UNIVERSITAT DE BARCELONA
Facultat de Farmàcia i Ciències de l'Alimentació

UNIVERSIDAD AUTONOMA DE CHILE

Servicio de Salud Maule
Región del Maule
Ministerio de Salud

HOSPITAL REGIONAL DE TALCA

Característiques i factors de risc de la Malaltia Pulmonar Obstructiva Crònica (MPOC) en poblacions llatinoamericanes

Jordi Olloquequi González

Departament de Bioquímica i Fisiologia

Secció de Fisiologia

Seminari de Recerca

2 de març de 2023

PHARMACOLOGICAL STRATEGIES FOR NEUROPROTECTION

Principal Investigators

CARME AULADELL
Associate Professor

Prevention of neuronal death by apoptosis in neurodegenerative processes

ANTONI CAMINS
Full professor

Therapeutic strategies for the treatment of Alzheimer's disease focused on cognitive improvement.

Research Interest

Our research is mainly focused on the identification of new molecular therapeutic targets to prevent neuronal-degeneration and cognitive-loss. Specifically, we are interested in the role of C-Jun-N-terminal-kinases (JNKs) and protein-tyrosine-phosphatase-1B (PTP1B) in the control of these processes.

Through different preclinical mouse models of epilepsy, obesity/type-2-diabetes mellitus, Alzheimer's disease and Huntington's disease, we have identified an important effect of Licochalcone-A (LicA) and Epigallocatechin-3-gallate (EGCG) to prevent neurodegeneration and deficits in synaptic plasticity. In addition to intraperitoneal and intranasal injections of these compounds, we are improving new treatment methods. With this purpose, we have developed PEGylated-poly(lactic-co-glycolic)-acid-nanoparticle (NPs) with ascorbic-acid (AA).

Besides, we are also studying the role of JNK isoforms in adult hippocampal neurogenic activity in the different preclinical murine models. To achieve this goal, we use stereotaxic methods to label newborn cells with GAG-GFP to determine the dendritic arborisation along neuronal maturation process. In addition, using intraperitoneal injections of bromodeoxyuridine, we analyze the activity of the different neurogenic subpopulations


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Edifici Mediterrània

DUC IN ALTUM

UA

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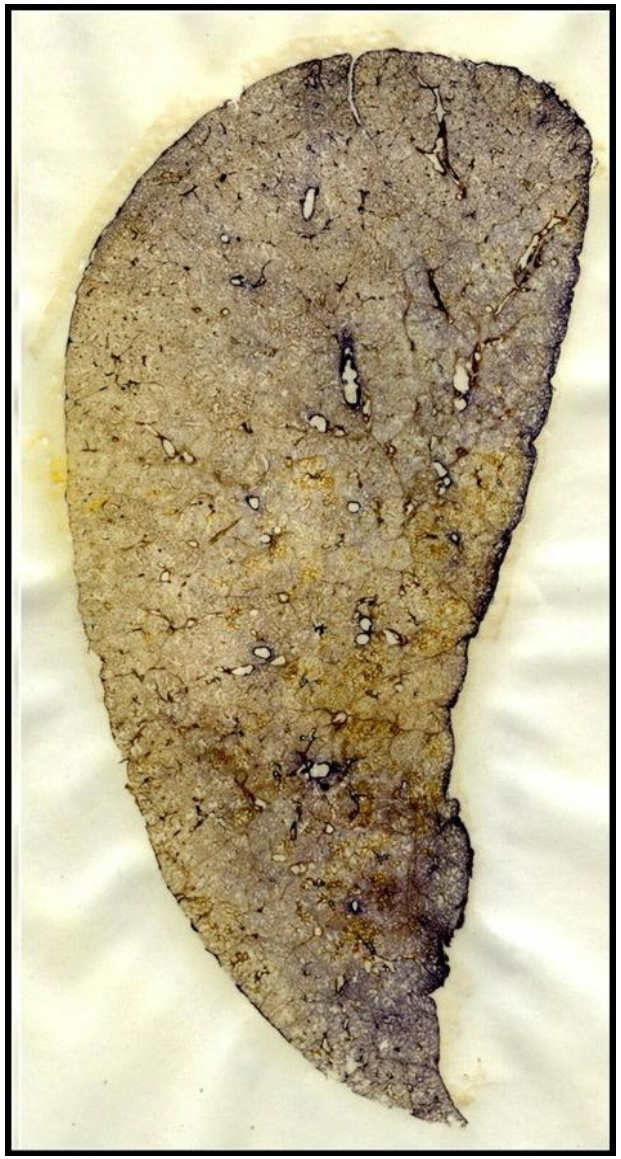
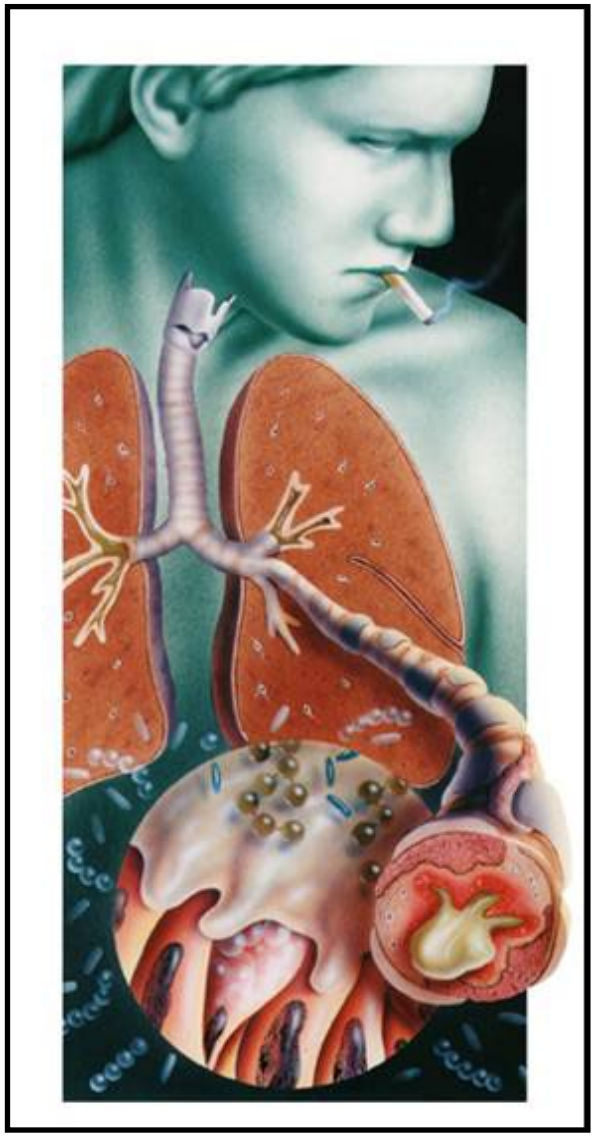
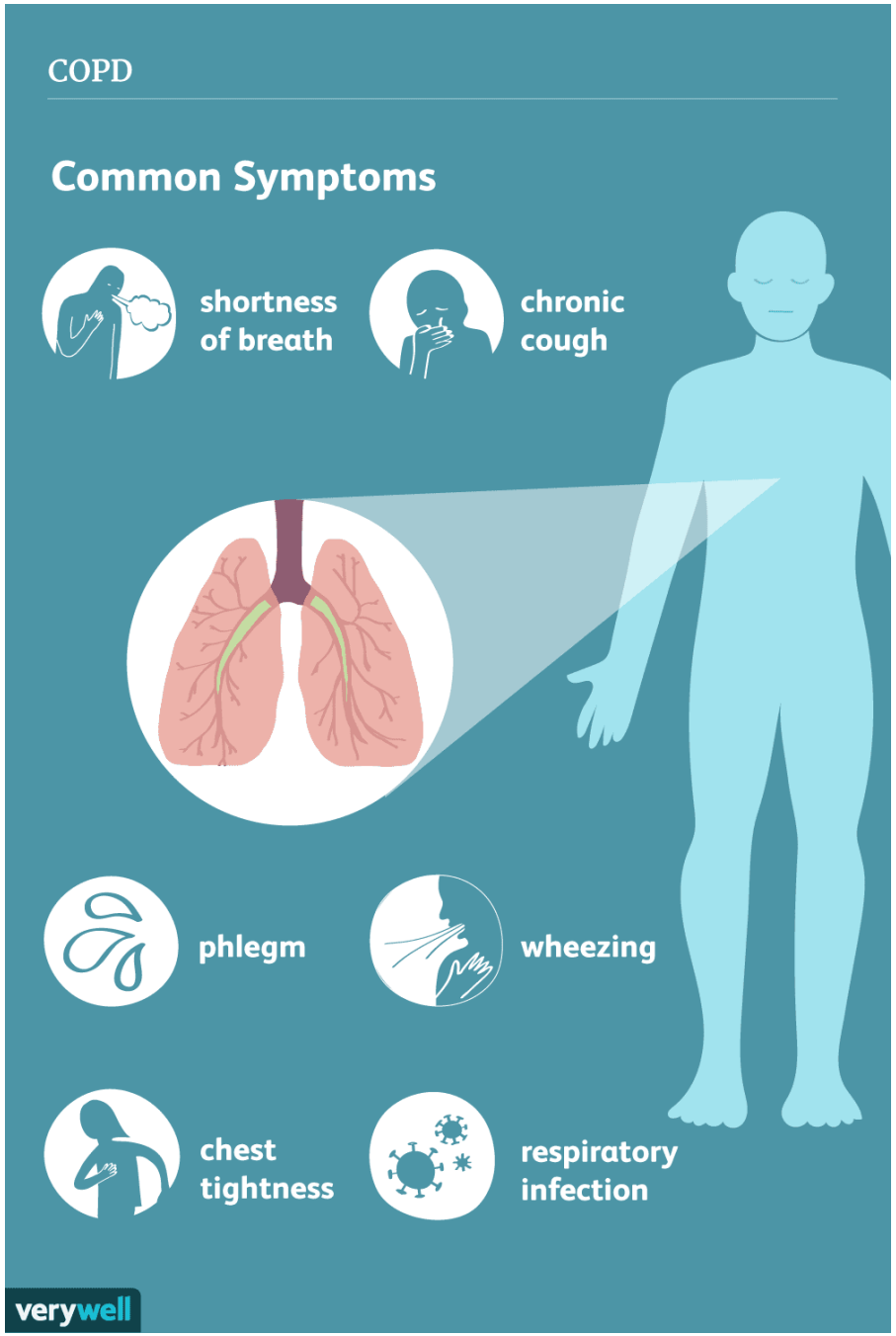
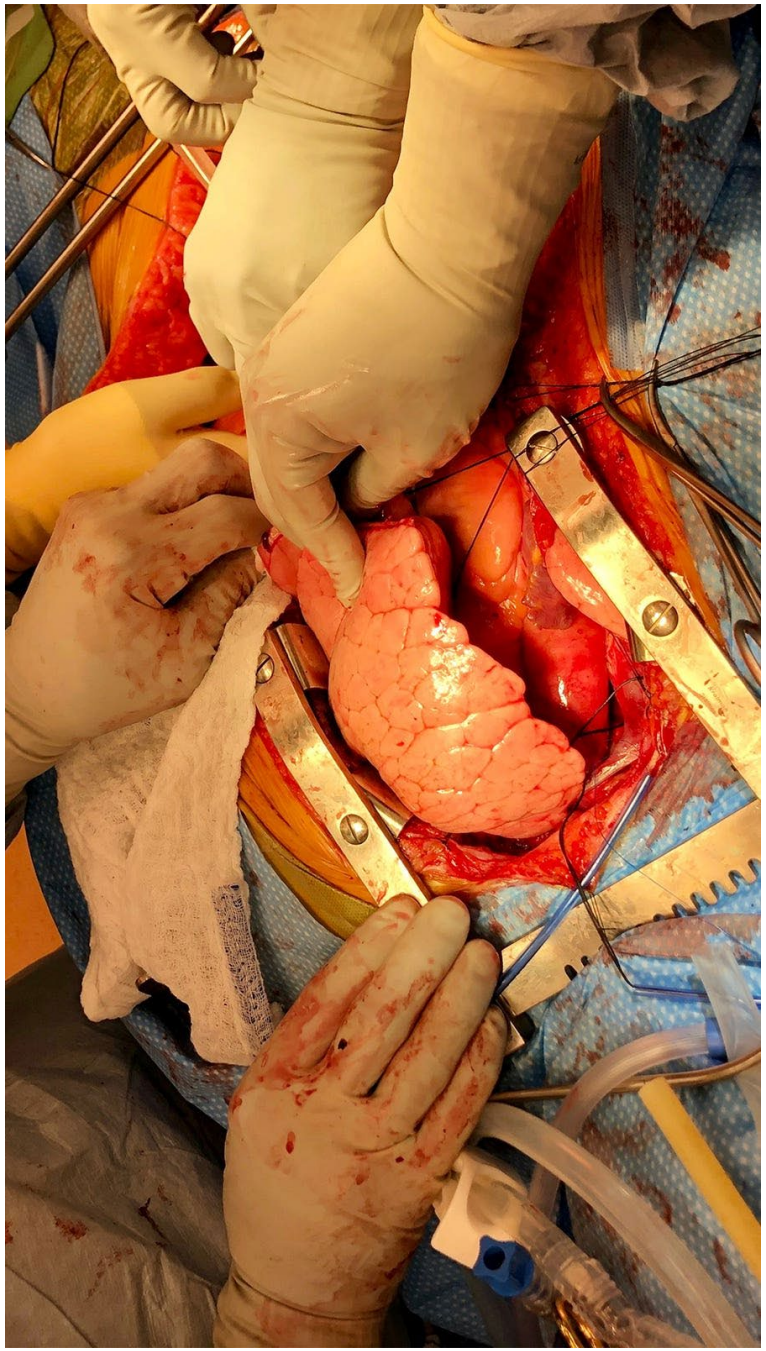
Malaltia Pulmonar Obstructiva Crònica (MPOC, EPOC, COPD)



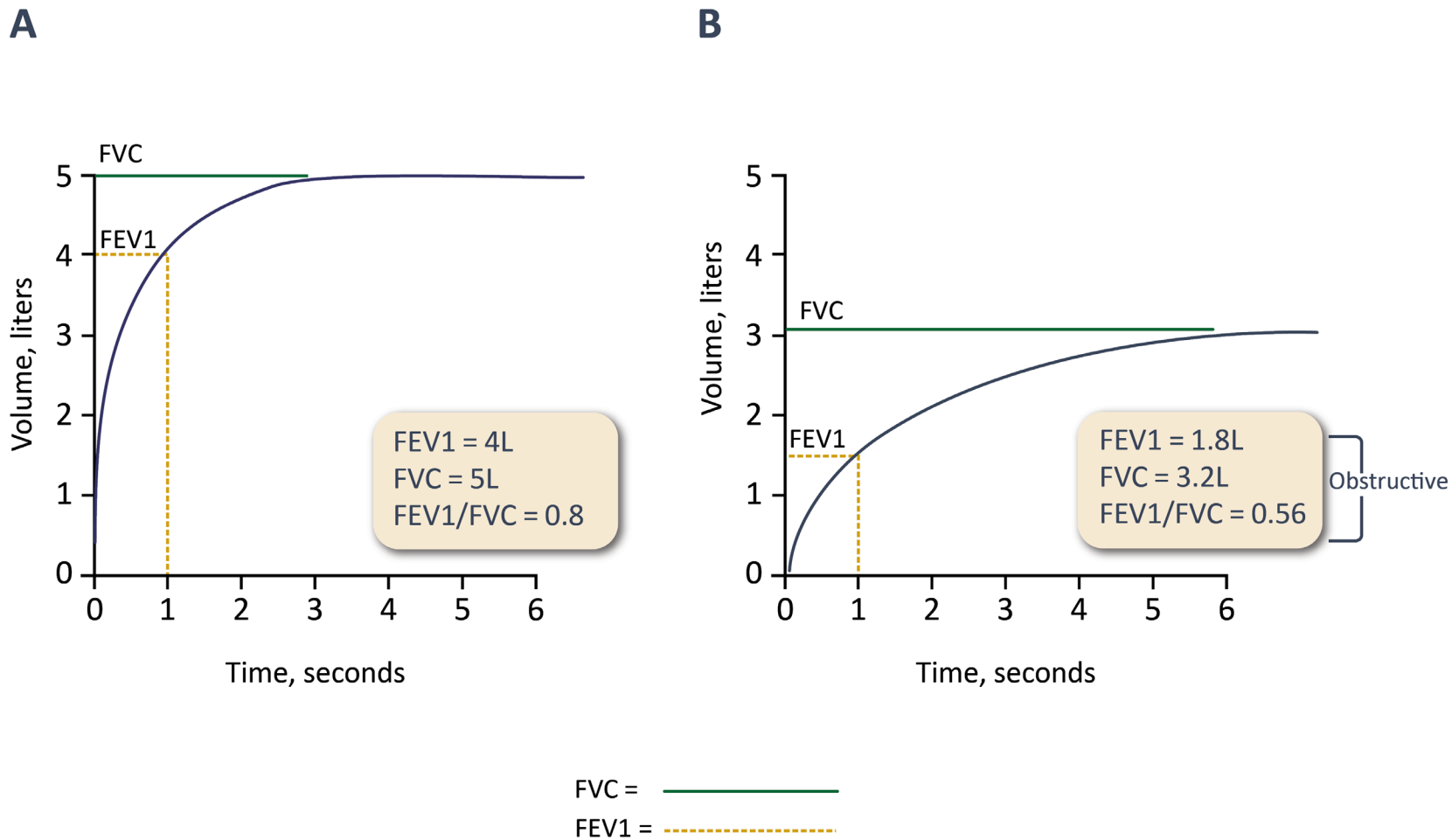


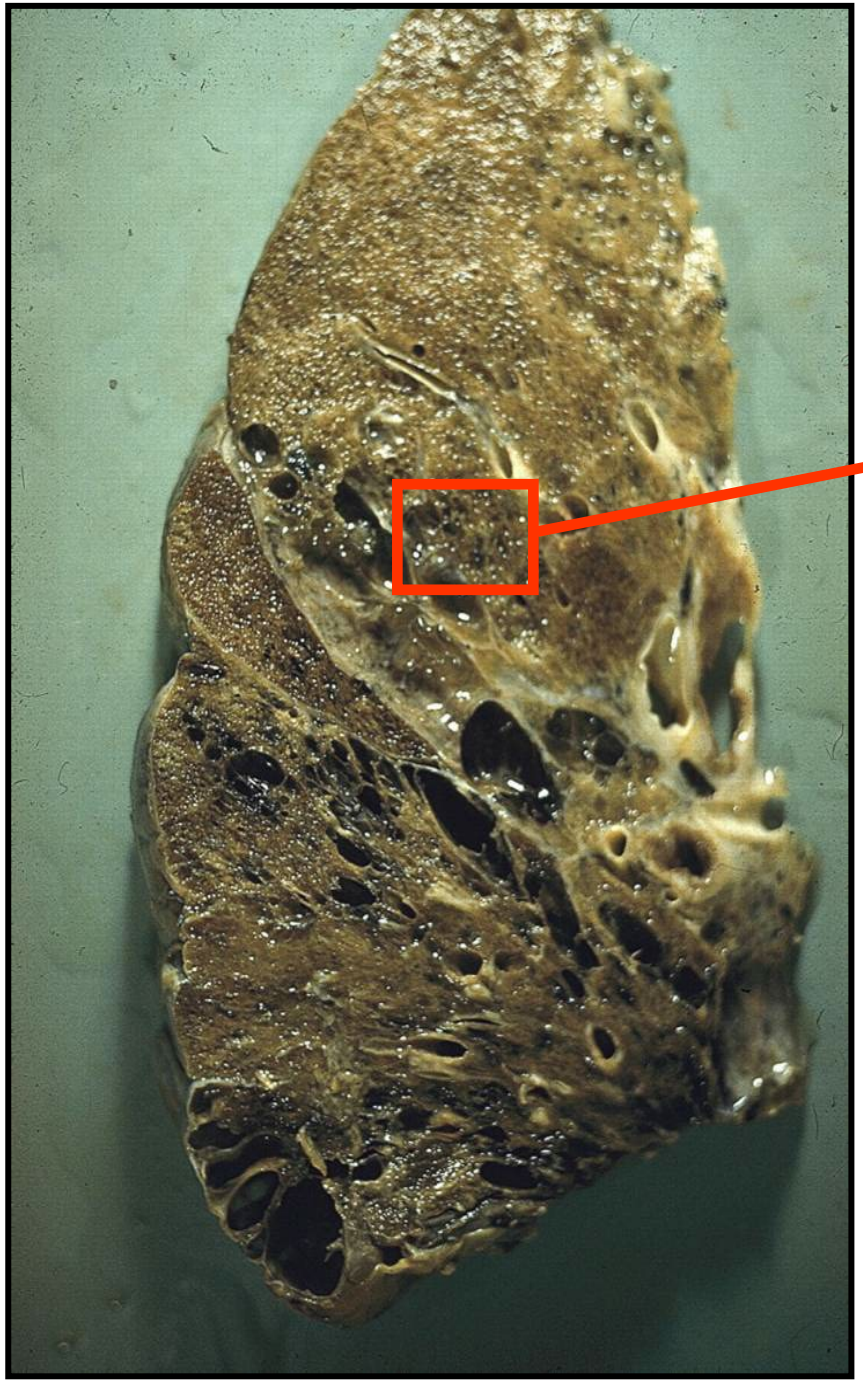

COPD
Common Symptoms
shortness of breath
chronic cough
phlegm
wheezing
chest tightness
respiratory infection
verywell

