Factors genètics implicats a la progressió de la malaltia renal crònica

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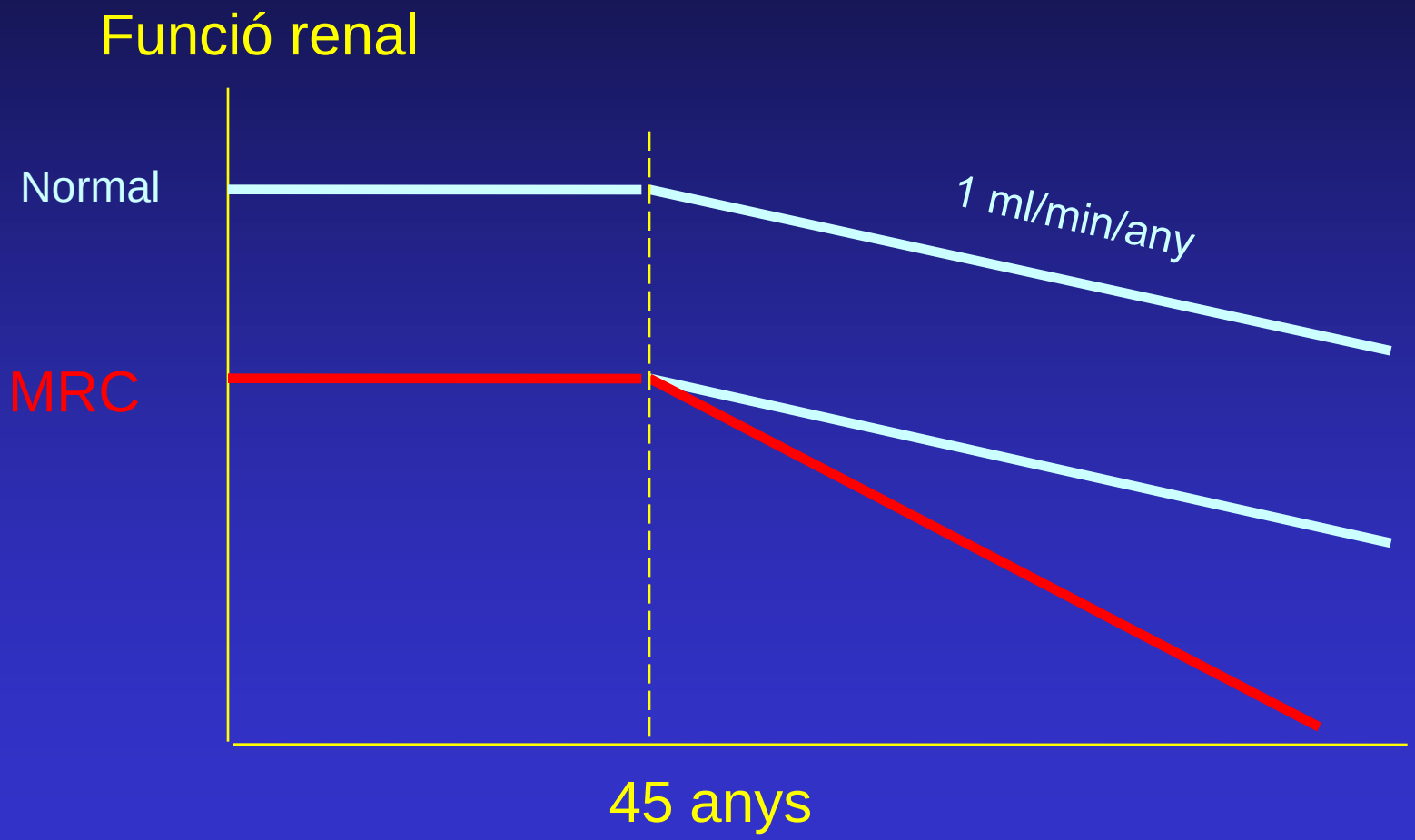
Fundació Puigvert

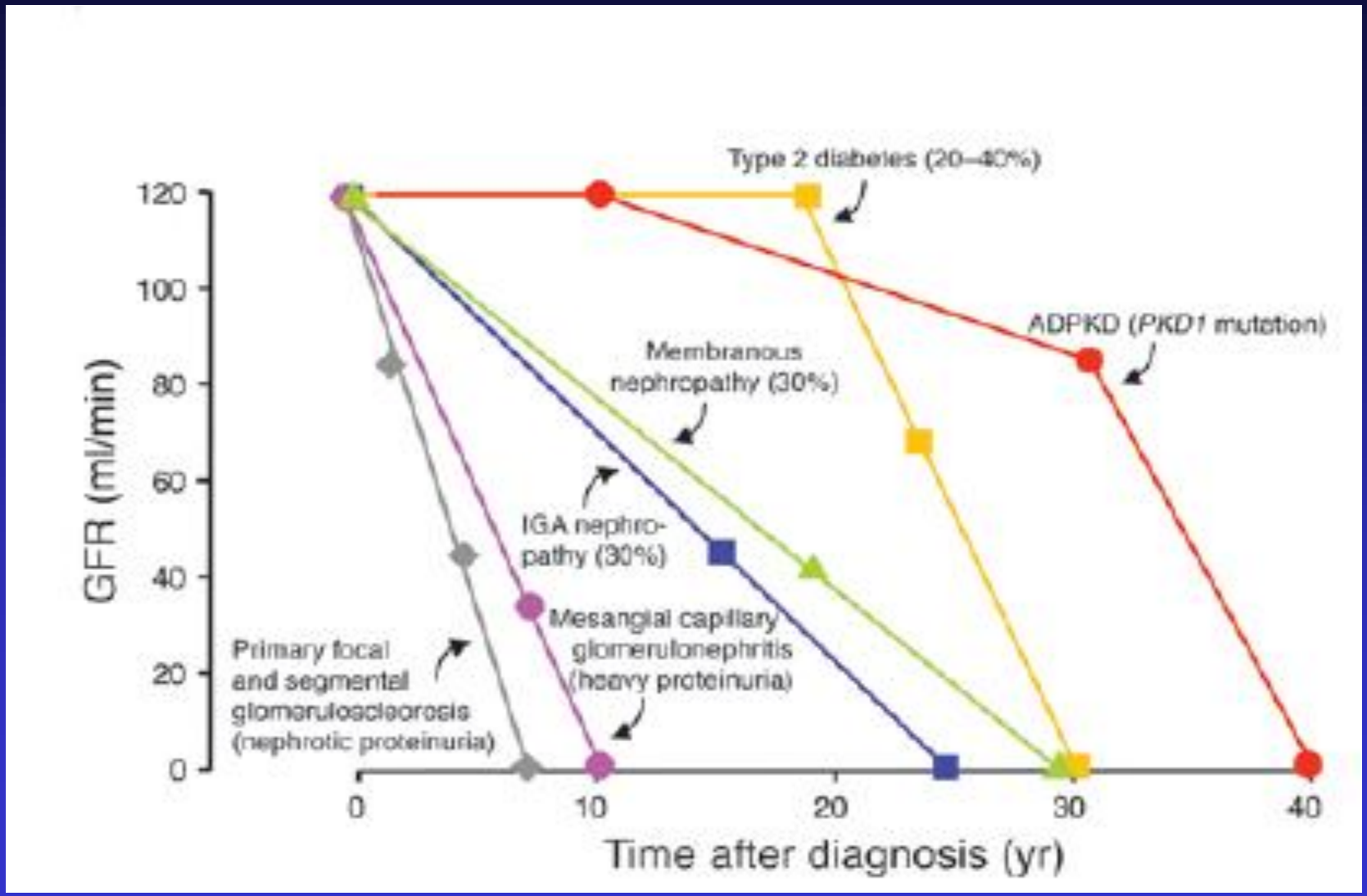
Index

1. Progressió de la MRC
2. Estudis genetics en MRC
3. SRAA
4. Factors de creixement
5. Citokines/inflamació
6. MYH9
7. Altres

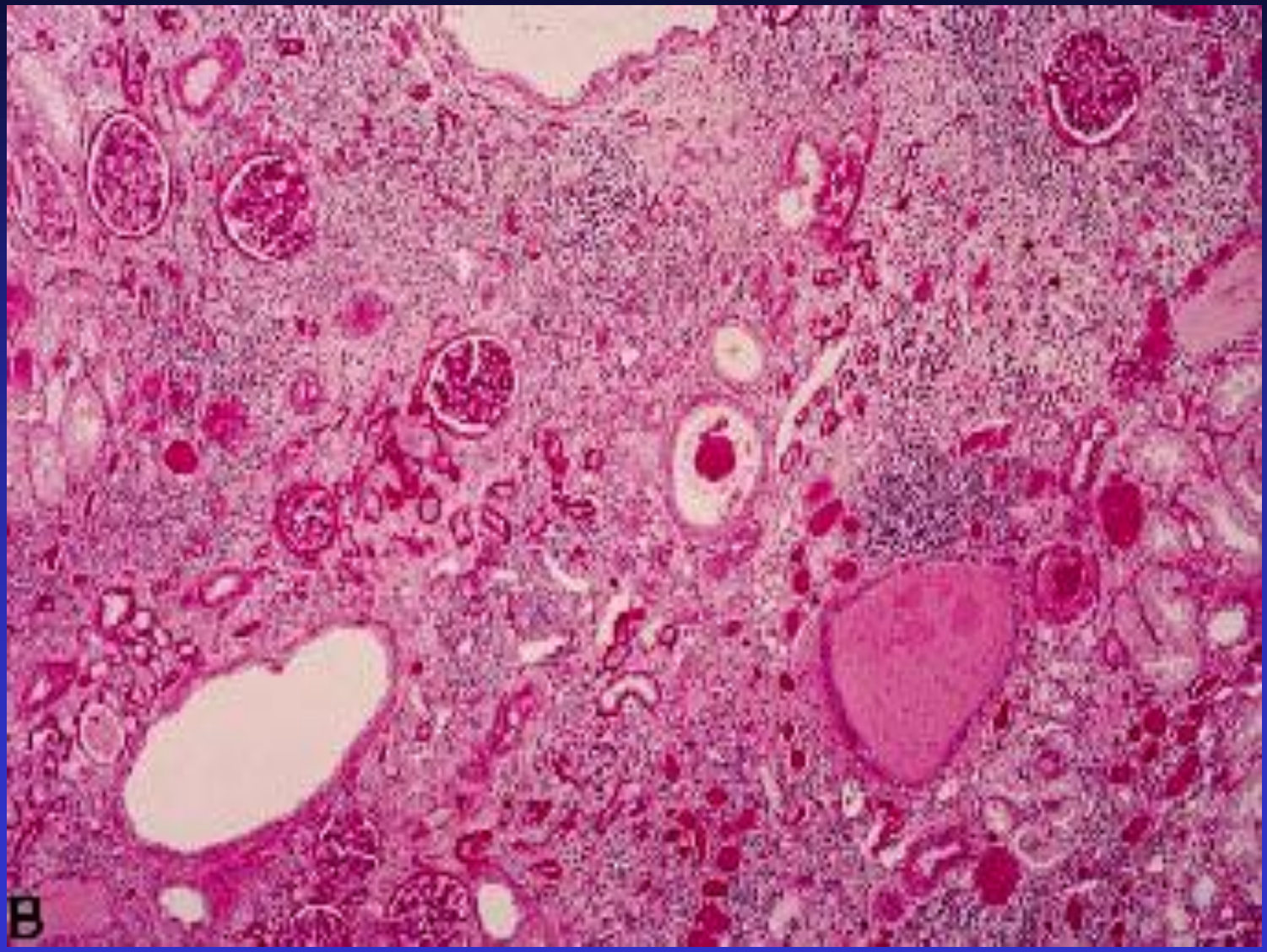
Progressió



Progressio de la MRC segons la nefropatia de base



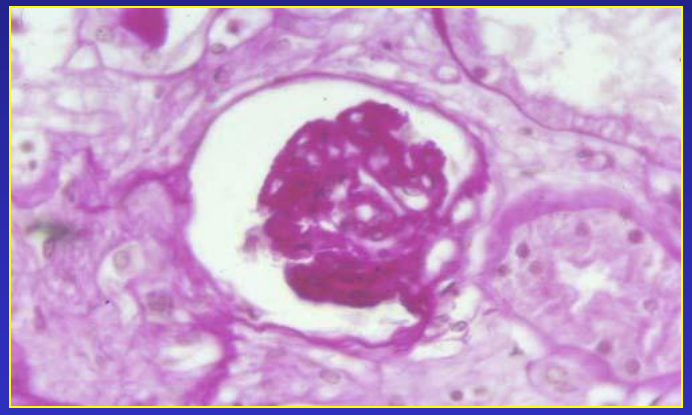
Malaltia renal crónica

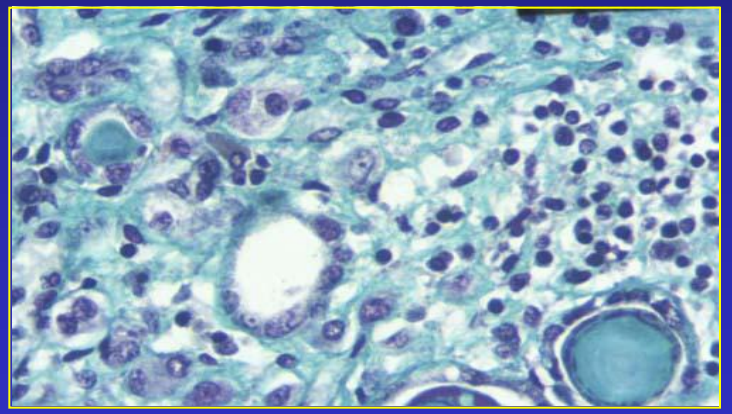


MRC: Mecanismes de progressió

LESIÓ HISTOLÒGICA:

