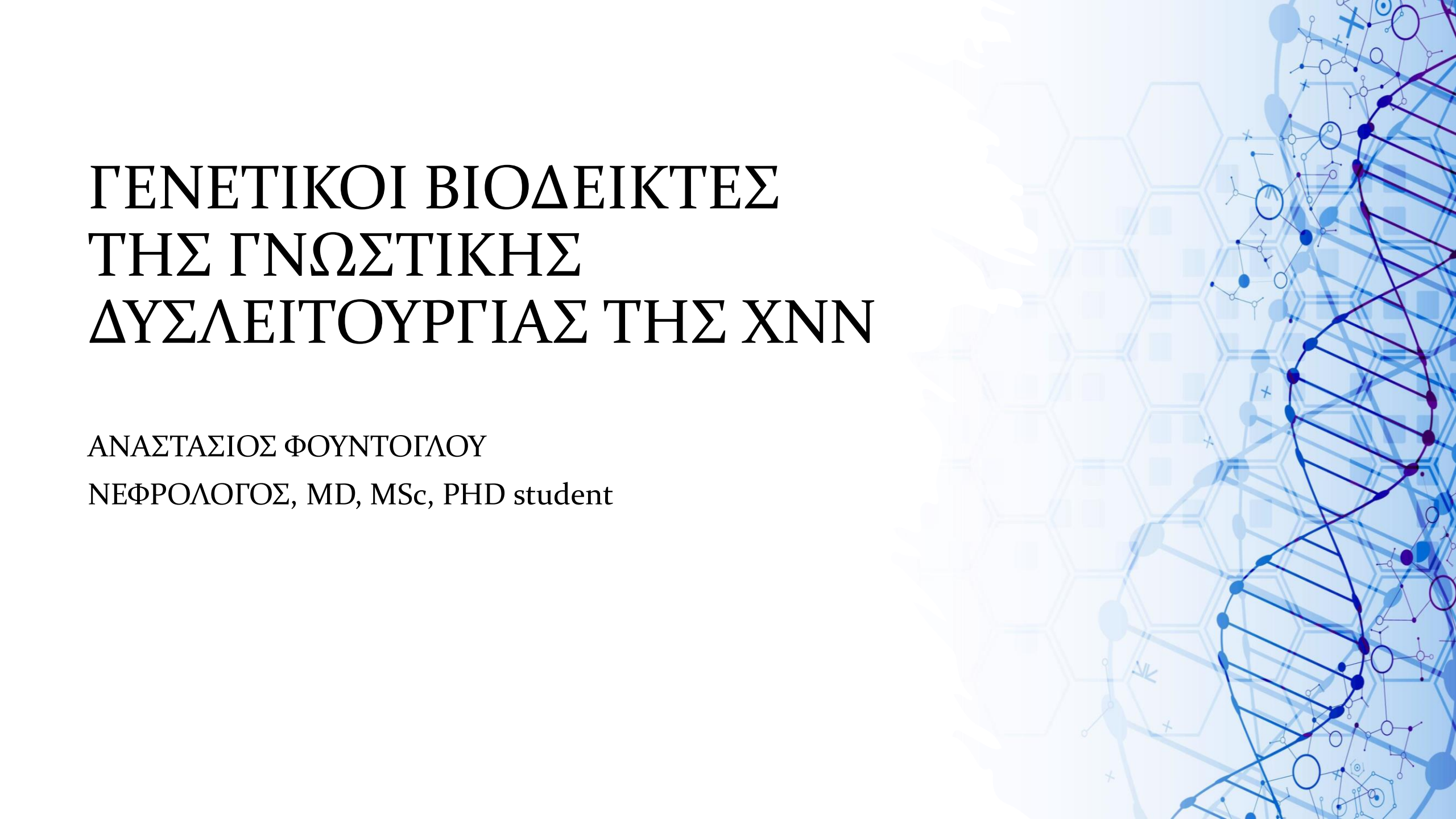
ΓΕΝΕΤΙΚΟΙ ΒΙΟΔΕΙΚΤΕΣ ΤΗΣ ΓΝΩΣΤΙΚΗΣ ΔΥΣΛΕΙΤΟΥΡΓΙΑΣ ΤΗΣ ΧΝΝ

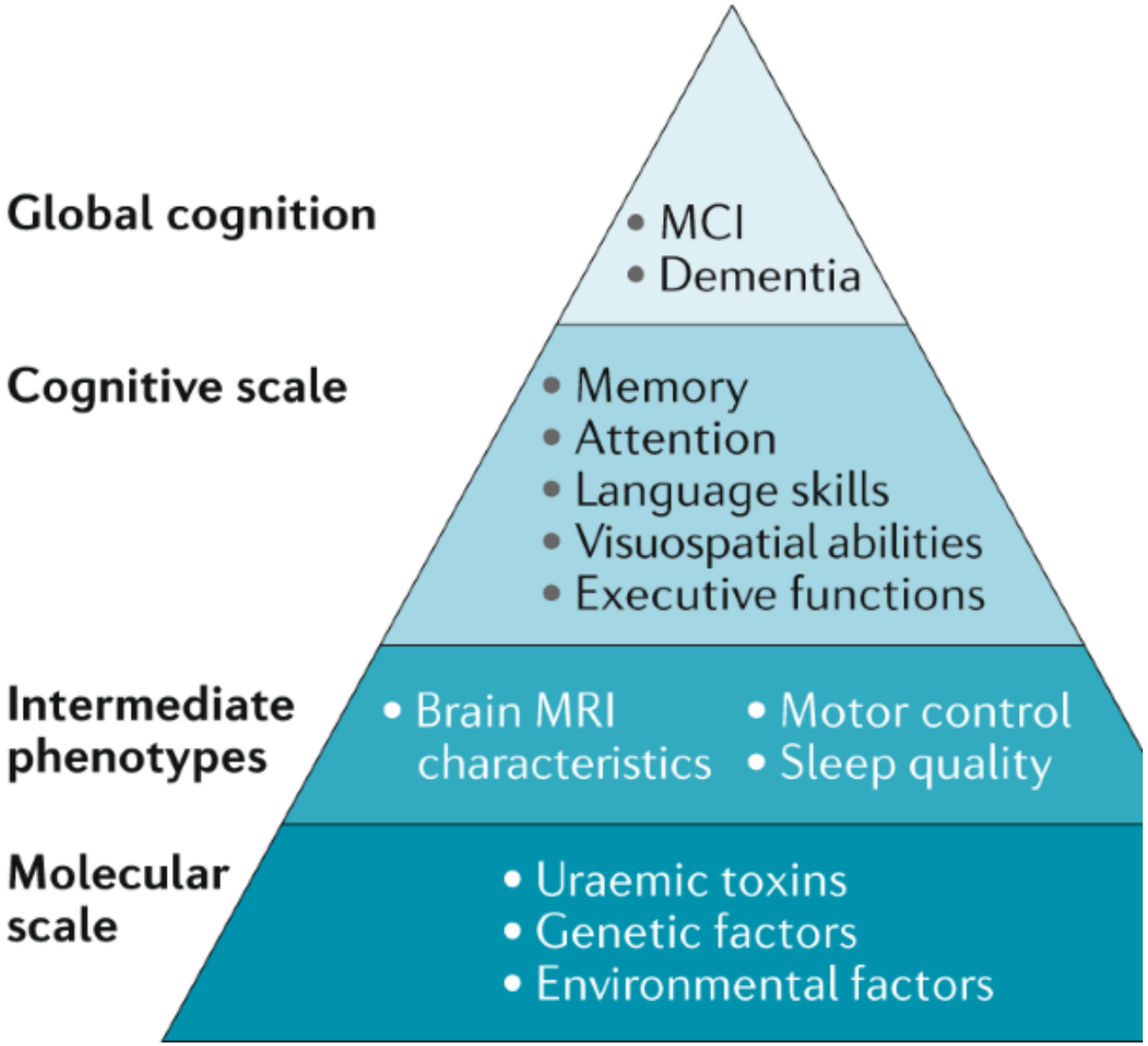
ΑΝΑΣΤΑΣΙΟΣ ΦΟΥΝΤΟΓΛΟΥ

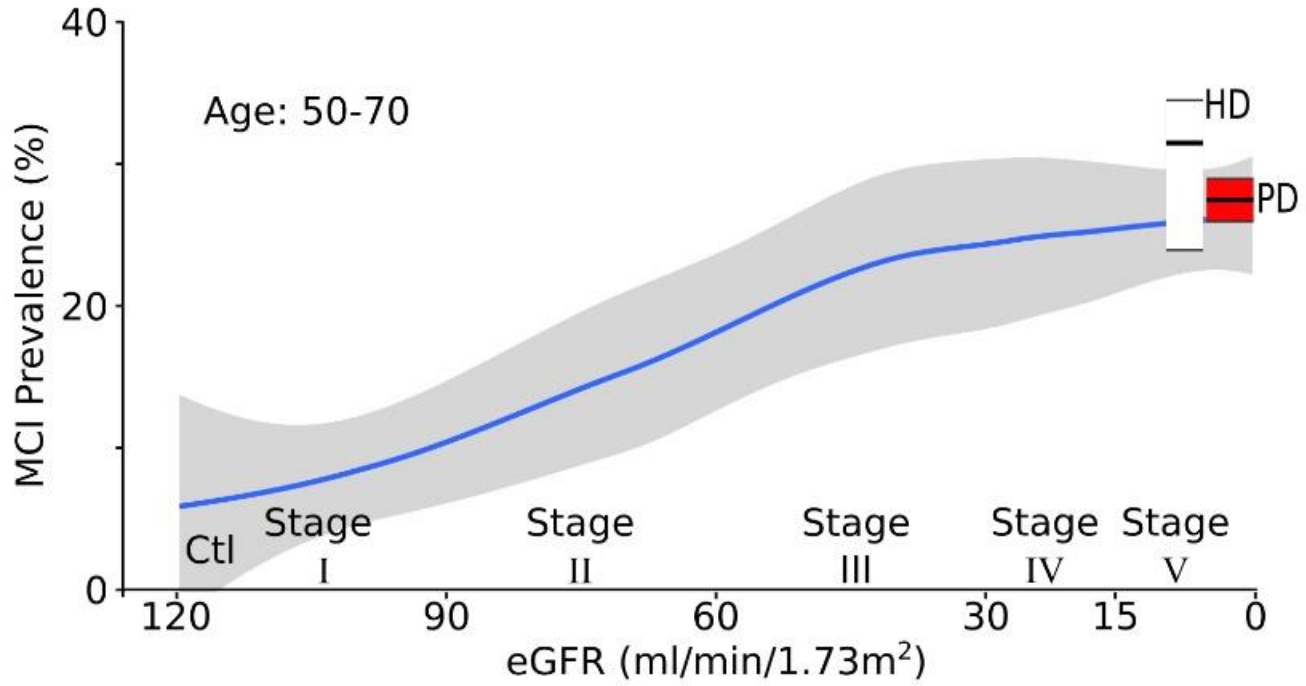
ΝΕΦΡΟΛΟΓΟΣ, MD, MSc, PHD student



γνωστική δυσλειτουργία

- ασθενείς με ΧΝΝ έχουν αυξημένο κίνδυνο ανάπτυξης διαταραχών της γνωστικής τους λειτουργίας
- ο βαθμός της γνωστικής δυσλειτουργίας αυξάνεται με την εξέλιξη της ΧΝΝ
- η γνωστική δυσλειτουργία κυμαίνεται από την ήπια γνωστική δυσλειτουργία (MCI) μέχρι και την εγκατάσταση άνοιας

