Folic acid supplementation, *MTHFR* and *MTRR* polymorphisms and the risk of childhood leukaemia: the ESCALE study

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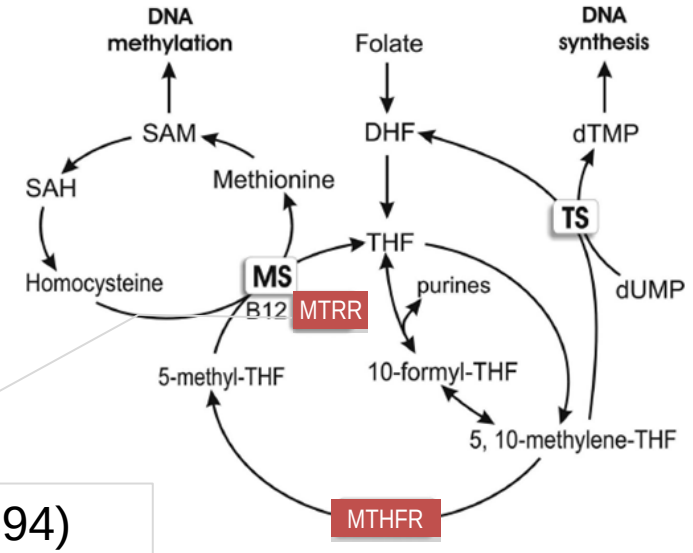
Hypotheses

- Does maternal folate supplementation during pregnancy decrease the risk of childhood acute leukaemia?
- Are *MTHFR* (C677T and A1298C) and *MTRR* (A66G and C524T) genetic variants associated with childhood AL and effect modifiers in the relationship between folic acid supplementation and childhood leukemia?



MTRR A66G (rs1801394)
MTRR C524T (rs1532268)
±
lower affinity for MS

MTHFR C677T (rs1801133)
MTHFR A1298C (rs1801131)
decreased MTHFR activity

The ESCALE study

- **Case and control selection (2003-2004)**
  764 cases identified through the national registry (participation rate: 91%)
  1681 contemporaneaous population controls (participation rate: 71%)
  493 cases and 441 controls of European descent (genotyping)
- **Standardized telephone interviews of biological mothers**
  Maternal supplementation during the index pregnancy
- **Biological material and genotyping**
  DNA extracted from blood for the cases and from saliva for the controls

  High throughput genotyping (*MTHFR* C677T and *MTRR* C524T)
  - genome wide for the cases (Illumina 370K quad)
  - subsample of 4500 SNPs for the controls (Illumina iSelect)

  Imputation of non genotyped SNPs (*MTHFR* A1298C and *MTRR* A66G)

Childhood leukaemia and periconceptional folic acid supplementation

		ALL			ANLL		
	Controls	Cases	OR	95%CI	Cases	OR	95%CI
Never	1439	584	**1.0**	Ref.	105	**1.0**	Ref.
Any folid acid suppl.	172	28	**0.4**	[0.3-0.6]	4	**0.3**	[0.1-0.9]
Pre- / 1st trimester	70	9	**0.3**	[0.2-0.7]	1		
2nd trimester	56	13	**0.6**	[0.3-1.1]	2		
3rd trimester	37	3	**0.2**	[0.1-0.8]	1		

Childhood leukaemia and *MTHFR* and *MTRR* polymorphisms

		ALL			ANLL		
	Co	Ca	OR	95%CI	Ca	OR	95%CI
***MTHFR* C677T and A1298C**							
Both ancestral	48	34	**1.0**	Ref.	5	**1.0**	Ref.
≥ 1 variant, none homozygous	278	273	**1.3**	[0.8-2.2]	33	**0.9**	[0.3-2.6]
Homozygous for at least 1 variant	101	99	**1.3**	[0.8-2.4]	19	**1.5**	[0.5-4.5]
***MTRR* A66G and C524T**							
Both ancestral	44	45	**1.0**	Ref.	7	**1.0**	Ref.
A66G variant only	51	67	**1.4**	[0.7-2.5]	3	**0.5**	[0.1-2.0]
C524T variant only	137	99	**0.8**	[0.4-1.3]	18	**0.9**	[0.4-2.5]
Both variants	209	198	**0.9**	[0.6-1.6]	28	**0.9**	[0.4-2.4]
MTHFR and MTRR combined							
Both MTHFR ancestral	48	34	**1.0**	Ref.			
≥ 1 MTHFR variant, none hom.	278	273	**1.3**	[0.8-2.1]			
≥ 1 MTHFR hom. < 2 MTRR variant	58	41	**1.0**	[0.5-1.8]			
≥ 1 MTHFR hom. 2 MTRR variant	43	50	**1.7**	[0.9-3.2]			

MTHFR, *MTRR* and maternal folic acid supplementation

No interaction between folic acid and MTHFR/MTRR polymorphisms

Conclusion

- The results reported herein support the hypothesis that maternal folic acid supplementation before or during pregnancy may reduce the risk of AL.
- They also suggest that the genotype homozygous for at least one *MTHFR* variant and carrying both *MTRR* variants may be a risk factor for AL.

Acknowledgements

- Case detection, recruitment, information
  INSERM U1018, Environmental Epidemiology of Cancer
  French National Registry of Childhood Blood Malignancies
- Control selection: Institut CSA
- Participants interviews: Callson
- Biological collection: Biological Resource Center of Saints-Pères, INSERM U775
- Genotyping: CEPH, Centre National du Génotypage & IntegraGen
- Société Française de lutte contre les Cancers de l'Enfant et de l'Adolescent (SFCE)
- Financial support: INSERM, Fondation de France, Association pour la Recherche sur le Cancer (ARC), Agence Française de Sécurité Sanitaire des Produits de Santé (AFSSAPS), Agence Française de Sécurité Sanitaire de l'Environnement et du Travail (AFSSET), association Cent pour sang la vie, Institut National du Cancer (INCa), Agence Nationale de la Recherche (ANR), Cancéropôle Ile de France.

Thank you for your attention