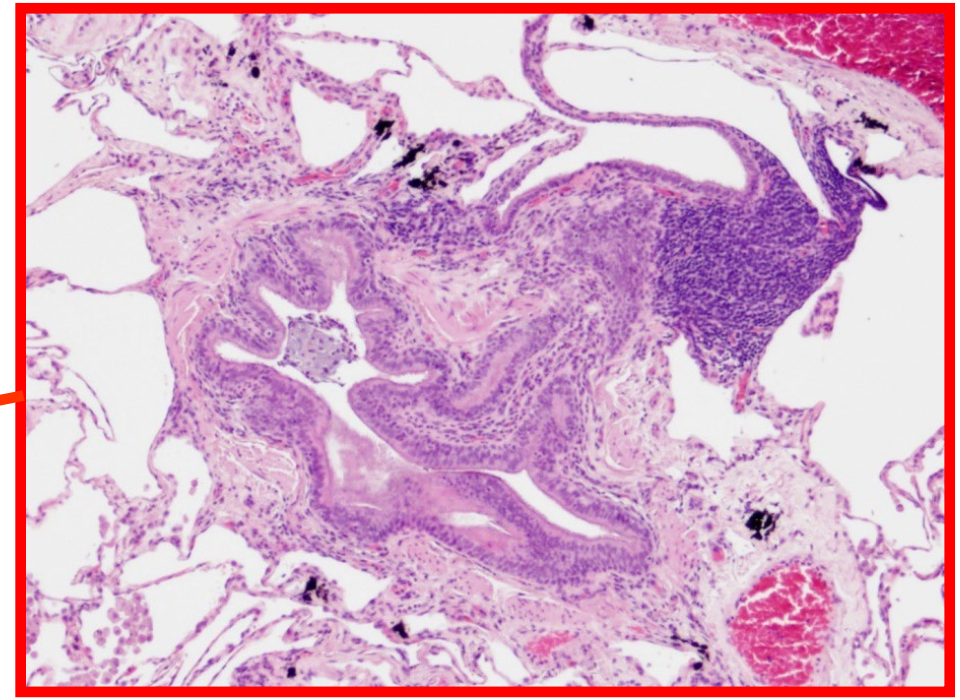


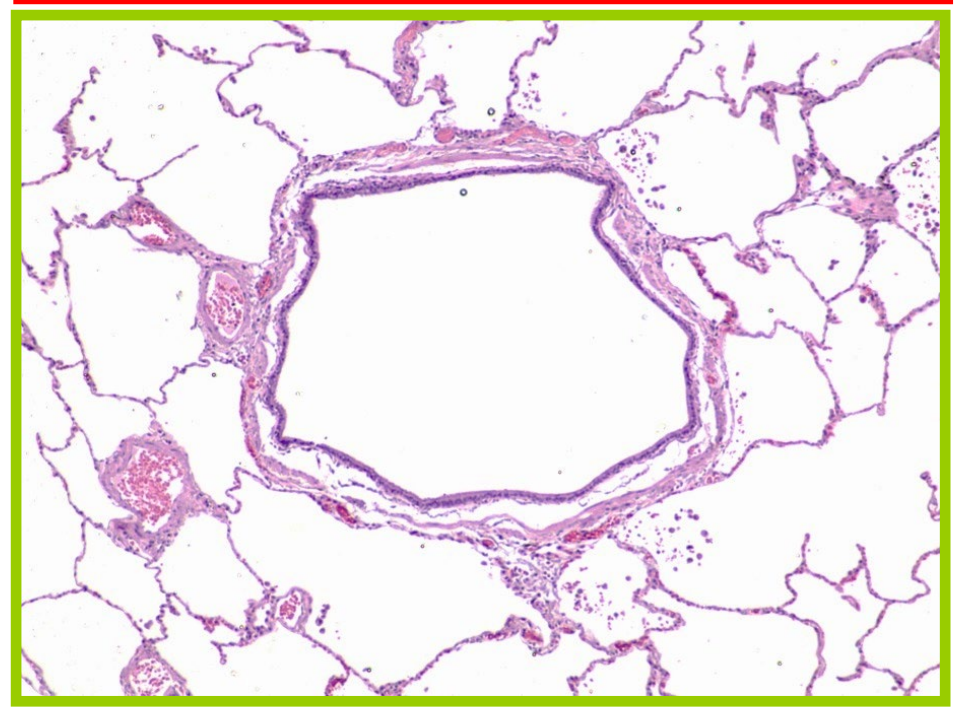
A. Spirometry - Normal Trace B. Spirometry - Airflow Obstruction

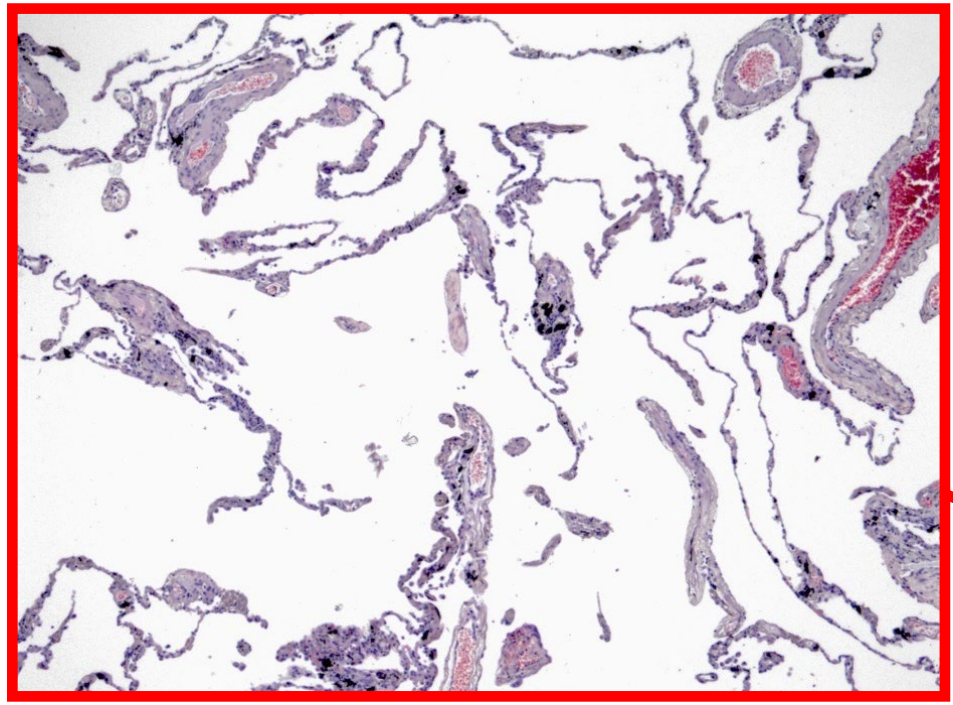
Figure 2.1

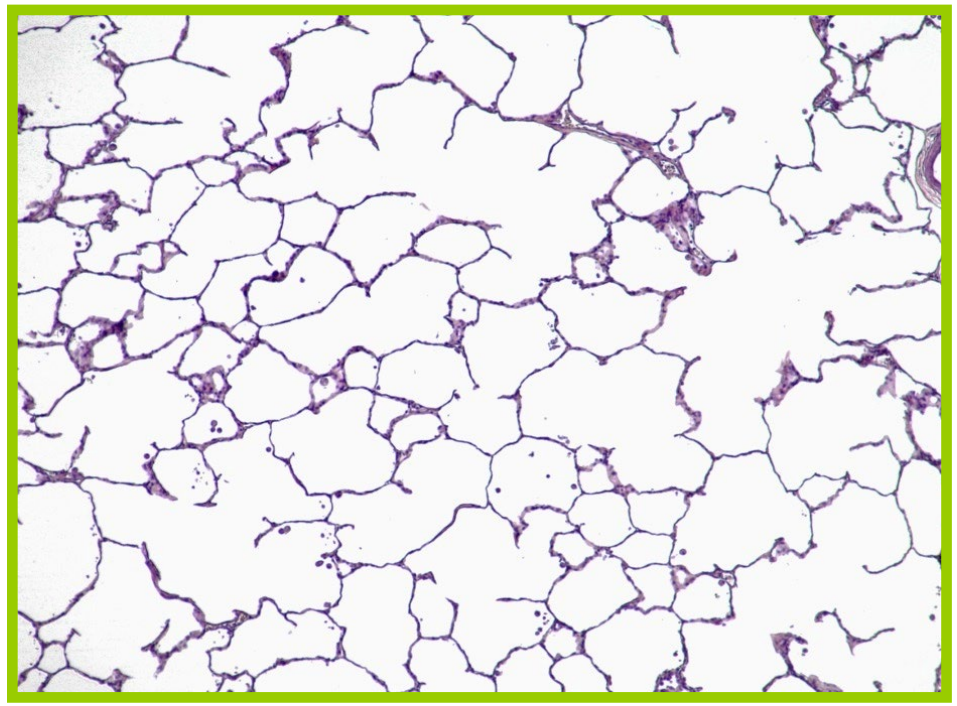


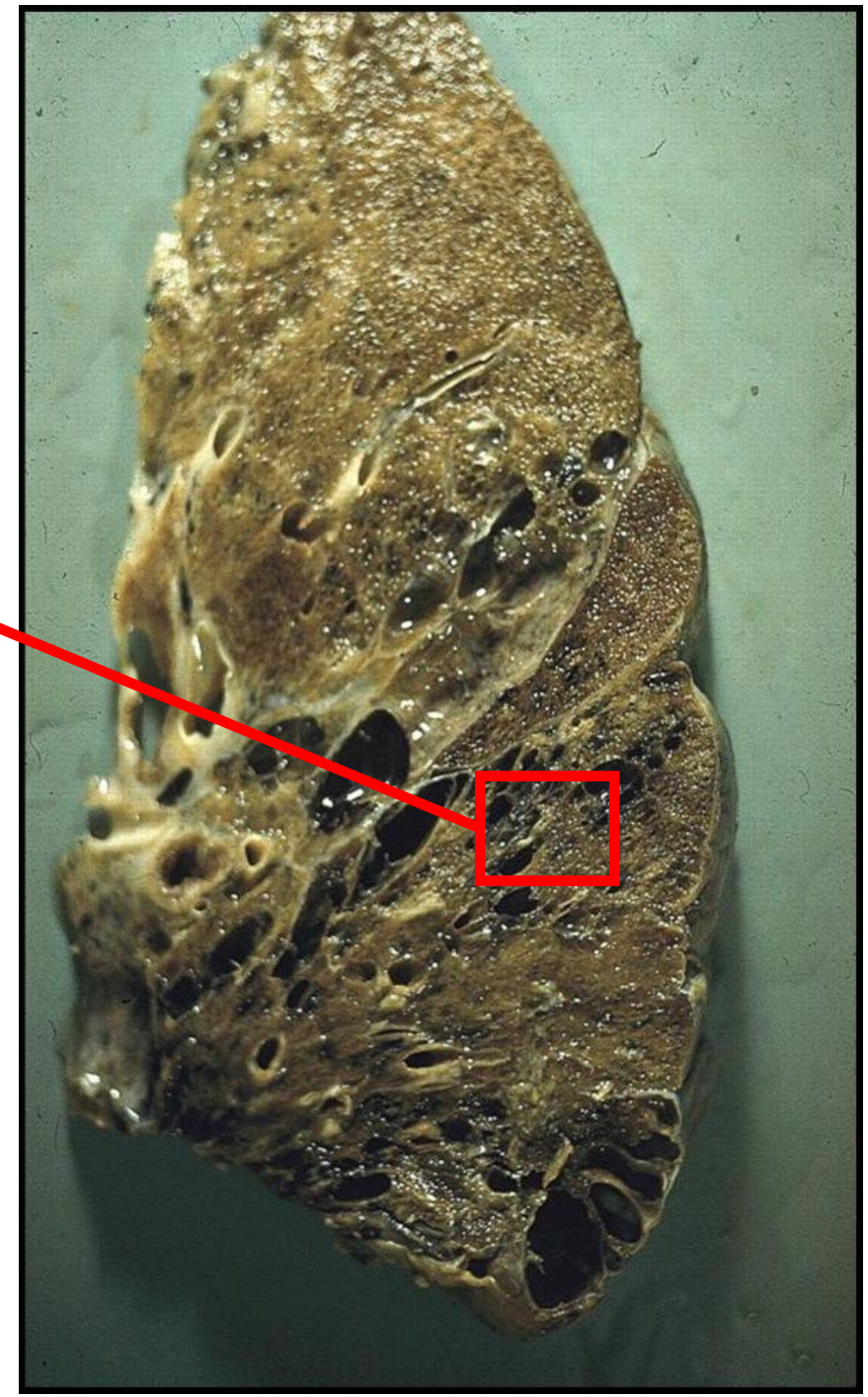


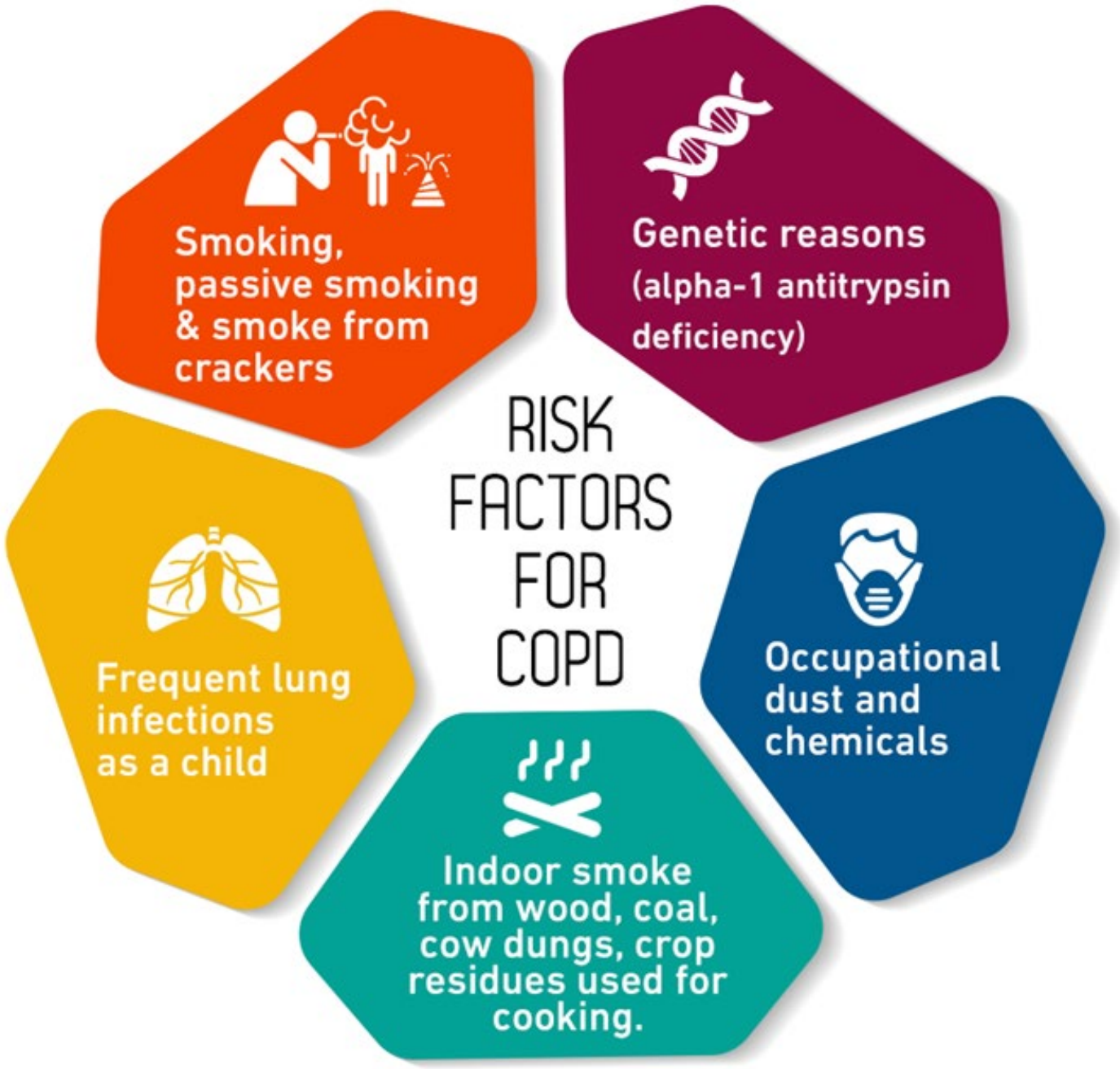












- **70%** de casos d'MPOC s'atribueixen al **tabaquisme**

- **10%** de casos d'MPOC s'atribueixen a exposició a gasos/partícules en l'àmbit laboral

- Asma, historial d'infeccions respiratòries a la infància, baix pes en néixer

- Exposició a contaminants intradomiciliaris (fum de biomassa)

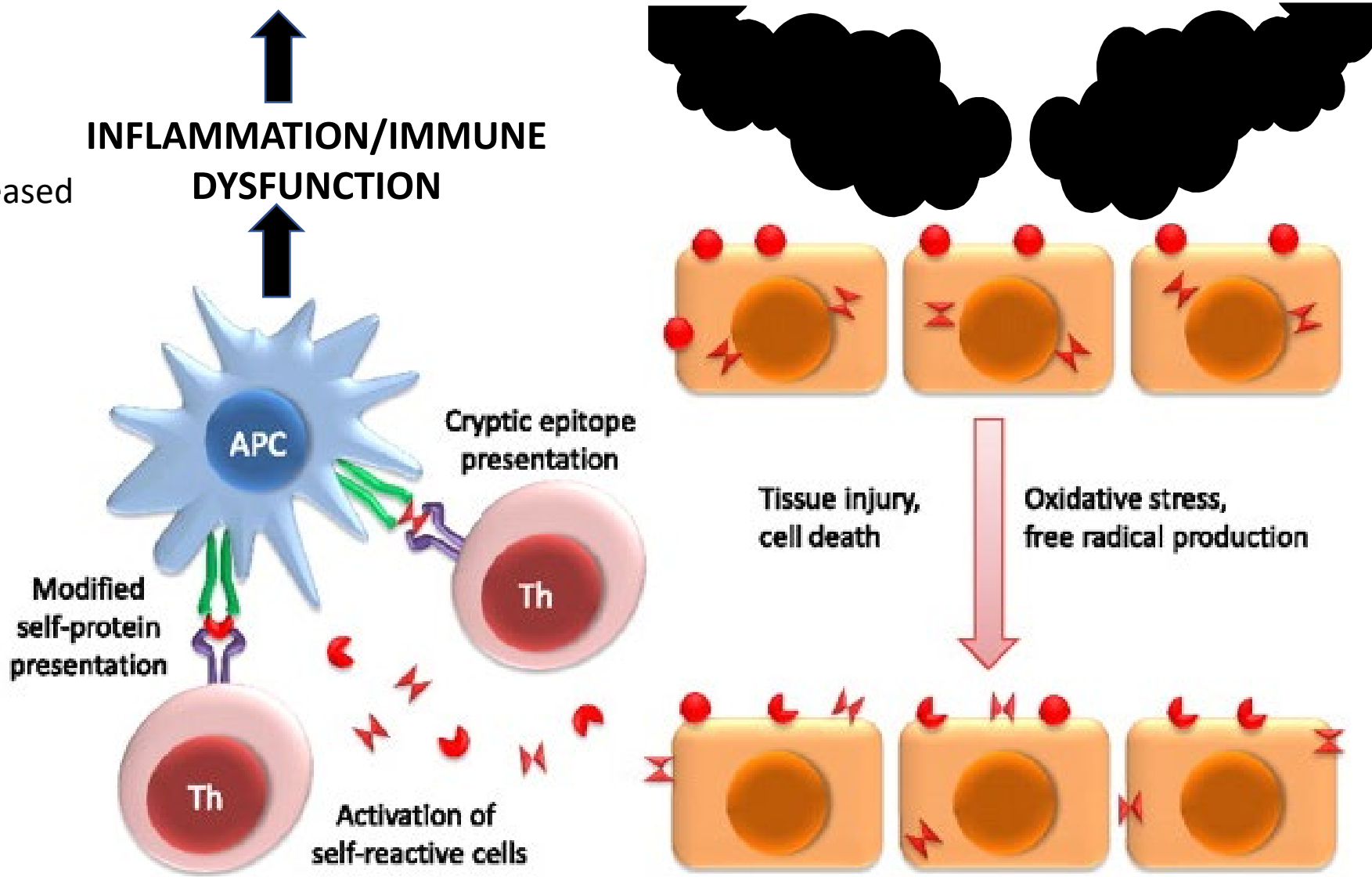
- Factors genètics

World Health Organization

- **Tercera** causa de mort a tot el món (3.23 milions de morts el 2019)
- Més de 5.4 milions de morts anuals abans del 2060.
- Prevalença global del **10.3%** (95% CI, 8.2%-12.8%)
- 38.6 bilions d'Euros/any a la Unió Europea
- 40 bilions de Dollars als Estats Units

HIPÒTESI DE L'AUTOIMMUNITAT

- Ongoing COPD after smoking cessation
- Pulmonary lymphoid fol·licles and increased numbers of T and B cells in COPD
- Circulating autoantibodies anti-elastin and anti-pulmonary epithelium and endothelium in COPD



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CALIDAD EN LOS PROCESOS DE ATENCIÓN EN SALUD
ACREDITADO
SUPERINTENDENCIA DE SALUD

MaulEPOC Study

AIMS:

i) Assess the epidemiological profile of Maulean subjects suffering from COPD.

Tabla 1. Características Sociodemográficas de 127 pacientes con EPOC de la Región del Maule

	Grupo A	Grupo B	Grupo C	Grupo D
Población muestral, n (%)	32 (25,19)	41 (32,28)	11 (8,66)	43 (33,85)
Género				
Masculino, n (%)	23 (71,87)	19 (43,34)	4 (44,44)	24 (55,81)
Femenino, n (%)	9 (28,12)	22 (53,65)	5 (45,45)	19 (44,18)
Edad, años*	68,31 ± 8,36	70,85 ± 9,56	69,72 ± 7,21	70,47 ± 8,41
Escolarización, años completados	7,13 ± 4,59	7,71 ± 4,83	6,00 ± 4,63	5,63 ± 3,83

*Edad en años: Valores expresados con la media ± desviación estándar.

Tabla 2. Características Clínicas de 127 pacientes con EPOC de la región del Maule agrupados según GOLD

	Grupo A	Grupo B	Grupo C	Grupo D
IMC, kg/m^2	28,9 ± 4,48	27,45 ± 4,63	29,27 ± 6,15	26,27 ± 4,49
VEF_1, % del predicho	75,47 ± 22,29	68,07 ± 9,93[a]	41,81 ± 8,29[a,b]	29,93 ± 9,35[a,b,c]
VEF_1/CVF, %	60,44 ± 7,15	61,75 ± 5,17	53,09 ± 10,31[a,b]	46,00 ± 10,57[a,b,c]
DL_{CO}, % del predicho	14,23 ± 18,74	12,58 ± 19,97	11,51 ± 19,24	9,39 ± 11,21 [a,b]
Oximetría , %	94,08 ± 3,51	94,00 ± 4,21	89,75 ± 5,44[a,b]	89,93 ± 3,79[a,b]
Caminata 6 min, m	445,50 ± 106,89	365,96 ± 139,04	322,13 ± 131,84[a]	271,19 ± 164,74[a,b]
mMRC	1,30 ± 0,75	2,73 ± 1,14[a]	2,20 ± 0,63[a]	3,29 ± 0,74[a,b,c]
CAT	5,97 ± 2,64	14,35 ± 2,55[a]	15,57 ± 7,64[a]	17,23 ± 5,19[a,b]

Valores expresados con la media ± desviación estándar. [a]Indica una diferencia significativa respecto a A ($p < 0,05$). [b]Indica una diferencia significativa respecto a B ($p < 0,05$). [c]Indica una diferencia significativa respecto a C ($p < 0,05$). VEF_1: volumen espiratorio forzado en el primer segundo; CVF: capacidad vital forzada; DL_{CO}; capacidad de difusión del monóxido de carbono; C6M: test de caminata en 6 min; mMRC: escala de disnea modificada del *Medical Research Council*; CAT: Test del calidad de vida "*COPD Assessment Test*".