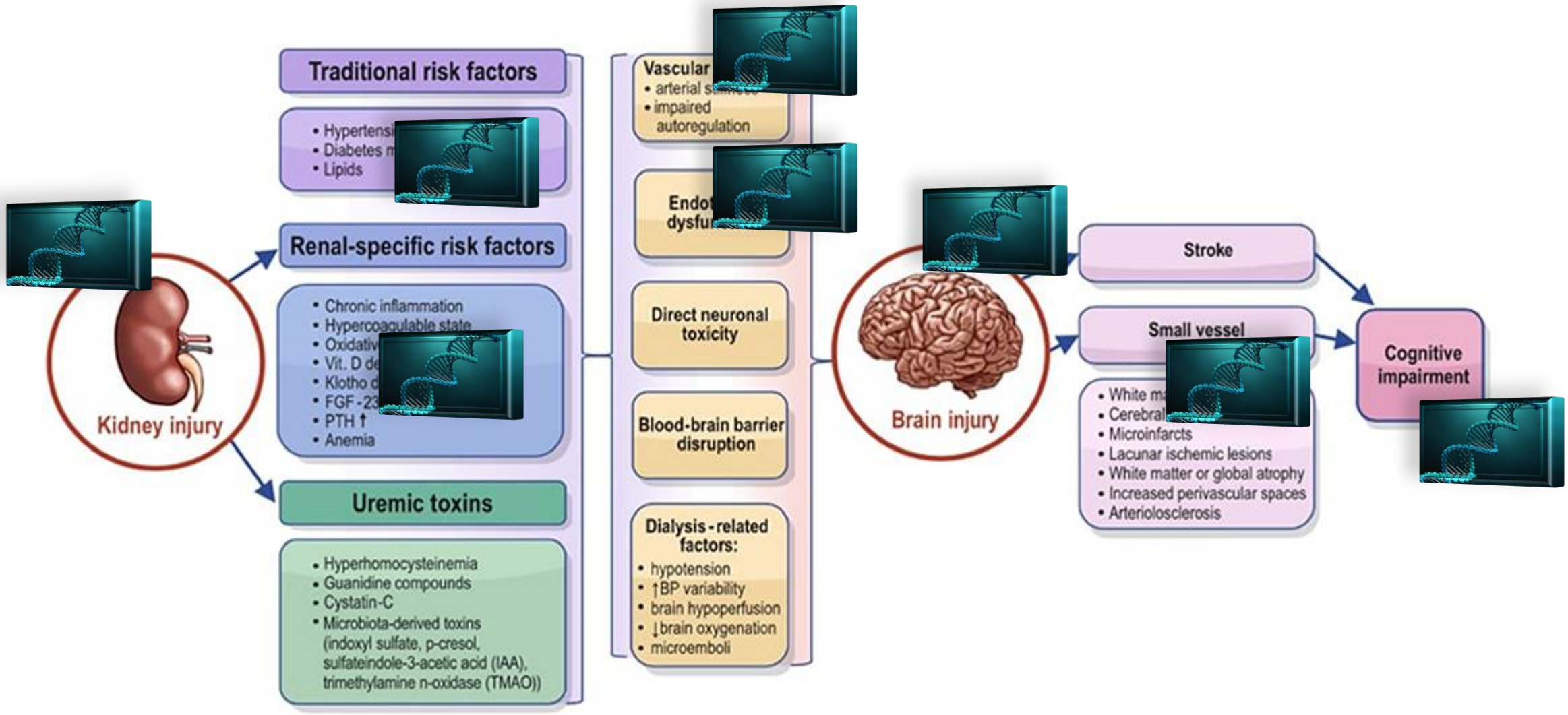


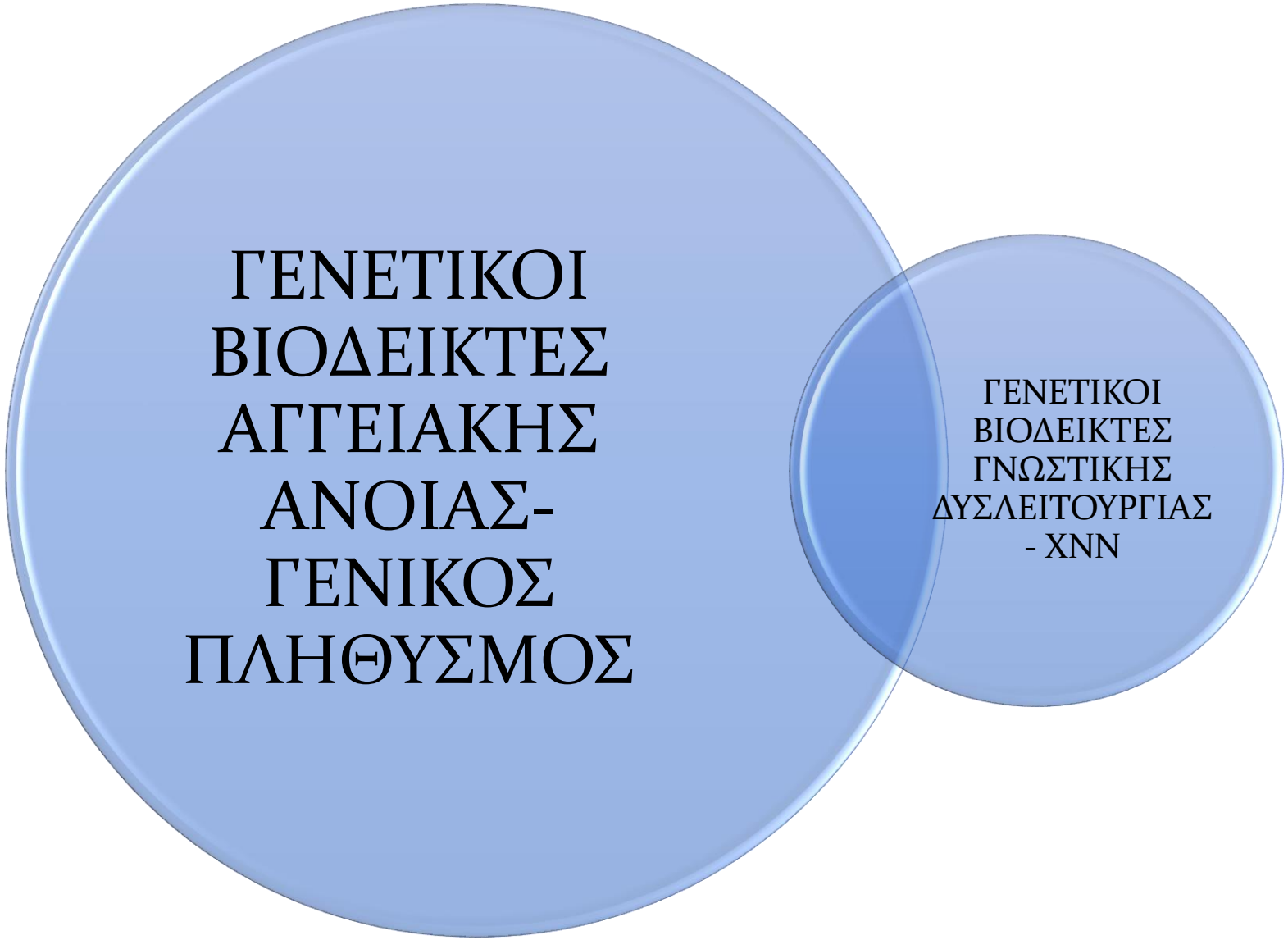


Cognitive impairment in hemodialysis patients is common

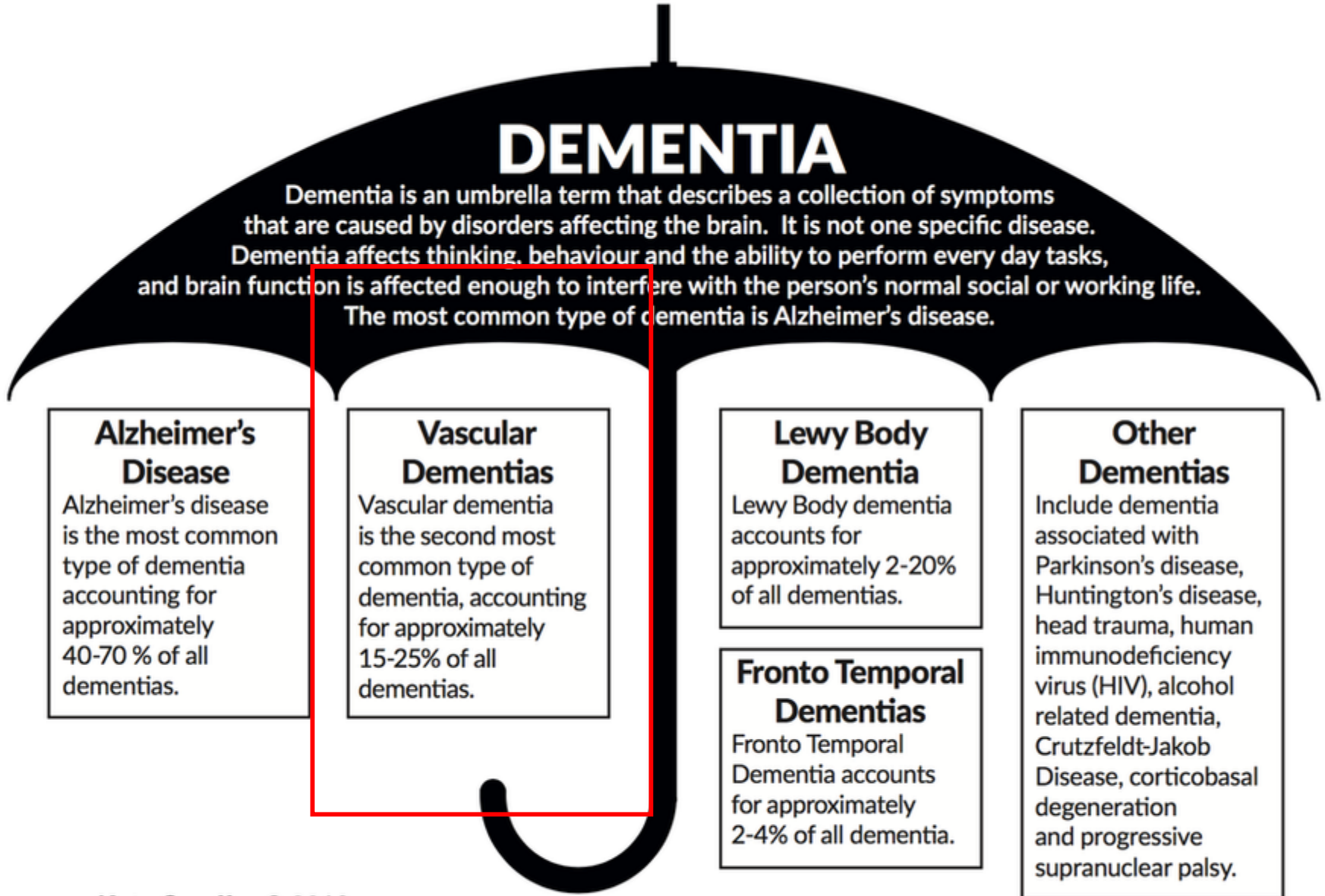
A M Murray [1], D E Tupper, D S Knopman, D T Gilbertson, S L Pederson, S Li, G E Smith, A K Hochhalter, A J Collins, R L Kane

Results: Of 338 subjects who completed testing in at least two of the three cognitive domains, 13.9% (95% CI 10.4, 18.1) were classified with mild impairment, 36.1% (31.0, 41.5) with moderate impairment, 37.3% (32.1, 42.7) with severe impairment, and 12.7% (9.4, 16.8) with normal cognition. Only 2.9% had a documented history of cognitive impairment. Factors associated with severe cognitive impairment on adjusted logistic regression were stroke (adjusted OR [AOR] 1.95; 95% CI 1.08, 3.49; $p < 0.03$), equilibrated Kt/V > 1.2 (1.67; 1.01, 2.75; $p < 0.05$), and education >12 years (0.32; 0.14, 0.72; $p < 0.01$). The AOR for severe cognitive impairment in a random sample of 101 hemodialysis patients vs an age-matched comparison group was 3.54 (1.28, 9.78; $p < 0.02$).


Kidney injury
Traditional risk factors
• Hypertens
• Diabetes
• Lipids
Renal-specific risk factors
• Chronic inflammation
• Hypercoagulable state
• Oxidativ
• Vit. D d
• Klotho
• FGF-23
• PTH ↑
• Anemia
Uremic toxins
• Hyperhomocysteinemia
• Guanidine compounds
• Cystatin-C
• Microbiota-derived toxins (indoxyl sulfate, p-cresol, sulfateindole-3-acetic acid (IAA), trimethylamine n-oxidase (TMAO))
Vascular
• arterial s
• impaired autoregulation
Endot dysfu
Direct neuronal toxicity
Blood-brain barrier disruption
Dialysis-related factors:
• hypotension
• ↑BP variability
• brain hypoperfusion
• ↓brain oxygenation
• microemboli
Brain injury
Stroke
Small vessel
• White ma
• Cerebral
• Microinfarcts
• Lacunar ischemic lesions
• White matter or global atrophy
• Increased perivascular spaces
• Arteriolosclerosis
Cognitive impairment


ΓΕΝΕΤΙΚΟΙ ΒΙΟΔΕΙΚΤΕΣ ΑΓΓΕΙΑΚΗΣ ΑΝΟΙΑΣ- ΓΕΝΙΚΟΣ ΠΛΗΘΥΣΜΟΣ