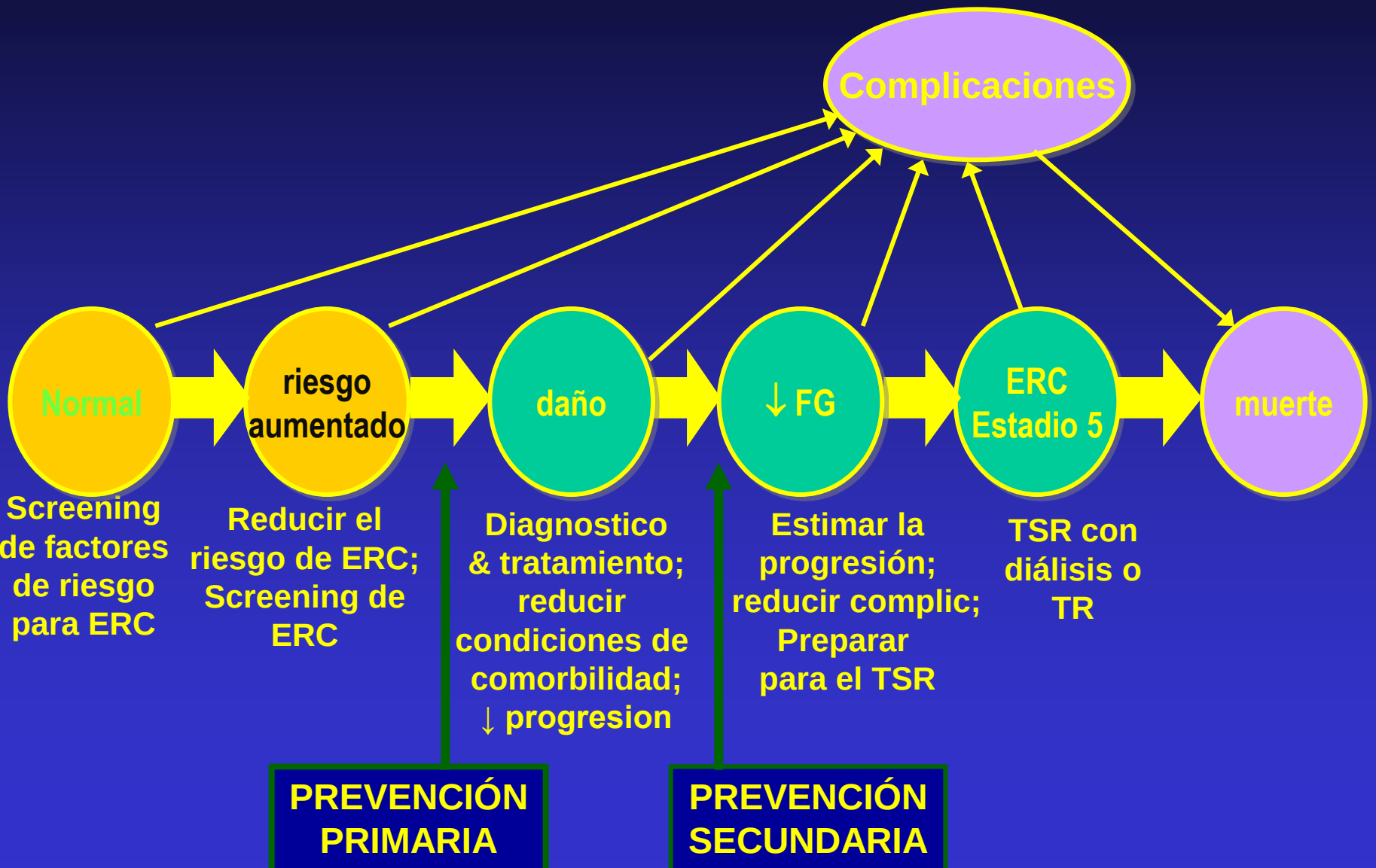
Disminució de la massa renal





Fibrosi ⟷ Progressió IR

Estadiatges en la progressió de la MRC i estrategies terapèutiques



Fisiopatología

Vía final común

DAÑO RENAL

↓

Disminución de la masa nefronal

↓

Hipertensión capilar glomerular

↓

Aumenta la permeabilidad glomerular a las macromoleculas

↓

Elevada filtracion de proteinas plasmaticas

↓

Elevada reabsorción tubular de proteinas

↓

Inflamación túbulointersticial

↓

FIBROSIS RENAL

Aumento PA

Factores hemodinámicos

Proteinuria

Factores de crecimiento

National Kidney Foundation of the NATIONAL CAPITAL AREA

IRC:Progressió

Factors Predisponents

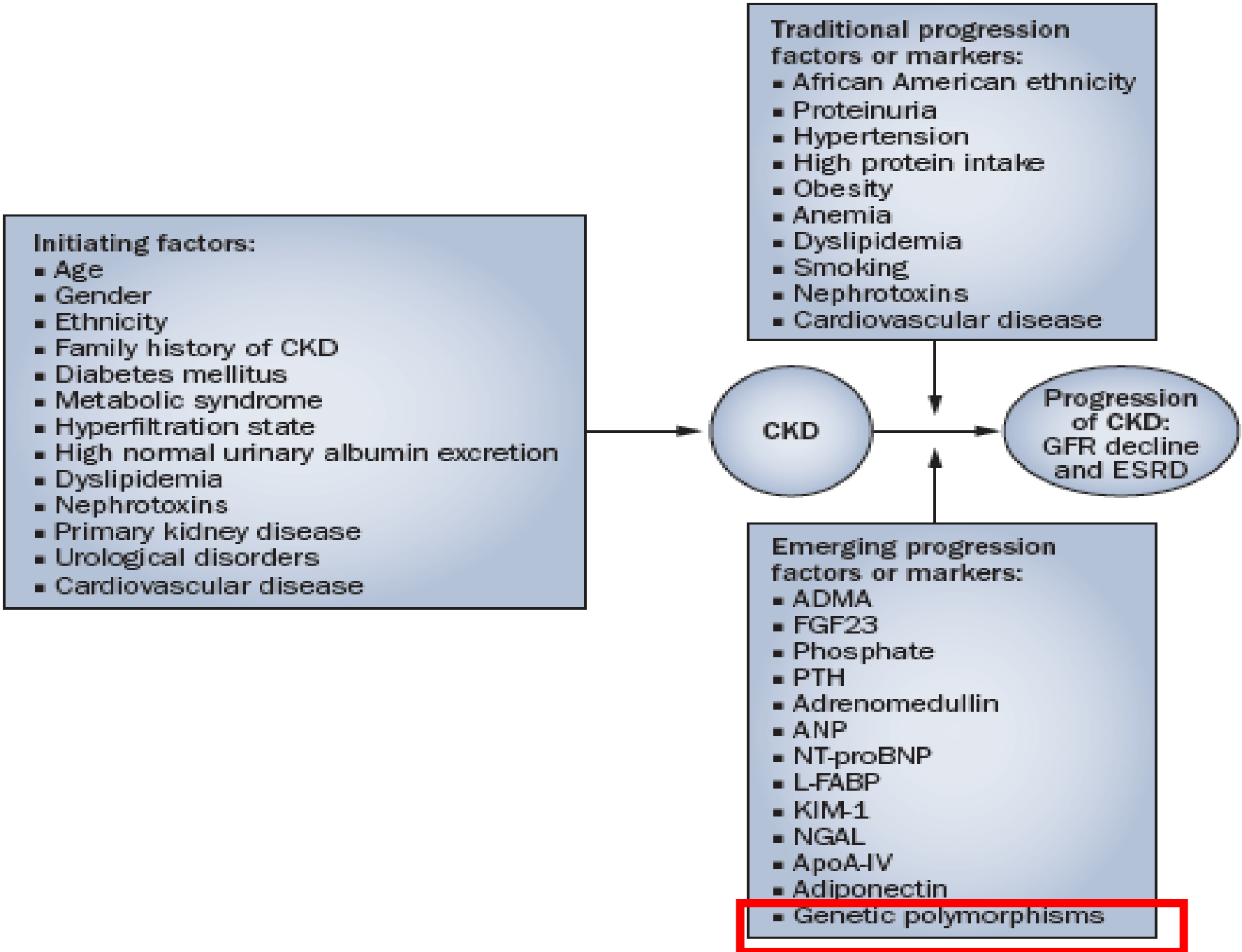
1. *Etiologia nefropatia*
2. *Sexe*
3. *Raça*
4. *Dislipèmia*
5. *Edat*
6. *Tabaquisme*
7. *Hiperglicèmia*
8. *Hiperhomocisteinèmia*
9. *Hiperfosfatèmia*
10. *Anemia*
11. *Factors prenatals*
12. *Drogues d´abús*

Fc Mediadors Comuns

1. *Hemodinàmica*
2. *Hipòxia*
3. ***Proteïnúria***
4. ***HTA***
5. *Activació del complement*
6. ***SRAA***
7. *Altres mediadors clínics*
   - **TGF-β**
   - PAI-1
   - ↓Òxid Nítric
   - Endotelina
   - PDGF-BB

Fisiopatología

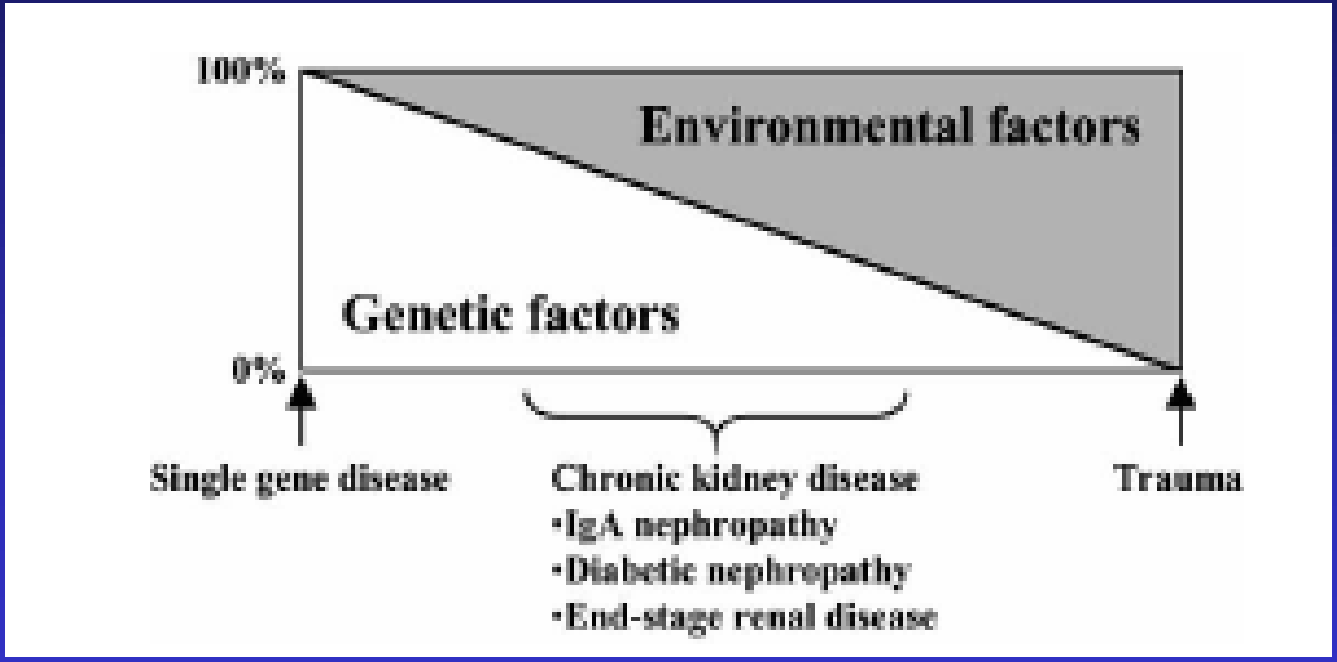
	Definición	Ejemplos
Factores de susceptibilidad	**Aumento de la susceptibilidad al daño renal**	**Edad avanzada, disminución de la masa renal , bajo peso al nacer, minoria racial, historia familiar, pobreza, inflamación, dislipemia**
Factores de iniciación	**Inician el daño renal directamente**	**DM, HTA, enfermedades autoinmunes, PQR, toxicidad farmacológica**
Factores de progresión	**Producen deterioro del daño renal y rápida disminución del FG**	**Hiperglicemia en DM, HTA, proteinuria, tabaquismo**
Factores en la ERC-5	**Aumentan la morbi-mortalidad en la ERC**	**Baja dosis de HD(Kt/V), acceso vascular temporal anemia, hipoalbuminemia, derivación tardía**


Initiating factors:
Age
Gender
Ethnicity
Family history of CKD
Diabetes mellitus
Metabolic syndrome
Hyperfiltration state
High normal urinary albumin excretion
Dyslipidemia
Nephrotoxins
Primary kidney disease
Urological disorders
Cardiovascular disease
Traditional progression factors or markers:
African American ethnicity
Proteinuria
Hypertension
High protein intake
Obesity
Anemia
Dyslipidemia
Smoking
Nephrotoxins
Cardiovascular disease
CKD
Progression of CKD: GFR decline and ESRD
Emerging progression factors or markers:
ADMA
FGF23
Phosphate
PTH
Adrenomedullin
ANP
NT-proBNP
L-FABP
KIM-1
NGAL
ApoA-IV
Adiponectin
Genetic polymorphisms

Contribució dels factors genetics i ambientals a les patologies

	Malaltia per un unic gen	Malaltia multifactorial	Malaltia no genetica
Factors	1 factor genetic	Factors genetics I factors ambientals	Factors ambientals
Gen	Gen responsable	Susceptibilitat genetica	no
Malaltia	Malalties hereditaries (Alport, PQHR)	Malalties comuns (HTA, DM, MRC)	accidents

MRC com a malaltia multifactorial



Susceptibilitat genètica en MRC

Evidències clíniques:

- NAE: susceptibilitat a desenvolupar IRT (alguns pacients l'assoleixen malgrat bon control PA)

Evidències experimentals:

- Gen RF1 a rates HTA risc de IR (no efectes sobre la PA)
- Transplantament de ronyons de rates normoTA a rates HTA → ronyons de les normotenses són més susceptibles al dany induït per la HTA