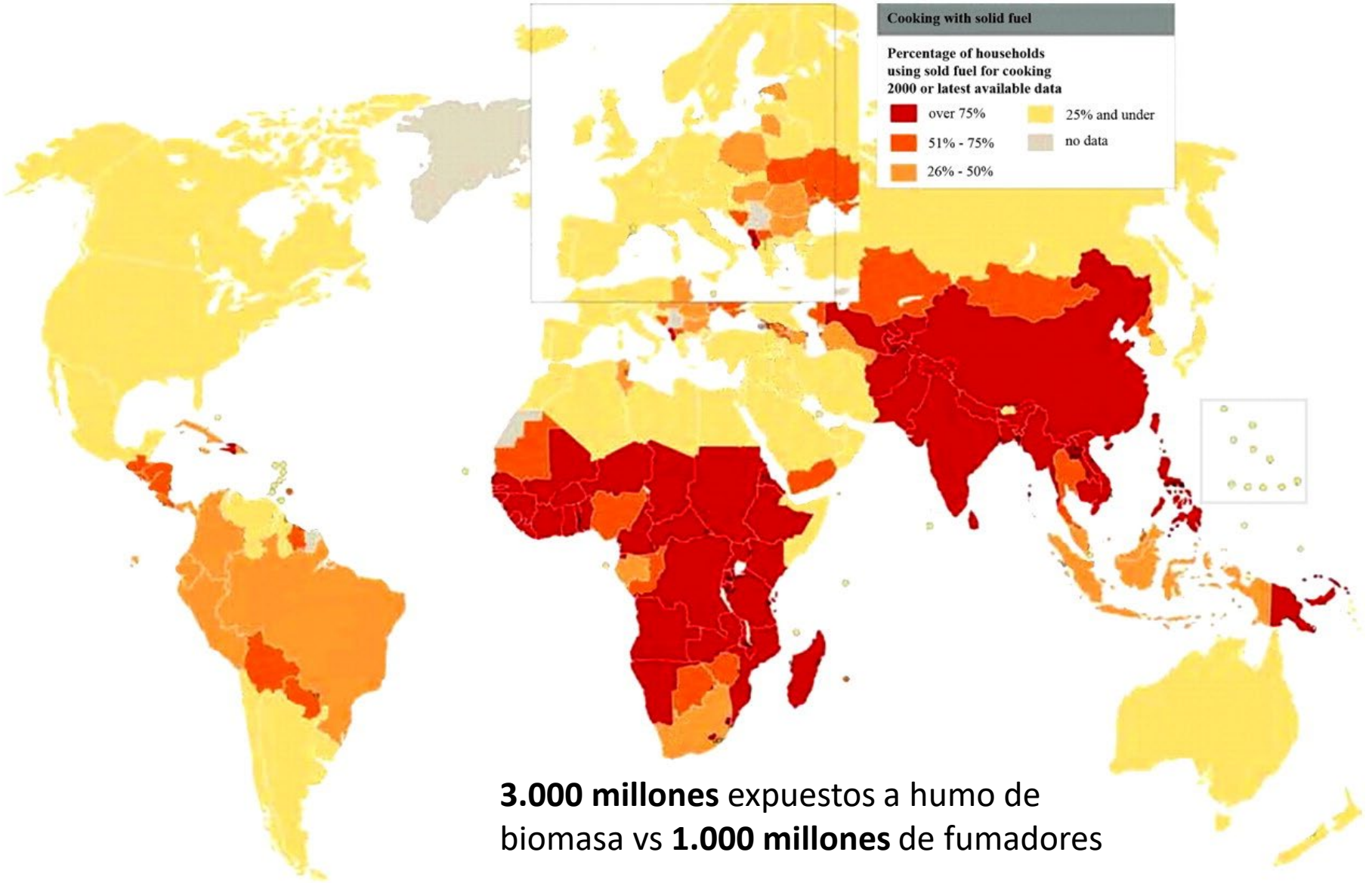
Olloquequi et al. Rev Chil Enferm Respir 2017; 33: 284-292

Tabla 3. Exposición a factores de riesgo

	Grupo A	Grupo B	Grupo C	Grupo D
Estatus tabáquico				
Nunca fumó, n (%)	3 (9,37)	6 (14,63)	3 (27,27)	4 (9,30)
Fumador actual, n (%)	4 (12,5)	5 (12,19)	1 (9,09)	5 (11,63)
Exfumador, n (%)	25 (78,12)	30 (73,17)	7 (77,77)	34 (79,06)
Índice paquete-año	40,98 ± 3,86	28,71 ± 28,49	24,27 ± 24,61	42,34 ± 34,68
Exposición a humo de biomasa, n (%)	27 (84,3)	36 (87,80)	8 (88,88)	38 (88,37)
Exposición a biomasa, horas-año	130,32 ± 124,87	217,45 ± 193,98	174,90 ± 113,95	261,37 ± 248,77
Exposición ocupacional, n (%)	22 (68,75)	18 (43,90)	1 (11,11)	25 (58,13)

Valores expresados como número de sujetos (porcentaje) o con la media ± desviación estándar.

Olloquequi et al. Rev Chil Enferm Respir 2017; 33: 284-292

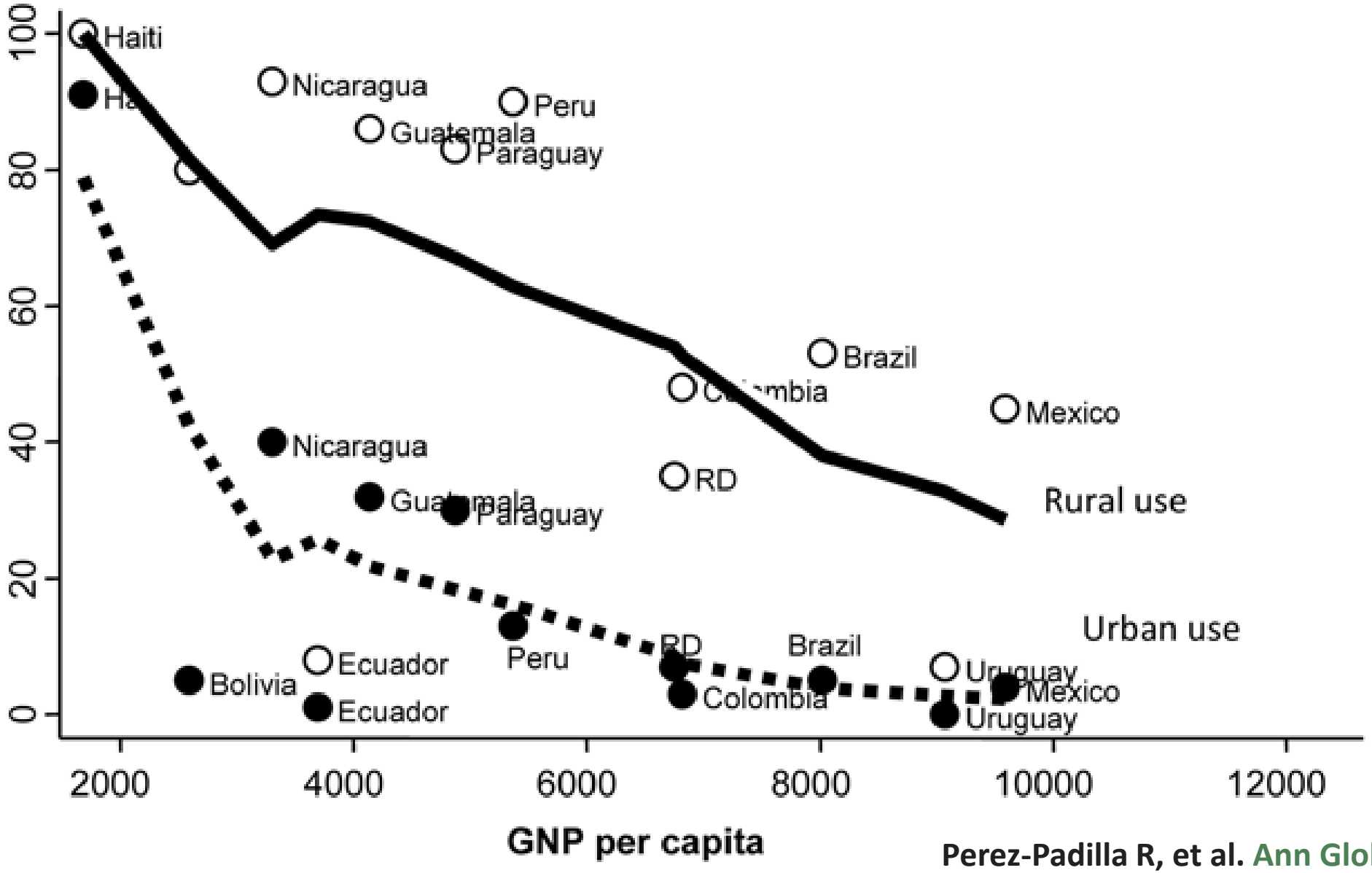


3.000 millones expuestos a humo de biomasa vs **1.000 millones** de fumadores

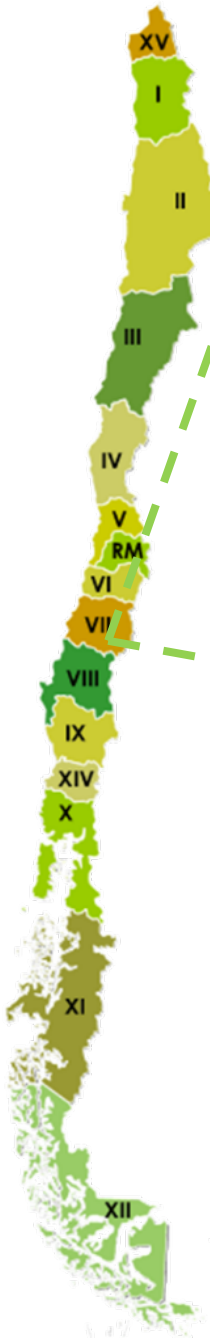
Worldwide solid fuel use for cooking. (Modified from: Children's environmental health. Part 2: Global environmental issues [Internet]. Geneva, Switzerland: World Health Organization [© 2008]. Map 9. Indoor smoke: breaking down respiratory defences. Available from: www.who.int/ceh/publications/en/map09b.jpg.)

Published in: Carlos Torres-Duque; Darío Maldonado; Rogelio Pérez-Padilla; Majid Ezzati; Giovanni Viegi; *Proc Am Thorac Soc* **2008,** 5, 577-590.

Dependence of biomass fuel use on socioeconomic status

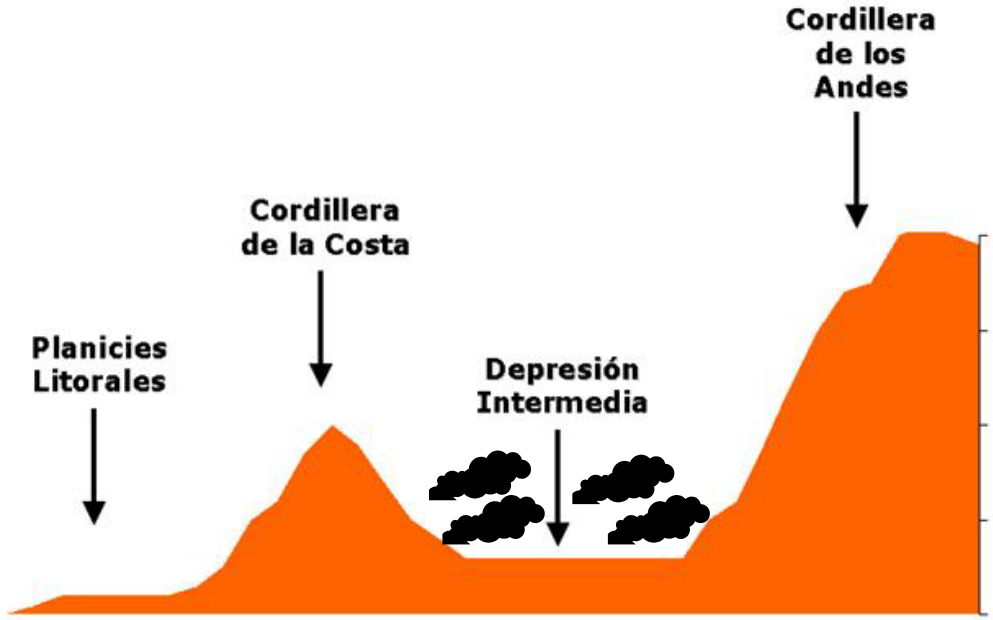


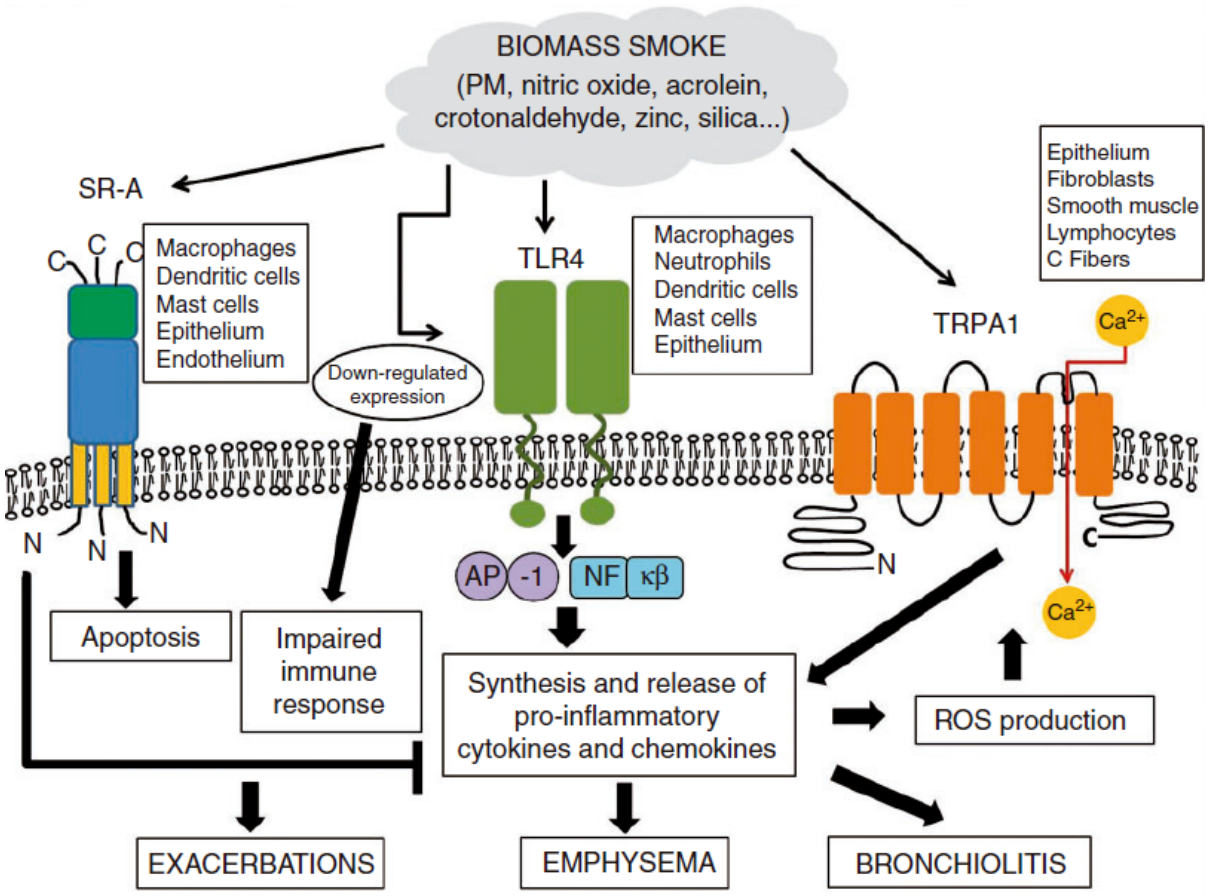
Perez-Padilla R, et al. Ann Glob Health. 2019.

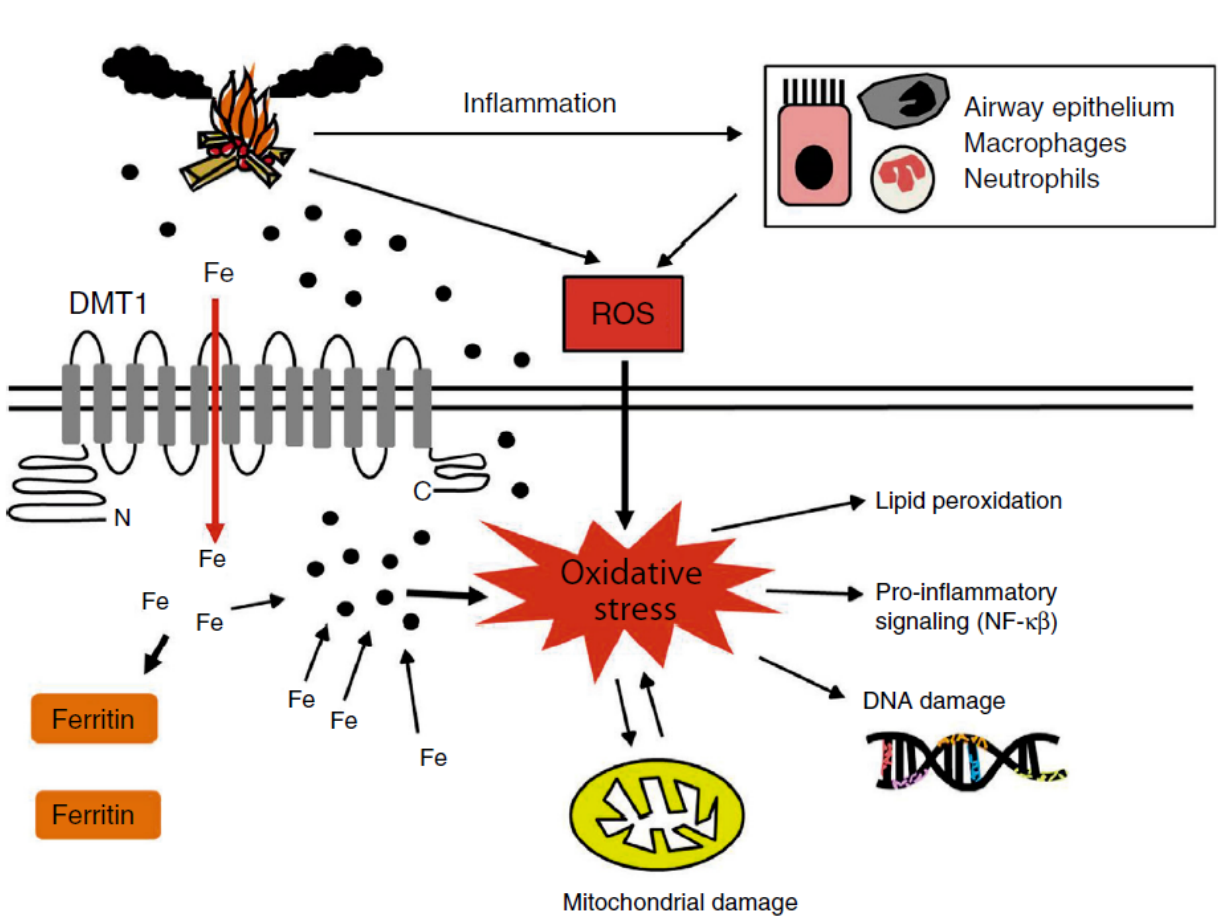

XV
I
II
III
IV
V
RM
VI
VII
VIII
IX
XIV
X
XI
XII


OCEANO PACIFICO
Curicó
Curicó
TALCA
Talca
Cauquenes
Cauquenes
Linares
Linares
ARGENTINA


Ministerio del Medio Ambiente
Gobierno de Chile
CHILE LO HACEMOS TODOS
80%
RESIDENCIAL


Cordillera de los Andes
Cordillera de la Costa
Planicies Litorales
Depresión Intermedia





Arch Bronconeumol. 2015;51(6):285–292

Innate Immun. 2016;22(5):373–381

BS may initiate pulmonary signalling through **PM–TLR2/TLR4 binding**, thus activating NF-κB and activator protein (AP)-1 pathways, and leading to the synthesis and release of **pro-inflammatory cytokines and chemokines**.

On the other hand, biomass smoke also decreases TLR expression and macrophage activity. Moreover, unlike the pro-inflammatory response initiated after PM–TLR2/TLR4 binding, the activation of **SR-A** by BS components seems to trigger an **attenuation of inflammation**. These processes thus contribute to **lung infeccions and COPD exhacerbations**

Biomass smoke increases production of **ROS, cytokines, lipid peroxidation products and oxidative DNA damage, and impairs antioxidant mechanisms**. Oxidative stress, then, appears to have a significant role in activating the harmful effects of this pollutant.

MaulEPOC Study

AIMS:

i) Assess the epidemiological profile of Maulean subjects suffering from COPD.

ii) Elucidate whether clinical, functional and molecular differences exist between patients exposed to tobacco and biomass smoke.