ΓΕΝΕΤΙΚΟΙ ΒΙΟΔΕΙΚΤΕΣ ΓΝΩΣΤΙΚΗΣ ΔΥΣΛΕΙΤΟΥΡΓΙΑΣ - ΧΝΝ

Γενετικοί βιοδείκτες στην άνοια


DEMENTIA
Dementia is an umbrella term that describes a collection of symptoms
that are caused by disorders affecting the brain. It is not one specific disease.
Dementia affects thinking, behaviour and the ability to perform every day tasks,
and brain function is affected enough to interfere with the person's normal social or working life.
The most common type of dementia is Alzheimer's disease.
Alzheimer's Disease
Alzheimer's disease is the most common type of dementia accounting for approximately 40-70 % of all dementias.
Vascular Dementias
Vascular dementia is the second most common type of dementia, accounting for approximately 15-25% of all dementias.
Lewy Body Dementia
Lewy Body dementia accounts for approximately 2-20% of all dementias.
Fronto Temporal Dementias
Fronto Temporal Dementia accounts for approximately 2-4% of all dementia.
Other Dementias
Include dementia associated with Parkinson's disease, Huntington's disease, head trauma, human immunodeficiency virus (HIV), alcohol related dementia, Crutzfeldt-Jakob Disease, corticobasal degeneration and progressive supranuclear palsy.
Kate Swaffer © 2016


Μονογονιδιακά αίτια
Αγγειακή άνοια
Πολυγονιδιακά αίτια

μονογονιδιακά αίτια σχετιζόμενα με νόσο μικρών αγγείων

Disease	CADASIL	Fabry disease	RVCL	COL4A1	CARASIL
OMIM	#125310	#301500	#192315	#120130	#60142
Pattern of inheritance	Autosomal dominant	X-linked recessive	Autosomal dominant	Autosomal dominant	Autosomal recessive
Gene	*NOTCH3*	α-GAL A gene (GLA)	TREX1	COL4A1	HTRA1
Locus	19p13	Xq22	3p21.3-p21.2	13q34	10q25
Gene product	Notch 3 receptor	Alpha galactosidase A enzyme	DNA specific 3'-5' exonuclease DNase III	Type IV collagen α1	HTRA1 serine peptidase/protease 1

- σπάνιες σχετικά αιτίες
- σημαντικά ποσοστά υποεκτίμησης
- απαιτούνται μεγαλύτερες μελέτες προκειμένου να ταυτοποιηθεί ο πραγματικός επιπολασμός τους