Potencial de la genètica de les malalties complexes

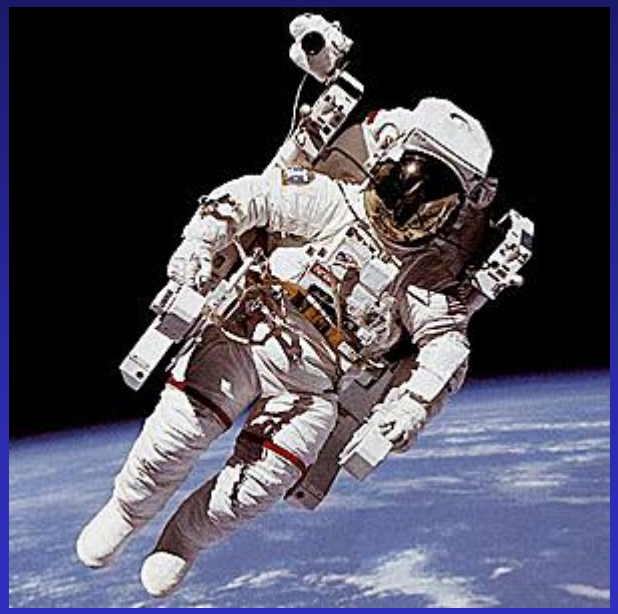
- Contribuir a la comprensió de la patogènia al definir els mecanismes fisiopatològics primaris.
- Oportunitat del diagnòstic pre-clínic.
- Possibilitat de desenvolupar terapèutiques específiques al identificar vies i dianes d´intervenció

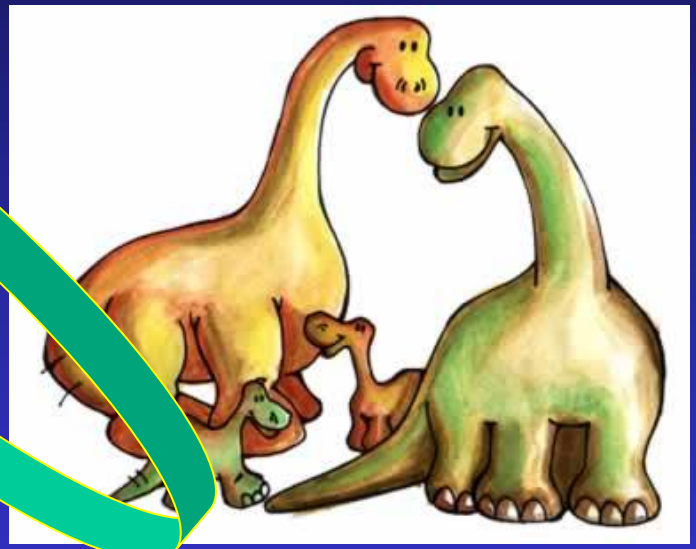
Polimorfisme

- Importants en l'estudi de patologies amb patrons hereditaris complexes
- Canvi en la seqüència de DNA (desde 1 nucleotid fins a cents de pb) ➡ Al.lels
- Detectable en $\geq$ 1% de la població
- Pot influir en el fenotip o ser un marcador d´utilitat clínica
- A introns o exons
- Per a detectar-los: PCR o Southern Blotting

Estudis genetics en MRC

1- Estudis d'associació utilitzant polimorfismes genetics



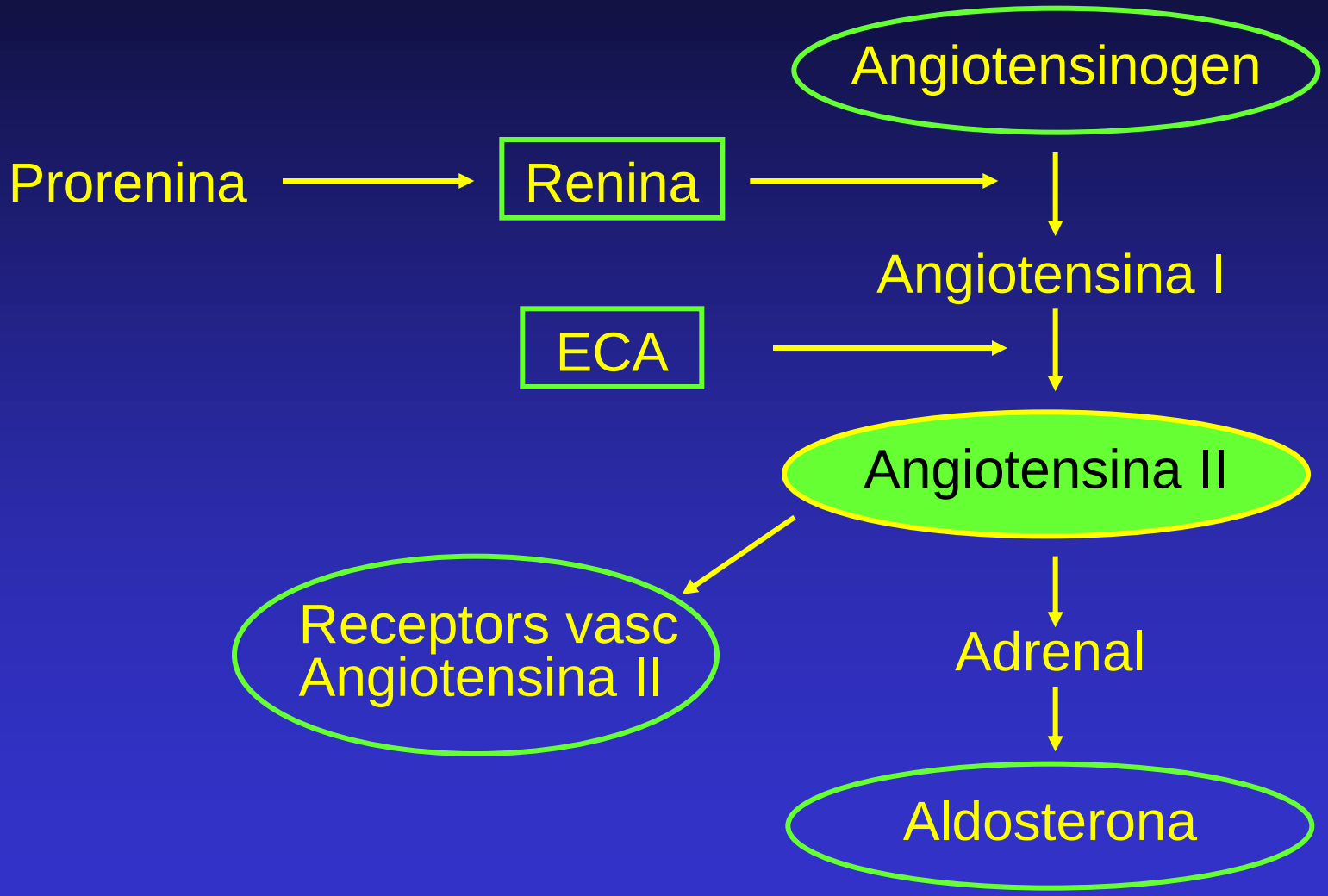


2- Estudis d'associació investigant una gran quantitat de variants genètiques

Gens implicats en la progressió de la MRC

GEN	Polimorfisme
ECA	Intron 16 I/D
Angiotensinogen	Met235Thr
Receptor tipus 1 angiotensina	A1166C
Aldosterona sintasa	-344C/T
IL-1beta	-511T/C, -31C/T
Antagonista receptor IL-1	Intro 2
IL-2	-330 T/G
IL-4	Intro 3
IL-6	-174 G/C
IL-10	-1082 A/G,
TGF-beta1	Codo 10, codo 25, -509 C/T
TNF-alfa	-308G/A
MYH9	Rs7078, rs12107, rs735853, rs5756130, rs4821480, rs2032487, rs4821481, rs3752462, rs5756152, rs1557539, rs1005570, rs16996674,rs16996677
APO E	Epsilon 2/epsilon 4
TCF7L2	Rs12255372, rs7903146, rs7901695, rs11196205
MTHFR	C677T

SRAA


Angiotensinogen
Prorenina
Renina
Angiotensina I
ECA
Angiotensina II
Receptors vasc
Angiotensina II
Adrenal
Aldosterona

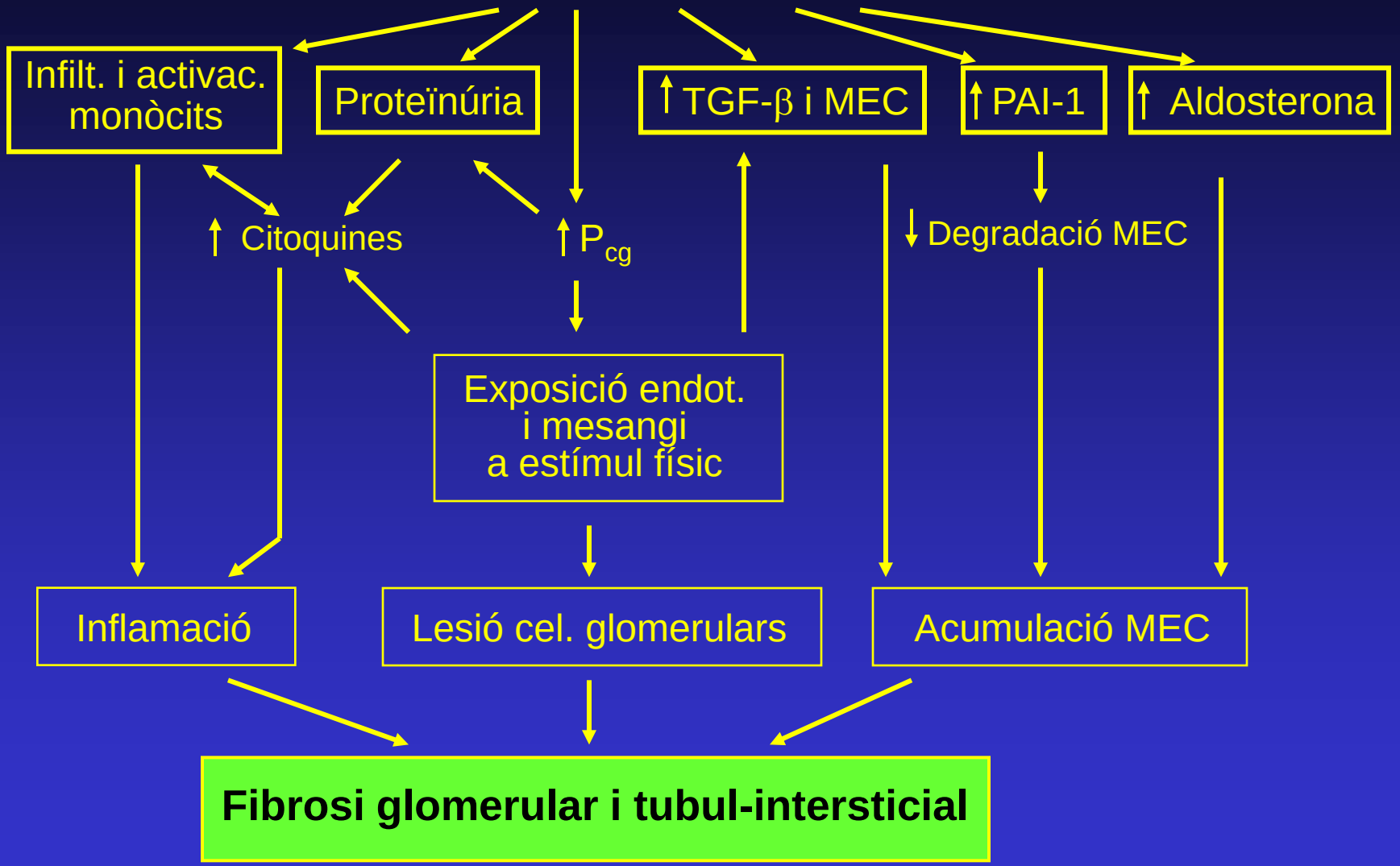
SRAA i ronyó

Plasmàtic	Tisular
endocrí	autocrí- paracrí
regulació aguda	regulació crònica
concentració <<	concentració >>

Vasoconstrictor

Factor de creixement

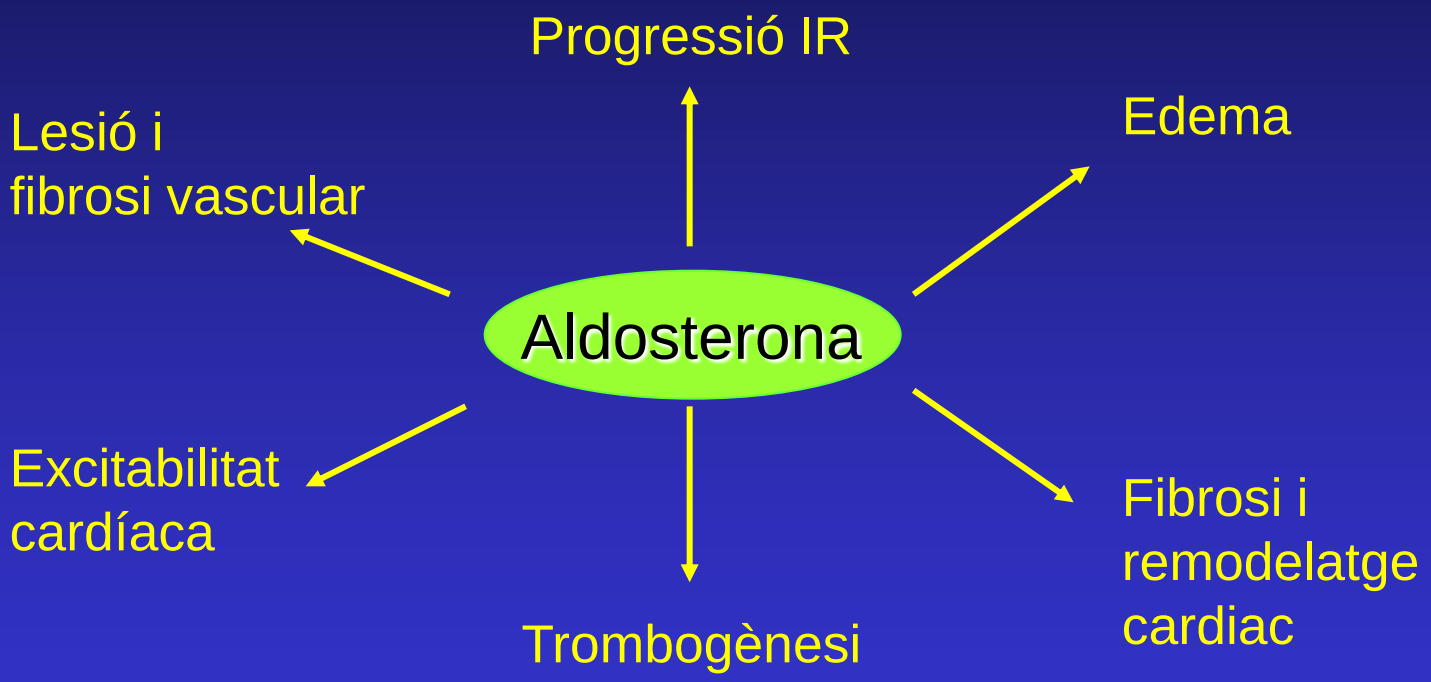
Angiotensina II



Kidney Int 2000; 57: 1803

SRAA i Ronyó: evidències experimentals

Transferència de gens de renina i angiotensinogen humans a ronyons de rates indueix glomeruloesclerosi (no canvis PA)



