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Transfer of recent evidences concerning genetic and epigenetic risk factors of complex diseases on clinical practice

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The goal of translating genomic testing for complex diseases into clinical practice

has not yet been reached in Italy

and predictive genetics have currently only few clinical applications

However for the first time (March 2013) the Italian Ministry of Health has introduced a policy strategic plan on genomics and predictive medicine within the National Prevention Plan, supported by the Italian Network for Genomics in Public Health (GENISAP)

AIM ⟶ to transfer the most recent findings on genetic risk factors for complex diseases into public health care system, and to give correct information to the citizens.

“The policy of public health genomics in Italy” Simone et al., Health Policy 110 (2013) 214– 219

Summary of evidence and knowledge available on the use of genomics for prevention

Genomic tests or predictive genetic tests

What is a predictive genetic test?

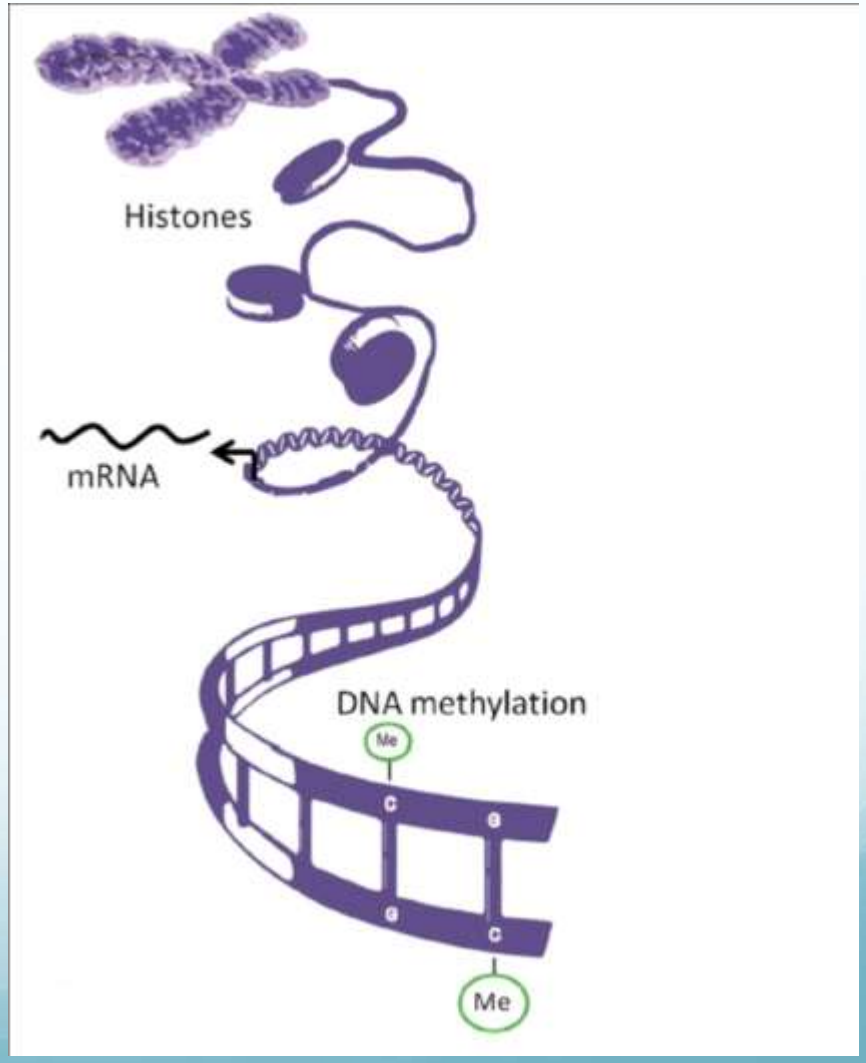
- A predictive genetic test can provide information about the possibility that a person will develop or has a chance of developing a specific disease that usually occurs later in life (EuroGenTest)
- Analysis of the DNA of an individual for tens, hundreds of disease alleles to identify predisposition to complex diseases

But…

- Susceptibility genes for many complex diseases, in their allelic forms, usually confer low relative risk (low OR values).
- Growing and uncontrolled availability of predictive genetic testing for complex diseases (DTC: Direct to consumer tests, available online)

- Lack of information from the best available scientific evidence on the real applications and the implications on the health of the individual, lack of trained operators in health care..