317 COPD patients (participation rate 97.8%) and 254 Control subjects (participation rate 85%)

Questionnaires on demographics, risk factors, symptoms and occupation

Medical evaluation (including respiratory function tests)

Blood samples

Table 1 Demographic and clinical data

	Control Subjects	TS COPD	BS COPD	TS + BS COPD
Sex, Male (%)/Female (%)	15(29)/37(71)	35(71)/14(29)	12(39)/19(61)	26(63)/20(37)
Age, years	70.34 ± 5.95	69.41 ± 8.69	72.29 ± 9.49	69.93 ± 7.19
Smoking history, pack-years	–	41.57 ± 25.62	–	55.46 ± 47.12
Biomass exposure, hour-years	–	–	340.90 ± 206.09	345.15 ± 193.16
Scolarship, years	13.21 ± 2.06	7.56 ± 4.25[a]	5.20 ± 3.59[a, b]	6.09 ± 3.93[a, b]
BMI, kg/m^2	30.09 ± 5.54	27.67 ± 5.08[a]	26.57 ± 3.06[a]	27.35 ± 5.69[a]
Exacerbations in the previous year	–	1.10 ± 1.37	0.58 ± 0.42	0.69 ± 1.29
FEV_1, % predicted	110.19 ± 17.46	56.88 ± 19.37[a, c]	68.09 ± 32.30[a]	53.79 ± 18.67[a, c]
FEV_1/FVC, % predicted	103.87 ± 8.13	67.75 ± 14.00[a,c]	74.16 ± 10.69[a]	67.56 ± 15.97[a, c]
DL_{CO}, % predicted	81.52 ± 21.21	66.60 ± 19.82[a]	73.73 ± 17.16	61.22 ± 24.98[a, c]
Oxygen Saturation, %	96.91 ± 1.36	92.65 ± 4.55[a]	93.94 ± 4.04[a]	90.52 ± 4.90[a, b, c]
6 MW, meters	492.48 ± 78.51	355.96 ± 163.02[a]	375.29 ± 143.75[a]	344.09 ± 161.12[a]
mMRC	–	2.38 ± 1.47	2.37 ± 1.16	2.67 ± 1.03
CAT	–	15.49 ± 8.21	14.84 ± 6.69	13.18 ± 6.69
BODE	–	2.88 ± 5.71	2.71 ± 6.35	3.87 ± 7.72

Data presented as mean ± standard deviation, unless otherwise indicated. Definition of abbreviations: *BMI* body-mass index, *FEV_1* forced expiratory volume in 1 s, *FVC* forced vital capacity. *DL_{CO}* carbon monoxide diffusing capacity, *6 MW* 6 min walking test, *mMRC* modified Medical Research Council scale *CAT* COPD assessment test, *BODE* Body-mass, airflow Obstruction, Dyspnea and Exercise index

[a]Different from control subjects ($p < 0.05$, by ANOVA)

[b]Different from TS COPD ($p < 0.05$, by ANOVA)

[c]Different from BS COPD ($p < 0.05$, by ANOVA)

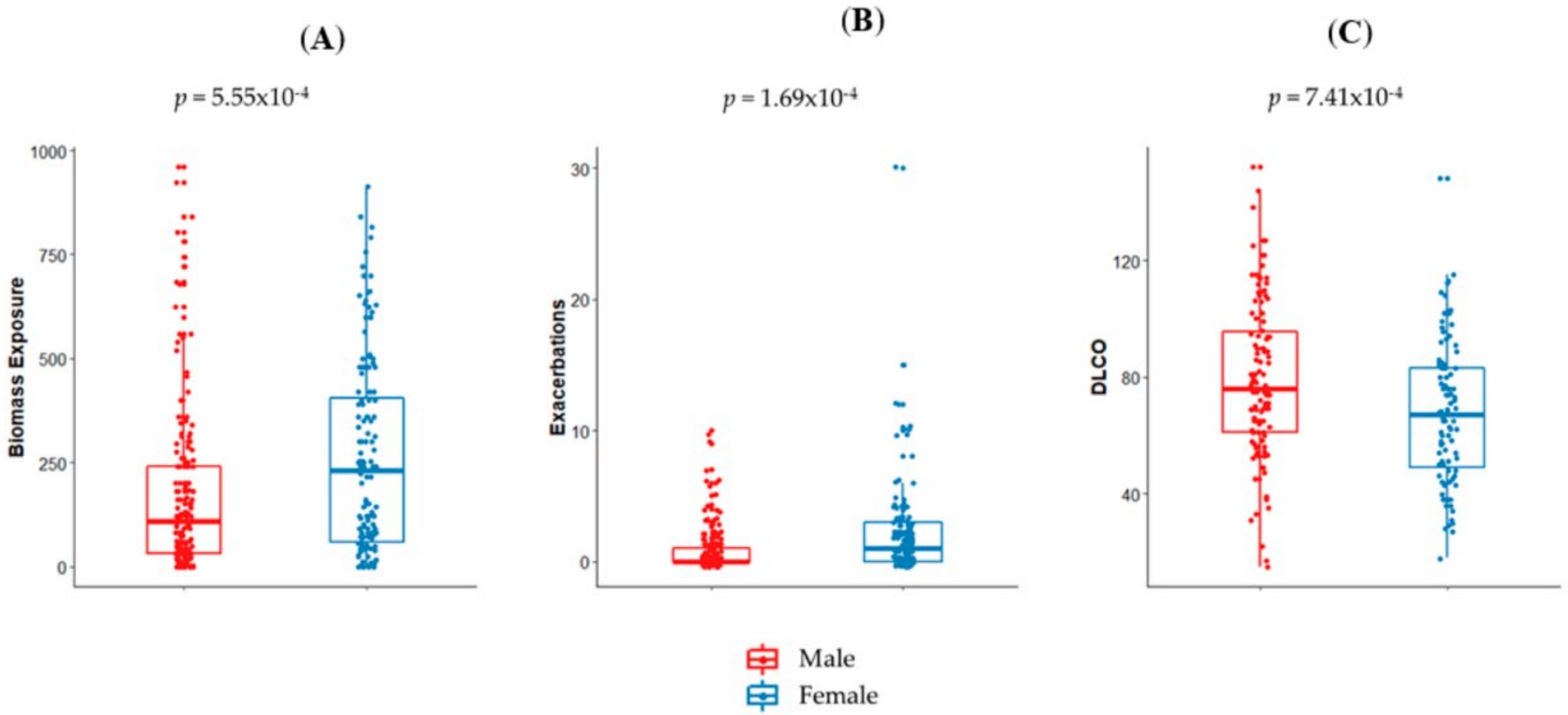


Figure 1. Sex differences in clinical and exposure parameters in chronic obstructive pulmonary disease (COPD) patients. Female COPD patients showed an increased exposure to in-home biomass smoke (**A**) and exacerbations in the previous year (**B**), whereas males exhibited a better carbon monoxide diffusing capacity of the lung (DL_{CO}) (**C**).

Olloquequi et al., J. Pers. Med. 2020, 10, 93

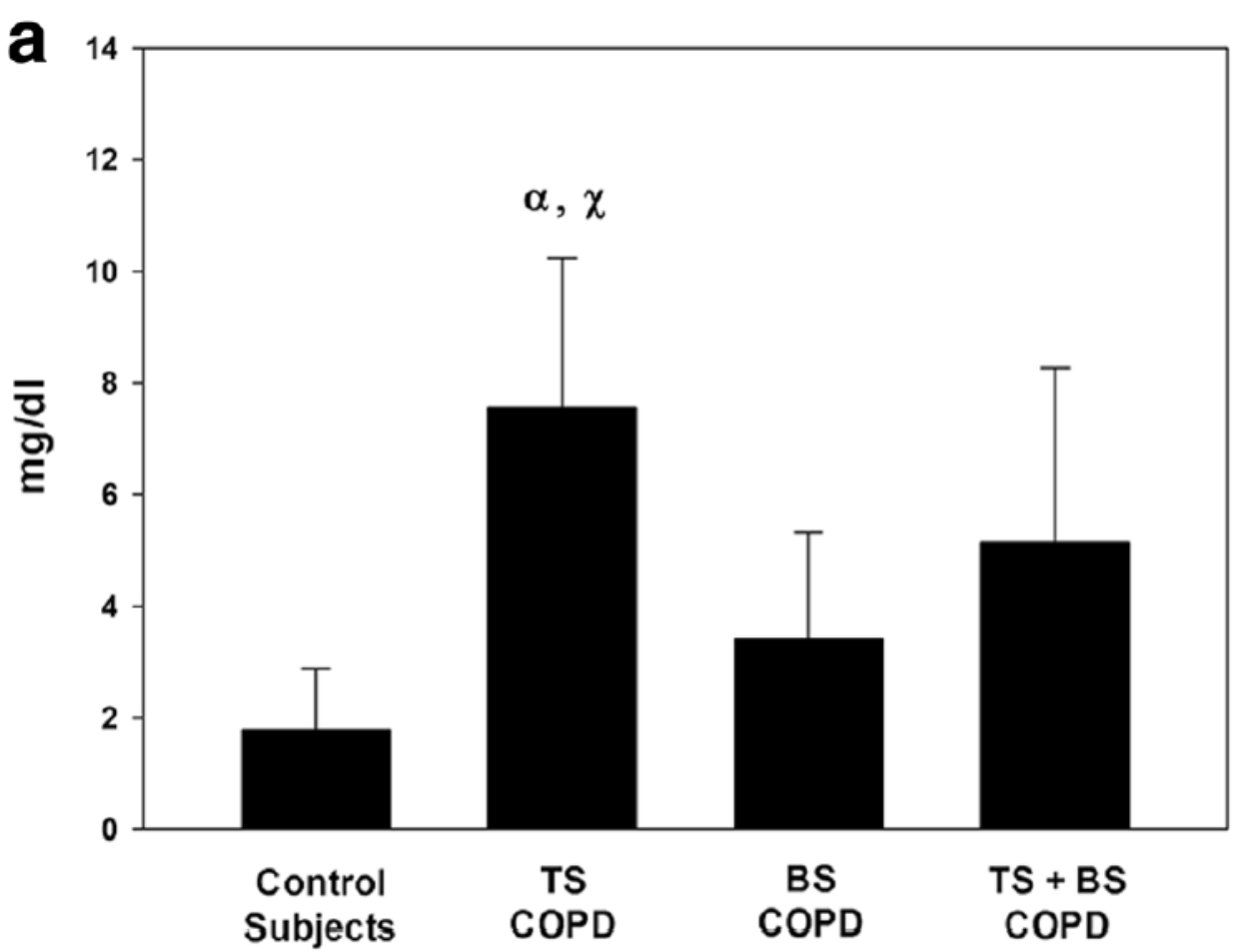
Table 2 Blood cell counts

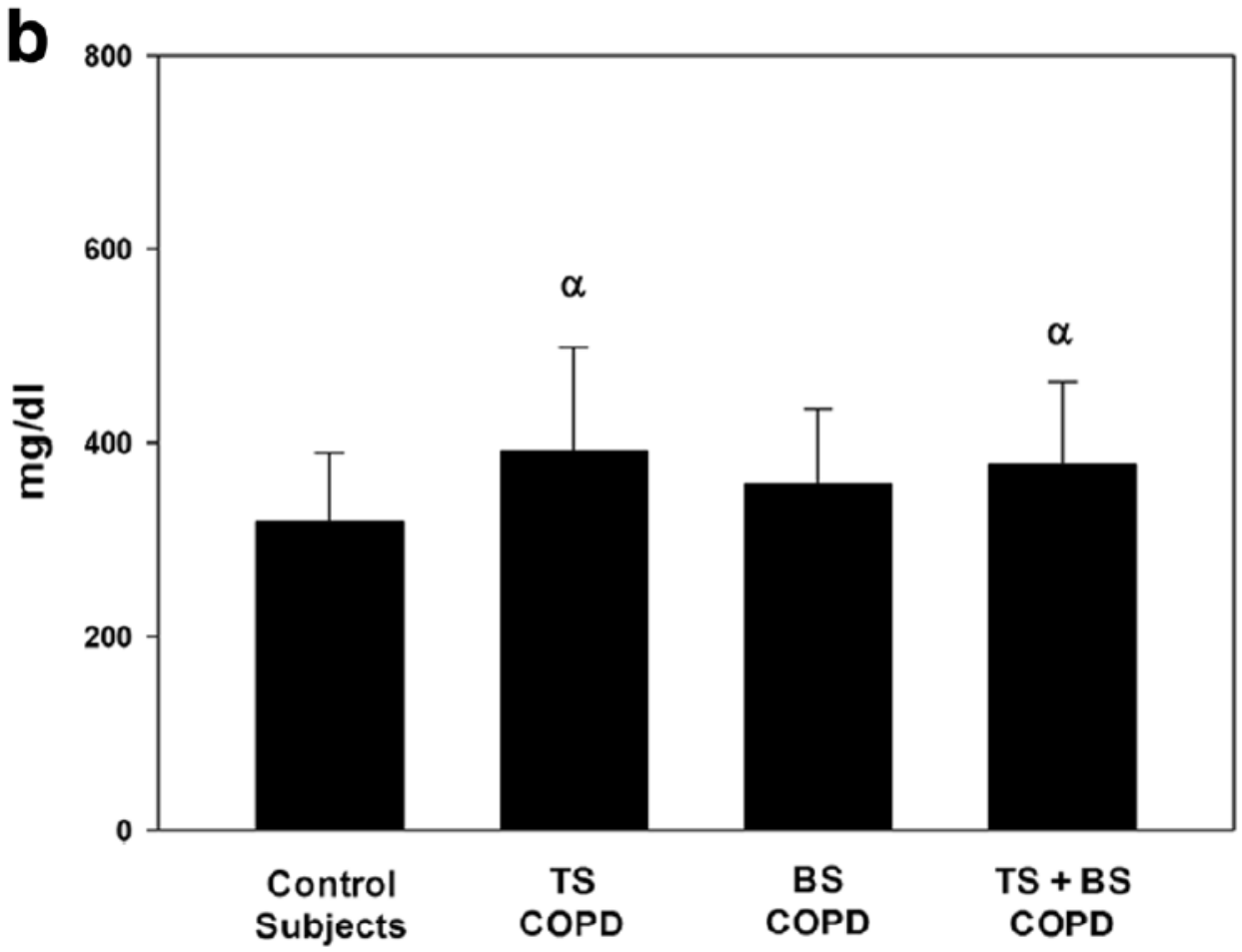
	Control Subjects $n = 52$	TS COPD $n = 49$	BS COPD $n = 31$	TS + BS COPD $n = 46$
Eritrocytes, 1×10^6 µl	4.53 (3.11–5.51)	4.64 (3.49–5.83)	4.54 (3.65–6.04)	4.79 (3.92–5.88)
Platelets, 1×10^3 µl	251.00 (142.00–477.00)	251.00 (118.00–553.00)	243.00 (132.00–389.00)	236.00 (144.00–360.00)
Leucocytes, 1×10^3 µl	7.40 (3.50–10.80)	8.80 (4.10–12.60)[a, c]	7.90 (4.10–11.70)	8.20 (5.30–11.80)[a, c]
Neutrophils, 1×10^3 µl	4.20 (2.00–7.00)	5.60 (2.50–8.10)[a]	5.20 (2.20–7.80)[a]	4.90 (2.80–7.50)[a]
Eosinophils, 1×10^2 µl	0.20 (0.00–0.30)	0.20 (0.00–0.30)	0.10 (0.00–0.60)	0.20 (0.00–0.70)
Basophils, 1×10 µl	0.50 (0.00–2.20)	0.40 (0.00–1.20)	0.50 (0.00–1.00)	0.50 (0.00–1.00)
Monocytes, 1×10^3 µl	0.50 (0.20–0.70)	0.60 (0.40–6.00)[a, c]	0.50 (0.30–1.10)	0.60 (0.40–1.60)[a, c]
Lymphocytes, 1×10^3 µl	2.38 (1.20–3.90)	2.06 (0.80–3.80)[a]	1.76 (1.00–2.80)[a]	2.11 (1.00–3.60)[a]
NLR	1.76 (0.87–3.00)	2.46 (1.36–5.14)[a]	2.94 (1.09–6.10)[a]	2.48 (0.88–4.18)[a]

Data presented as median (range). NLR: neutrophil-to-lymphocyte ratio
[a]Different from control subjects ($p < 0.05$, by Kruskall-Wallis test)
[b]Different from TS COPD ($p < 0.05$, by Kruskall-Wallis test)
[d]Different from BS COPD ($p < 0.05$, by Kruskall-Wallis test)

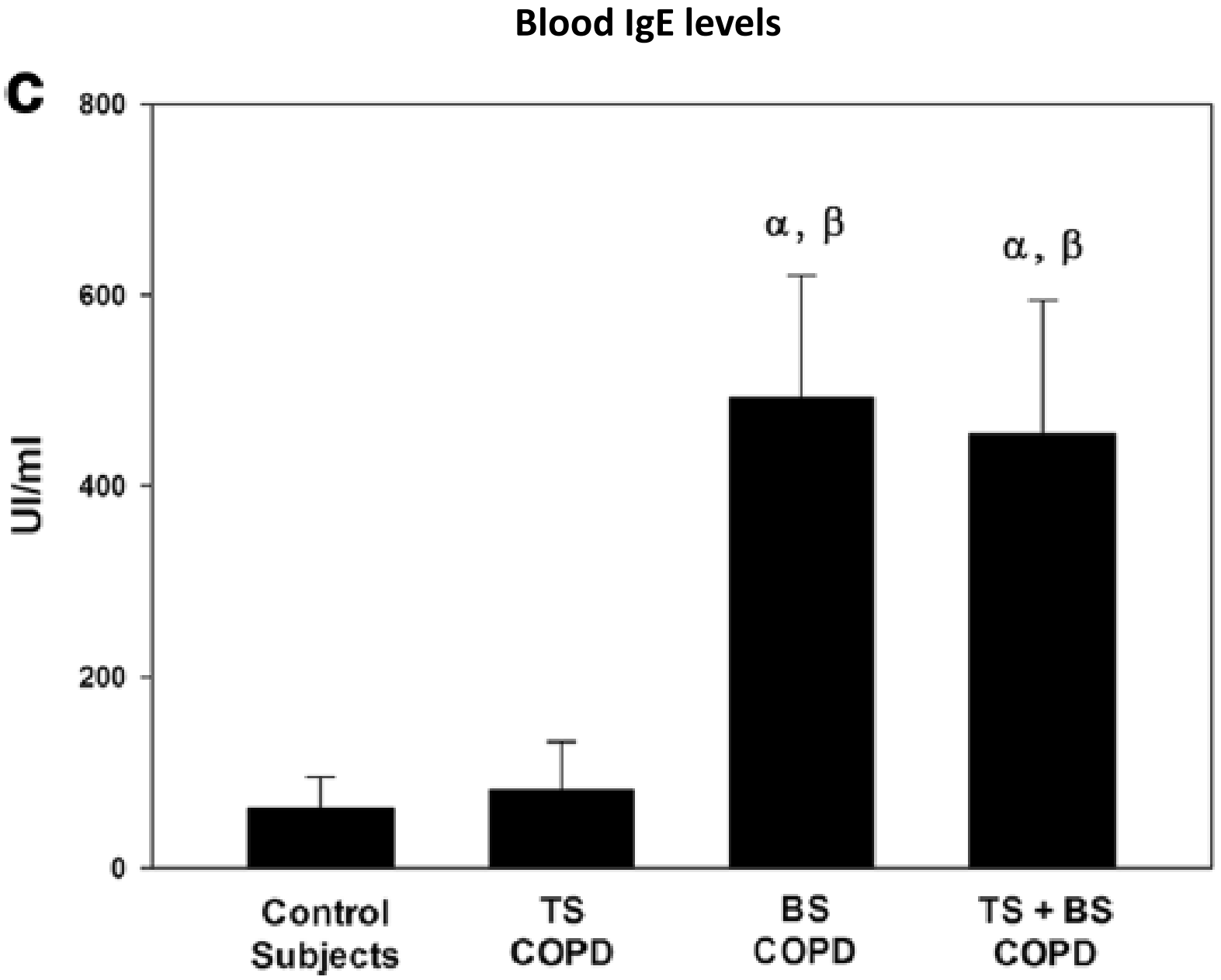
Blood CRP levels

Blood Fibrinogen levels





Olloquequi *et al. Respiratory Research* (2018) 19:13

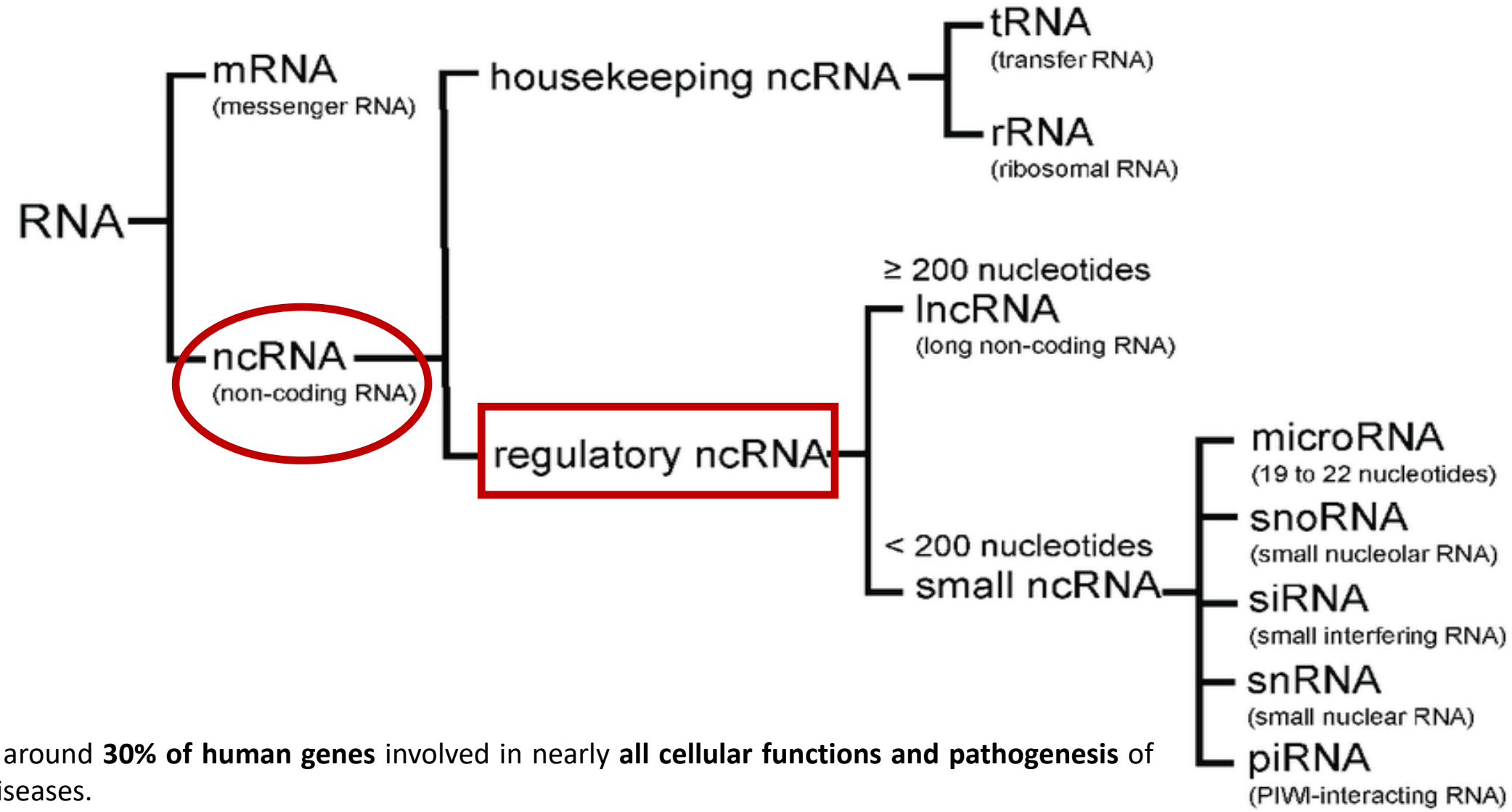


- COPD patients exposed to biomass smoke **have higher levels of IgE** in the blood (specific Th2 inflammatory response).

