TRATAMIENTO PERSONALIZADO – CENTRADO EN EL PACIENTE

IX REUNION GRUPO EPOC – SEMI

13 y 14 de marzo de 2014

Francisco Javier Cabrera Aguilar

Hospital General Universitario Gregorio Marañón de Madrid

Arch Bronconeumol. 2009; 45(Supl 5): 27-34

Archivos de Bronconeumología

www.archbronconeumol.org

Tratamiento individualizado de la EPOC: una propuesta de cambio

Marc Miravitlles

Características	Tipo A Enfisema	Tipo B Bronquitis crónica	Tipo C Enfisema/bronquitis crónica	Tipo D Fumador con asma crónica	Tipo E Asma/bronquitis crónica
BD de corta duración	++	++	++	+++	+++
LABA	++	+++	++	+++	+++
LAMA	+++	+++	+++	++	++
CI	-	+	+	+++	++
Teofilinas	++	++	++	+	+
Mucolíticos	-	+	+	-	+
Antibióticos	-	+	++	-	+

BD: broncodilatadores; LABA: β_2-adrenérgicos de larga duración; LAMA: anticolinérgicos de larga duración; CI: corticoides inhalados; +: escasa evidencia de su eficacia, indicado en algunas situaciones; ++: eficaz, indicado como tratamiento de segunda línea o asociado a otro más activo; +++: muy eficaz, indicado como tratamiento de primera línea; -: no evidencia de su eficacia o evidencia de su falta de eficacia, no indicado.

Tenemos que tener en cuenta que la EPOC ha carecido siempre de investigación propia en farmacología y que la mayor parte de los medicamentos utilizados se desarrollaron para el asma y posteriormente fueron heredados por unos pacientes que tienen características y necesidades diferentes

Educación al Paciente y su Familia

Guía práctica de la SALUD

semFYC
Sociedad Española de Medicina de Familia y Comunitaria

Inicio

Créditos

Arch Bronconeumol. 2011;47(2):59–60

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Editorial

La acreditación de las Unidades Especializadas en Tabaquismo

Accreditation of Specialist Stop Smoking Units

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[b] *Presidente de la Sociedad Española de Neumología y Cirugía Torácica, SEPAR*

Arch Bronconeumol. 2006;42(3):104-12

ORIGINALES

Efectividad y eficiencia de una consulta monográfica hospitalaria para pacientes con EPOC e insuficiencia respiratoria

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Med Clin (Barc). 2011;136(15):665–668

www.elsevier.es/medicinaclinica

Original breve

Hospital de día de enfermedades respiratorias: impacto sobre la tasa de ingresos hospitalarios por exacerbaciones de la enfermedad pulmonar obstructiva crónica

Luis Fernando Casas Méndez [a,*], Concepción Montón Soler [a], Marisa Baré Mañas [b], Jordi Casabon Salas [a], Xavier Pomares Amigó [a] y Urko Aguirre Larracoechea [c]

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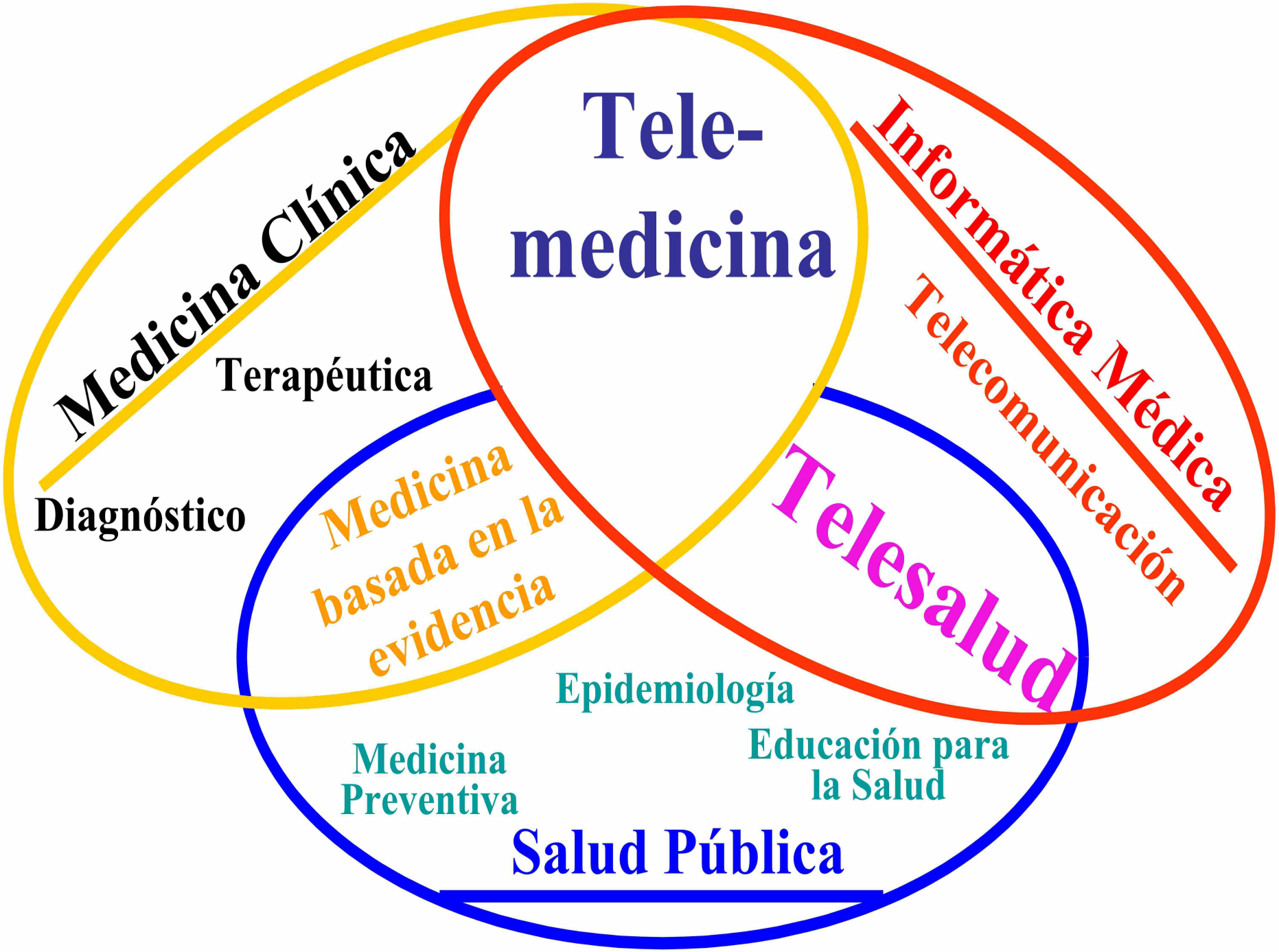
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Informática Médica
Telecomunicación
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Telesalud
Epidemiología
Medicina
Preventiva
Educación para
la Salud
Salud Pública