An emerging scenario: not only testing for genetic markers, but also for epigenetic ones.



Epigenetics

The missing link between the genome and the environment

Epigenetics

Hereditary changes that do not involve alteration of the DNA sequence

Epigenetic markers

- DNA methylation
- Histone tails modifications
- ncRNA

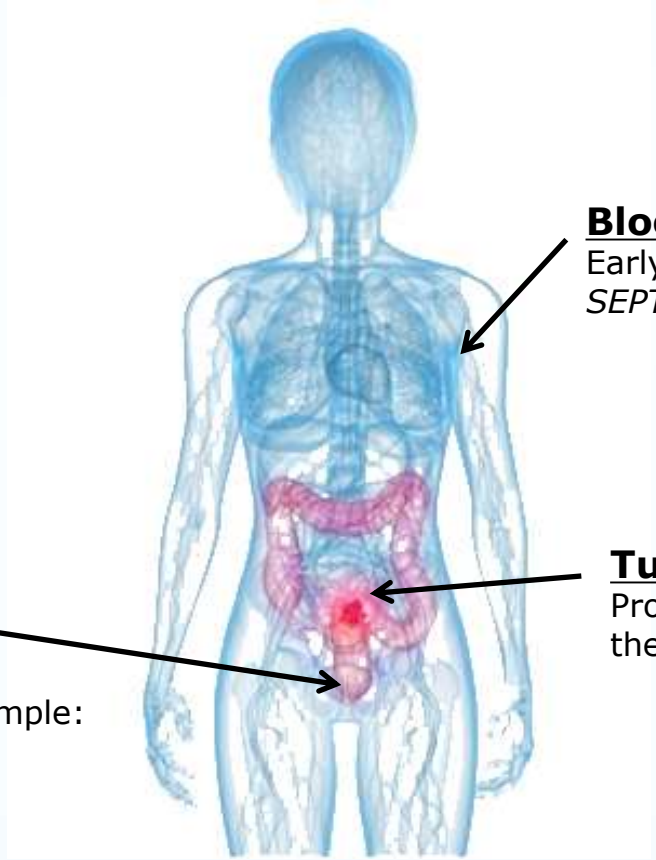
Aberrant DNA methylation, histone tails modifications, ncRNAs deregulation have been linked to a number of age related disorders including cancer, autoimmune disorders, cardiovascular diseases, neurodegeneration, behavioural diseases and other degenerative diseases

Epigenetics at the Epicenter of Modern Medicine
JAMA. 2008; 299(11):1345-1350 Andrew P. Feinberg

Epigenetics and environment

The epigenome is an important target of environmental modifications

Methylation as diagnostic, prognostic and treatment marker (CRC)



Blood DNA
Early diagnosis (example: *SEPT9*)

Tumor sample DNA
Prognosis/staging/choice of therapy

Fecal DNA
Early diagnosis (example: *VIM*)

World J Gastroenterol. 2014 Jan 28;20(4):943-56. doi: 10.3748/wjg.v20.i4.943.
Genetic and epigenetic biomarkers for diagnosis, prognosis and treatment of colorectal cancer. Coppedè F, Lopomo A, Spisni R, Migliore L.

Our contributions

Myasthenia Gravis

PLOS ONE Volume 8 | Issue 11 | e80846

Association of the *DNMT3B* -579G>T Polymorphism with Risk of Thymomas in Patients with Myasthenia Gravis

Fabio Coppedè[1*], Roberta Ricciardi[2,3], Maria Denaro[1], Anna De Rosa[2], Carlo Provenzano[4], Emanuela Bartoccioni[4], Angelo Baggiani[1], Marco Lucchi[3], Alfredo Mussi[3], Lucia Migliore[1]

1 paper

Alzheimer's disease

Folate, Homocysteine, Vitamin B12, and Polymorphisms of Genes Participating in One-Carbon Metabolism in Late-Onset Alzheimer's Disease Patients and Healthy Controls

Fabio Coppedè, Pierpaola Tannorella, Ilaria Pezzini, Francesca Migheli, Giulia Ricci, Elena Caldarazzo-Jenco, Irene Piaceri, Antonio Polini, Benedetta Nacmias, Fabio Monzani, Sandro Sorbi, Gabriele Siciliano, and Lucia Migliore

