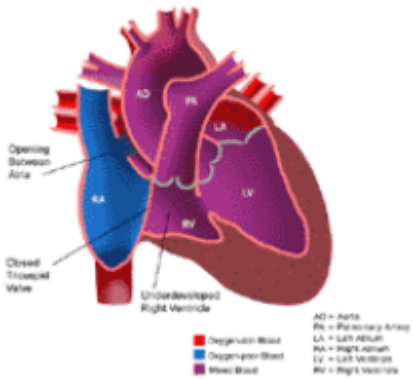
Patent Ductus Arteriosus (PDA)



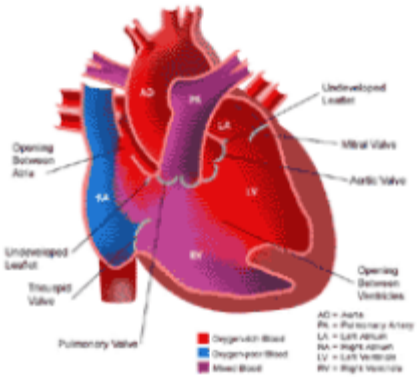
Atrial Septal Defect (ASD)



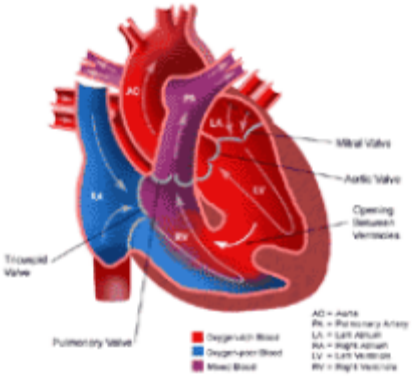
Tricuspid Atresia



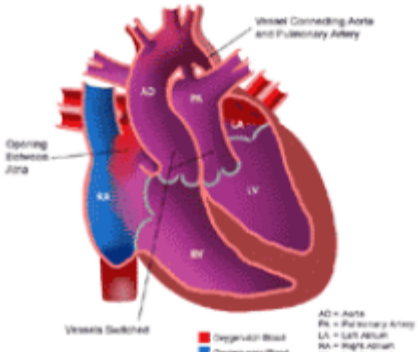
Atrioventricular Canal Defect



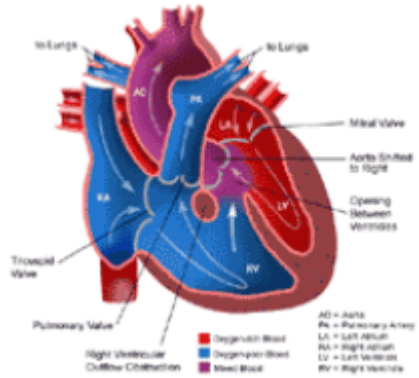
Ventricular Septal Defect (VSD)



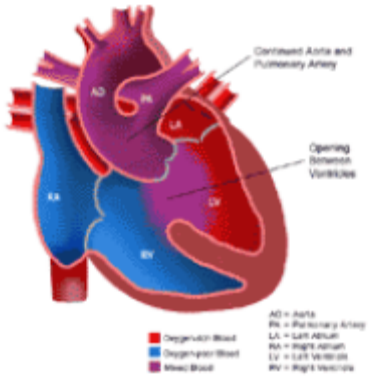
Transposition of Great Arteries



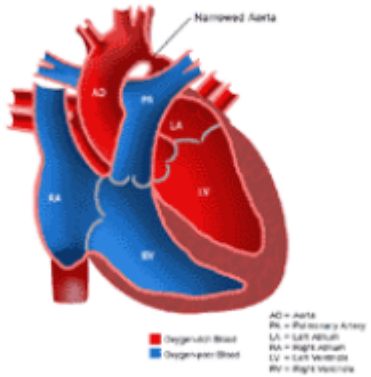
Tetralogy of Fallot (TOF or "Tet")



Truncus Arteriosus



Coarctation of the Aorta



https://www.stanfordchildrens.org/en/topic/default?id=congenital-heart-disease-90-P02346

Altered folate metabolism and congenital defects

Several evidences have emerged that mothers with congenital defects children may have altered folate or methionine metabolism, which suggests the folate methionine cycle may play a key role in the etiology of birth defects.