EQUIPO BASICO PARA EL DESARROLLO DE LA TELEMEDICINA

Arch Bronconeumol. 2011;47(1):35–40

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Revisión

Medicina P4: el futuro a la vuelta de la esquina

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INFORMACIÓN DEL ARTÍCULO

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Genética
Investigación
Redes libres de escala
Sistemas complejos

RESUMEN

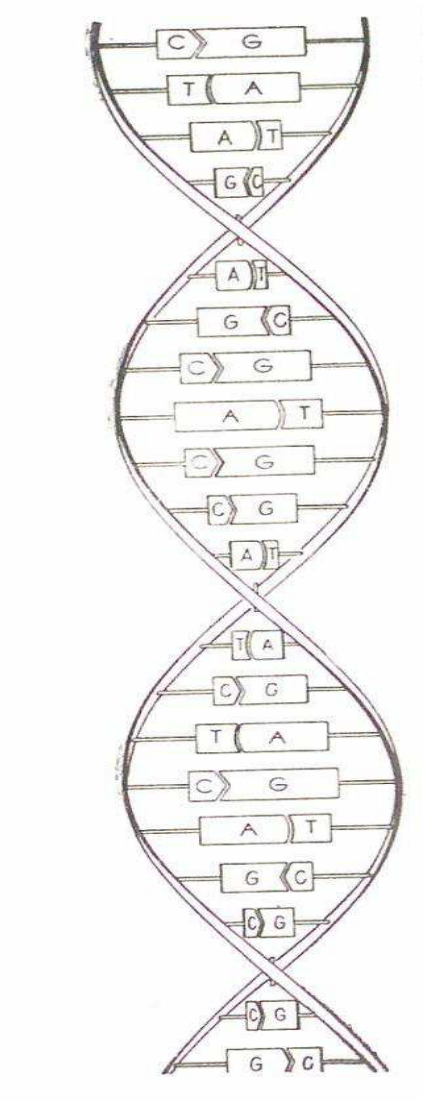
La práctica médica tradicional ha sido "reactiva" (el médico interviene cuando hay enfermedad). Los avances teóricos (redes libres de escala y sistemas complejos), tecnológicos (tecnologías "ómicas" de alta eficiencia) y conceptuales (biología de sistemas) habidos en la última década, permiten anticipar la transición hacia una medicina "anticipatoria", centrada en la salud (no en la enfermedad). Esta revisión establece las bases conceptuales fundamentales y discute los principales aspectos de esta nueva medicina, denominada "Medicina P4" por ser personalizada, predictiva, preventiva y participatoria.

Predictiva
Preventiva
Personalizada
Participativa

Medicina P4

¿EN QUE SE BASA LA MEDICINA PERSONALIZADA POSTGENOMICA?