Kidney Int 57: 1408, 2000

Gen de l´angiotensinògen: variants genètiques **M235T (MM MT TT)**

TT Associat a:

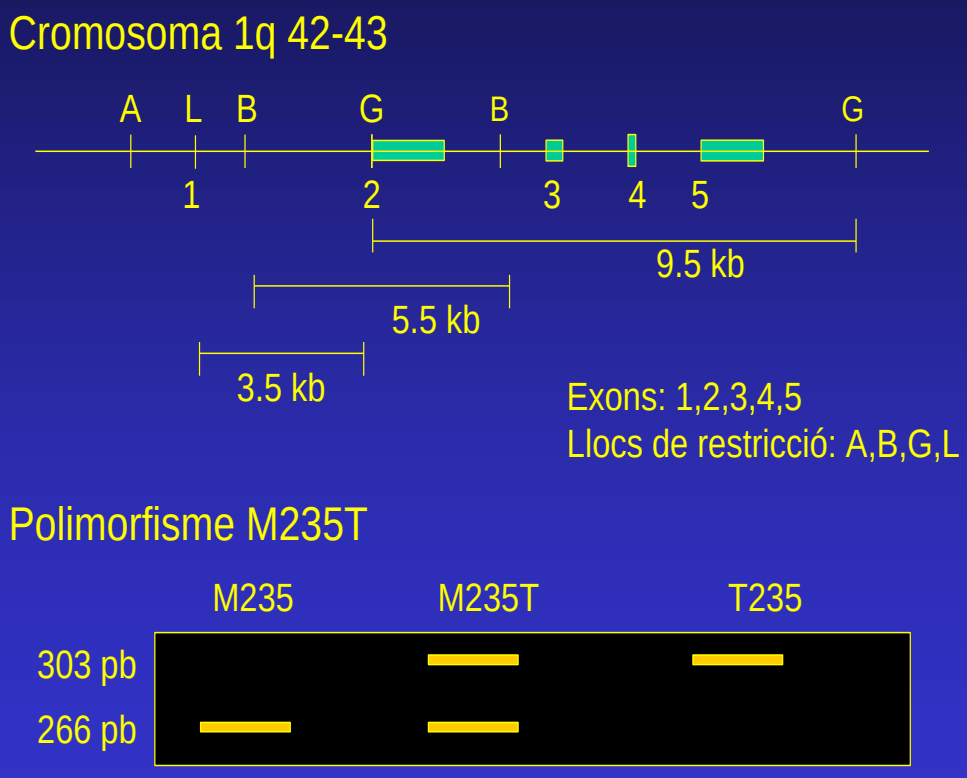
–N- Nivells plasma d´AGT

–p- Preeclàmpsia

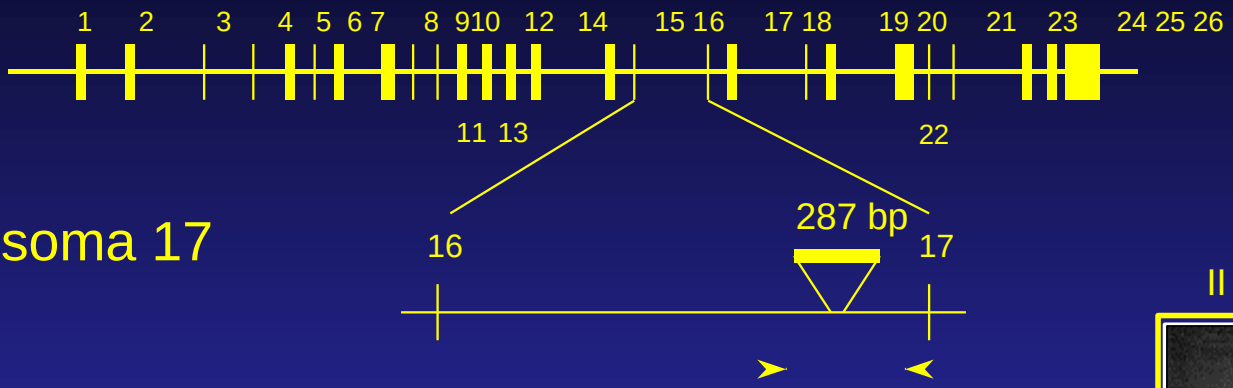
–r- Risc de HTA

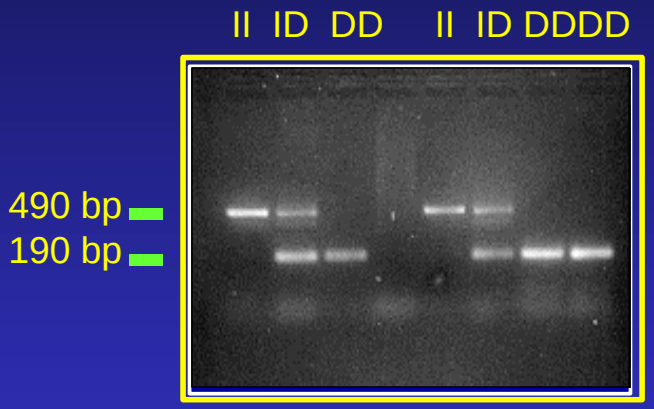
- Patologia coronària

- Progressió ràpida a IRT (nefropatia IgA)



Gen de la ECA





Associacions:

Nivells plasmàtics d´ECA: DD>DI>II

Hipertensió: alguns estudis negatius.

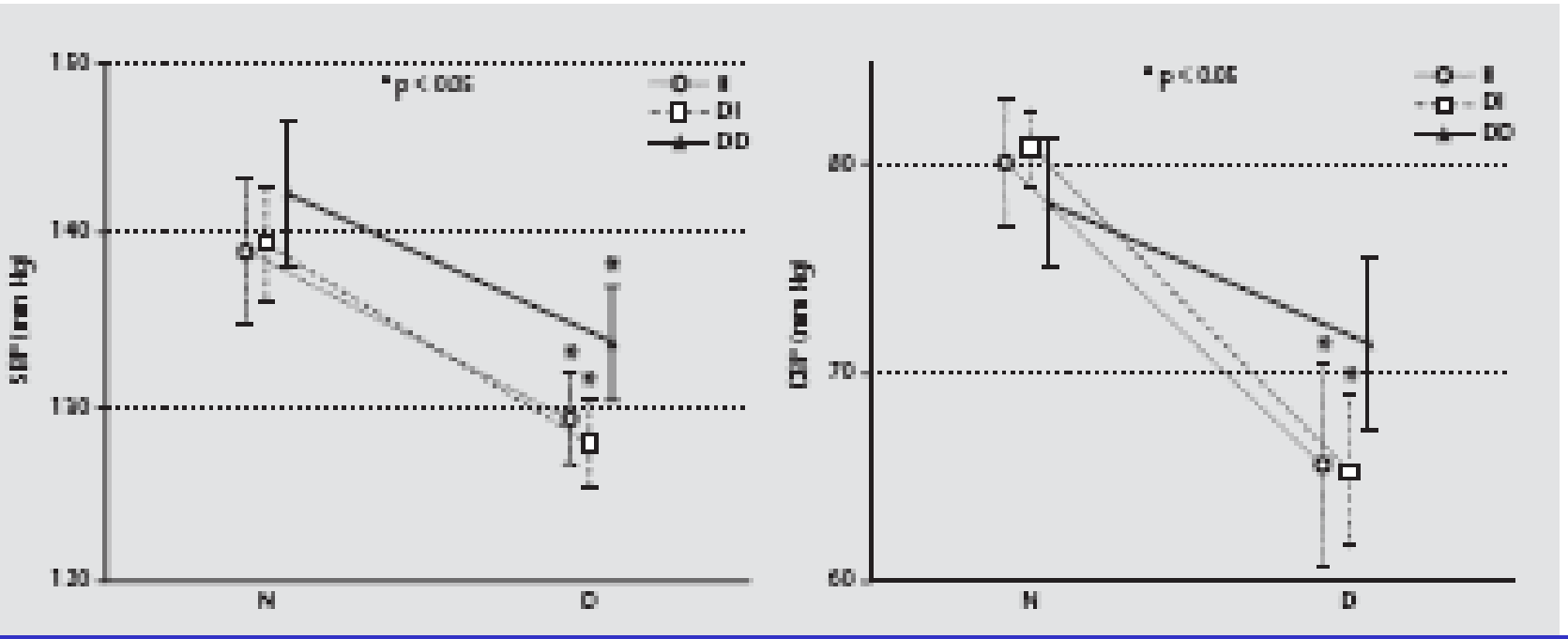
Fenotips HTA: sensibilitat a la sal, lesió endotelial, insulinR.

Complicacions HTA: HVE, μalbuminuria, NAE.

Patologia cardiovascular: IAM, HVE, miocardiopatia dilatada, aterosclerosi carotídea, ACV.

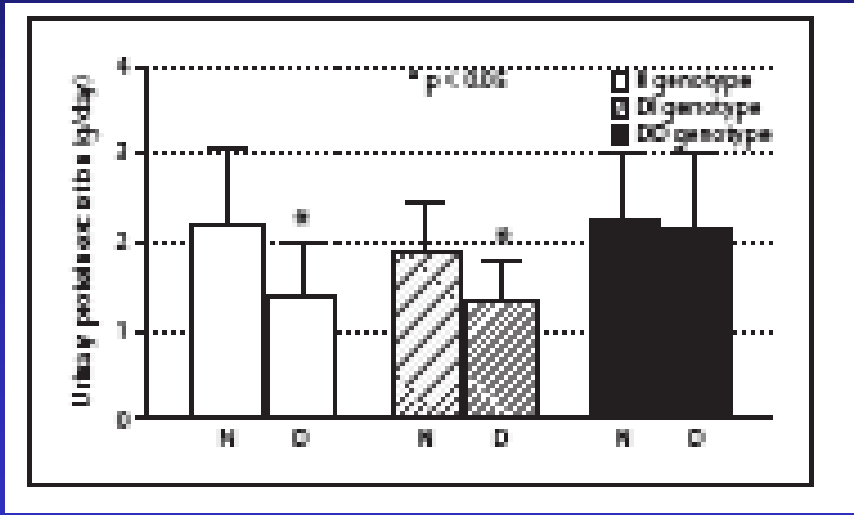
Ronyó: major dany renal i progressió IRC (DM, HTA, IgA, PQR).

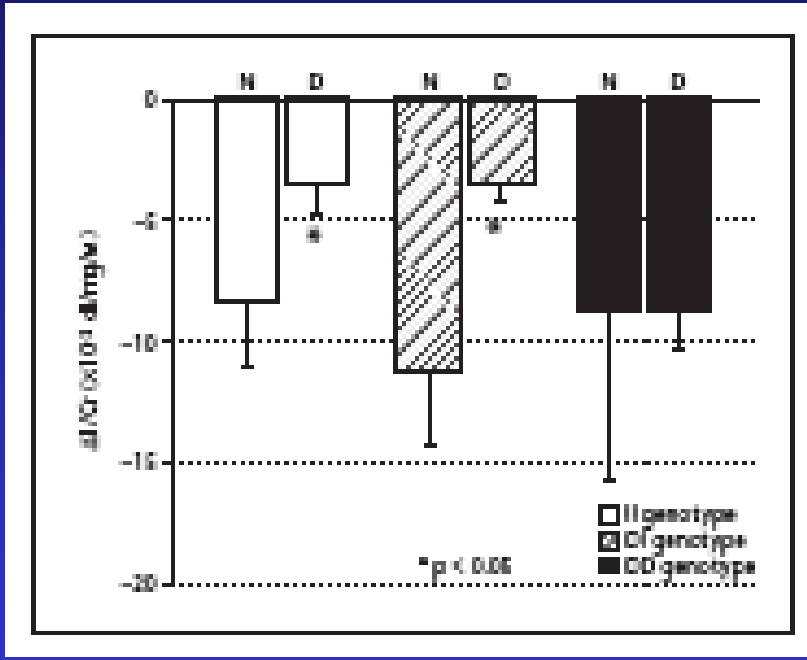
Gen de la ECA I resposta al tractament amb IECA-ARA-II



Nakayama Y et al. Nephron Clin Pract 2009; 111: c240.