Humans cannot synthesize folic acid, and folate is essential for

de novo synthesis of nucleotide

methylation reaction i.e. cytosine, histone, lipid.

Chronic folate/methyl deficiency in vivo and in vitro has been associated with:

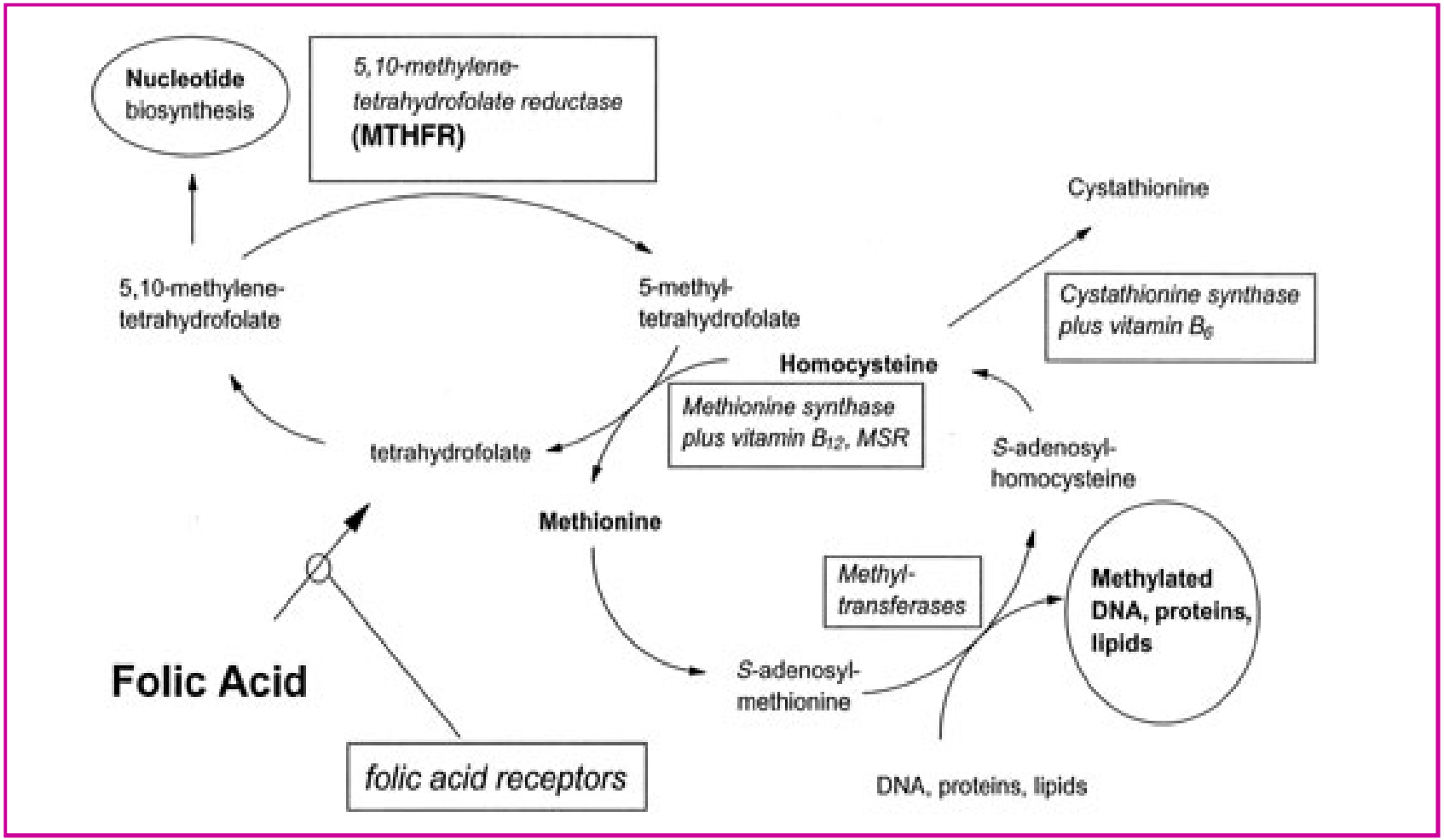
abnormal DNA methylation

DNA strand breaks

altered chromosome recombinations

aberrant chromosome segregations

Folic acid Pathway



1.Methylene tetrahydrofolate reductase; 2. Methionine synthase ; 3.Methionine synthase reductase ; 4. SAH hydrolase ; 5. DNA methyltransferase; 6. Cystathionine b synthase

Hobbs et al., 2000

Methylene Tetrahydrofolate Reductase(MTHFR)