ANTIOXIDANTS & REDOX SIGNALING
Volume 17, Number 2, 2012
© Mary Ann Liebert, Inc.
DOI: 10.1089/ars.2011.4388

9 papers

Amyotrophic Lateral sclerosis

Neuroscience Letters 420 (2007) 163–168

Association of the *hOGG1* Ser326Cys polymorphism with sporadic amyotrophic lateral sclerosis

Fabio Coppedè[a,*], Michelangelo Mancuso[a], Annalisa Lo Gerfo[a], Cecilia Carlesi[a], Selina Piazza[a], Anna Rocchi[a], Lucia Petrozzi[a], Claudia Nesti[a], Dario Micheli[a], Andrea Bacci[a], Lucia Migliore[b], Luigi Murri[a], Gabriele Siciliano[a]

3 papers

Parkinson's disease

Neuroscience Letters 473 (2010) 248–251

The *hOGG1* Ser326Cys polymorphism is not associated with sporadic Parkinson's disease

Fabio Coppedè[a,*], Roberto Ceravolo[a], Francesca Migheli[b], Francesca Fanucchi[b], Daniela Frosini[a], Gabriele Siciliano[a], Ubaldo Bonuccelli[a], Lucia Migliore[b]

6 papers

Huntington's disease

Toxicology 278 (2010) 199–203

The *hOGG1* Ser326Cys polymorphism and Huntington's disease

Fabio Coppedè[a,*], Francesca Migheli[b], Roberto Ceravolo[a], Elisa Bregant[c], Anna Rocchi[a], Lucia Petrozzi[a], Elisa Unti[a], Renata Lonigro[c], Gabriele Siciliano[a], Lucia Migliore[b]

1 paper

Colorectal cancer

Epigenetics. 2014 Jan 31;9(4). [Epub ahead of print]

Gene promoter methylation in colorectal cancer and healthy adjacent mucosa specimens: Correlation with physiological and pathological characteristics, and with biomarkers of one-carbon metabolism.

Coppedè F[1], Migheli F[2], Lopomo A[3], Failli A[4], Legitimo A[5], Consolini R[5], Fontanini G[6], Sensi E[6], Servadio A[6], Seccia M[6], Zocco G[6], Chiarugi M[6], Spisni R[6], **Migliore L**[1].

3 papers

Down syndrome

Human Reproduction, Vol.28, No.2 pp. 545–550, 2013

***DNMT3B* promoter polymorphisms and maternal risk of birth of a child with Down syndrome**

Fabio Coppedè[1,*], Paolo Bosco[2], Pierpaola Tannorella[3], Carmelo Romano[2], Ivana Antonucci[4], Liborio Stuppia[4], Corrado Romano[2], and Lucia Migliore[1,3]