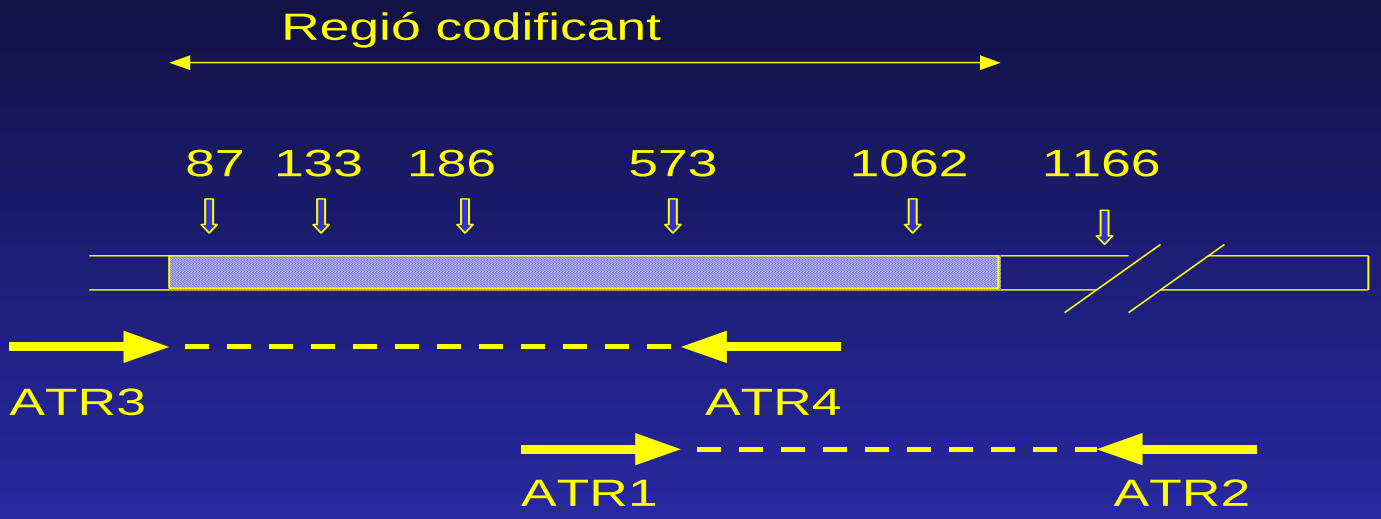
Gen de la ECA I resposta al tractament amb IECA-ARA-II





Nakayama Y et al. Nephron Clin Pract 2009; 111: c240.

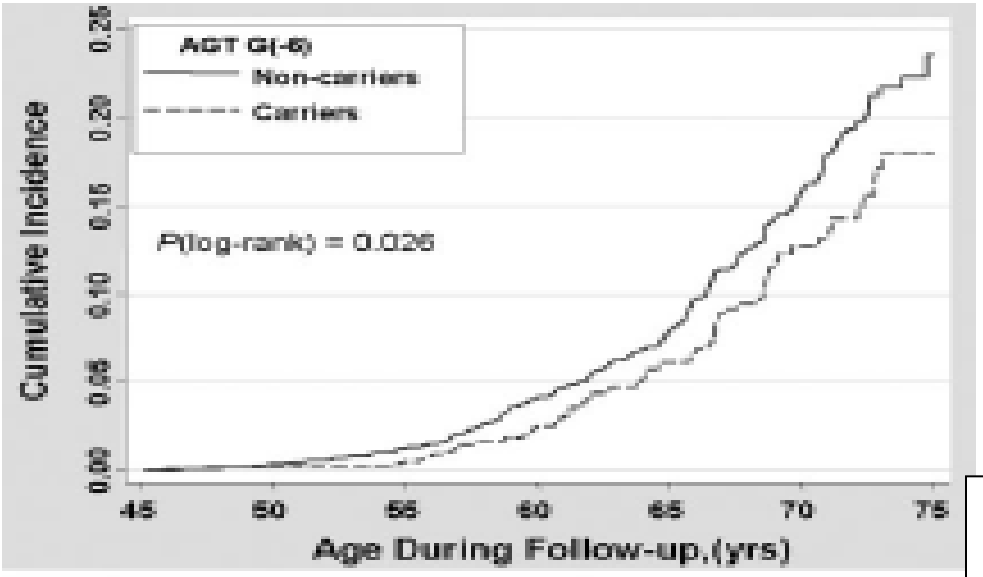
Gen del AT1R: Cromosoma 3

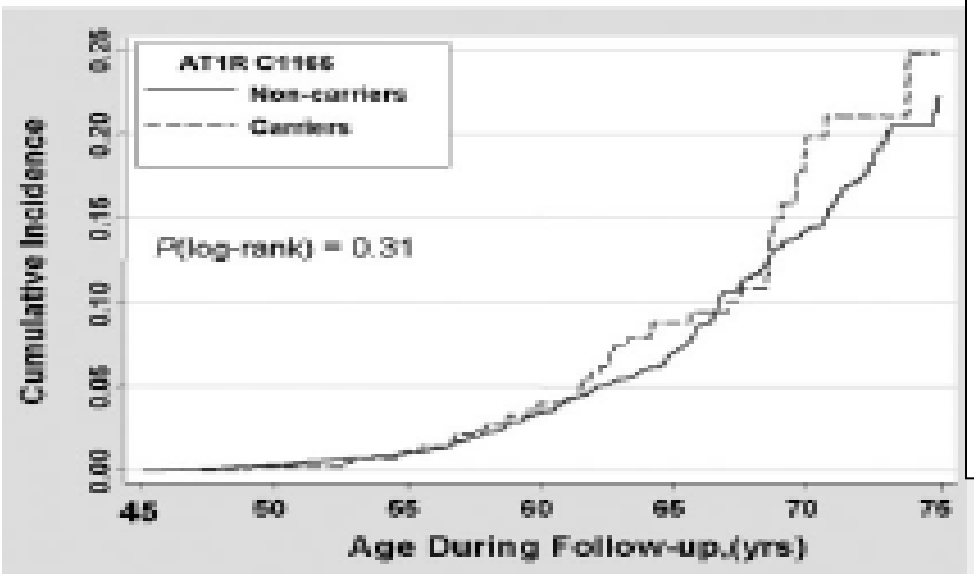


Polimorfisme A1166C associat a: Al.lel C

- HTA, HTA greu, HTA precoç, HTA a l´embaraç
- Nefropatia diabètica
- Rigidesa aòrtica
- HVE
- > VC arterial a l´angiotensina II
- Progressió més ràpida de la MRC

Angiotensinogen i ATR-1





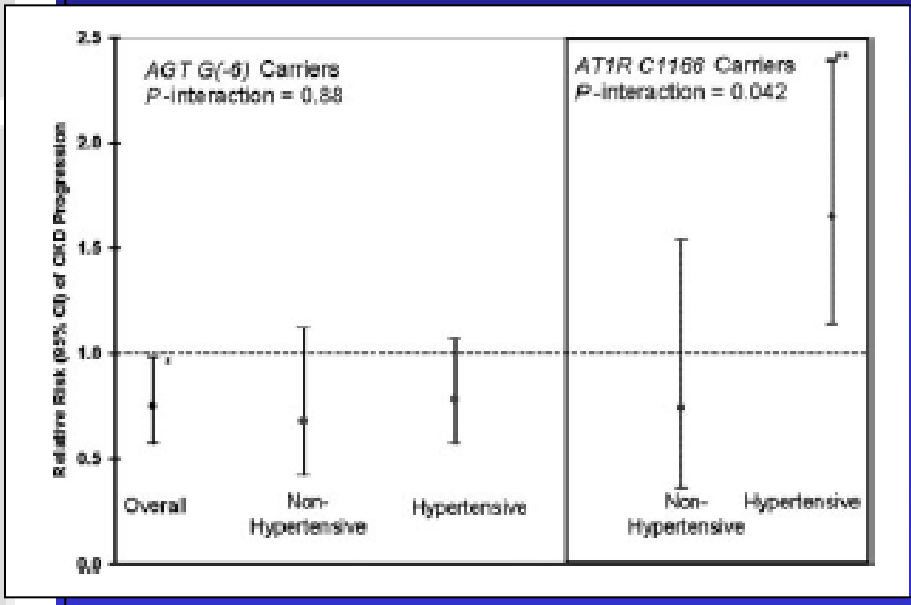
Polimorfisme del promotor al nucleotid -6 GA

L'al·lel A augmenta la transcripcio basal de ATG, incrementant nivells de ATG.

Al.lel G progressio més lenta de la MRC (indepependent de la PA) en raça negra

Polimorfisme A1166C del ATR1

L'al·lel C progressio més rápida de la MRC en els individus HTA



Hsu CC, JASN 17; 504, 2006

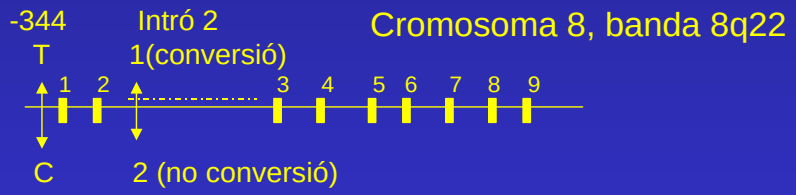
Gen de la aldosterona sintasa (CYP11B2)

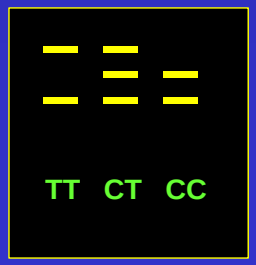
Variantes genètiques:

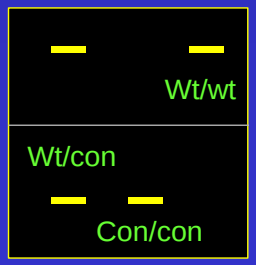
- *Promotor*
-344 C/T
- *Intron 2*
conversió/no conversió
(inserció sec. CYP11B1)

Fenotips associats amb -344C/T:

- HVE (C)[1]
- >PAS y > U aldo (TT)
- HTA renina baixa (C)[2]
- IAM (CC)[3] sols si
  - Fumador RR 3,51
  - HDL baixa RR 3,20
  - PAS alta RR 2,21
- MRC[4]

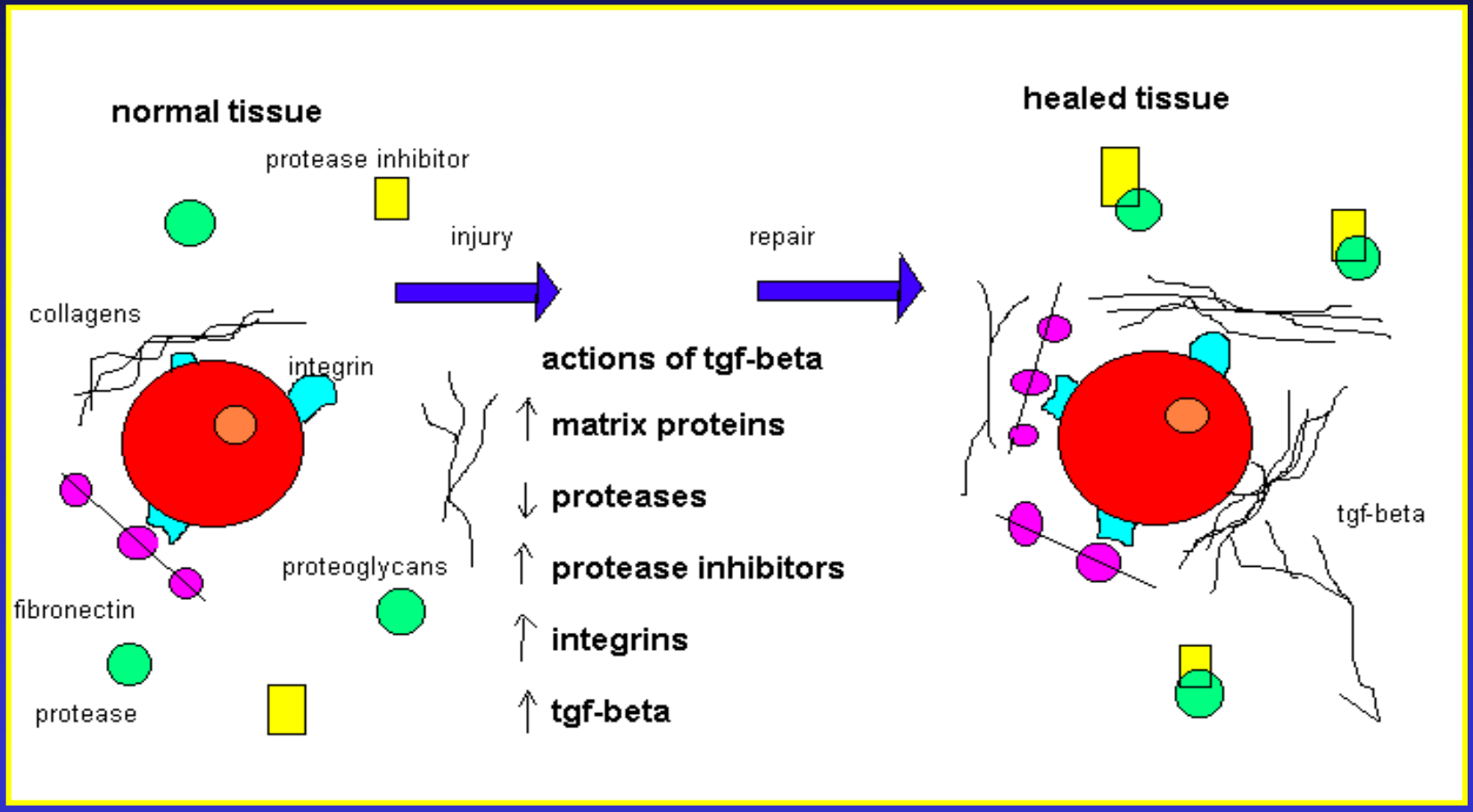






[1]*Circulation* 1998;97:569
[2]*Hypertension* 2000;35:699
[3]*Circulation* 1999;100:2213
[4]*J Nephrol 2004*

TGF-β


normal tissue
protease inhibitor
injury
repair
healed tissue
collagens
integrin
actions of tgf-beta
matrix proteins
proteases
protease inhibitors
integrins
tgf-beta
proteoglycans
fibronectin
protease
tgf-beta

TGF-β i ronyó

Evidències experimentals:

- rates amb sobreexpressió de TGF-beta ➡ fibrosi renal ràpida
- injecció antiserum que neutralitza TGF-beta a rates amb GN bloqueja l´acúmul de la MEC