MTHFR enzyme plays an important role in folate and homocysteine metabolism by catalyzing the reduction of 5,10-methylene tetra hydrofolate to 5-methyl tetra hydro folate, which acts as methyl group donor (Scott and Weir, 1994) and donate methyl group for the synthesis of methionine from homocystein.

MTHFR variant: C677T

C677T mutation (ala222val) is within the catalytic domain of the enzyme, and in hetero/homozygous conditions the enzyme activity declines by about 35% and 70% respectively.

The reduction in enzyme activity associated with the C677T MTHFR polymorphism raises the dietary requirement for folic acid to maintain normal remethylation of homocysteine to methionine.

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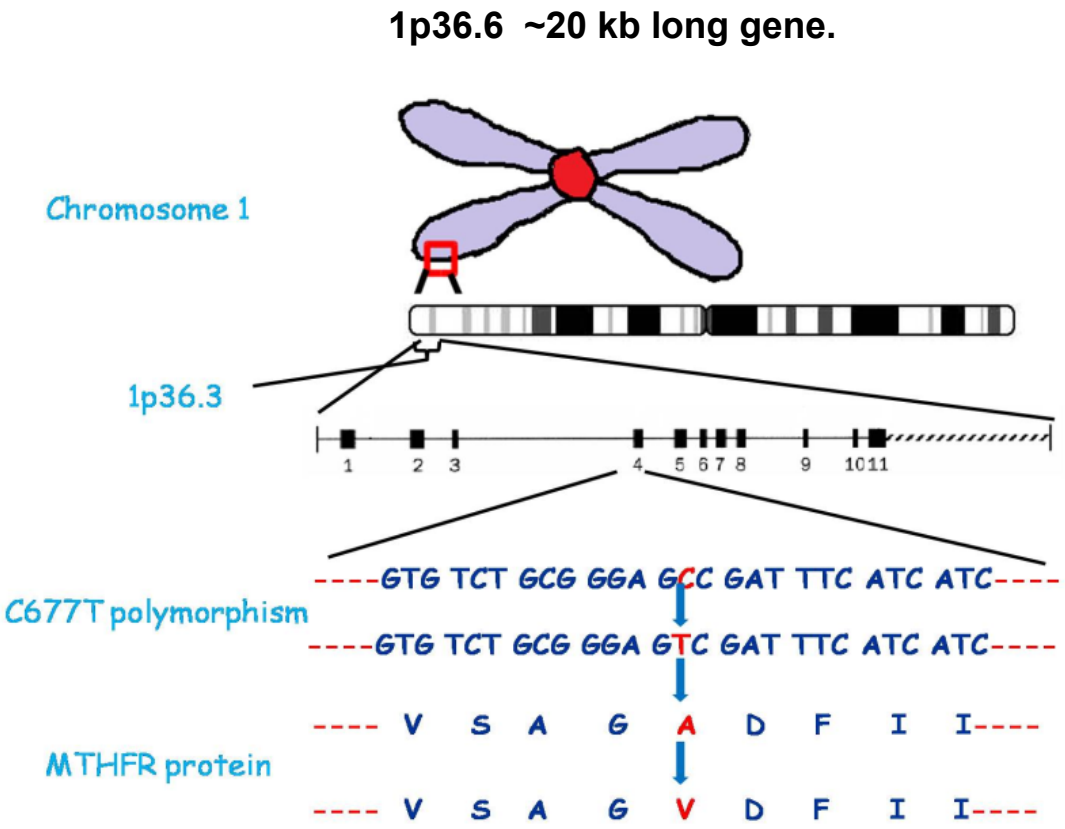