- **Hours of exposure to biomass smoke** correlate with **total blood leukocyte levels** (R=0.69, $p < 0.01$), **total lymphocytes** (R=0.55, $p < 0.05$) and **neutrophil-to-lymphocyte ratio** (NLR, R=0.52, $p < 0.05$).

- **BS-COPD** and **TS-COPD** are different.

Olloquequi *et al. Respiratory Research* (2018) 19:13



Regulate around **30% of human genes** involved in nearly **all cellular functions and pathogenesis** of human diseases.

Some immunity- or inflammation-related diseases were reported to be **associated with abnormal expression of miRNAs**, and COPD is also categorized in this group.

Toxicants that interfere with the biogenesis and expression of these RNAs are likely to produce adverse effects.

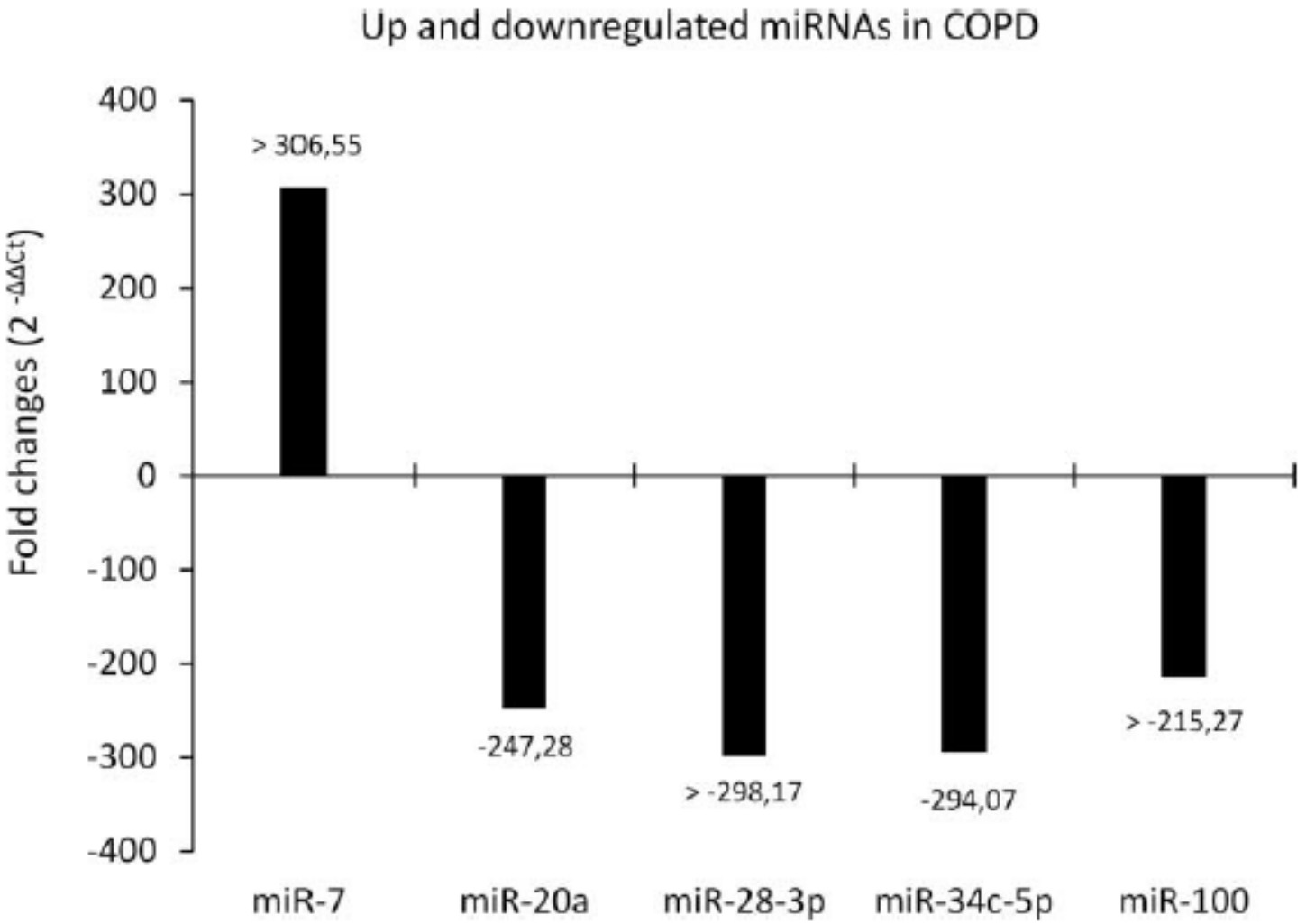
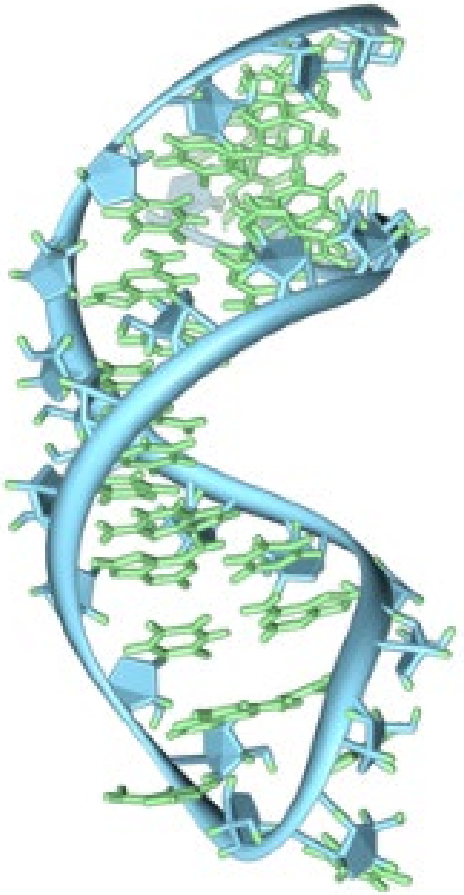


FIGURE 2 Dysregulated serum miRNAs in COPD patients versus healthy controls. According to qRT-PCR results, 4 miRNAs were down-regulated and 1 miRNA was up-regulated. C_t value at 40 adjusted was cutoff point and over this value was evaluated as unexpressed. Expression levels of selected miRNAs were normalized to U6snRNA and are presented as fold changes ($2^{-\Delta\Delta CT}$). Fold change indicated with ">" means at least.



Experimental Lung Research, 38, 286–294, 2012

MaulEPOC Study

AIMS:

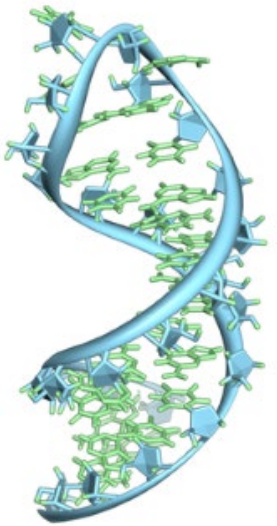
i) Assess the epidemiological profile of Maulean subjects suffering from COPD.

ii) Elucidate whether clinical, functional and molecular differences exist between patients exposed to tobacco and biomass smoke.

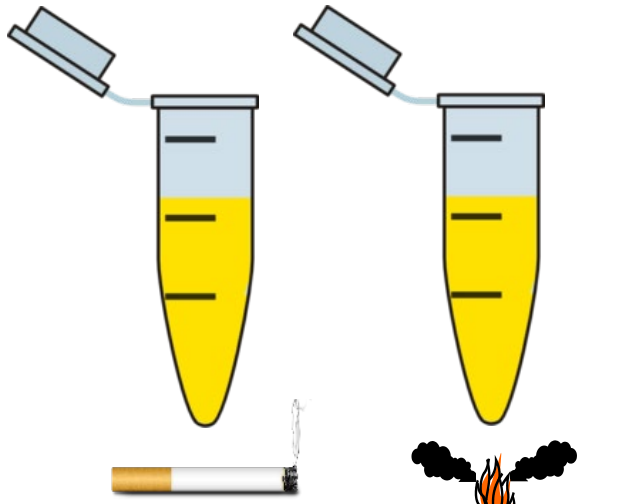
CIGARETTE SMOKING

BIOMASS SMOKE

CS COPD
BS COPD

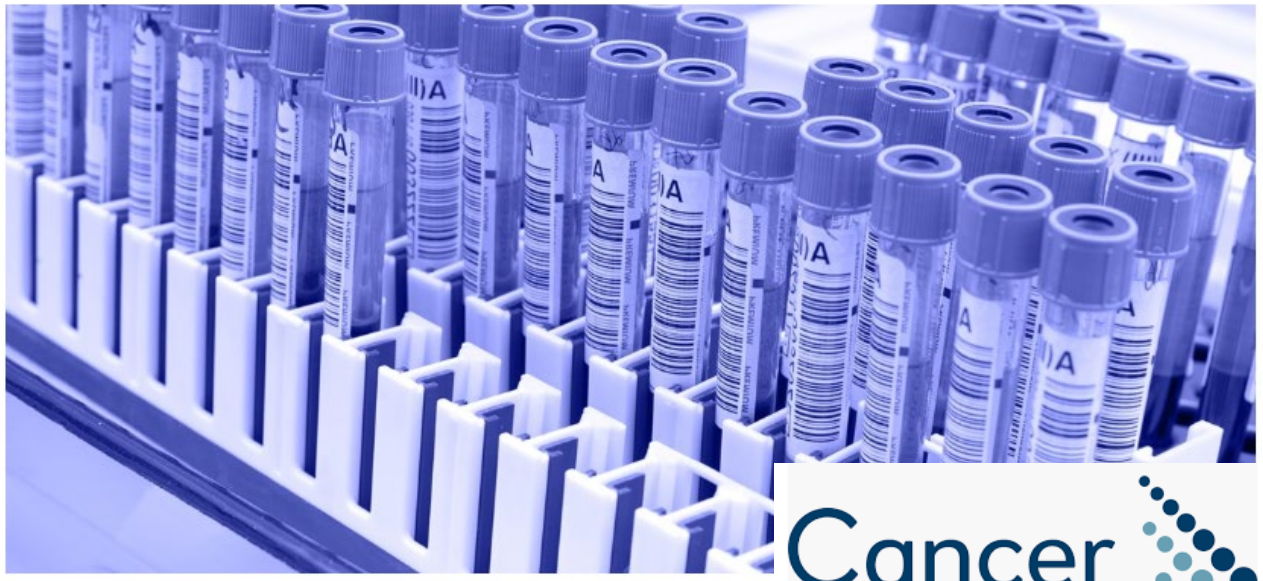


?



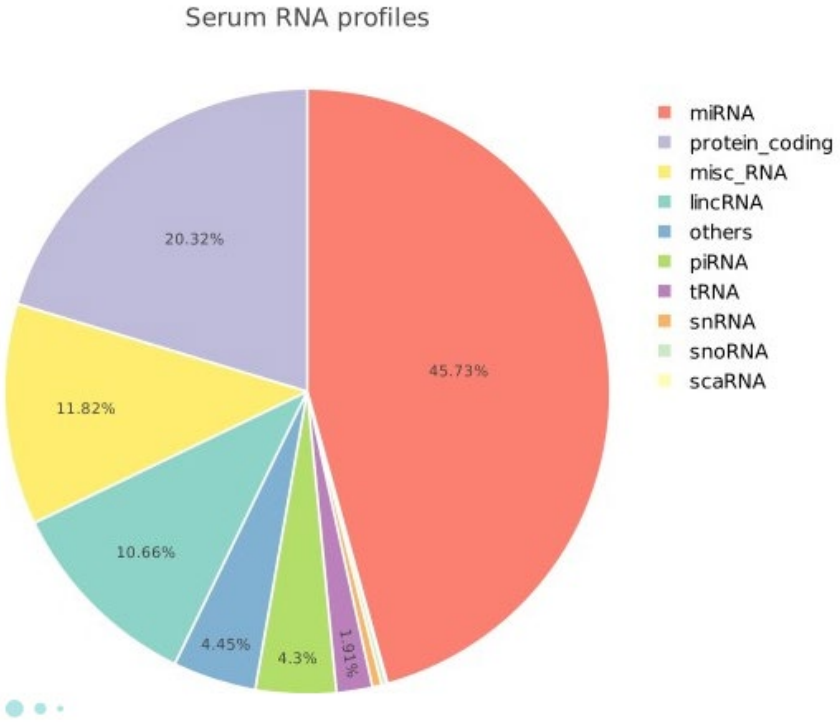
15 CS COPD

15 BS COPD



JANUS SERUM BANK

Cancer Registry of Norway

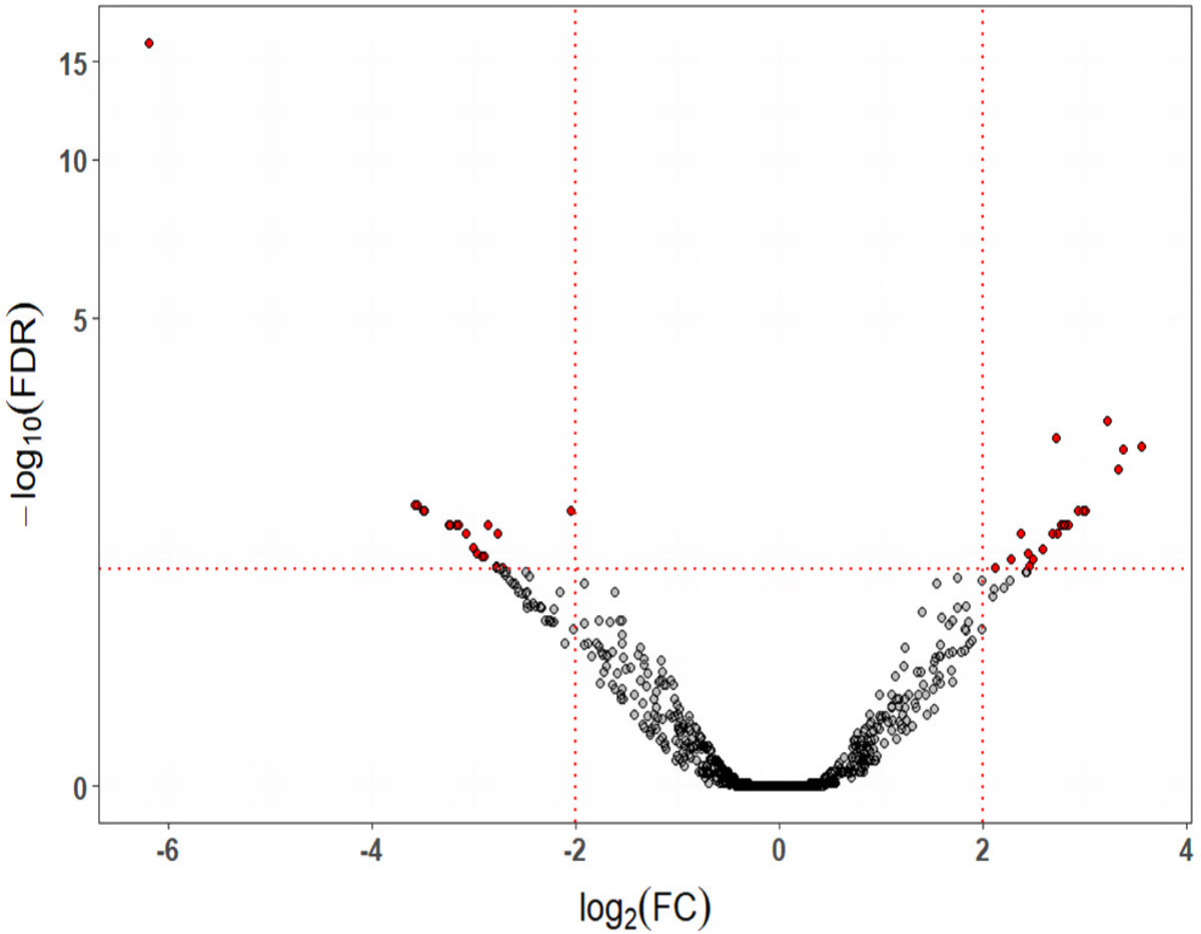


- **sncRNA expression profiles** from **more than 2000 cancer cases and 600 healthy controls** using pre-diagnostic serum samples from the Janus Serum Bank, on an Illumina HiSeq platform.

- We compared the levels of **2609 circulating miRNAs** in patients with COPD associated to cigarette smoking (CS) and in never-smoking BS-COPD patients, exploring **the hub genes and pathways associated** with these differentially expressed miRNAs.

- **45 miRNAs differentially expressed in CS- and BS-COPD**
- **FDR ≤ 0,01 → 9 upregulated and 6 downregulated in BS-COPD**

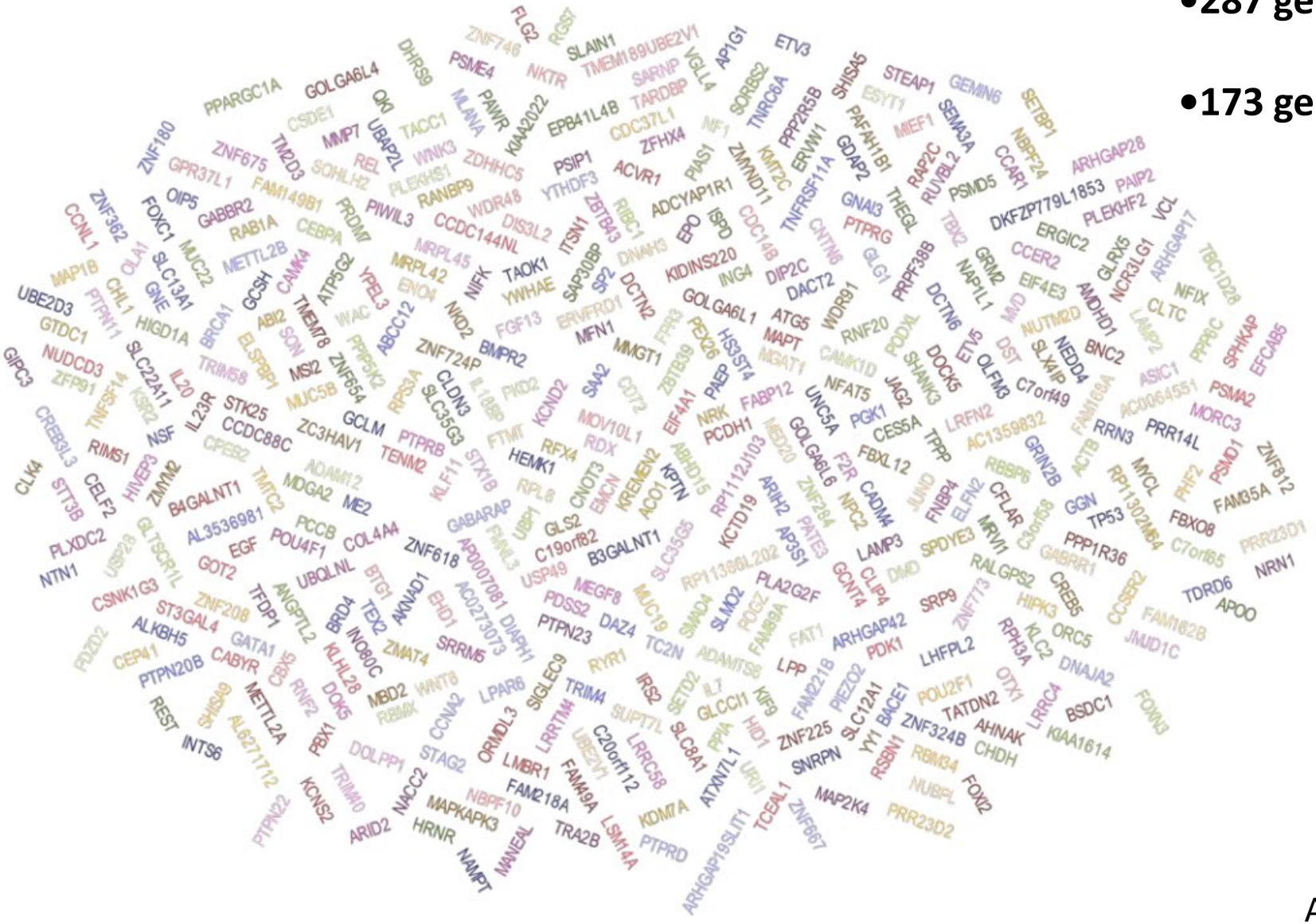
BS COPD



Up BS-COPD				Down BS-COPD			
miRNAs	Log Fold Change	pvalue	FDR	miRNAs	Log Fold Change	pvalue	FDR
hsa-miR-6748-3p	3.22	1.56e-06	0.0009	hsa-miR-125b-1-3p	-6.20	5.21e-20	6.01e-17
hsa-miR-1262	2.71	4.25e-06	0.002	hsa-miR-4742-5p	-3.59	7.87e-05	0.01
hsa-miR-6746-5p	3.56	7.33e-06	0.002	hsa-miR-4658	-3.55	7.95e-05	0.01
hsa-miR-1537-3p	3.38	1.02e-05	0.002	hsa-miR-4754	-3.49	0.0001	0.01
hsa-miR-6851-5p	3.33	2.20e-05	0.004	hsa-miR-6855-3p	-3.50	0.0001	0.01
hsa-miR-876-3p	3.01	0.0001	0.01	hsa-miR-3168	-2.06	0.0002	0.01
hsa-miR-548at-3p	2.98	0.0002	0.01	hsa-miR-4477b	-3.25	0.0003	0.02
hsa-miR-6854-3p	2.99	0.0002	0.01	hsa-miR-3685	-3.24	0.0004	0.02
hsa-miR-7153-3p	2.93	0.0002	0.01	hsa-miR-6858-5p	-2.86	0.0004	0.02
hsa-miR-215-3p	2.84	0.0003	0.02	hsa-miR-6718-5p	-3.16	0.0004	0.02
hsa-miR-4477a	2.78	0.0003	0.02	hsa-miR-6132	-3.18	0.0004	0.02
hsa-miR-6085	2.77	0.0004	0.02	hsa-miR-6748-5p	-3.08	0.0006	0.02
hsa-miR-6803-5p	2.80	0.0004	0.02	hsa-let-7g-3p	-2.76	0.0006	0.02
hsa-miR-3650	2.73	0.0005	0.02	hsa-miR-4299	-3.08	0.0006	0.02
hsa-miR-3199	2.37	0.0005	0.02	hsa-miR-6849-5p	-3.01	0.0009	0.03
hsa-miR-6791-3p	2.68	0.0006	0.02	hsa-miR-4463	-2.93	0.001	0.04
hsa-miR-1247-5p	2.59	0.0009	0.03	hsa-miR-6735-3p	-2.90	0.001	0.04
hsa-miR-4785	2.44	0.001	0.04	hsa-miR-6751-5p	-2.97	0.001	0.04
hsa-miR-1237-3p	2.49	0.001	0.04	hsa-miR-7853-5p	-2.78	0.002	0.05
hsa-miR-6839-5p	2.27	0.001	0.04	hsa-miR-570-3p	-2.78	0.002	0.05
hsa-miR-6779-5p	2.27	0.001	0.04	hsa-miR-1193	-2.73	0.002	0.05
hsa-miR-4723-5p	2.46	0.002	0.05	hsa-miR-3139	-2.78	0.002	0.05
hsa-miR-4777-3p	2.11	0.002	0.05				