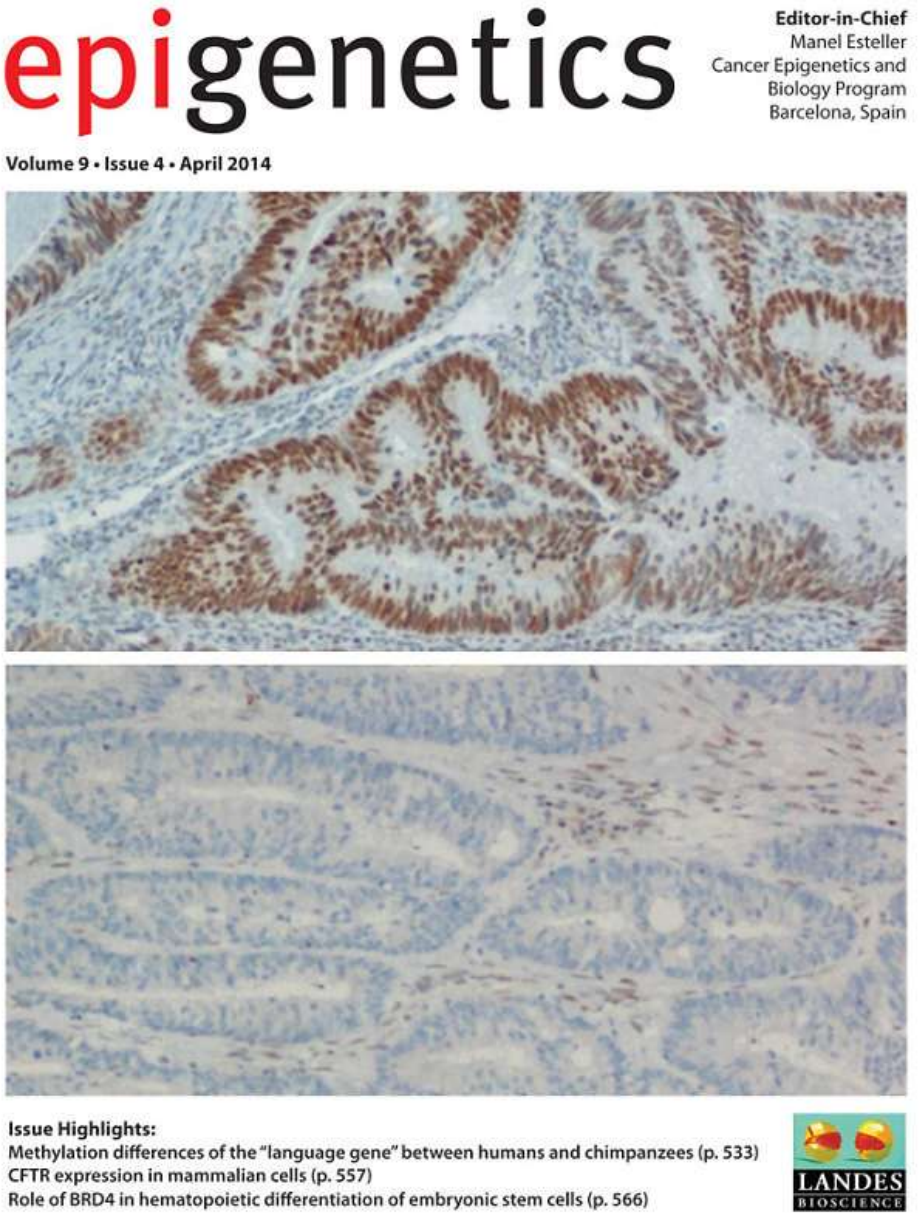
9 papers

13 Review

“Gene promoter methylation in colorectal cancer and healthy adjacent mucosa specimens: correlation with physiological and pathological characteristics, and with biomarkers of one-carbon metabolism”

Coppedè F, Migheli F, Lopomo A, Failli A, Legitimo A, Consolini R, Fontanini G, Sensi E, Servadio A, Seccia M, Zocco G, Chiarugi M, Spisni R, **Migliore L**.

Epigenetics. 2014 Apr 1;9(4):621-33



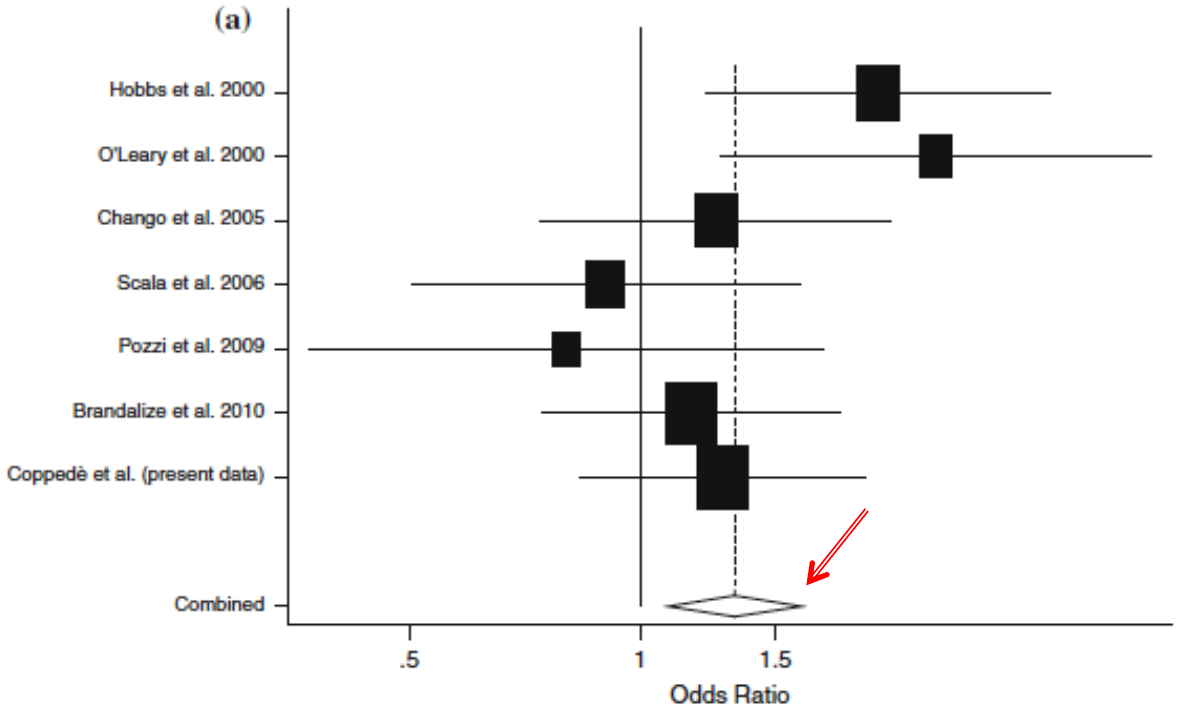
How best to use all this data?