T allele Frequency

- Among European populations there is considerable variation in the T allele (UK 0.29-0.38; Italy 0.4-0.44; Germany 0.28; Holland 0.31- 0.36) .
- Saudi Arab region (14.8%), Bahrain (12.6%), Jordan (16%),Lebanon (49%), Turkey (33.1%).
- However, it was higher than was reported in other Mediterranean countries such as Italy (25%), and Asian countries such as Japan (16%),Srilanka (13% in Sinhalese, 9% in Tamils, and 9% in Moors) and India (10%).
- Middle Eastern and Mediterranean countries such as Iran (32.5%), Turkey (27.8%) ,Lebanon (30.4%), Tunisia (29.2%), Morocco (28.9%), Greece (35%), Saudi Arab region (14.8%), Bahrain (12.6%), Jordan (16%)and Italy (25-45%).

In the Greek population the allele frequency was 35.5%,

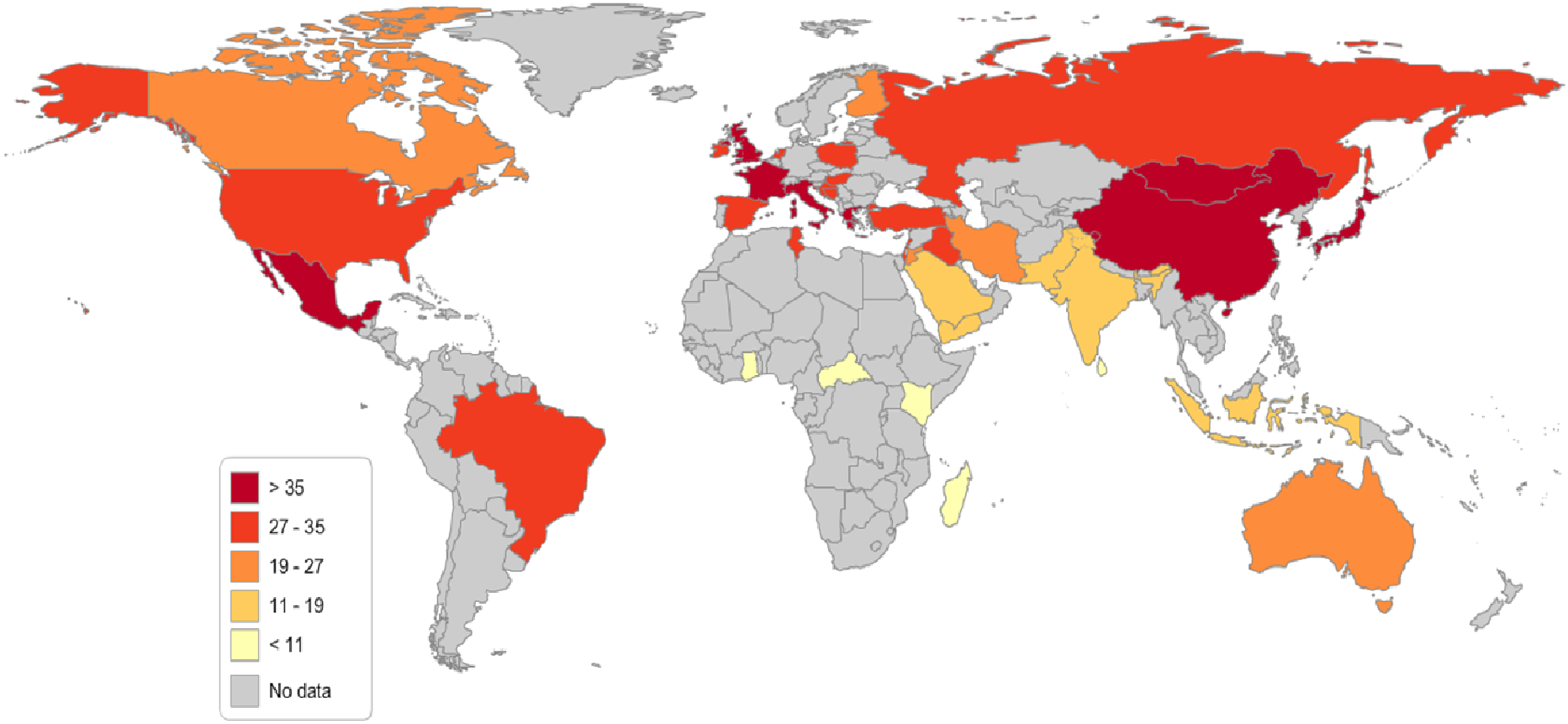
among the French it was 36.1%,

in Italy it was 52.7%, and

in Spain 54.5%.

Population	**T allele Freq.**	**Study**
European	0.20 to 0.55	Van der Put et al.,1997
American	0.11 to 0.35	Schneider et al.,1998
African	0.063 to 0.094	Pepe et al.,1998
Asian	0.04 to 0.38	Spirinidova et al., 2004

Worldwide distribution of T allele



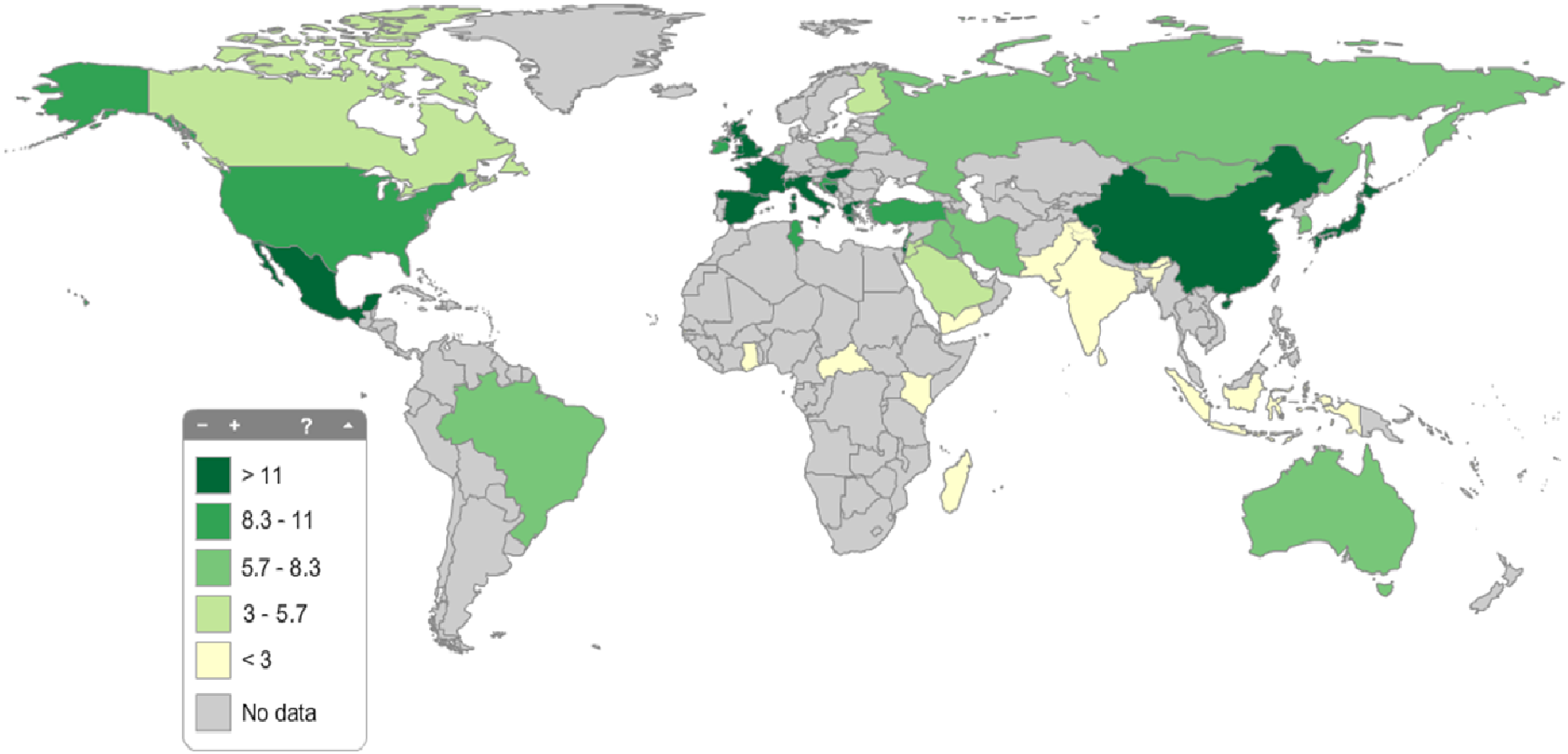
Yadavet al., 2017, Ind J Clin Biochem DOI 10.1007/s12291-016-0619-0