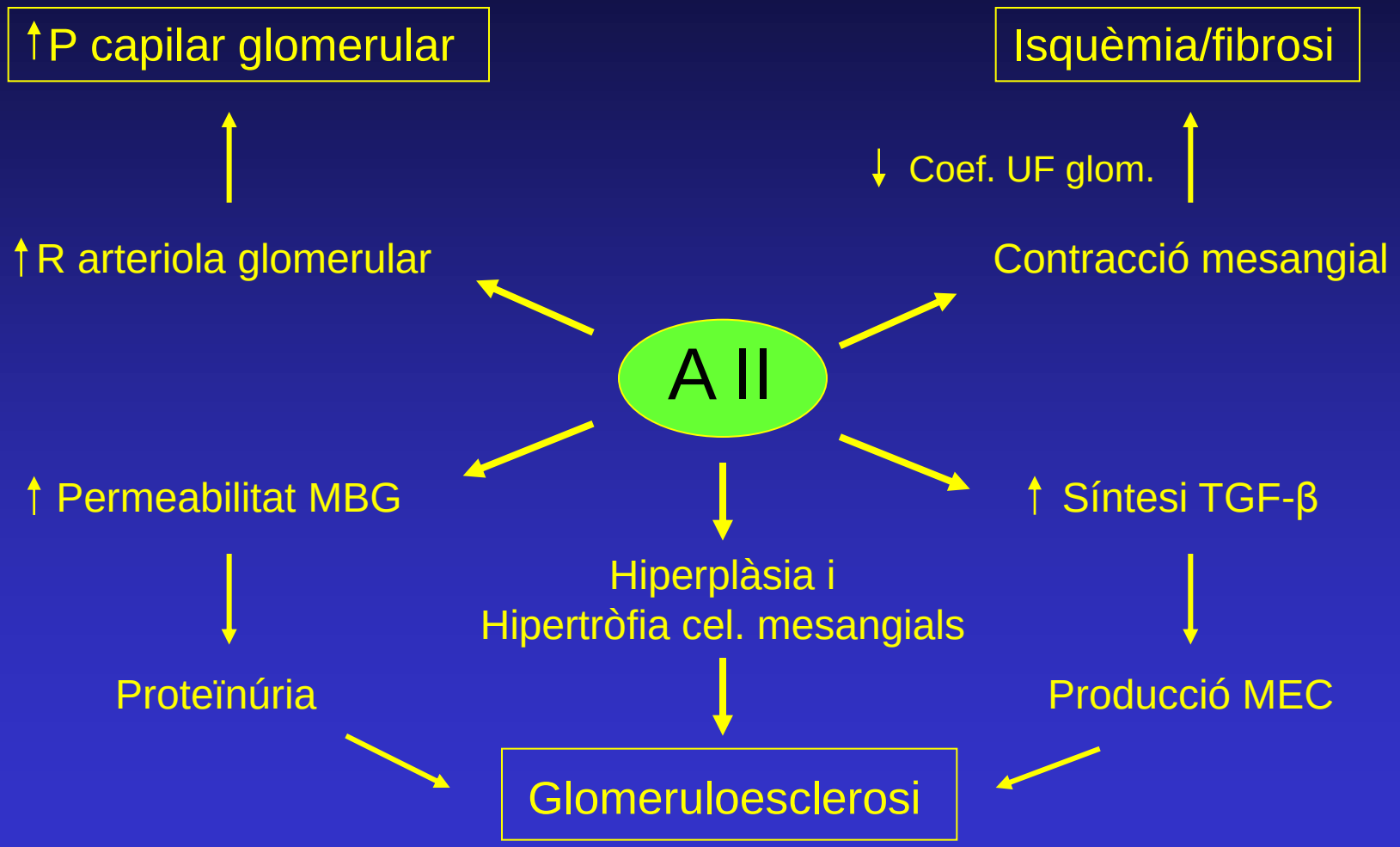
Evidències clíniques:

- augment de producció de TGF-beta a GN, ND, NAE i nefropatia de l´empelt

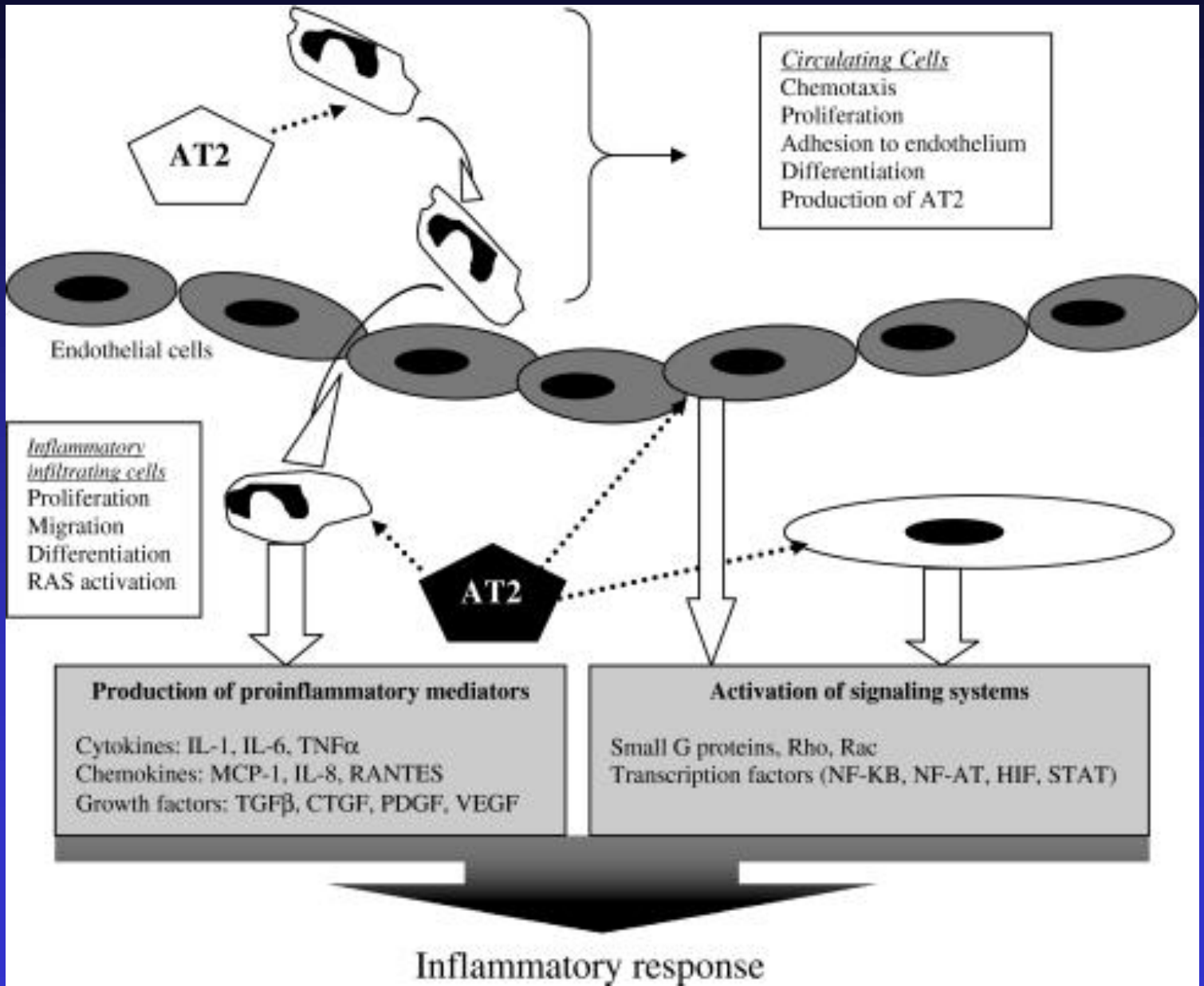
Interaccions SRAA i TGF-β

- Fluid “shear stress” ↑ l’expressió TGF-beta i (+) SRAA de les cèl. endotelials
- Hipovolèmia i hipokaliemia augmenten la producció de renina i TGF-beta a l´aparell juxtaglomerular
- A-II activa la producció de TGF-beta i ↑ la seva activació a cultius cel·lulars

Interaccions SRAA i TGF-β



SRAA- resposta inflamatòria

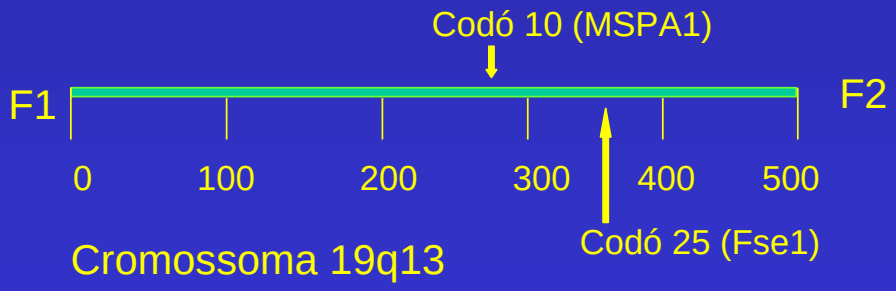


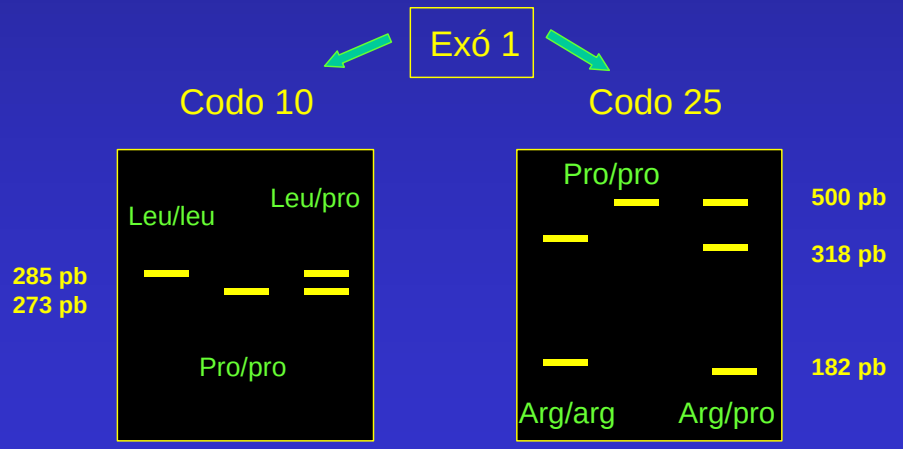
Gen del TGF-β

8 polimorfismes:

2 situats a la seqüència peptídica del senyal: { Leu10Pro, Arg25Pro

- Genotip Arg/Arg (codo 25) més freqüent a HTA
- Genotip Pro/Pro (codo 10) associat a > [ ] de TGF-beta en IAM
- Al.lel Pro (25) associat a > risc de IAM
- Al.lel Leu (10) associat a IAM, nef.diabètica, IgA
- PLM codo 10 i 25 associats a MRCT





Citokines /Inflamació

Les citokines són moduladors de la inflamació.

El balanç entre les CK pro I antiinflamatories determina si la intensitat de la resposta inflamatoria es troba dins del rango fisiologic o patologic.

MRC es caracteritza per nivells elevats de CK proinflamatories I altres marcadors de la inflamació.

Les CK modulen el risc de progressio de la MRC I la susceptibilitat a la malaltia CV.

PLM de citokines i fenotips

Table 3 | Cytokine gene polymorphisms known to be related to progression and severity of renal and cardiovascular diseases

Authors	Genotype	Clinical significance
IL-1		
Amoli *et al.*[28]	−511 C/T	Severity of renal involvement in Henoch-Schonlein purpura
IL-1Ra		
Blakemore *et al.*[29]	IL1RN*2	Development of diabetic nephropathy in type I and type II diabetes
Shu *et al.*[42,43]	IL2RN*2	Progression in IgA nephropathy and risk for ESRD
IL-6		
Kitamura *et al.*[44]	−634 C/G	Progression of diabetic nephropathy
Liu *et al.*[45]	−174 G/C	Risk for CVD among dialysis patients
Losito *et al.*[32]	−174 G/C	LVH in hemodialysis patients, especially those with diabetes
TGF-β		
Khalil *et al.*[46]	Arg^{25}	Associated with severity of proteinuria and glomerulosclerosis
Sato *et al.*[47]	−509 CC and 869 CC	Heavy proteinuria and mesangial cell proliferation
Rao *et al.*[48]	G/C substitution at codon 25	Risk for prevalent vascular disease, new onset cardiac morbidity and cardiac mortality in HD patients
TNF-α		
Thibaudin *et al.*[49]	−308 G/A TNFd2 allele	Susceptibility to idiopathic membranous nephropathy
IL-10		
Girndt *et al.*[33]	−1082A*	Lower production of IL-10 and increased CV morbidity

CVD, cardiovascular disease; ESRD, end-stage renal disease; HD, hemodialysis; IL, interleukin; LVH, left ventricular hypertrophy.