Arch Bronconeumol, 58, 177–179, 2022

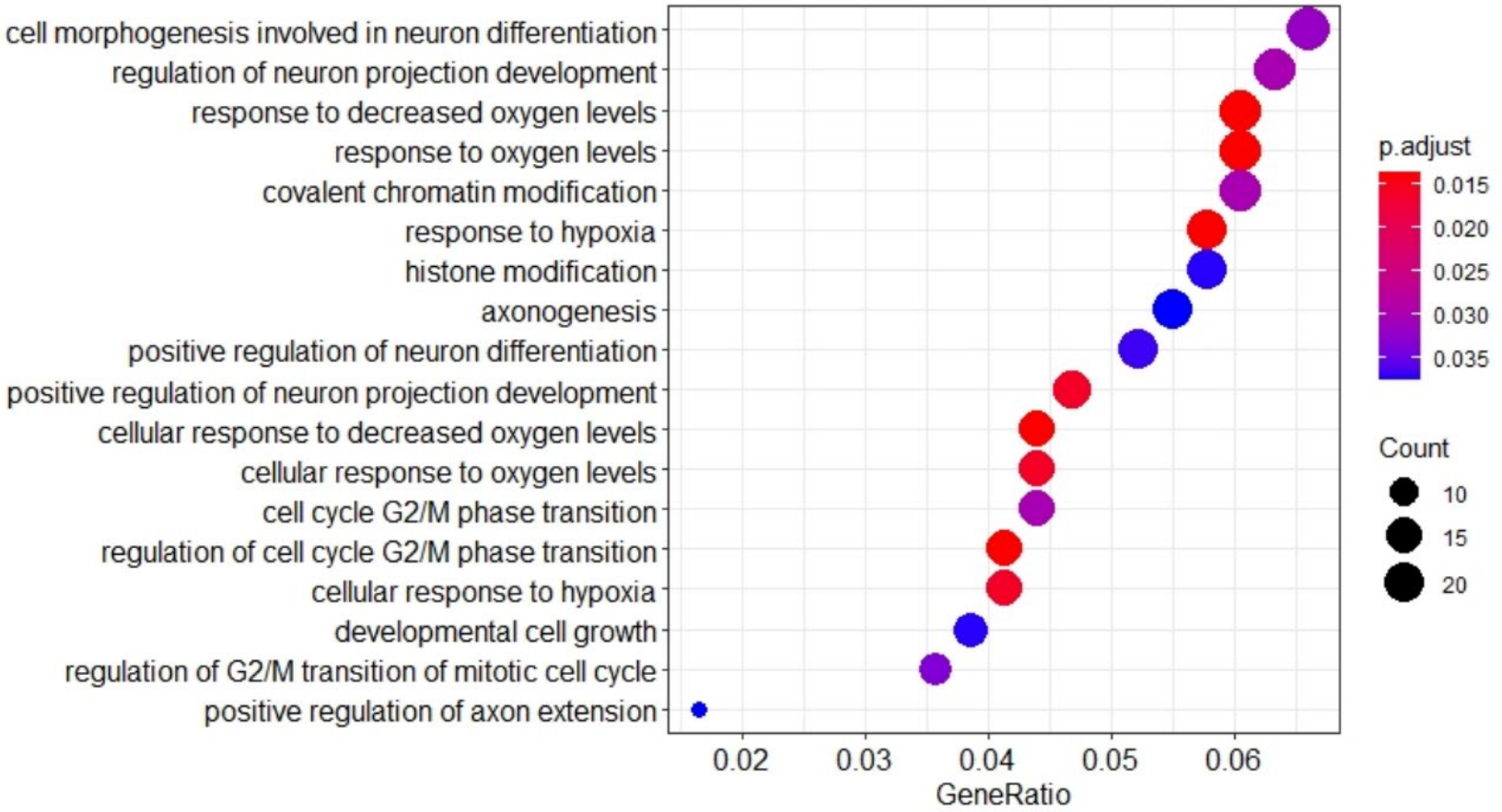
Figure S1. Genes related to differentially expressed miRNAs in BS-COPD with an FDR ≤ 0.01, compared to CS-COPD



- **287 genes related to upregulated miRNAs**
- **173 genes related to downregulated miRNAs**

Arch Bronconeumol, 58, 177–179, 2022

Figure S2. Dotplot depicting the activity of biological processes terms.



Arch Bronconeumol, 58, 177–179, 2022

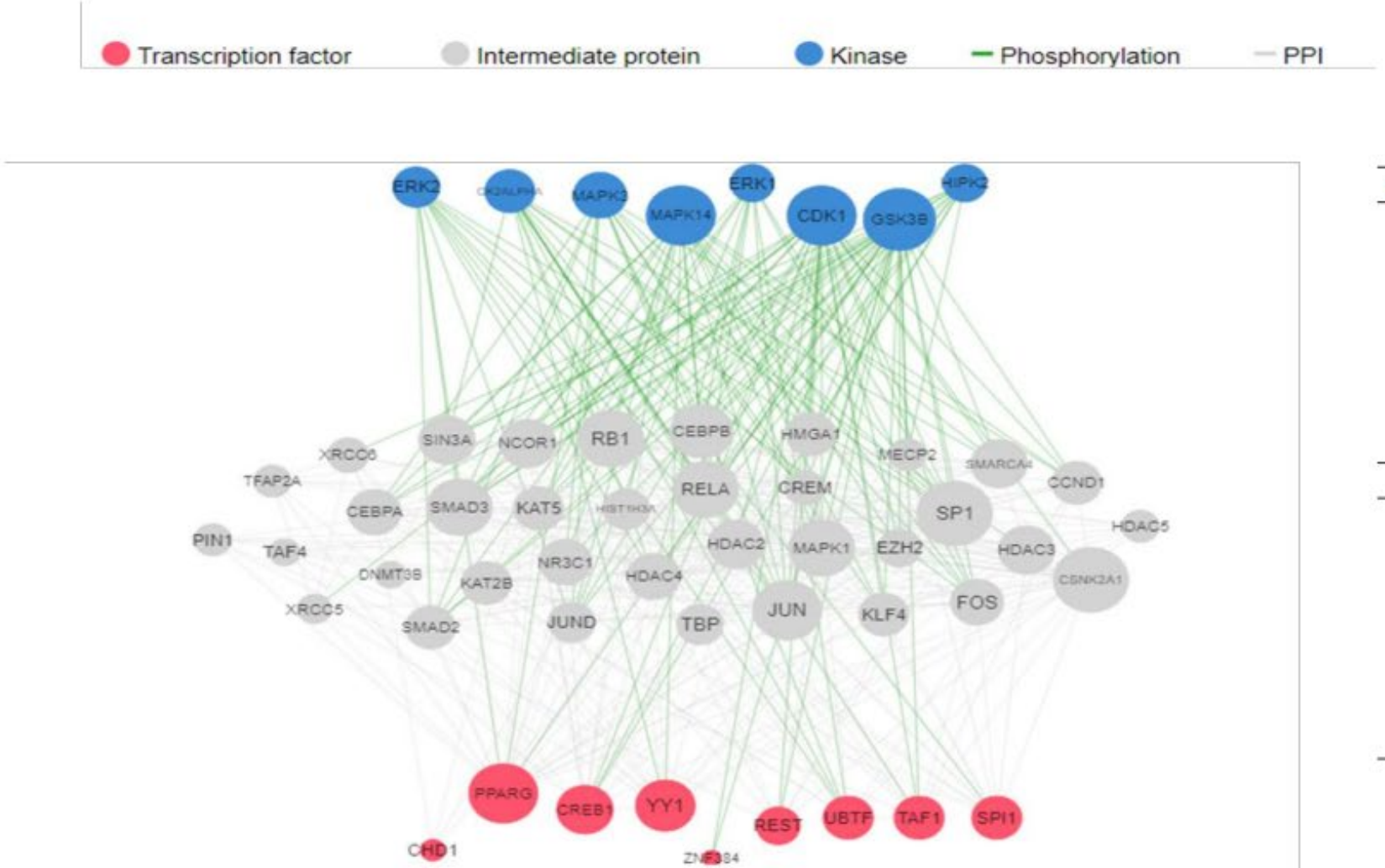
1. Resposta cel·lular davant la hipòxia

2. Modificació de la cromatina i histones

3. Desenvolupament i diferenciació neuronals

neuron-specific enolase → cognitive dysfunction in COPD

Figure S4. Upstream regulatory network of the differentially expressed miRNAs.



Transcription Factor¤	Hypergeometric p-value¤	Enriched Targets¤
CREB1¤	2.76×10^{-6}¤	61 targets¤
CHD1¤	6.68×10^{-5}¤	32 targets¤
UBTF¤	1.71×10^{-4}¤	60 targets¤
SPI1¤	2.12×10^{-4}¤	43 targets¤
TAF1¤	8.41×10^{-4}¤	102 targets¤
REST¤	9.75×10^{-4}¤	47 targets¤
YY1¤	1.22×10^{-3}¤	86 targets¤
PPARG¤	1.68×10^{-3}¤	24 targets¤
Protein Kinase¤	**Hypergeometric p-value¤**	**Enriched Substrates¤**
CK2ALPHA¤	2.26×10^{-11}¤	14 substrates¤
ERK2¤	3.81×10^{-11}¤	12 substrates¤
MAPK14¤	6.91×10^{-11}¤	21 substrates¤
CDK1¤	1.87×10^{-10}¤	26 substrates¤
HIPK2¤	2.11×10^{-10}¤	11 substrates¤
GSK3B¤	5.24×10^{-10}¤	28 substrates¤
MAPK3¤	5.88×10^{-10}¤	14 substrates¤
ERK1¤	1.12×10^{-9}¤	11 substrates¤

X2K was used to analyse the upstream regulatory network of genes of interest. Enriched transcription factors and kinases were ranked based on hypergeometric p value, and the inferred network was constructed and visualized.

Arch Bronconeumol, 58, 177–179, 2022

TRANSCRIPTION FACTORS

PPARG

Peroxisome proliferator-activated receptor gamma

→ Alveolar macrophages, epithelium, endothelium, smooth muscle →

ANTI-INFLAMMATORY EFFECT

CREB1

CAMP responsive element binding protein 1

→ ↑↑↑ Activation in alveolar hypoxia →

RESPONSE TO DECREASED OXYGEN LEVELS

Yin Yang 1

→ Altered expression and localization in COPD →

REGULATION OF LUNG DEVELOPMENT

KINASES

GSK3β

Glycogen synthase kinase-3β

→ Oxidation-mediated signalling → **CHRONIC MUCUS HYPERSECRETION**

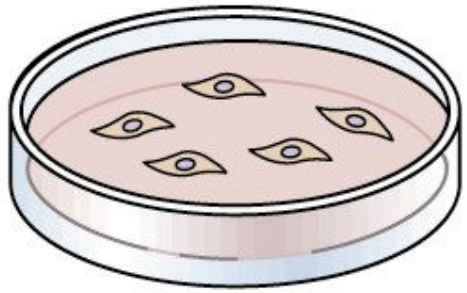
CDK-1

Cyclin-dependent kinase-1

MAPK-14

Mitogen-activated kinase-14

→ Cell proliferation
Cell differentiation
Cell death →



THERAPEUTIC POTENTIAL IN COPD

MaulEPOC Study

AIMS:

i) Assess the epidemiological profile of Maulean subjects suffering from COPD.

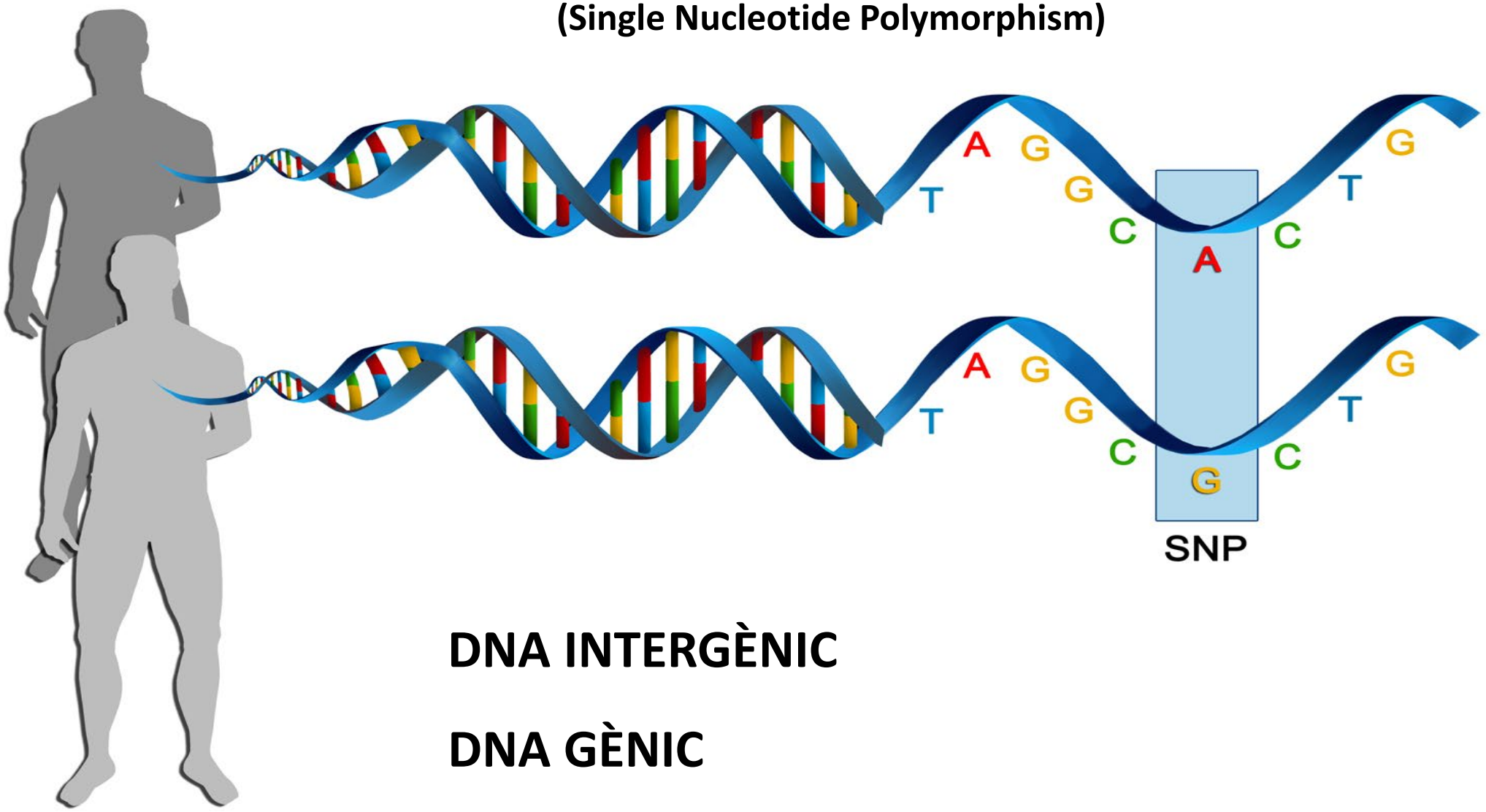
ii) Elucidate whether clinical, functional and molecular differences exist between patients exposed to tobacco and biomass smoke.

iii) Investigate genetic susceptibility to COPD in Chileans.

- GWAS

SNP

(Single Nucleotide Polymorphism)