TT genotype frequency worldwide

- It is high in European countries, mainly Italy (18%), France (16.8%), United Kingdom (16.0%), Ireland (10.8%),Germany (10.4%), Sweden (10.3%),Norway (9.5%)and Holland (9.9-12.4%).
- Meta analysis of studies among European populations has shown that the frequency of homozygous carriers ranges from 5–15% .
- High prevalence of the TT genotype was also seen in Southeast Asian countries, including South Korea (12%), Japan (11.0%), India (2.0%), Thailand (1.4%) and Taiwan (6.9%).
- It is even highly prevalent among Hispanics in California (20.7%), and in Colombians (25.3%) (Kostulas et al., 1998).
- It is also noteworthy that the highest prevalence of the TT genotype was encountered in Mexico with 34.8%.

- It is even highly prevalent among Hispanics in California (20.7%), and in Colombians (25.3%) (Kostulas et al., 1998).
- It is also noteworthy that the highest prevalence of the TT genotype was encountered in Mexico with 34.8%.
- US (11.9%)
- Brazil (10.3%)
- Australia (10.7%)
- Lebanon (3.9%)
- Turkey (9.6%)
- In India prevalence of TT genotype is 2.0%

Worldwide distribution of TT genotype



Yadav et al., 2017, Ind J Clin Biochem DOI 10.1007/s12291-016-0619-0

Mothers with MTHFR polymorphisms and lower enzyme activity cannot maintain the higher folate status during pregnancy, thus leading to an increased number of cases of developmental disorders like congenital defects.

Approximately 6.5 million children born annually are affected with a birth defects either genetic or partial genetic origin and there is paucity of data of congenital malformation in India, owing to limited diagnostic facilities, lack of birth surveillance and registry (IC verma,2000).

70% of birth in our country are home based, attended by traditional birth attendant. Therefore, no complete hospital data exists from our country.

In a developing country like India, cost of a management of birth defects/genetic disorders also gets substantial, not only in terms of monetary expenditure but also emotional and social distress due to them.

Therefore, early detection (prenatal diagnosis) of the anomaly, increasing