πολυγονιδιακοί φαινότυποι

- σποραδικές μορφές αγγειακής άνοιας
- πολλαπλές γενετικές παραλλαγές με χαμηλή διεισδυτικότητα
- αρκετοί από τους κλασικούς παράγοντες κινδύνου (διαβήτης, υπέρταση, δυσλιπιδαιμία) καθορίζονται επίσης γενετικά
- μελέτες γονιδίου στόχου (candidate gene studies) και GWAS μελέτες

APOE γονίδιο

- Απολιποπρωτείνη Ε
- APOE2, APOE3, and APOE4
- 6 πιθανοί γονότυποι: ε2/ε2, ε2/ε3, ε2/ε4, ε3/ε3, ε3/ε4, και ε4/ε4

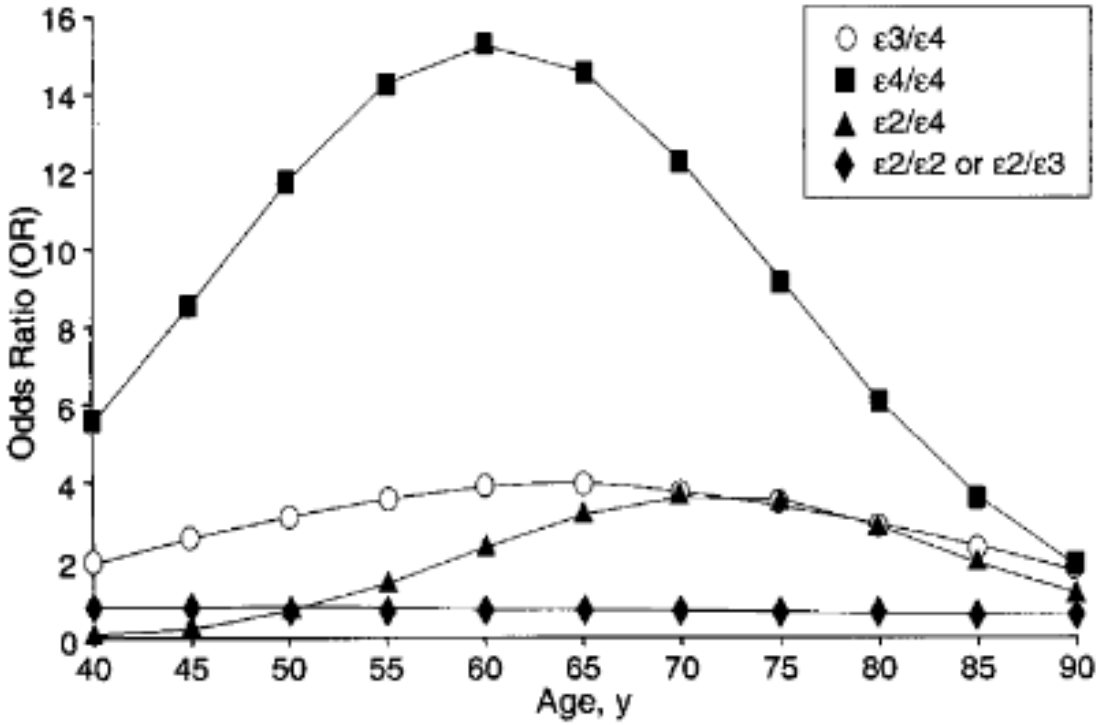
Association between apolipoprotein E gene polymorphism and the risk of vascular dementia: A meta-analysis

Yan-Wei Yin [1], Jing-Cheng Li [1], Jing-Zhou Wang, Bing-Hu Li, Yan Pi, Qing-Wu Yang, Chuan-Qin Fang, Chang-Yue Gao, Li-Li Zhang

The present meta-analysis of 29 studies including 1763 cases and 4534 controls provides most comprehensive analysis on the relationship between ApoE gene polymorphism and VaD. Our meta-analysis showed that individuals with ε3/ε4 genotype and ε4/ε4 genotype had a significantly higher risk of developing VaD (OR=1.65 and OR=3.17) compared to those with ε3/ε3 genotype. Moreover, the risk of developing VaD in individuals with ε4 allele was 1.72-fold higher than those without. Thus, it is reasonable…

Effects of age, sex, and ethnicity on the association between apolipoprotein E genotype and Alzheimer disease. A meta-analysis. APOE and Alzheimer Disease Meta Analysis Consortium

L A Farrer [1], L A Cupples, J L Haines, B Hyman, W A Kukull, R Mayeux, R H Myers, M A Pericak-Vance, N Risch, C M van Duijn



Γενετικοί βιοδείκτες στη γνωστική δυσλειτουργία στην ΧΝΝ

γνωστική δυσλειτουργία και ΧΝΝ

ΓΕΝΕΤΙΚΕΣ ΠΑΡΑΛΛΑΓΕΣ

ΧΝΝ → ΓΝΩΣΤΙΚΗ ΔΥΣΛΕΙΤΟΥΡΓΙΑ

ΓΕΝΕΤΙΚΕΣ ΠΑΡΑΛΛΑΓΕΣ

ΧΝΝ → ΓΝΩΣΤΙΚΗ ΔΥΣΛΕΙΤΟΥΡΓΙΑ

παιδιατρικοί πληθυσμοί

- η ΧΝΝ έχει σαφή γενετικό υπόστρωμα
- η γενετική διαταραχή ενδέχεται να προκαλεί τόσο ΧΝΝ όσο και γνωστική δυσλειτουργία
- ορισμένα σπάνια σύνδρομα προκαλούν τόσο νεφρική βλάβη όσο και γνωστική δυσλειτουργία
  - Bardet Biedl σύνδρομο
  - Fabry νόσος
  - Joubert σύνδρομο
  - Tuberous sclerosis (οζώδης σκλήρυνση)
  - Lowe σύνδρομο

Genomic Disorders and Neurocognitive Impairment in Pediatric CKD

Miguel Verbitsky [1], Amy J Kogon [2], Matthew Matheson [3], Stephen R Hooper [4 5], Craig S Wong [6], Bradley A Warady [7], Susan L Furth [8 9 10], Ali G Gharavi [11]

Children with CKD are at increased risk for neurocognitive impairment, but whether neurocognitive dysfunction is solely attributable to impaired renal function is unclear. Data from the CKD in Children Study Chronic Kidney Disease in Children (CKiD) Study indicate that a subset of children with CKD have unsuspected genomic disorders that predispose them to organ malformations and neurocognitive impairment. We therefore tested whether the CKiD Study participants with genomic disorders had impaired neurocognitive performance at enrollment. Compared with noncarriers (n=389), children with genomic disorders (n=31) scored significantly poorer on all measures of intelligence, anxiety/depressive symptoms, and executive function (differences of 0.6-0.7 SD; P=1.2×10^{-3}-2.4×10^{-4}). These differences persisted after controlling for known modifiers, including low birth weight, maternal education, seizure disorder, kidney disease duration, and genetically defined ancestry. The deleterious effect of genomic disorders on neurocognitive function was significantly attenuated in offspring of mothers with higher education, indicating the potential for modification by genetic and/or environmental factors. These data indicate that impaired neurocognitive function in some children with CKD may be attributable to genetic lesions that affect both kidney and neurocognitive development. Early identification of genomic disorders may provide opportunity for early diagnosis and personalized interventions to mitigate the effect on neurocognitive function.