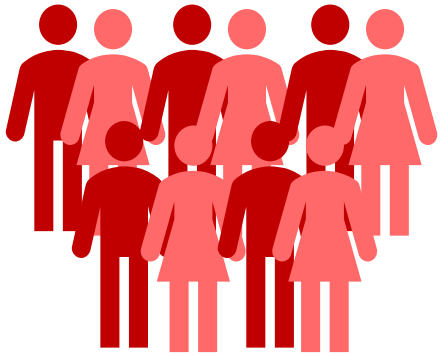


DNA INTERGÈNIC

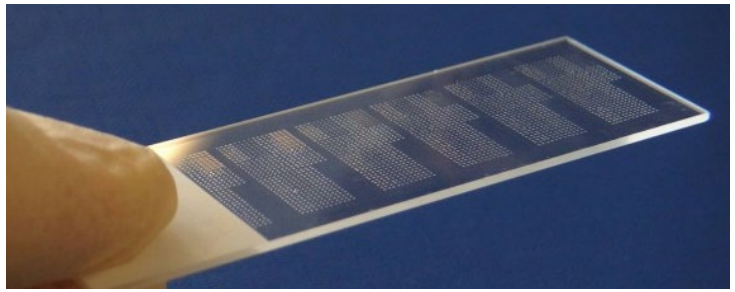
DNA GÈNIC

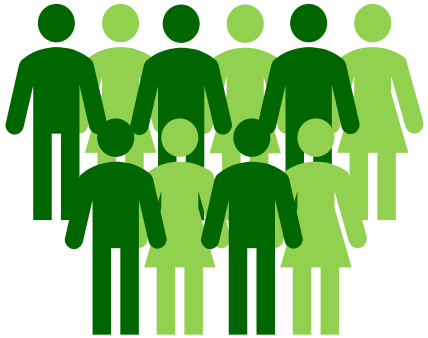
GWAS

Genome-wide association study

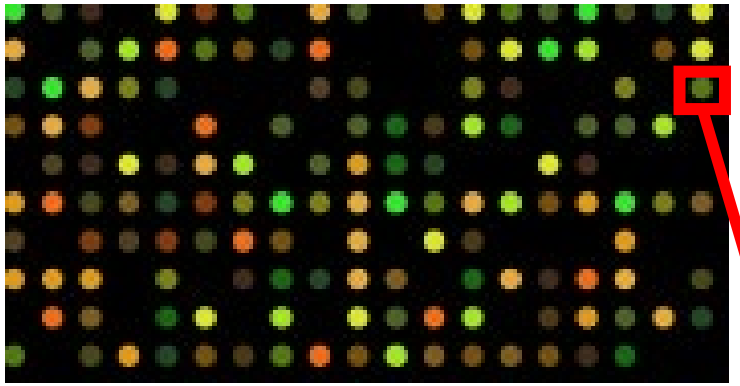


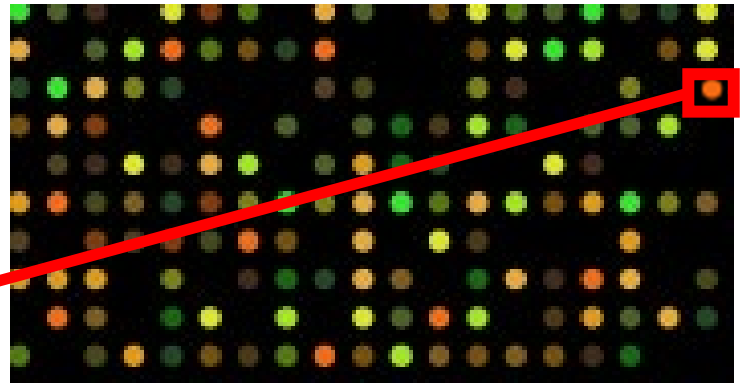
CASOS MPOC

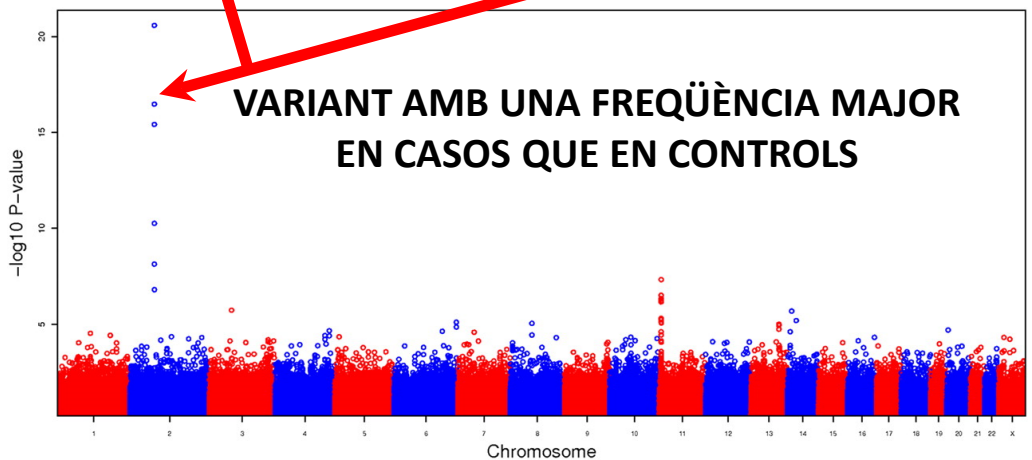




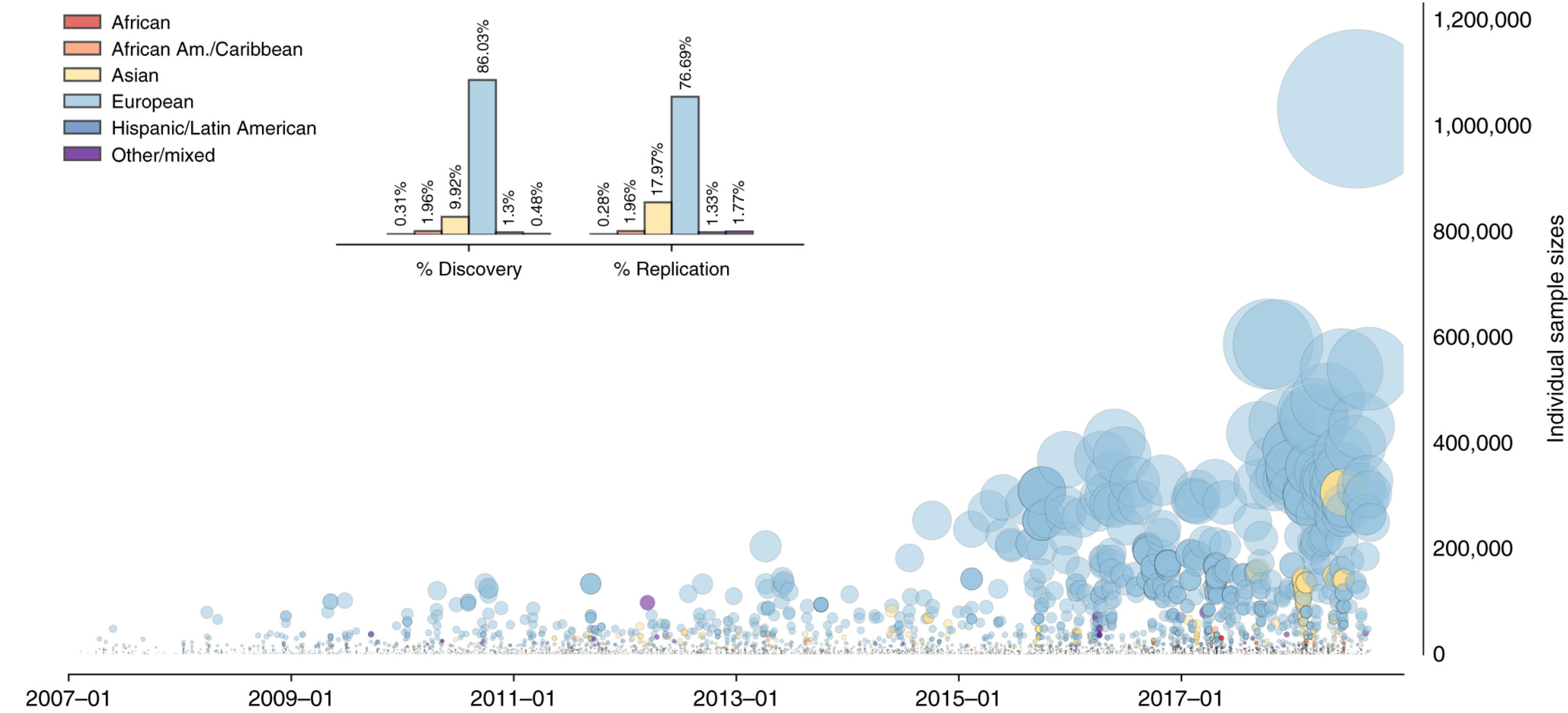
CONTROLS SANS



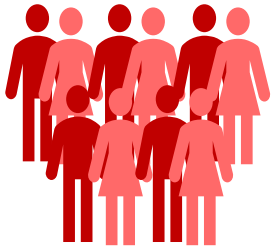




GWAS Participant Ancestry over Time, 2007–2017

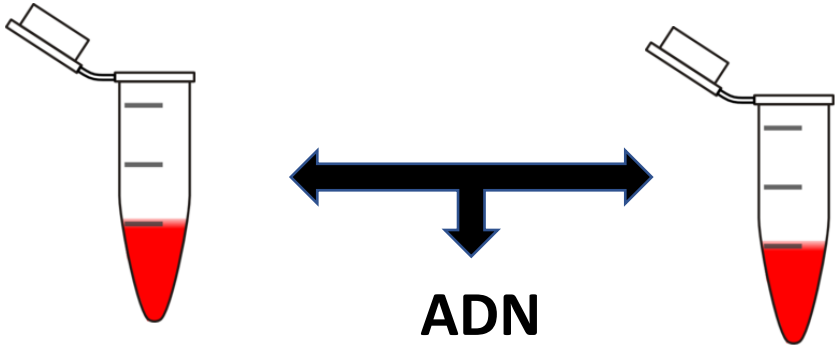


Mills & Rahal, Communications Biology, 2, 9 (2019)

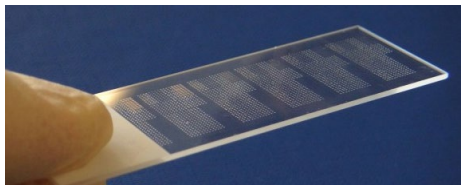


CASOS MPOC

CONTROLS SANS



ADN



Illumina Infinium Global Screenig Array
(754.159 SNPs)

455.564 SNPs

Table 1
Clinical and epidemiological data.

	Controls $n = 193$	COPD $n = 214$
Sex, M/W, N (%)	60 (31)/133 (69)	121 (57)/93 (43)*
Age, years	68.66 ± 3.25	70.97 ± 4.69
Smoking history, pack-years	7.75 ± 3.25	30.47 ± 14.82*
Smoking habit, n (%)		
Smokers	31 (16)	29 (13)
Former smokers	63 (33)	136 (64)
Never smokers, %	99 (51)	49 (23)
Exposure to biomass, hours/year	96.87 ± 32.57	225.62 ± 54.28*
Schooling, years completed	14.33 ± 2.57	7.21 ± 3.98*
BMI, kg/m²	29.45 ± 5.02	26.96 ± 5.02*
Exacerbations in the previous year	–	1.37 ± 1.50
FEV_1, % predicted	108.84 ± 18.40	61.47 ± 24.56*
FEV_1/FVC,%	83.00 ± 6.27	58.25 ± 10.48*
DL_{CO}, % predicted	87.43 ± 24.48	72.33 ± 25.13*
Oxygen saturation, %	96.14 ± 2.34	92.36 ± 4.76*
6MWT, meters	462.95 ± 87.82	351.50 ± 155.61*
mMRC	–	2.28 ± 1.39
CAT	–	14.94 ± 8.46
BODE	–	3.18 ± 2.74

Data displayed as mean ± standard deviation, except where otherwise noted.
6MWT: 6-minute walk test; BMI: body mass index; BODE: *Body mass, airflow obstruction, dyspnea and exercise*; CAT: COPD Assessment Test; DLCO: diffusing capacity of the lung for carbon monoxide; FEV_1: forced expiratory volume in 1 second; FVC: forced vital capacity; mMRC: modified Medical Research Council dyspnea scale.

* Indicates a significant difference compared to controls ($p < 0.05$).

GWAS

CHR	Position	SNP	*p* value	BONF	Gene	Location
21	43218520	rs1054761	2.22E–07	0.1012	PRDM15	Non-coding transcript variant/utr variant 3 prime
21	43236176	rs4075967	5.18E–07	0.2361	PRDM15	Non-coding transcript variant/synonymous variant
21	43229099	rs8184900	2.58E–06	1	PRDM15	Intron
10	13978235	rs10906545	3.12E–06	1	FRMD4A	Intron
8	54788251	rs7827611	4.06E–06	1	RGS20	Intron
1	241849659	rs9428513	5.61E–06	1	WDR64	Intron
12	30308868	rs12313180	8.13E–06	1	Intergenic	

Table 2. Association of GWAS identified *PRDM15* SNPs and COPD risk

CHR	SNP	BP	A1	MAF cases	MAF controls	A2	CHISQ	*p*	OR	SE	95% CI
21	**rs1054761**	**43218520**	**T**	**0.2196**	**0.386**	**C**	**26.83**	**2.22E–07**	**0.4477**	**0.1567**	**0.3293–0.6086**
21	rs2236696	43221826	T	0.3879	0.3031	C	6.426	0.01124	1.457	0.1487	1.088–1.95
21	**rs8184900**	**43229099**	**G**	**0.3107**	**0.4715**	**A**	**22.11**	**2.58E–06**	**0.5053**	**0.146**	**0.3796–0.6727**
21	rs62216232	43233770	A	0.09813	0.09067	G	0.1318	0.7166	1.091	0.2405	0.6811–1.748
21	**rs4075967**	**43236176**	**A**	**0.1916**	**0.3472**	**G**	**25.19**	**5.18E–07**	**0.4457**	**0.1628**	**0.3239–0.6133**
21	rs4075970	43236481	A	0.5467	0.4482	G	7.883	0.004989	1.485	0.1411	1.126–1.958
21	rs73375539	43240446	T	0.04907	0.04145	C	0.2712	0.6025	1.193	0.3395	0.6133–2.321
21	rs74357060	43240636	T	0.04907	0.0285	C	2.273	0.1316	1.759	0.379	0.8368–3.697
21	rs28360603	43242207	A	0.521	0.4508	G	4.009	0.04526	1.325	0.1408	1.006–1.747
21	rs28708536	43244905	A	0.229	0.1788	G	3.138	0.07647	1.364	0.1757	0.9668–1.925
21	rs76291974	43247564	A	0.03738	0.06477	G	3.182	0.07446	0.5608	0.3282	0.2947–1.067

Respiration. 2020;99(4):307-315

PRDM

Positive-regulatory domain gene family

19 TFs

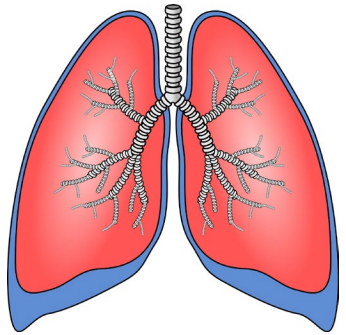
Cell development

Cell differentiation

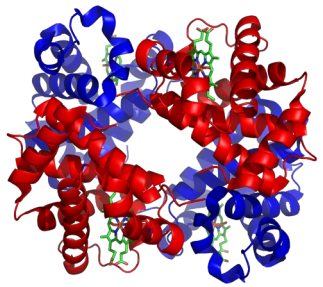
Hematopoiesis

PRDM15 $^{-/-}$

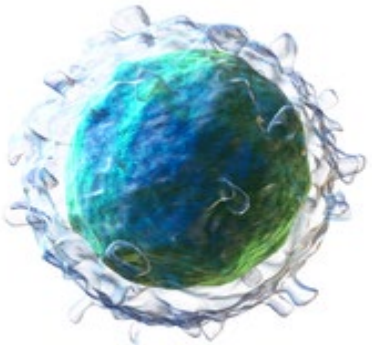
↑↑↑ MAPK-ERK



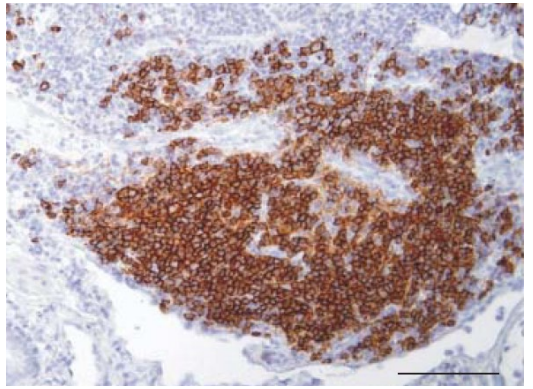
Lung Inflammation



↑↑↑PRDM15



B cell dysregulation/autoimmunity



Pulmonary tertiary lymphoid organs

GWAS

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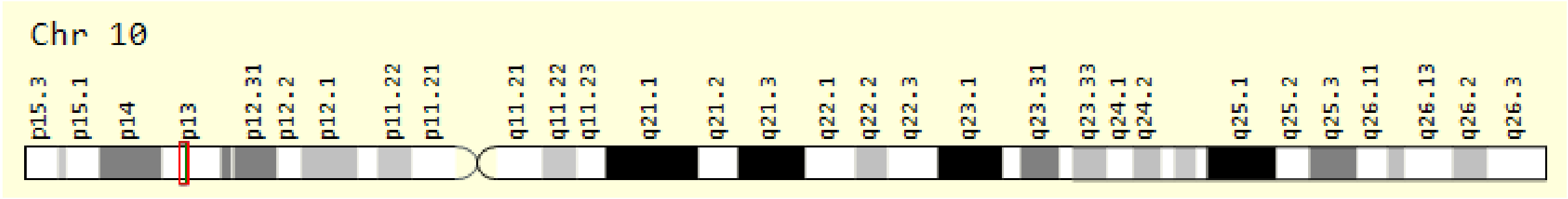
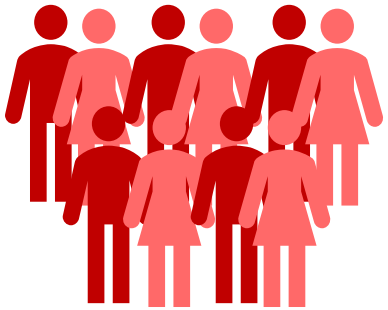
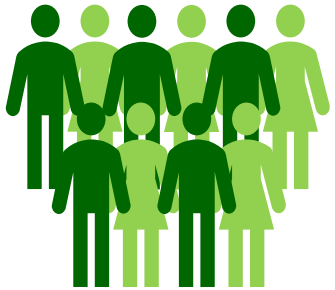
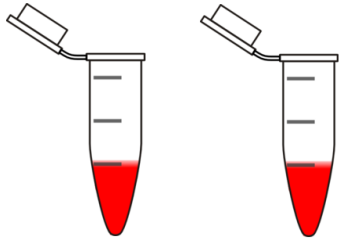
Respiration. 2020;99(4):307-315



FRDM4A







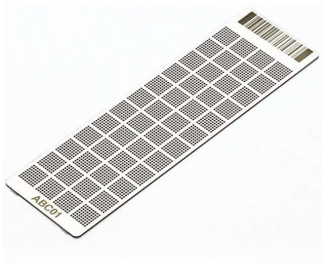
CASOS MPOC

CONTROLS SANS

➡ **DNA** ➡

FRDM4A

60 SNPs



OpenArray®TMTaqMan platform

Table 2
Variants significantly associated with COPD susceptibility in the overall study cohort (all subjects) and in smokers only.

All subjects								
SNP	Position	Odds ratio	95% CI	*p*-Value	Bonferroni *p*-value	A1	MAF cases	MAF controls
rs10906545	13978235	1.97	1.47–2.62	3.97×10^{-6}	2.38×10^{-4}	A	0.54	0.37
rs1218353	14318441	2.41	1.54–3.77	7.82×10^{-5}	4.69×10^{-3}	G	0.18	0.08

95% CI: 95% confidence interval; A1: low-frequency allele; MAF: minor allele frequency; SNP: single nucleotide polymorphism.
[a] 165 cases and 94 controls.

Arch Bronconeumol. 2022 May;58(5):454-456

FRMD4A

FERM domain containing protein 4A

+

Arf6

ADP-ribosylation factor 6

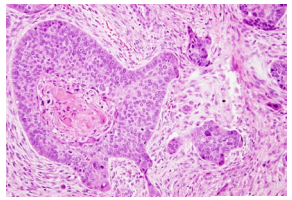
Cell signal transduction

Membrane traffic

Actin cytoskeleton

FRMD4A

Nicotine addiction



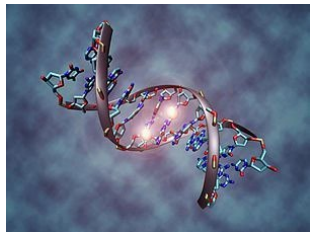
Non-small lung cell carcinoma

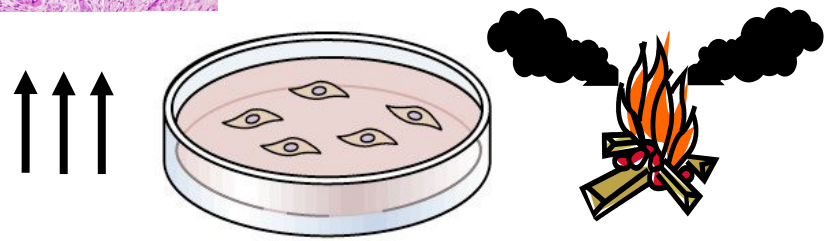
Genetic & Epigenetic variations in FRMD4A

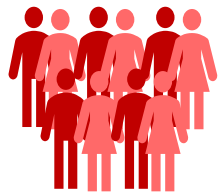
COPD Pathogenesis

FRMD4A

Methylation







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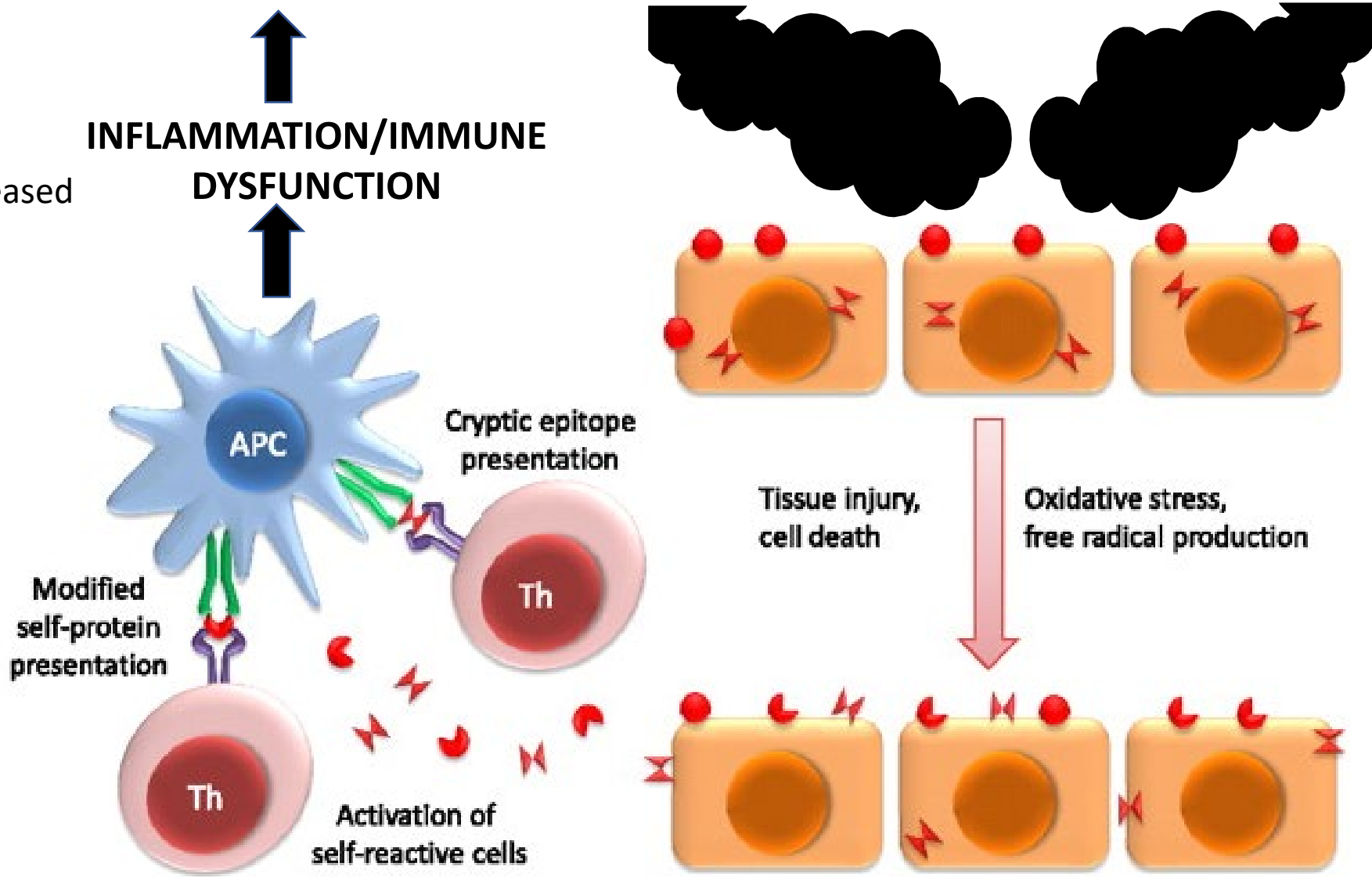
CASOS EPOC

CONTROLS SANS

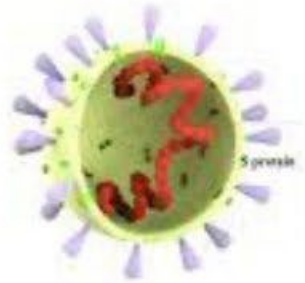
HIPÒTESI DE L'AUTOIMMUNITAT

- Ongoing COPD after smoking cessation
- Pulmonary lymphoid fol·licles and increased Numbers of T and B cells in COPD
- Circulating autoantibodies anti-elastin and anti-pulmonary epithelium and endothelium in COPD

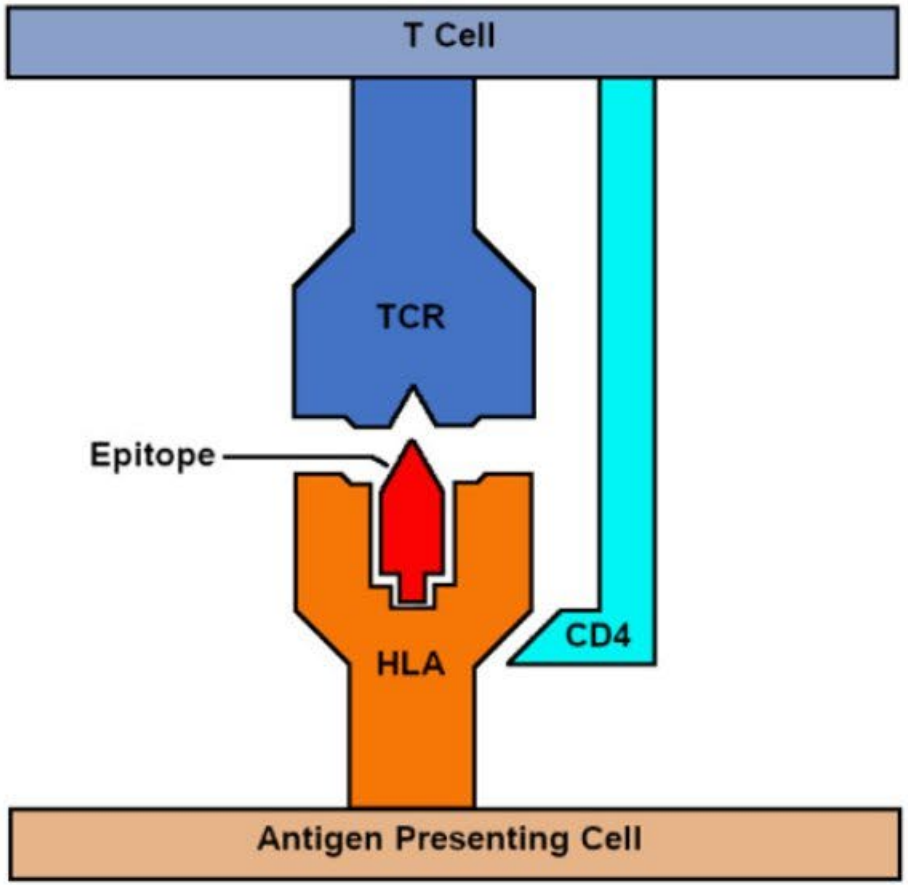


HLA Variants Bind to Self-Peptides to Cause Autoimmunity

Synapse of T-cell, peptide, and antigen presenting cell drives both immunity and autoimmunity



Pathogenic foreign antigens
Bind to many HLAs and trigger normal T cell immune response