Approach 1: meta-analysis

Mol Biol Rep
DOI 10.1007/s11033-014-3462-5

The *MTRR* 66A>G polymorphism and maternal risk of birth of a child with Down syndrome in Caucasian women: a case–control study and a meta-analysis

Fabio Coppedè · Paolo Bosco · Valentina Lorenzoni · Maria Denaro · Guido Anello · Ivana Antonucci · Concetta Barone · Liborio Stuppia · Corrado Romano · Lucia Migliore



Approach 2: combined genotypes

American Journal of Medical Genetics Part A 140A:1083–1091 (2006)

Folate Gene Polymorphisms and the Risk of Down Syndrome Pregnancies in Young Italian Women

Fabio Coppedè,[1] Giulia Marini,[1] Stefania Bargagna,[2] Liborio Stuppia,[3,4] Fabrizio Minichilli,[5] Ilaria Fontana,[1] Renato Colognato,[1] Guia Astrea,[2] Giandomenico Palka,[3,6] and Lucia Migliore[1]*

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[4]I.T.O.I. CNR, c/o IOR, Bologna, Italy
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[6]Human Genetic Division, Pescara Hospital, Pescara, Italy

Received 4 November 2005; Accepted 17 February 2006

TABLE V. Interaction Between *MTHFR* 1298A > C and *RFC*-1 80G > A Genotypes in Mothers of Down Syndrome Children (DS Mothers) and Control Mothers

*MTHFR*1298/*RFC1*-80 Genotype	Number of DS mothers (%)	Number of control mothers (%)	OR	95% CI	*P*
	64 (total)	87 (total)			
1298AA/80GG	16 (25)	11 (12.6)	1.0	Referent	
1298AC/80GG	10 (15.6)	12 (13.6)	0.57	0.18–1.79	0.337
1298CC/80GG	1 (1.6)	3 (3.45)	0.23	0.02–2.50	0.227
AC or CC/GG[a]	11 (17.2)	15 (17.05)	0.50	0.17–1.50	0.219
1298AA/80GA	11 (17.2)	20 (23)	0.38	0.13–1.09	0.073
1298AA/80AA	6 (9.4)	12 (13.8)	0.34	0.09–1.19	0.093
AA/GA or AA[b]	17 (26.6)	32 (36.8)	0.36	0.14–0.96	0.041
1298AC/80GA	13 (20.3)	20 (23)	0.45	0.16–1.26	0.128
1298AC/80AA	5 (7.8)	6 (6.9)	0.57	0.14–2.35	0.440
1298CC/80GA	2 (3.2)	1 (1.15)	1.37	0.11–17.09	0.804
AC or CC/GA or AA[c]	20 (31.3)	29 (33.35)	0.47	0.18–1.23	0.126