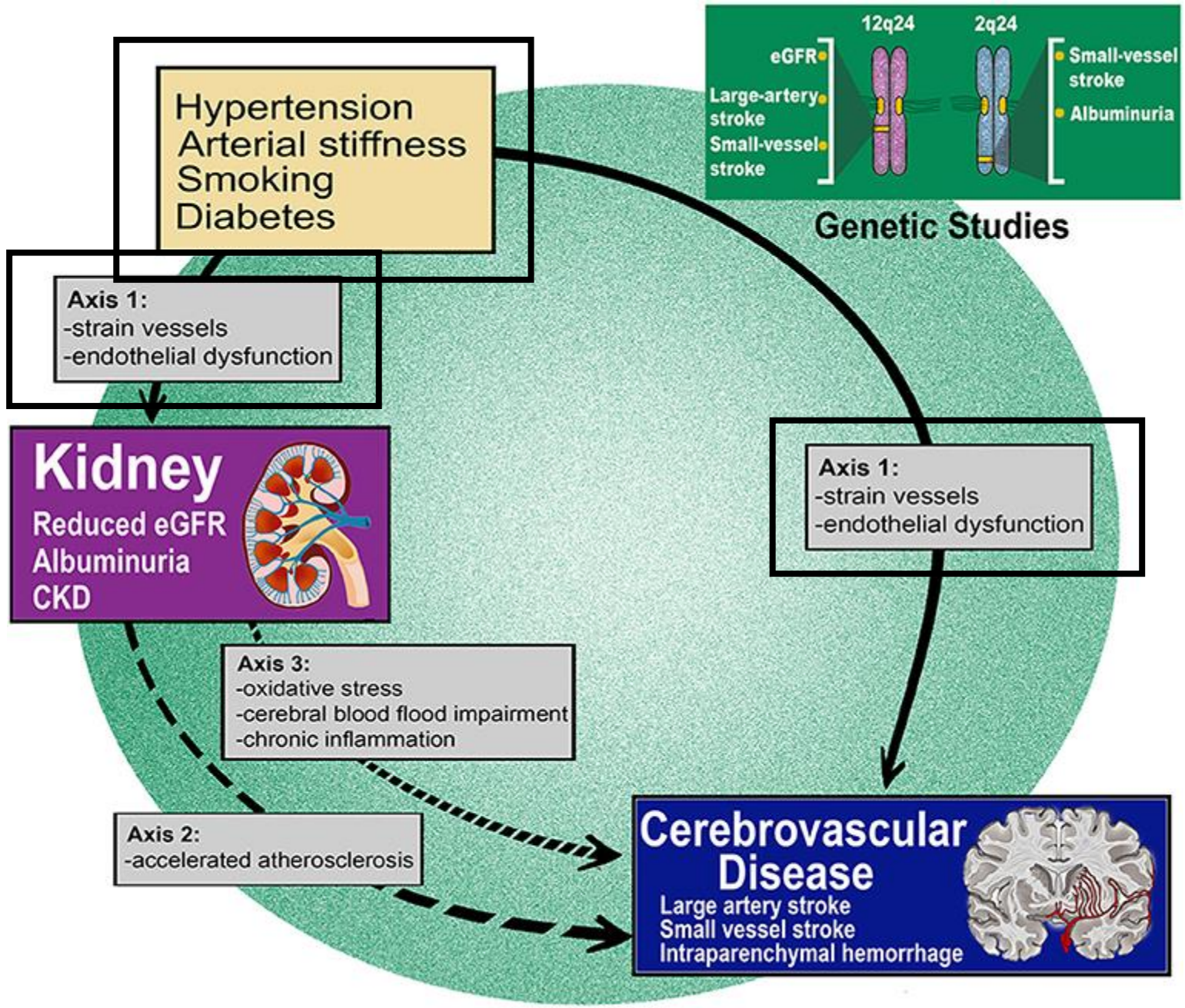
πληθυσμοί ενηλίκων

- γενετική αιτία αναγνωρίζεται στο 10-15% των ασθενών με ΧΝΝ ενώ σε αρκετές περιπτώσεις εμπλέκονται σύνθετοι πολυγονιδιακοί φαινότυποι
- η γενετική προδιάθεση της γνωστικής δυσλειτουργίας σε άτομα του γενικού πληθυσμού αφορά και τους ασθενείς με ΧΝΝ

γενετικά σενάρια

1. η νεφρική και η εγκεφαλική νόσος είναι το αποτέλεσμα ενός κοινού βιολογικού μηχανισμού βλάβης (μονογονιδιακά αίτια ΧΝΝ και εγκεφαλικής νόσου)
2. η νεφρική και η εγκεφαλική νόσος μοιράζονται κοινά παθογενετικά μονοπάτια
3. η νεφρική νόσος αυξάνει τον κίνδυνο εγκεφαλικής βλάβης

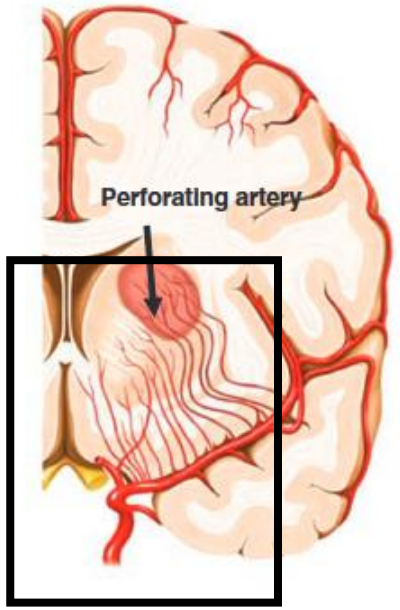
- γενετική παραλλαγή → νεφρική και εγκεφαλική νόσος
- παραδείγματα
  - ✓ Fabry νόσος → εναπόθεση γλυκοσφιγγολιπιδίων στο αγγειακό ενδοθήλιο του εγκεφάλου και του νεφρού → ΑΕΕ + ΧΝΝ
  - ✓ COL4A1 γενετικές παραλλαγές → νόσος μικρών αγγείων → ισχαιμικό ΑΕΕ + ΧΝΝ (HANAC σύνδρομο, CAKUT)
  - ✓ NOTCH3 γενετικές παραλλαγές → CADASIL → ΧΝΝ και υψηλός κίνδυνος ισχαιμικού ΑΕΕ

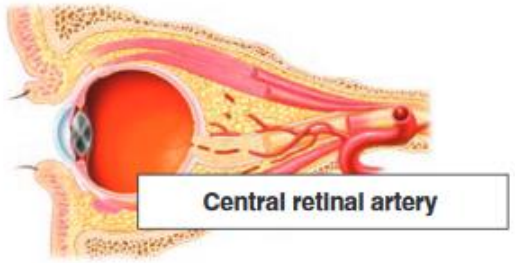

Hypertension
Arterial stiffness
Smoking
Diabetes
Axis 1:
-strain vessels
-endothelial dysfunction
Kidney
Reduced eGFR
Albuminuria
CKD
Axis 3:
-oxidative stress
-cerebral blood flood impairment
-chronic inflammation
Axis 2:
-accelerated atherosclerosis
12q24
2q24
eGFR
Large-artery stroke
Small-vessel stroke
Small-vessel stroke
Albuminuria
Genetic Studies
Axis 1:
-strain vessels
-endothelial dysfunction
Cerebrovascular Disease
Large artery stroke
Small vessel stroke
Intraparenchymal hemorrhage

κοινή παθογενετική βάση

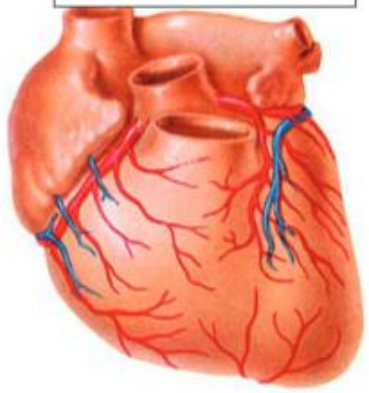
- κοινά αγγειακά γνωρίσματα νεφρών και εγκεφάλου
- οι μικρές αρτηρίες τους είναι μοναδικές καθώς δέχονται συνεχώς υψηλού όγκου αιματικές ροές έναντι χαμηλών αγγειακών αντιστάσεων (strain vessels)
- τα αγγεία τους είναι ιδιαίτερα δεκτικά στην πρόκληση μικροαγγειακής βλάβης ως απάντηση στην γήρανση του οργανισμού και στην επίδραση μείζονων αγγειακών παραγόντων κινδύνου (ΣΔ,ΑΥ)
- ιδιαίτερα συχνή η συνύπαρξη της νόσου μικρών αγγείων στα δυο όργανα

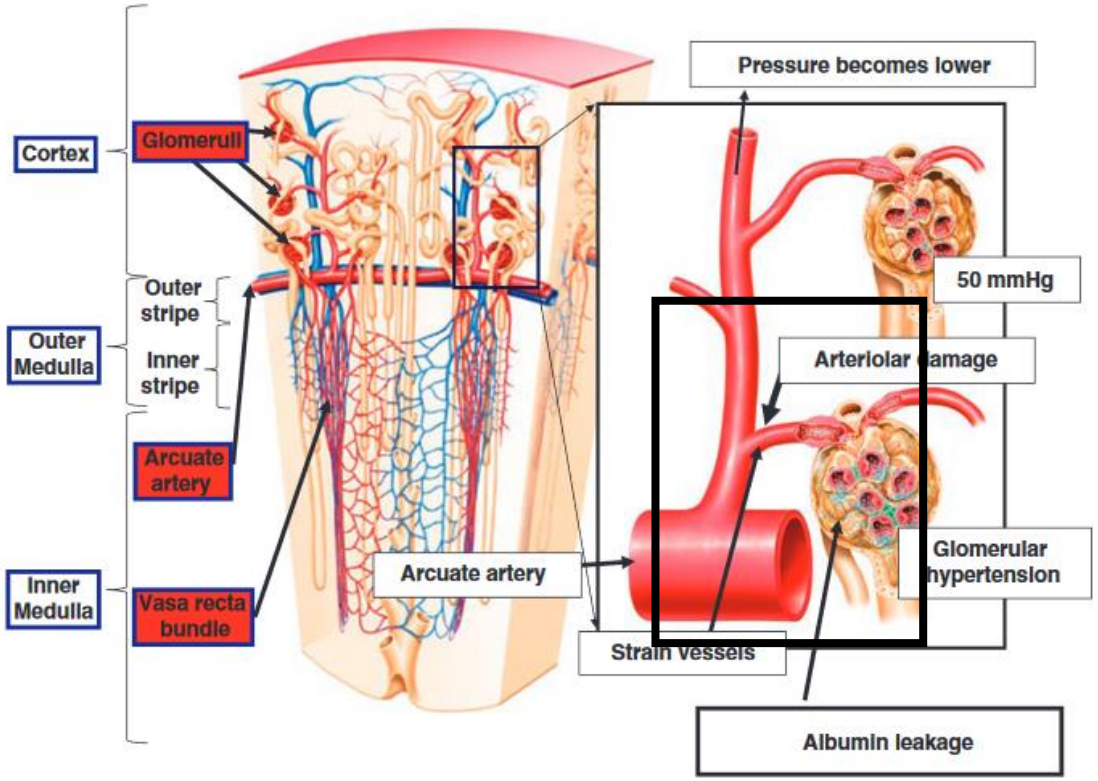
Strain Vessels





Coronary artery





Strain vessel hypothesis: a viewpoint for linkage of albuminuria and cerebro-cardiovascular risk