Self-antigens
Bind to specific HLA variants and trigger autoimmune response

GENOTYPE IMPUTATION

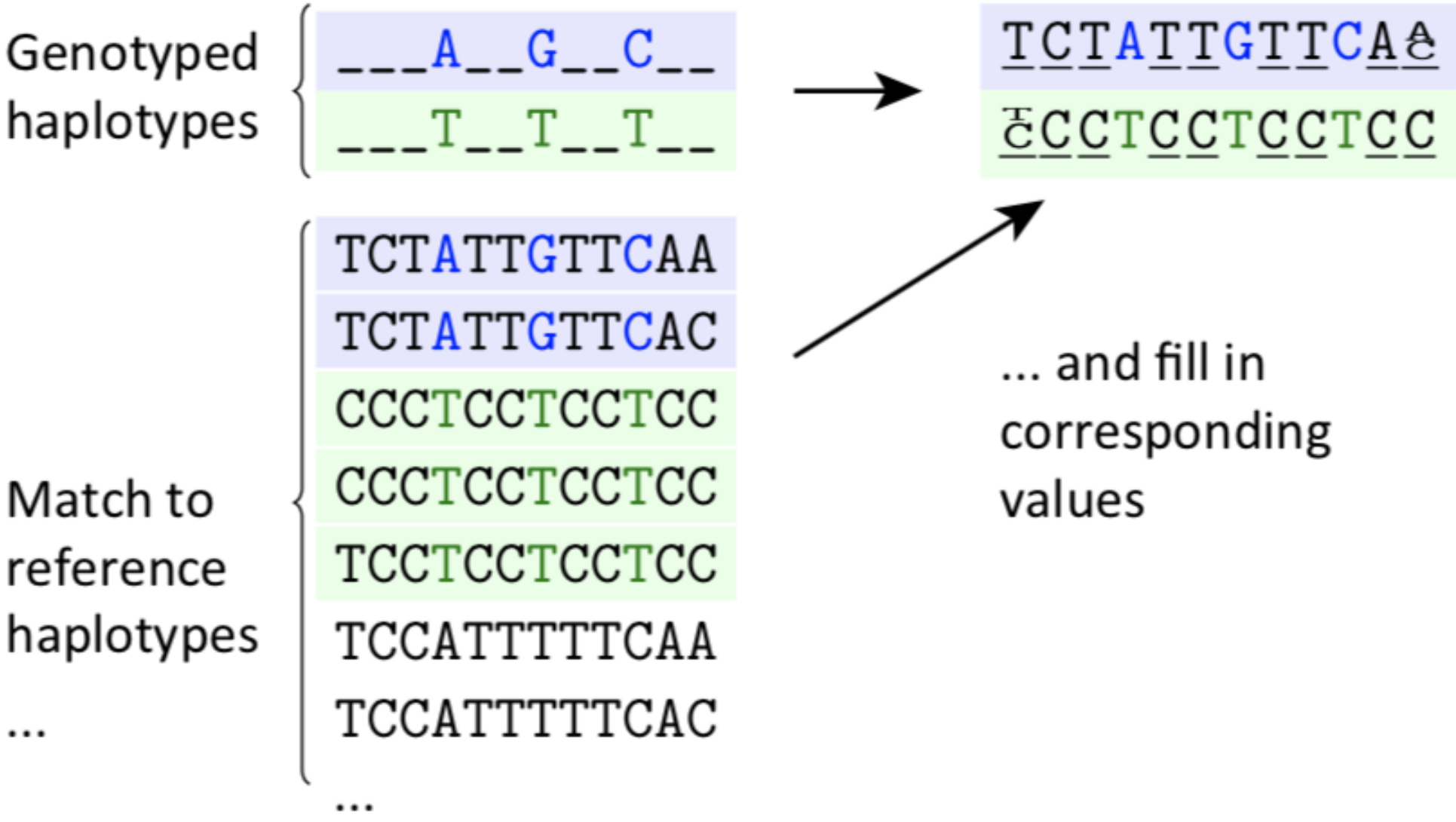
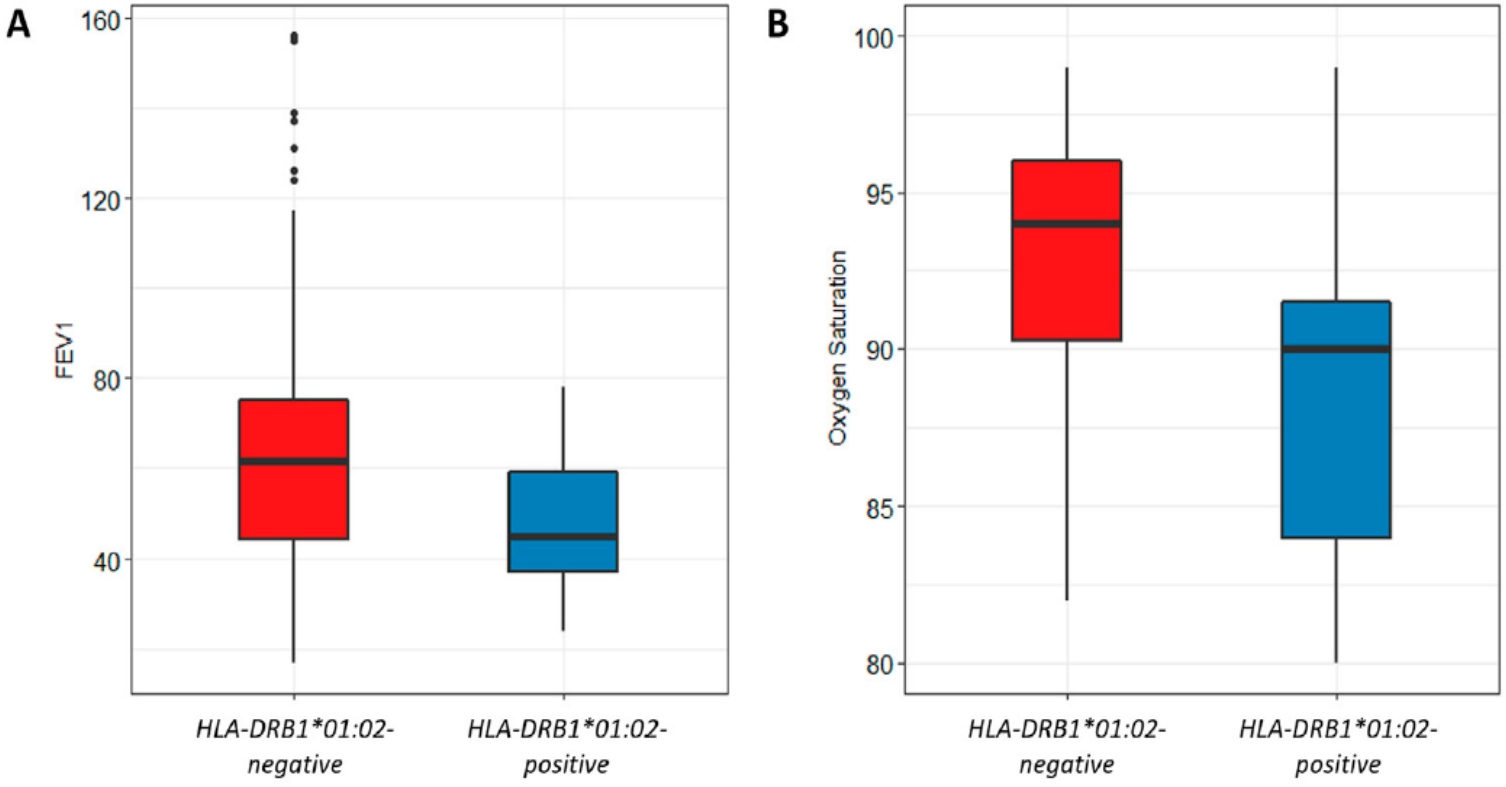


Table 4
Frequency distribution of HLA alleles between COPD cases and controls.

HLA Allele	COPD cases ($n = 214$)		Healthy controls ($n = 703$)		p value	OR	95% CI
	n	%	n	%			
DRB1*01:02	14	6.54	23	3.27	0.04	2.07	1.04–4.10
DRB1*14:02	23	10.75	48	6.83	0.08	1.64	0.97–2.77
DRB1*15:01	24	11.21	88	12.52	0.64	0.88	0.55–1.43

OR: odds ratio; CI: confidence interval.
p values were determined by Fisher's 2-tailed exact test.



Polymorphysms in HLA-II region

Self-antigens & autoantibodies in COPD

Autoimmune process, loss of lung function

Arch Bronconeumol, 57, 291–297, 2021

MaulEPOC Study

AIMS:

i) Assess the epidemiological profile of Maulean subjects suffering from COPD.

ii) Elucidate whether clinical, functional and molecular differences exist between patients exposed to tobacco and biomass smoke.

iii) Investigate genetic susceptibility to COPD in Chileans.

- GWAS
- Effect of genetic ancestry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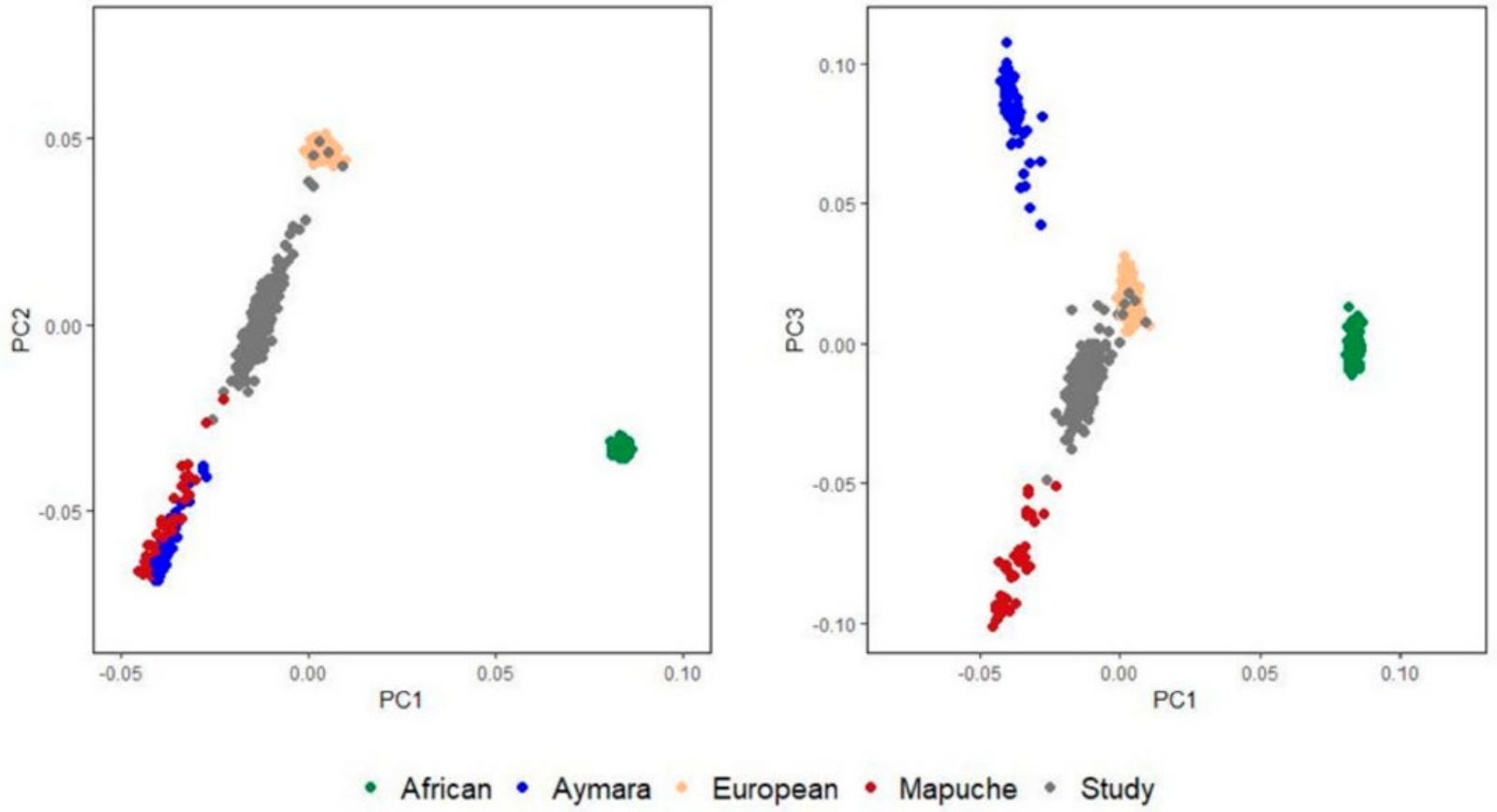
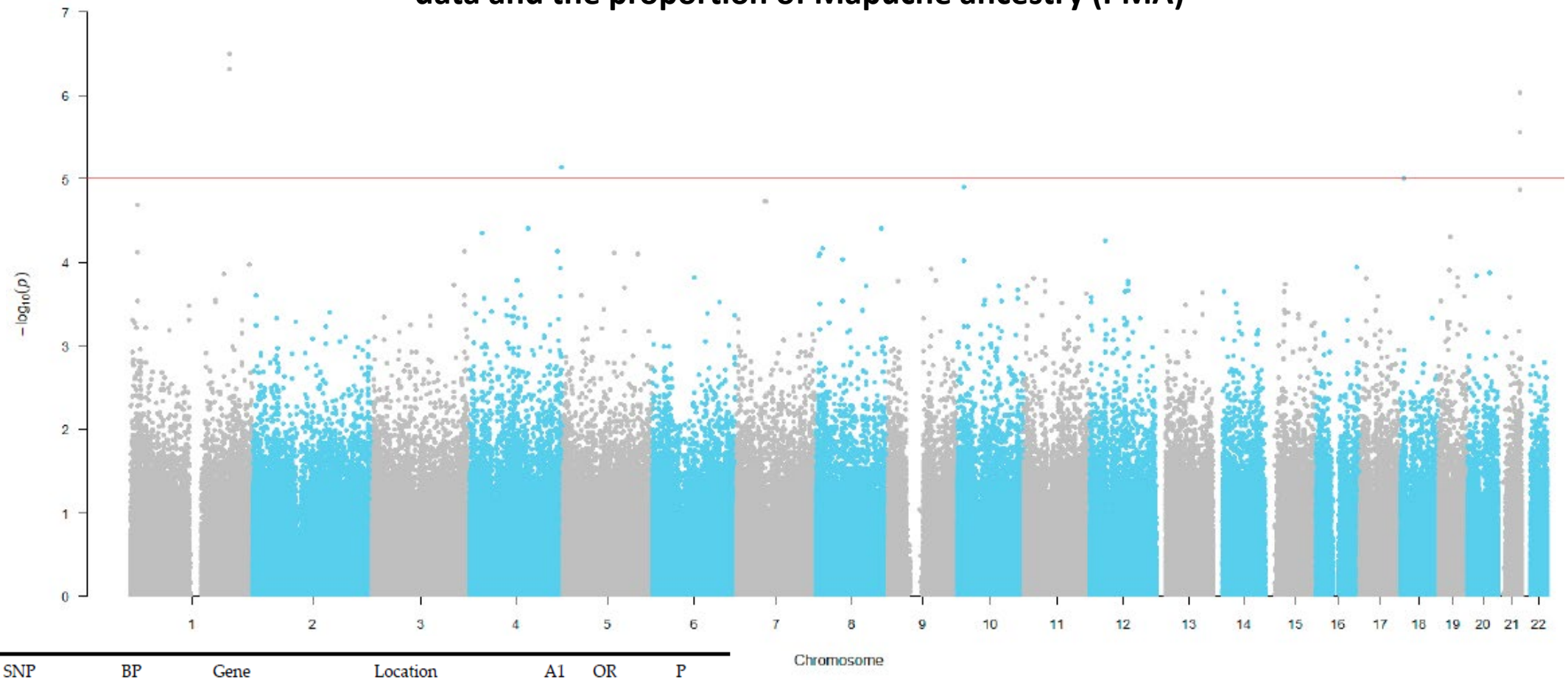


	Control Subjects	COPD Patients
European ancestry, %	55.93 ± 6.89	56.32 ± 10.27
African ancestry, %	1.73 ± 1.00	1.73 ± 1.12
Mapuche ancestry, %	35.39 ± 6.71	35.11 ± 8.54
Aymara ancestry, %	6.96 ±.45	6.73 ± 3.52

J. Pers. Med. 2020, 10, 93

Single-marker allelic association after controlling for age, sex, the first two principal components of a PCA based on genetic data and the proportion of Mapuche ancestry (PMA)



CHR	SNP	BP	Gene	Location	A1	OR	P
1	rs12741415	202474774	PPP1R12B	Non Coding Transcript Variant	A	3.01	3.18×10^{-7}
1	rs116062217	202431443	PPP1R12B	Intron	T	2.92	4.89×10^{-7}
21	rs1054761	43218520	PRDM15	Non Coding Transcript Variant	T	0.44	9.42×10^{-7}
21	rs4075967	43236176	PRDM15	Synonymous Variant	A	0.45	2.75×10^{-6}
4	rs4862451	185789995	Intergenic	-	G	2.47	7.21×10^{-6}

CHR: chromosome; SNP: single nucleotide polymorphism; BP: base pair; A1: minor allele frequency; OR: odds ratio; P: p-value.

PPP1R12B → **Asthma**

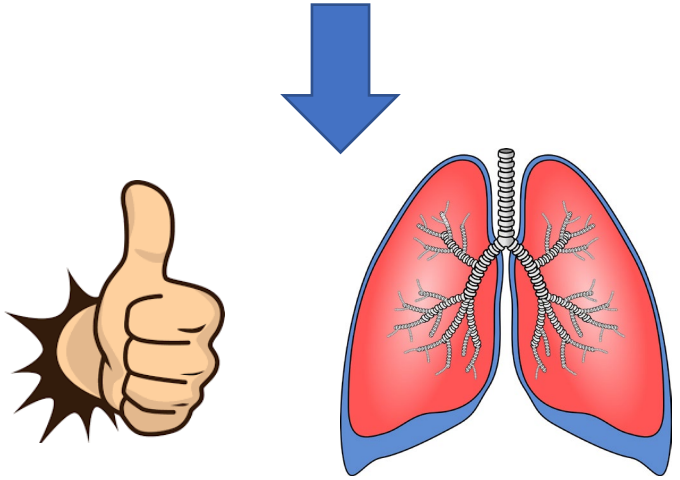
PPP1R12B → **Celiac disease autoimmunity**

J. Pers. Med. 2020, 10, 93

Table 3. Association between *PRMD15* SNPs and COPD risk in participants with low and high PMA (proportion of Mapuche ancestry, <35% vs. ≥35%).

Low PMA							
SNP	A1	OR1	95%CI	*p*	*OR2	95%CI	*p*
rs1054761	T	0.31	0.18–0.51	7.24×10^{-7}	0.23	0.09–0.89	0.02
rs2236696	T	2.45	1.5–3.99	1.89×10^{-4}	10.41	1.99–54.59	1.00×10^{-3}
rs8184900	G	0.4	0.26–0.62	9.99×10^{-6}	0.40	0.11–1.49	0.16
rs4075967	A	0.27	0.16–0.46	9.46×10^{-8}	0.22	0.04–1.12	0.05
rs4075970	A	2.43	1.57–3.78	3.32×10^{-5}	6.76	1.84–24.84	8.25×10^{-4}
rs28360603	A	2.26	1.46–3.48	1.24×10^{-4}	7.55	2–28.54	5.41×10^{-4}
rs7275618	C	1.79	1.18–2.71	4.75×10^{-3}	2.04	0.57–7.30	0.25
rs35109371	C	1.87	1.24–2.82	2.16×10^{-3}	2.02	0.56–7.26	0.27
High PMA							
SNP	A1	OR1	95%CI	*p*	*OR2	95%CI	*p*
rs1054761	T	0.63	0.41–0.96	0.03	0.41	0.13–1.25	0.10
rs2236696	T	1.02	0.7–1.5	0.92	2.34	0.80–6.92	0.11
rs8184900	G	0.73	0.5–1.08	0.12	0.58	0.29–1.16	0.12
rs4075967	A	0.73	0.47–1.13	0.15	0.45	0.15–1.40	0.15
rs4075970	A	0.98	0.68–1.43	0.93	2.08	0.77–5.64	0.13
rs28360603	A	1.22	0.82–1.79	0.32	1.04	0.34–3.17	0.94
rs7275618	C	1.18	0.77–1.83	0.44	0.81	0.22–3.01	0.75
rs35109371	C	1.32	0.88–1.96	0.17	1.08	0.31–3.71	0.90

SNP: single nucleotide polymorphism; A1: minor allele nucleotide; OR: odds ratio; *p*: *p*-value; CI: confidence interval; PMA: proportion of Mapuche ancestry.*OR adjusted for sex, smoking status, biomass exposure, scholarship, and body mass index.



J. Pers. Med. 2020, 10, 93

CONCLUSIONS

i) Un **nivell d'estudis baix** i l'exposició a **fum de biomassa** són factors de risc clau per a l'MPOC en poblacions llatinoamericanes, especialment en **dones**.

ii) L'MPOC causada per exposició a **fum de biomassa** presenta diferents trets **fisiològics i moleculars** comparada amb l'MPOC causada pel tabac. En concret, implica:

- una **pitjor oxigenació de la sang**
- una resposta inflamatòria de tipus **Th2**
- una major rellevància de mecanismes relacionats amb la **hipoxèmia** i la **hipersecreció de moc**

iii) Les poblacions llatinoamericanes presenten tant **variants genètiques específiques** relacionades amb el risc de desenvolupar MPOC, situades als gens ***PRDM15***, ***FRDM4A*** i ***PPP1R12B***, com variants genètiques prèviament descrites en altres poblacions, com al·lels d'**HLA-DRB1**.

iv) Aquestes variants genètiques podrien contribuir a la patogènia de l'MPOC mitjançant mecanismes de **disfunció immune i autoimmunitat.**

v) El fet de tenir un bagatge genètic **Amerindi (Maputxe)** podria conferir certa **protecció davant l'MPOC**.

vi) Els avenços en la medicina personalitzada passen per una **millor caracterització genètica dels diversos grups ètnics**.

UNIVERSITAT DE BARCELONA
Facultat de Farmàcia i Ciències de l'Alimentació

UNIVERSIDAD AUTONOMA DE CHILE

Servicio de Salud Maule
Región del Maule
Ministerio de Salud

HOSPITAL REGIONAL DE TALCA

Característiques i factors de risc de la Malaltia Pulmonar Obstructiva Crònica (MPOC) en poblacions llatinoamericanes

Jordi Olloquequi González

Departament de Bioquímica i Fisiologia

Secció de Fisiologia

Seminari de Recerca

2 de març de 2023