Rao M et al. Kidney Int 2007; 72: 549

Polimorfismes de la PCR

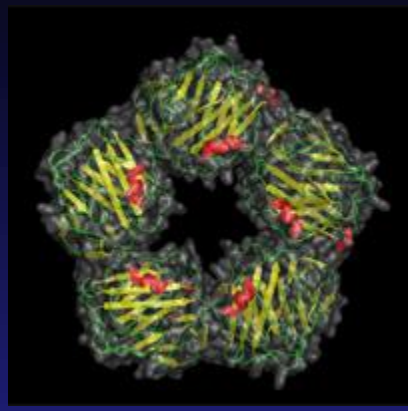
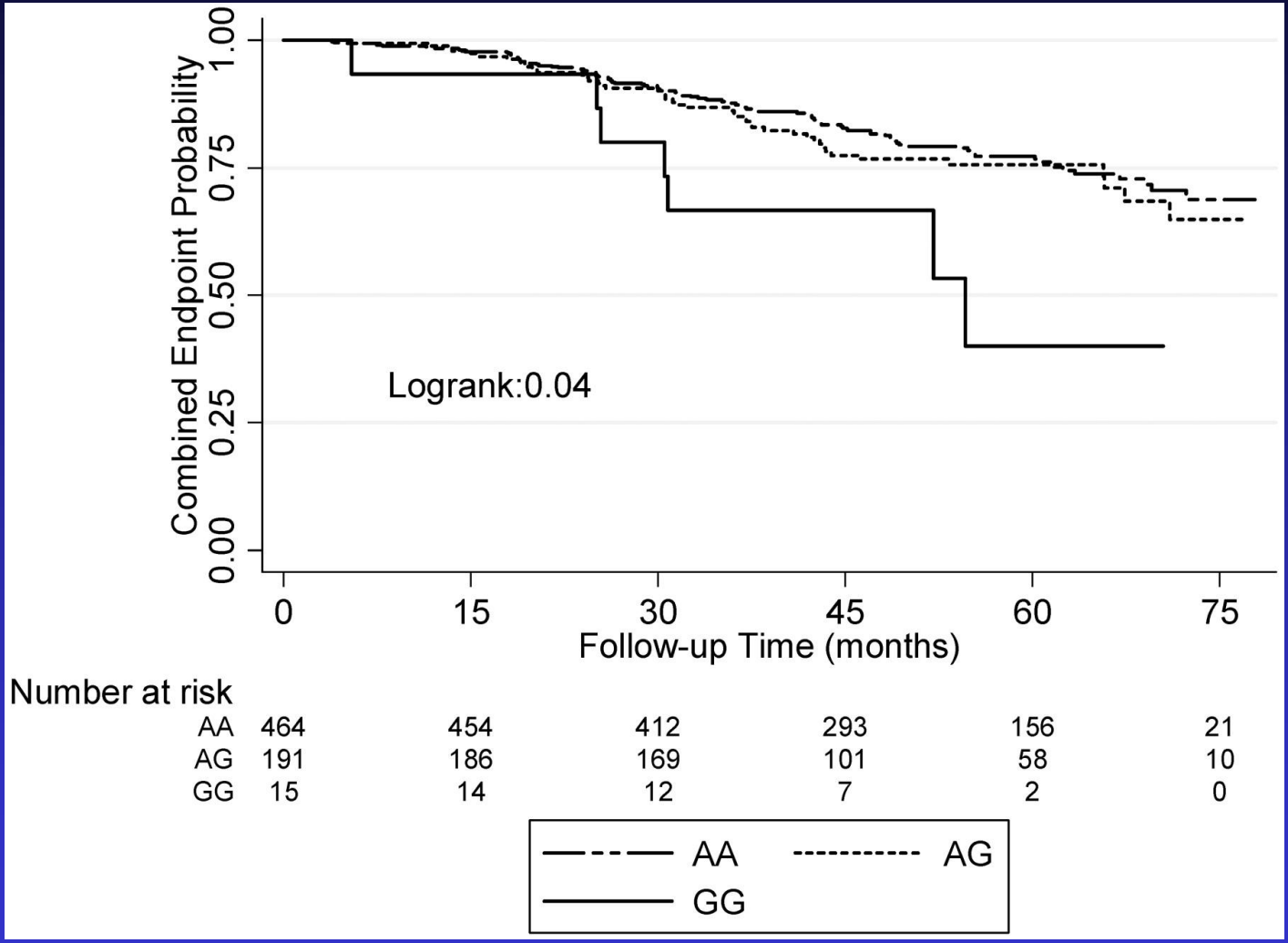


Table 2. CRP SNP allele frequencies for African Americans from NHANES III and AASK participants

CRP SNPs	Location	Alleles	Allele Frequencies		P Value[a]
			NHANES III (n = 450)	AASK (n = 642)	
rs2808630	3′-flanking region	A	86%	83%	0.03[b]
		G	14%	17%	
rs1205	3′-flanking region	A	21%	18%	0.03[b]
		G	79%	82%	
rs3093066	5′-flanking region	A	24%	22%	0.3
		C	76%	78%	
rs1417938	Intron 1	A	87%	88%	0.3
		T	13%	12%	
rs3093058	5′-flanking region	A	84%	81%	0.08
		T	16%	19%	
rs1800947[c]	Exon 2	C	1%	1%	0.6
		G	99%	99%	

Hung A M et al. CJASN 2010;5:24-33

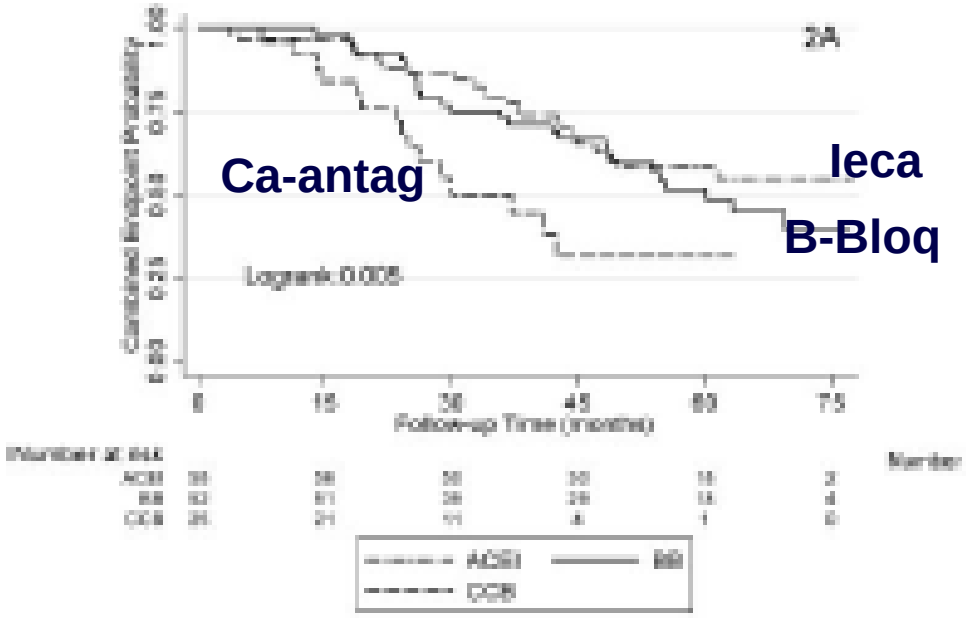
Genotip rs2808630 de la PCR



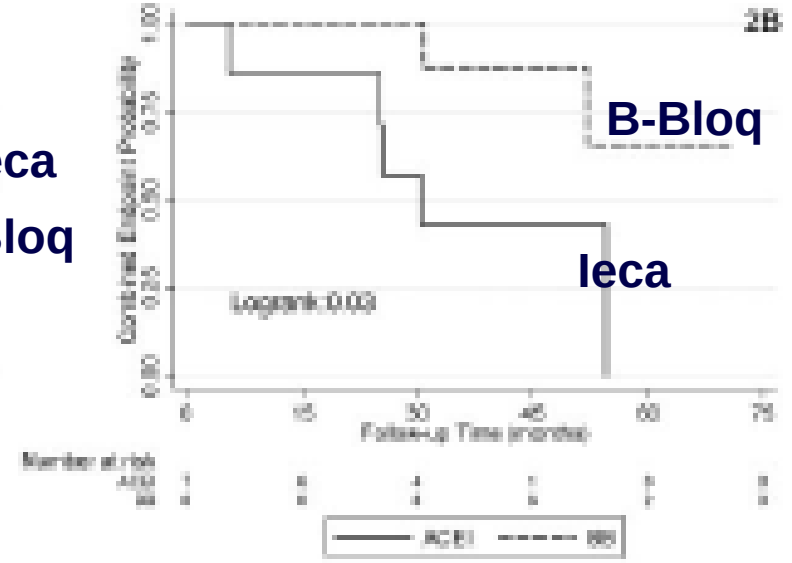
Hung A M et al. CJASN 2010;5:24-33

Efecte de diferents hipotensors sobre la progressio en portadors de genotip rs2808630GA

Genotip AA



Genotip GG

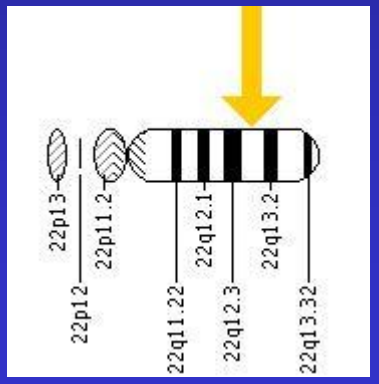


Hung A M et al. CJASN 2010;5:24-33

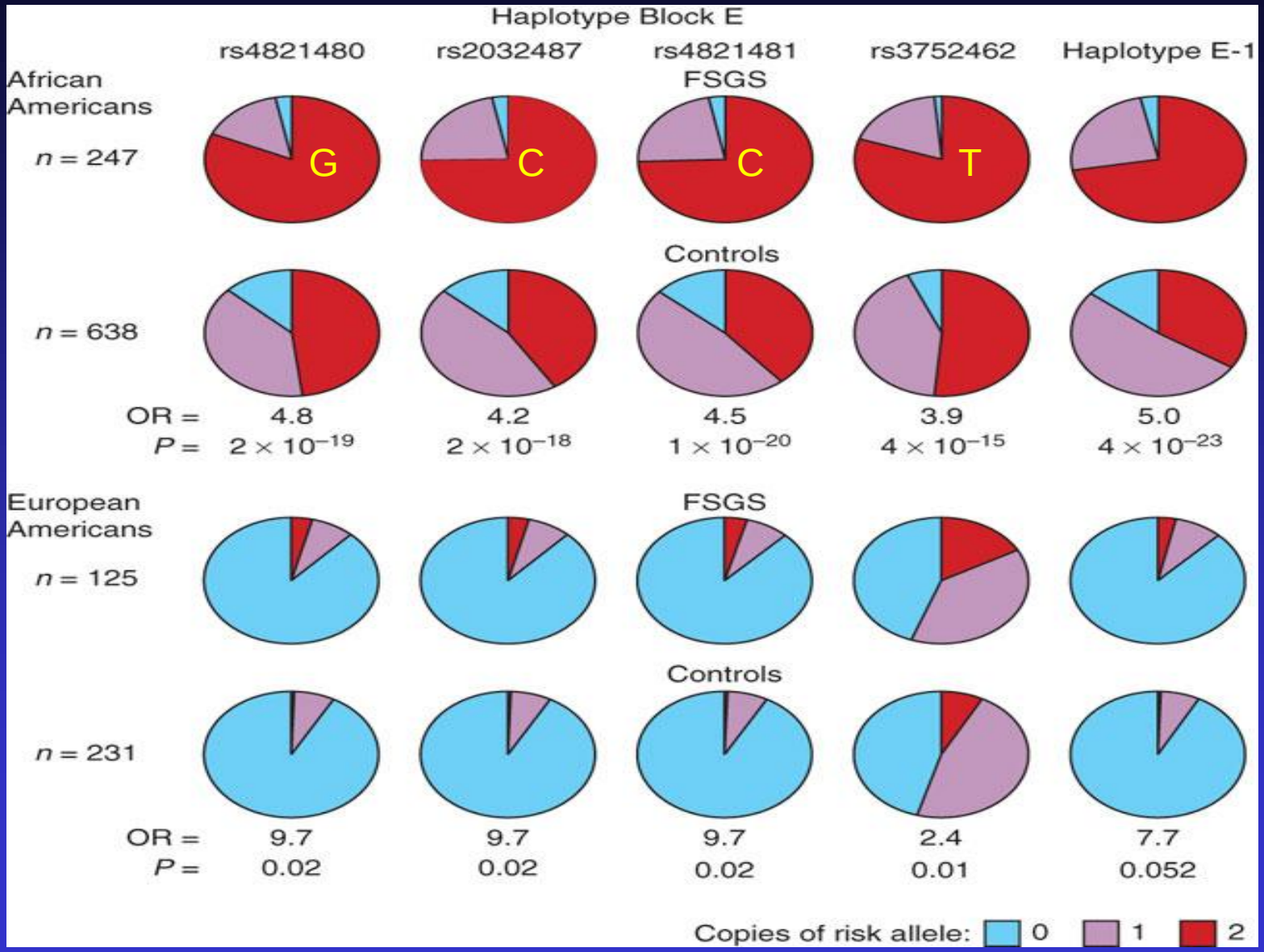
Polimorfismes del gen MYH9

Situat al cromossoma 22
Codifica la cadena pesada d'una proteina no muscular de la miosina IIA
En fases inicials la miosina IIA es situa a nivell podocitari i indueix alteracions estructurals

Recentment NAE hipertensiva: lesio estructural disminucio nº total de podocits I de l'expressió intrarrenal de gens de proteines com la nefrina, la podocina i la sinaptopodina, relacio amb el FG I el grau de fibrosi renal.