Sadayoshi Ito, Tasuku Nagasawa, Michiaki Abe and Takefumi Mori

Therefore, **albuminuria may be an early sign of vascular damages imposed on 'strain vessels' such as perforating arteries and juxtamedullary afferent arterioles**. Coronary circulation also occurs under unique hemodynamic conditions, in which the entire epicardial segments are exposed to very high pressure with little flow during systolic phases. From the evolutionary point of view, we speculate that such circulatory systems in the vital organs are mandatory for survival under the danger of hypoperfusion due to difficult access to salt and water as well as high risks of wound injuries

June 16, 2020; 94 (24) ARTICLE

Genetic overlap and causal inferences between kidney function and cerebrovascular disease

Sandro Marini, Marios K. Georgakis, Jaeyoon Chung, Jonathan Q.A. Henry, Martin Dichgans, Jonathan Rosand, Rainer Malik, Christopher D. Anderson

Multiple pleiotropic loci were identified between kidney function traits and cerebrovascular disease phenotypes, with 12q24 associated with eGFR and both LAS and small vessel stroke (SVS), and 2q33 associated with UACR and both SVS and WMH. Mendelian randomization revealed associations of both lower eGFR (odds ratio [OR] per 1-log decrement, 2.10; 95% confidence interval [CI], 1.38–3.21) and higher UACR (OR per 1-log increment, 2.35; 95% CI, 1.12–4.94) with a higher risk of LAS, as well as between higher UACR and higher risk of ICH.

Taken together, these data support the possibility that there are specific biological pathways, potentially involving the products of these genes, which once perturbed may lead to SVD pathology in those organs where small vessels are particularly represented, namely kidney and deep brain structures

Polygenic overlap between kidney function and large artery atherosclerotic stroke

Elizabeth G Holliday [1], Matthew Traylor [1], Rainer Malik [1], Stephen Bevan [1], Jane Maguire [1], Simon A Koblar [1], Jonathan Sturm [1], Graeme J Hankey [1], Christopher Oldmeadow [1], Mark McEvoy [1], Cathie Sudlow [1], Peter M Rothwell [1], Josef Coresh [1], Pavel Hamet [1], Johanne Tremblay [1], Stephen T Turner [1], Mariza de Andrade [1], Madhumathi Rao [1], Reinhold Schmidt [1], Peter A Crick [1], Antonietta Robino [1], Carmen A Peralta [1], J Wouter Jukema [1], Paul Mitchell [1], Sylvia E Rosas [1], Jie Jin Wang [1], Rodney J Scott [1], Martin Dichgans [1], Braxton D Mitchell [1], W H Linda Kao [1], Caroline S Fox [1], Christopher Levi [1], John Attia [1], Hugh S Markus [1]; CKDGen Consortium and the International Stroke Genetics Consortium

Background and purpose: Epidemiological studies show strong associations between kidney dysfunction and risk of ischemic stroke (IS), the mechanisms of which are incompletely understood. We investigated whether these associations may reflect shared heritability because of a common polygenic basis and whether this differed for IS subtypes.

Conclusions: This study suggests possible polygenic correlation between renal dysfunction and IS. The shared genetic components may be specific to stroke subtypes, particularly large artery atherosclerotic stroke. Further study of the genetic relationships between these disorders seems merited.

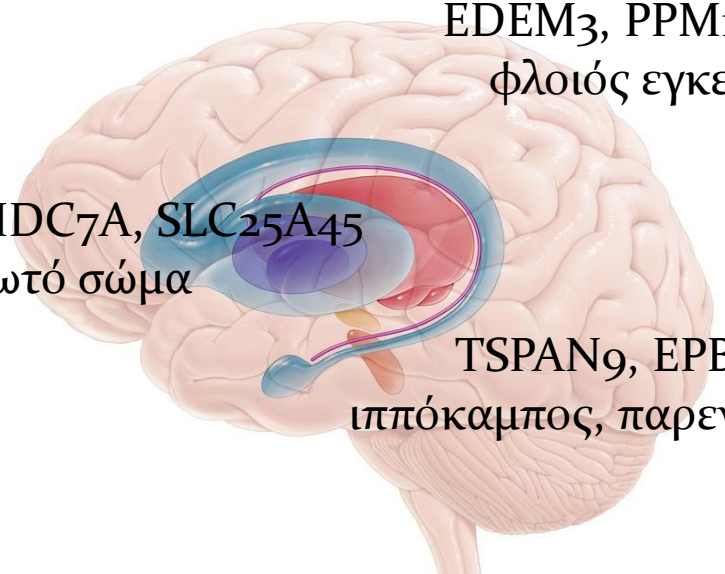
A catalog of genetic loci associated with kidney function from analyses of a million individuals

Matthias Wuttke [1 2], Yong Li [1], Man Li [3], Karsten B Sieber [4], Mary F Feitosa [5], Mathias Gorski [6 7], Adrienne Tin [8 9], Lihua Wang [5], Audrey Y Chu [10], Anselm Hoppmann [1], Holger Kirsten [11 12], Ayush Giri [13 14], Jin-Fang Chai [15], Gardar Sveinbjornsson [16], Bamidele O Tayo [17], Teresa Nutile [18], Christian Fuchsberger [19], Jonathan Marten [20], Massimiliano Cocca [21], Sahar Ghasemi [22 23], Yizhe Xu [3], Katrin Horn [11 12], Damia Noce [19], Peter J van der Most [24], Sanaz Sedaghat [25],