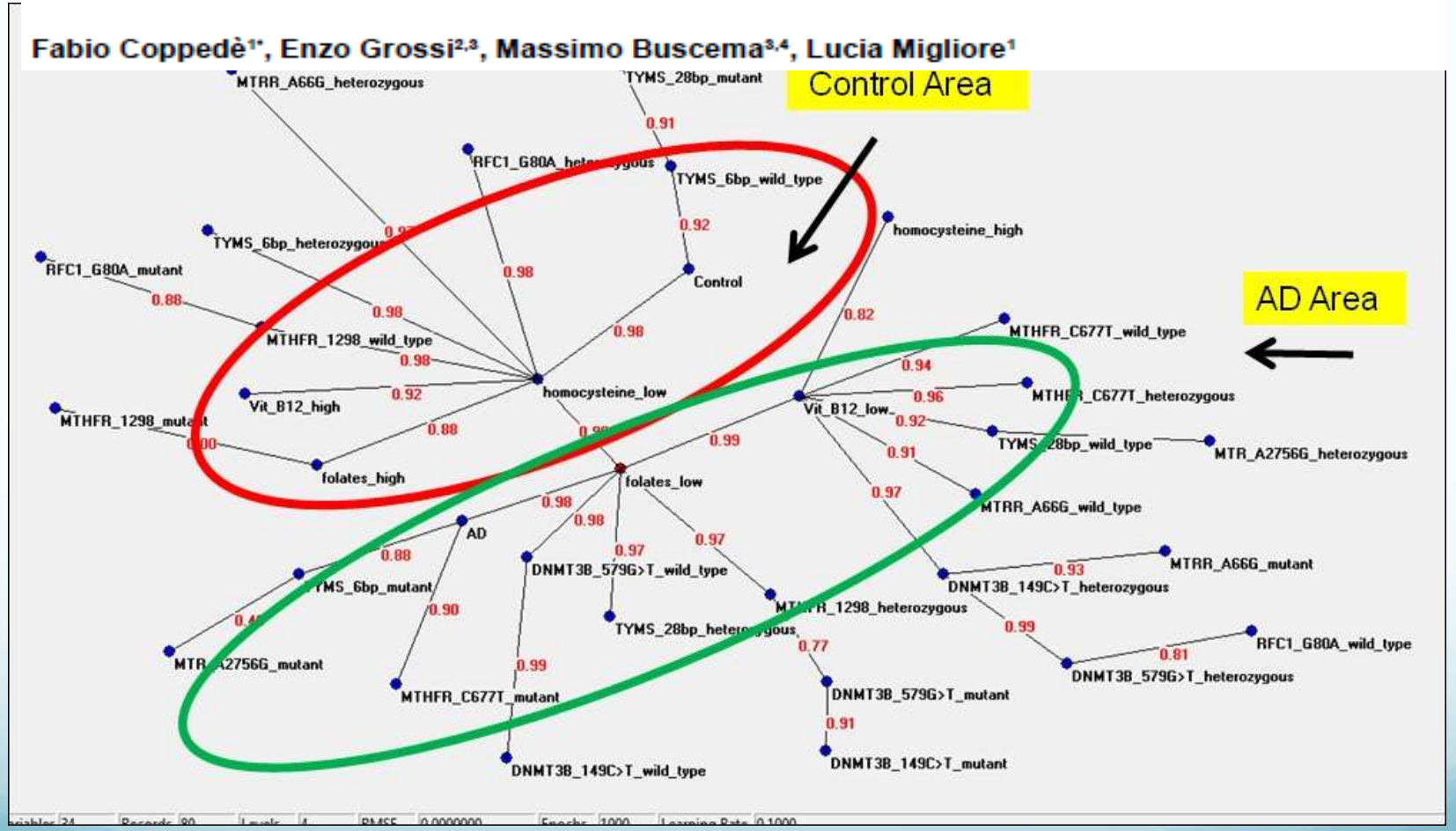
Missing combinations are due to the absence of DS mothers and/or control mothers with that particular genotype.
[a]Combined 1298(AA or CC)/80GG.
[b]Combined 1298AA/80(AG or AA).
[c]Combined1298(AC or CC)/80(GA or AA).

Approach 3: artificial neural networks

PLOS ONE Volume 8 | Issue 8 | e74012 2013

Application of Artificial Neural Networks to Investigate One-Carbon Metabolism in Alzheimer's Disease and Healthy Matched Individuals

Fabio Coppedè[1*], Enzo Grossi[2,3], Massimo Buscema[3,4], Lucia Migliore[1]



Semantic connectivity map showing connections among variables.

Values range from 0 (not connected) and 1 (highly connected)

Thank you for your attention!