Frequencies de 4 genotips i 1 haplotip del gen MYH9 segons raça i patologia



Kopp et al., Nat Genetics 2008

Progressió de la MRC en africans-americans: polimorfismes del gen MYH9

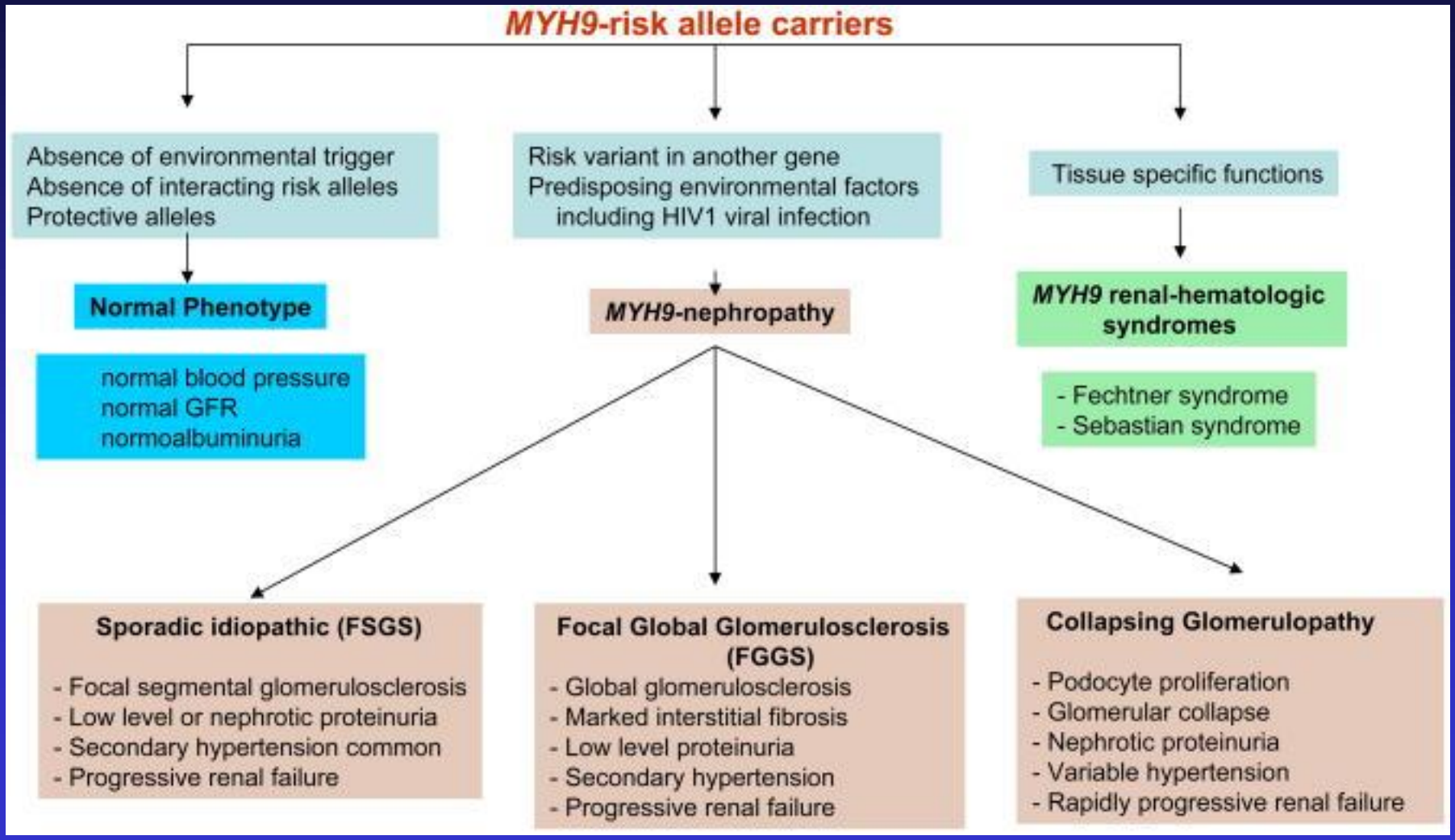
Freedman BI, et al: Non muscle myosin heavy chain 9 gene MYH9 associations in African Americans with clinically diagnosed type 2 diabetes mellitus-associated ESRD. *NDT* 2009; 24: 3366-3371.

Kopp, et al: *MYH9* is a major-effect risk gene for focal segmental glomerulosclerosis.
Nature Genetics 2008; 40:1175-1184

Kao, et al: *MYH9* is associated with nondiabetic end-stage renal disease in African Americans.
Nature Genetics 2008; 40:1185-1192

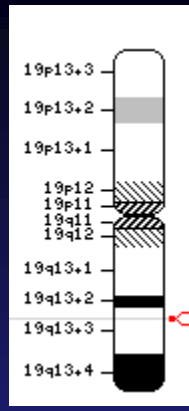
Freedman BI, and Sedor JR: Hypertension-associated kidney disease: Perhaps no more.
J Am Soc Nephrol 2008; 19:2047-2051

Nefropaties associades al MYH9 – mecanismes postulats



Murea M. Curr Opin Nephrol Hypertens 2010; 19: 235.

Altres polimorfismes



Gen de la APO E

Hsu CC et al. Apolipoprotein E and progression of chronic kidney disease. JAMA 2005; 293: 2892

Alel ε4 i alzheimer

Alel ε2 i hiperlipoproteinemia tipus III

Dades ARIC study

Figure 1. Incidence Rates of Chronic Kidney Disease Progression by *APOE* Genotype and Race

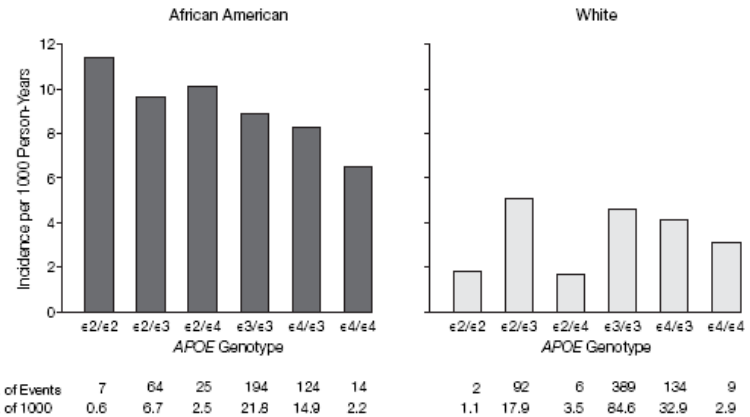


Table 2. Adjusted Relative Risk of CKD Progression by *APOE* Alleles, Summary Score, and Race*

Model†	Relative Risk per *APOE* Allele (95% CI) ε3	ε2	ε4	Relative Risk Per Unit Increase in *APOE* Summary Score (95% CI)‡	*P* Value
Both races					
Age, sex, and race adjusted (model 1)	1.00	1.04 (0.90-1.20)	0.85 (0.75-0.96)§	1.12 (1.03-1.22)	.009
Risk factor adjusted (model 2)	1.00	1.07 (0.93-1.24)	0.87 (0.77-0.98)§	1.12 (1.03-1.22)	.01
Risk factor and lipid adjusted (model 3)	1.00	1.08 (0.93-1.25)	0.85 (0.75-0.95)§	1.14 (1.05-1.24)	.003
African American					
Age and sex adjusted (model 1)	1.00	1.15 (0.94-1.42)	0.91 (0.77-1.08)	1.12 (0.99-1.27)	.06
Risk factor adjusted (model 2)	1.00	1.15 (0.93-1.41)	0.90 (0.76-1.07)	1.12 (0.99-1.27)	.06
Risk factor and lipid adjusted (model 3)	1.00	1.17 (0.95-1.45)	0.88 (0.74-1.05)	1.15 (1.01-1.31)	.03
White					
Age and sex adjusted (model 1)	1.00	0.95 (0.77-1.16)	0.80 (0.67-0.94)§	1.11 (0.99-1.25)	.07
Risk factor adjusted (model 2)	1.00	1.02 (0.83-1.24)	0.84 (0.71-0.99)	1.12 (0.99-1.26)	.07
Risk factor and lipid adjusted (model 3)	1.00	1.01 (0.82-1.24)	0.82 (0.69-0.97)	1.13 (1.00-1.27)	.047

Altres polimorfismes

gen del Transcriptor factor 7-like 2

Estudi ARIC

Polimorfismes del gen del TCF7L2 associats a DM2.

Table 2. Multivariable adjusted relative hazard of CKD progression during a median follow-up of 14 yr with *TCF7L2* variants in 10786 white and 3599 black ARIC participants[a]

Marker	White					Black				
	HR[b]	95% CI	*P*	Events	*n*	HR[b]	95% CI	*P*	Events	*n*
rs12255372										
overall	1.13	1.00 to 1.28	0.040	629	10,452	1.07	0.91 to 1.25	0.421	350	3522
no diabetes	1.12	0.98 to 1.29	0.099	474	9553	1.05	0.86 to 1.28	0.649	219	2963
diabetes	1.18	0.93 to 1.49	0.177	155	899	1.10	0.85 to 1.44	0.459	131	559
rs7903146										
overall	1.17	1.04 to 1.32	0.008	635	10,476	1.20	1.03 to 1.41	0.023	349	3537
no diabetes	1.18	1.03 to 1.35	0.019	477	9566	1.10	0.89 to 1.35	0.375	219	2980
diabetes	1.19	0.94 to 1.51	0.150	158	910	1.32	1.03 to 1.71	0.031	130	557
rs7901695										
overall	1.19	1.06 to 1.34	0.002	636	10,527	1.27	1.09 to 1.48	0.002	350	3546
no diabetes	1.20	1.05 to 1.37	0.009	477	9613	1.22	1.01 to 1.48	0.036	220	2987
diabetes	1.21	0.96 to 1.52	0.111	159	914	1.36	1.05 to 1.76	0.018	130	559
rs11196205										
overall	1.15	1.03 to 1.29	0.011	635	10,524	1.06	0.88 to 1.28	0.514	351	3559
no diabetes	1.12	0.99 to 1.28	0.070	477	9608	0.97	0.77 to 1.21	0.779	220	2998
diabetes	1.26	1.00 to 1.58	0.045	158	916	1.21	0.88 to 1.67	0.238	131	561

[a]Results obtained from a model adjusting for baseline gender, BMI, SBP, antihypertensive medication intake, fasting glucose, study center, smoking, and diabetes in the overall analyses.
[b]HR are for each copy of the known diabetes-susceptibility allele (rs12255372 [T]; rs7903146 [T]; rs7901695 [C]; rs11196205 [C]).

Kottgen A et al. JASN 2008; 19; 1989

Altres polimorfismes

• Crawford A et al. **Glutation peroxidase, superoxide dismutase and catalase genotypes** and activities and the progression of CKD. NDT 20011

• Narita I et al. Role of **uteroglobin G38A polymorphism** in the progression of IgA nephropathy in Japanese patients. Kidney int 2002; 61: 1853.

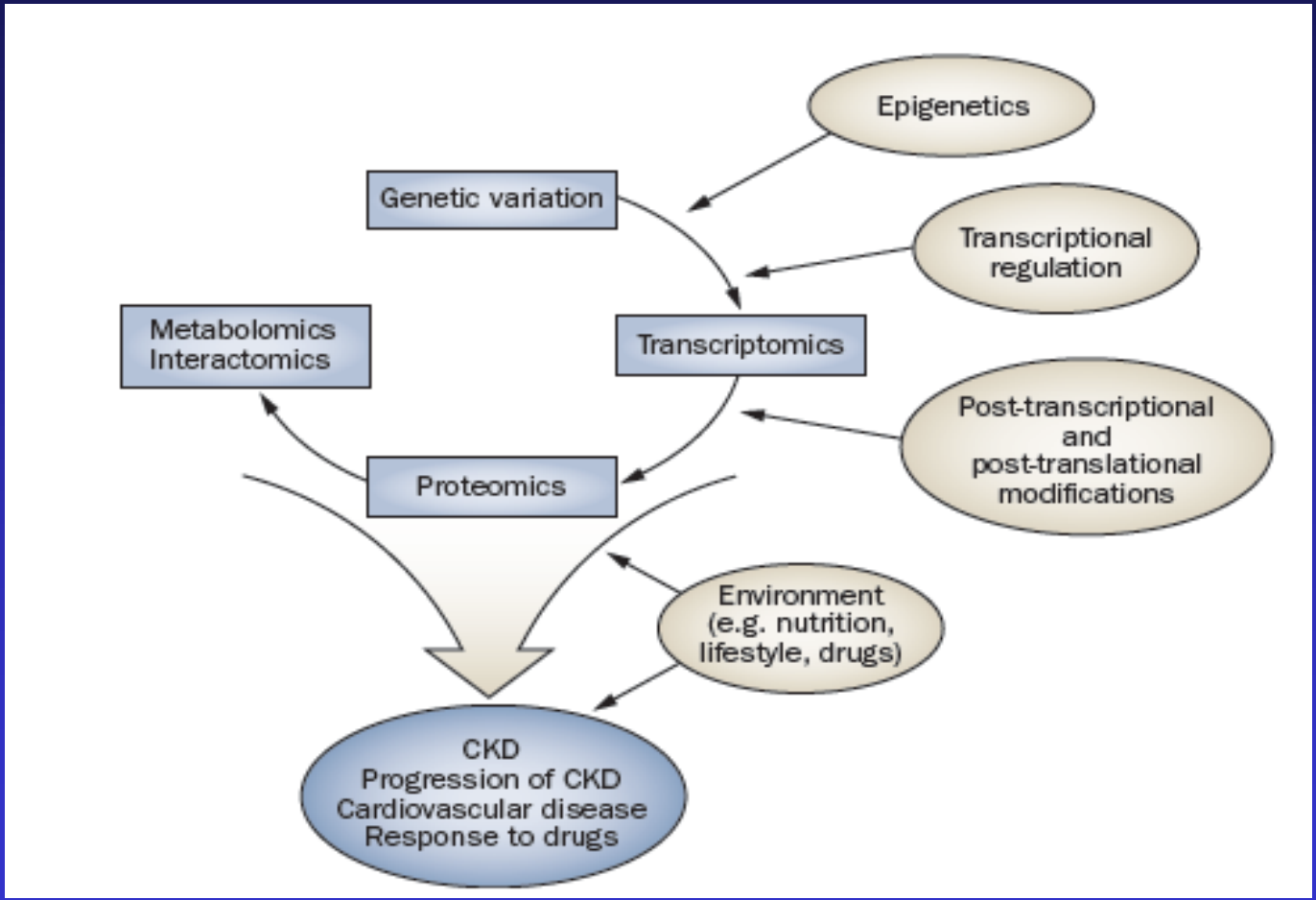
• Prasad et al. association of TGF beta 1, TNF alpha, **CCR2 and CCR5 gene polymorphisms** in type 2 diabetes and renal insufficiency among Asian Indians. BCM Med Genet 2007; 8:20.

• Tripathi G et al. Role of thrombotic risk factors in ESRD. Clin Appl Thromb Hemost 2010; 16: 132. **MTHFR genotypes and Factor V leiden mutation.**

Conclusions

- Existeix una susceptibilitat genètica a desenvolupar insuficiència renal terminal.
- Existeix una susceptibilitat genètica a una progressió més ràpida cap a la HD.
- La progressió de la IR és un procés multifactorial en el que interaccionen factors clínics amb genètics.

El futur


Epigenetics
Genetic variation
Transcriptional regulation
Metabolomics
Interactomics
Transcriptomics
Post-transcriptional and post-translational modifications
Proteomics
Environment (e.g. nutrition, lifestyle, drugs)
CKD
Progression of CKD
Cardiovascular disease
Response to drugs

Gracies per la vostra atenció