147 γενετικοί τόποι σχετιζόμενοι με ΧΝΝ

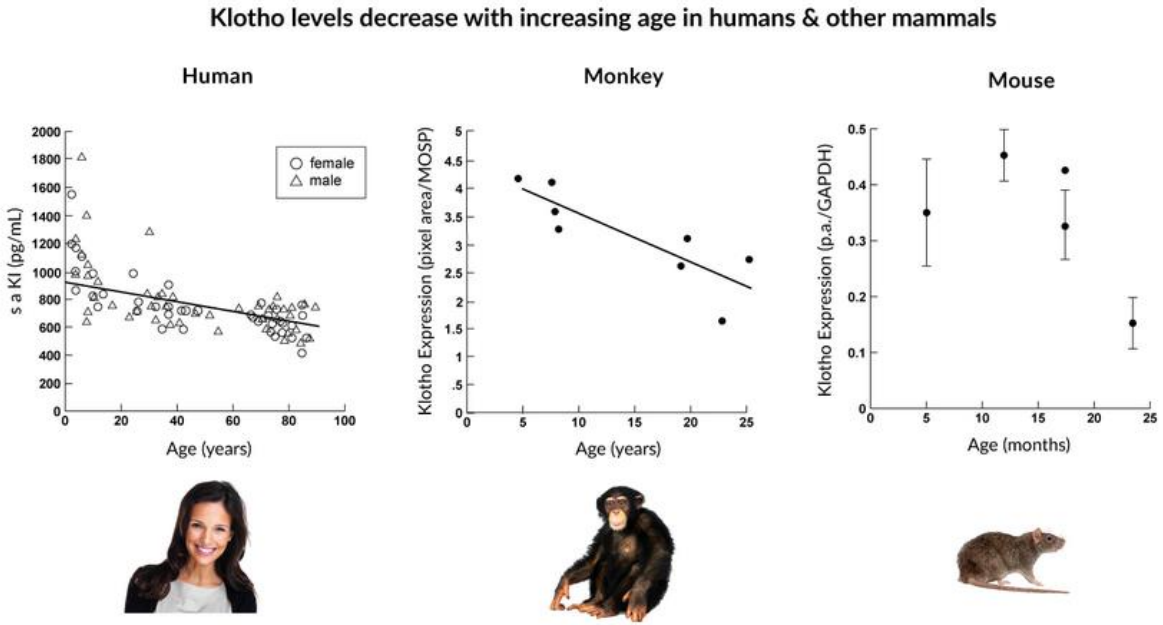
EDEM3, PPM1J, CERS2
φλοιός εγκεφάλου

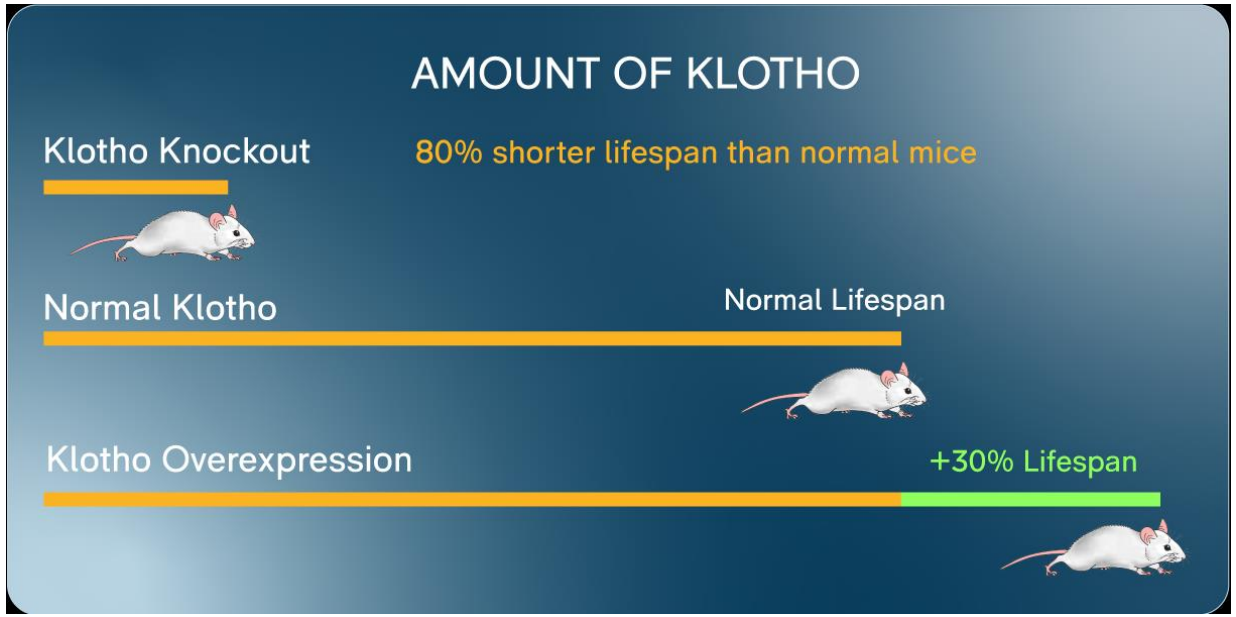
SLC47A1, KLHDC7A, SLC25A45
ραβδωτό σώμα

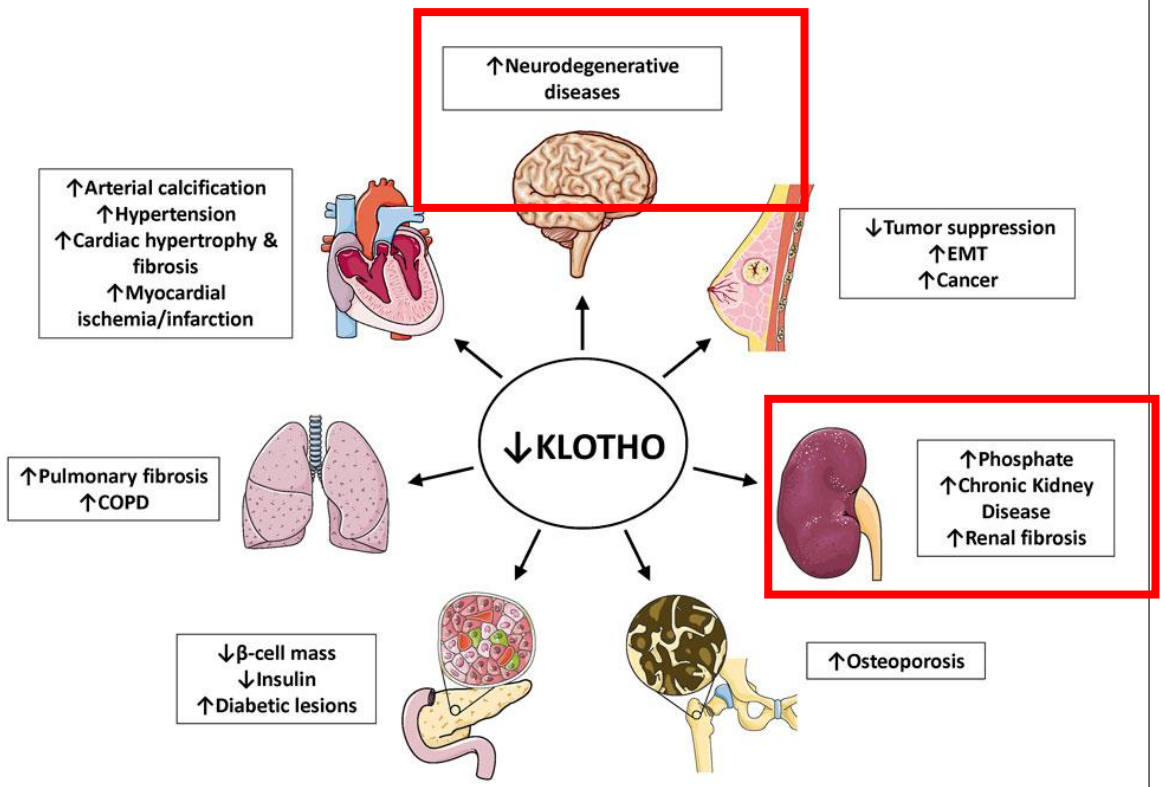


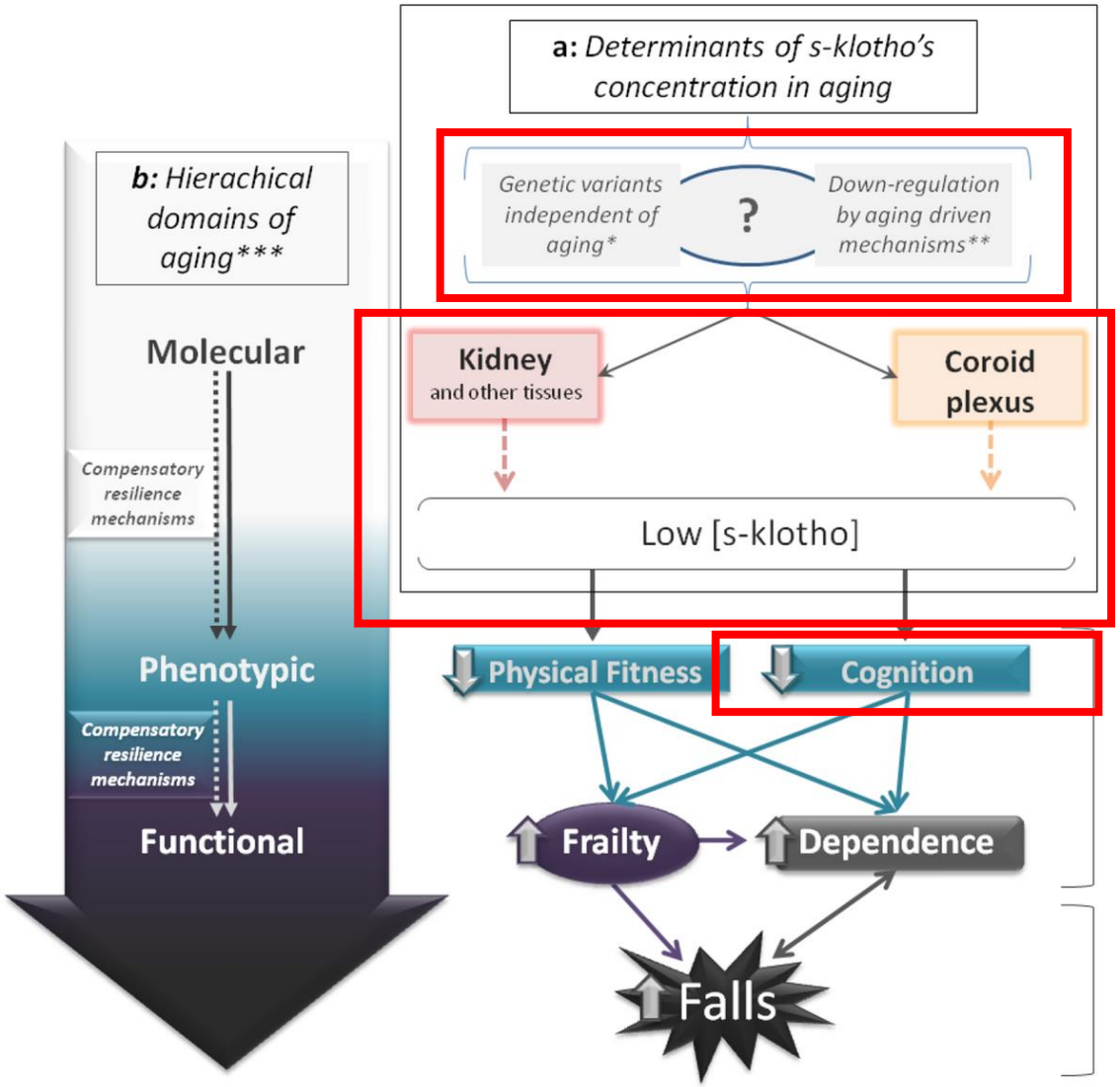
TSPAN9, EPB41LP
ιππόκαμπος, παρεγκεφαλίδα

Klotho


Klotho levels decrease with increasing age in humans & other mammals
Human
Monkey
Mouse
female
male
s a Kl (pg/mL)
Klotho Expression (pixel area/MOSP)
Klotho Expression (p.a./GAPDH)
Age (years)
Age (years)
Age (months)


AMOUNT OF KLOTHO
Klotho Knockout
80% shorter lifespan than normal mice
Normal Klotho
Normal Lifespan
Klotho Overexpression
+30% Lifespan


↑Neurodegenerative diseases
↑Arterial calcification
↑Hypertension
↑Cardiac hypertrophy & fibrosis
↑Myocardial ischemia/infarction
↓Tumor suppression
↑EMT
↑Cancer
↓KLOTHO
↑Pulmonary fibrosis
↑COPD
↑Phosphate
↑Chronic Kidney Disease
↑Renal fibrosis
↓β-cell mass
↓Insulin
↑Diabetic lesions
↑Osteoporosis


a: Determinants of s-klotho's concentration in aging
Genetic variants independent of aging*
?
Down-regulation by aging driven mechanisms**
Kidney and other tissues
Coroid plexus
Low [s-klotho]
b: Hierachical domains of aging***
Molecular
Compensatory resilience mechanisms
Phenotypic
Compensatory resilience mechanisms
Functional
Physical Fitness
Cognition
Frailty
Dependence
Falls

Genetic Variants in KLOTHO Associate With Cognitive Function in the Oldest Old Group

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Abstract

Decline in cognitive abilities is a major concern in aging individuals. A potential important factor for functioning of the central nervous system in late-life stages is the KLOTHO (KL) gene. KL is expressed in various organs including the brain and is involved in multiple biological processes, for example, growth factor signaling. In the present study, 19 tagging gene variants in KL were studied in relation to 2 measures of cognitive function, a 5-item cognitive composite score and the Mini-Mental State Examination, in 1,480 Danes 92-100 years of age. We found that heterozygotes for the previously reported KL-VS had poorer cognitive function than noncarriers. Two other variants positioned in the 5' end of the gene, rs398655 and rs562020, were associated with better cognitive function independently of KL-VS, and the common haplotype AG was associated with poorer cognition, consistently across two cognitive measures in two cohort strata. The haplotype effect was stronger than that of KL-VS. Two variants, rs2283368 and rs9526984, were the only variants significantly associated with cognitive decline over 7 years. We discuss an age-dependent effect of KL and the possibility that multiple gene variants in KL are important for cognitive function among the oldest old participants.

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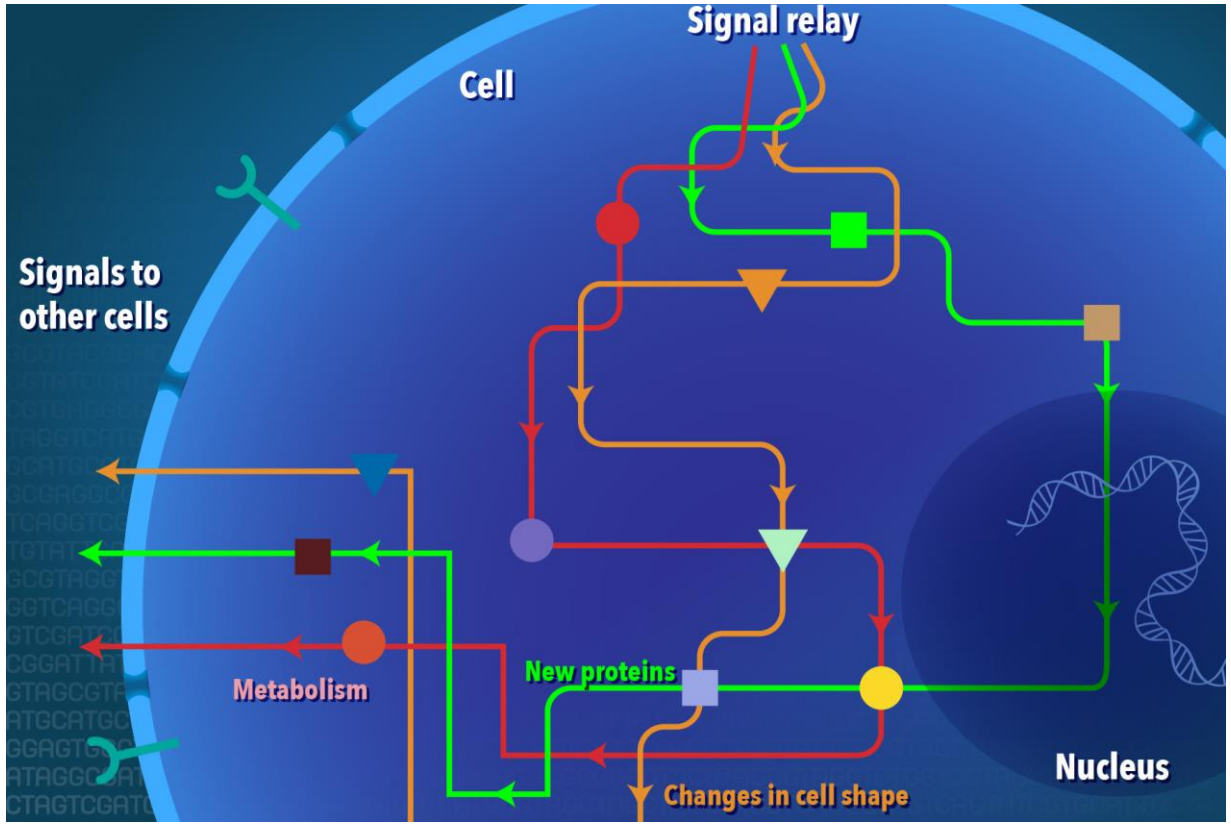
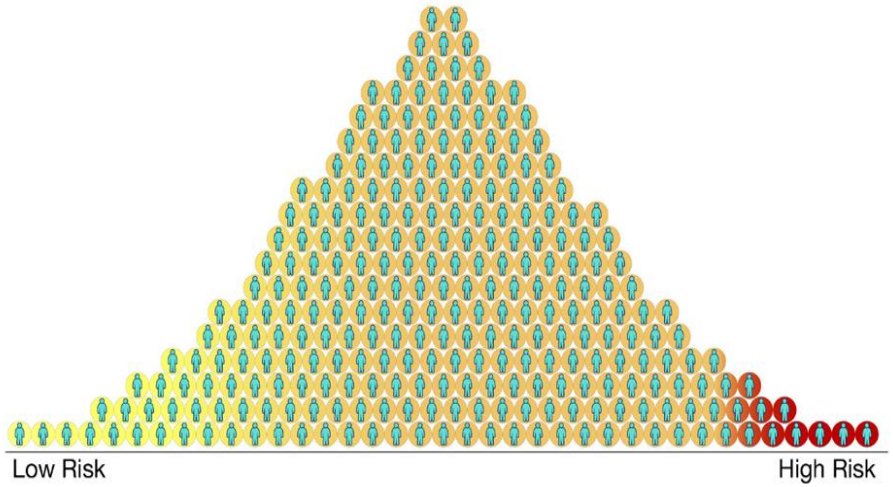
αποσαφήνιση βιολογικών μονοπατιών



εκτίμηση πολυγονιδιακού κινδύνου/ Genetic Risk Score- GRS



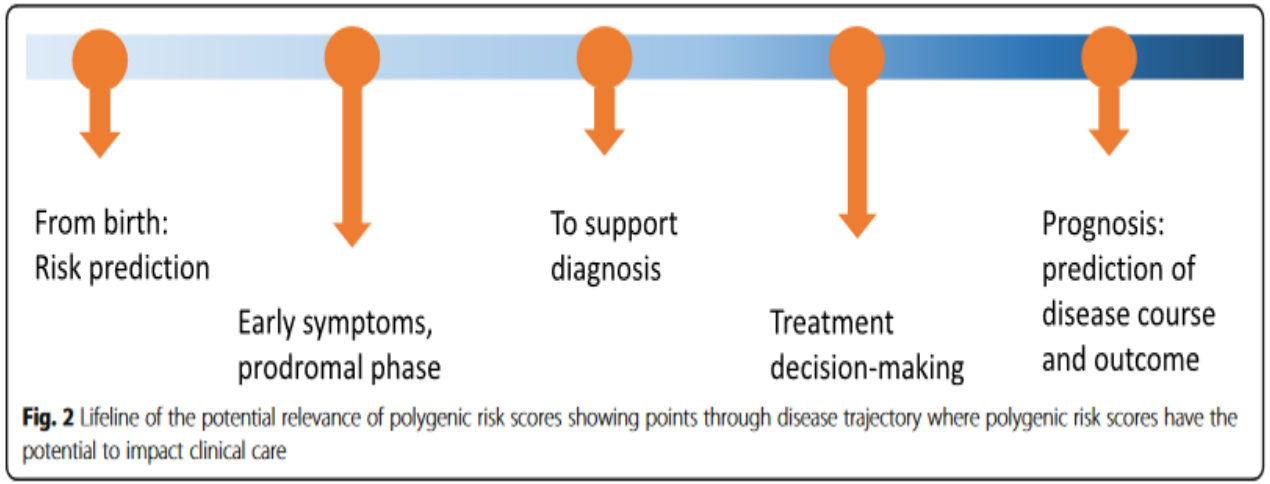


Fig. 2 Lifeline of the potential relevance of polygenic risk scores showing points through disease trajectory where polygenic risk scores have the potential to impact clinical care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