- Cada persona es genéticamente única
- La mayoría de los SNP pueden ocasionar una respuesta atenuada o exacerbada a un agente externo, que puede ser un fármaco, algún componente alimenticio o contaminantes ambientales
- Se dispone ya de bancos de datos que relacionan SNP con una respuesta normal o anormal a medicamentos, nutrientes y contaminantes
- En cada persona se podrá predecir su respuesta
- Se realizan estudios con miles de SNP con el fin de relacionarlos con la predisposición a determinadas enfermedades.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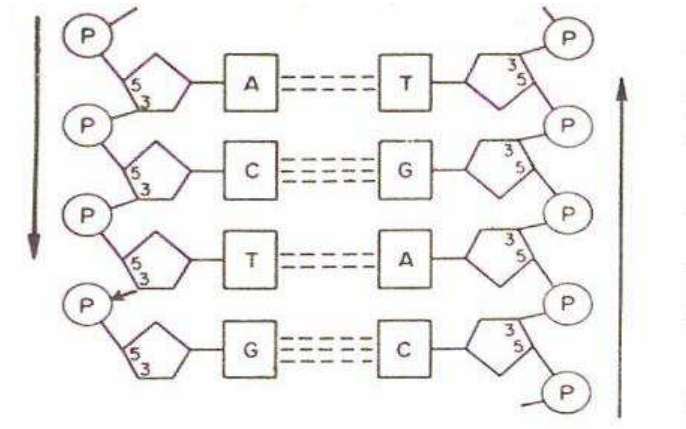
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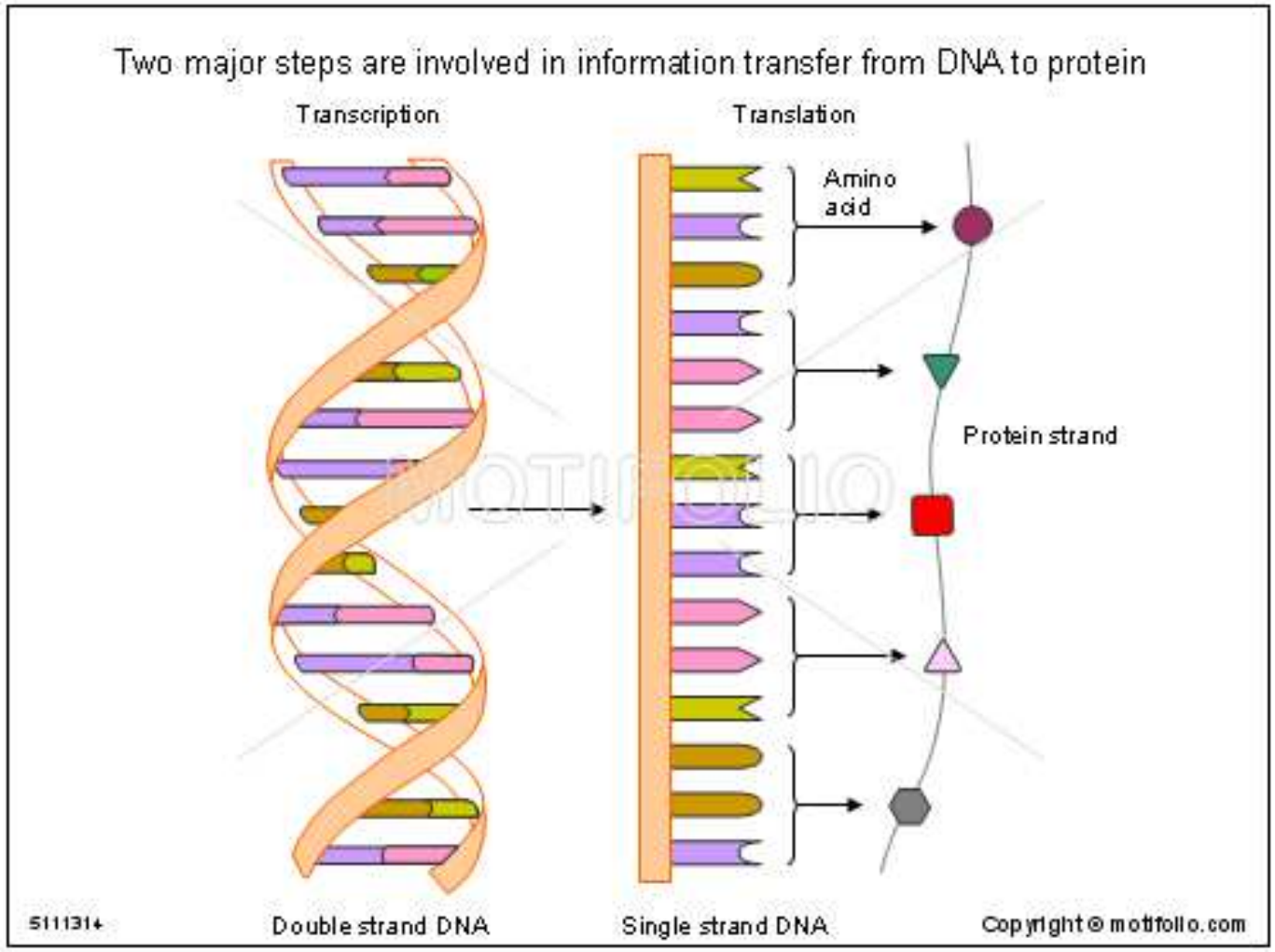
Two major steps are involved in information transfer from DNA to protein
Transcription
Translation
Amino acid
Protein strand
5111314
Double strand DNA
Single strand DNA
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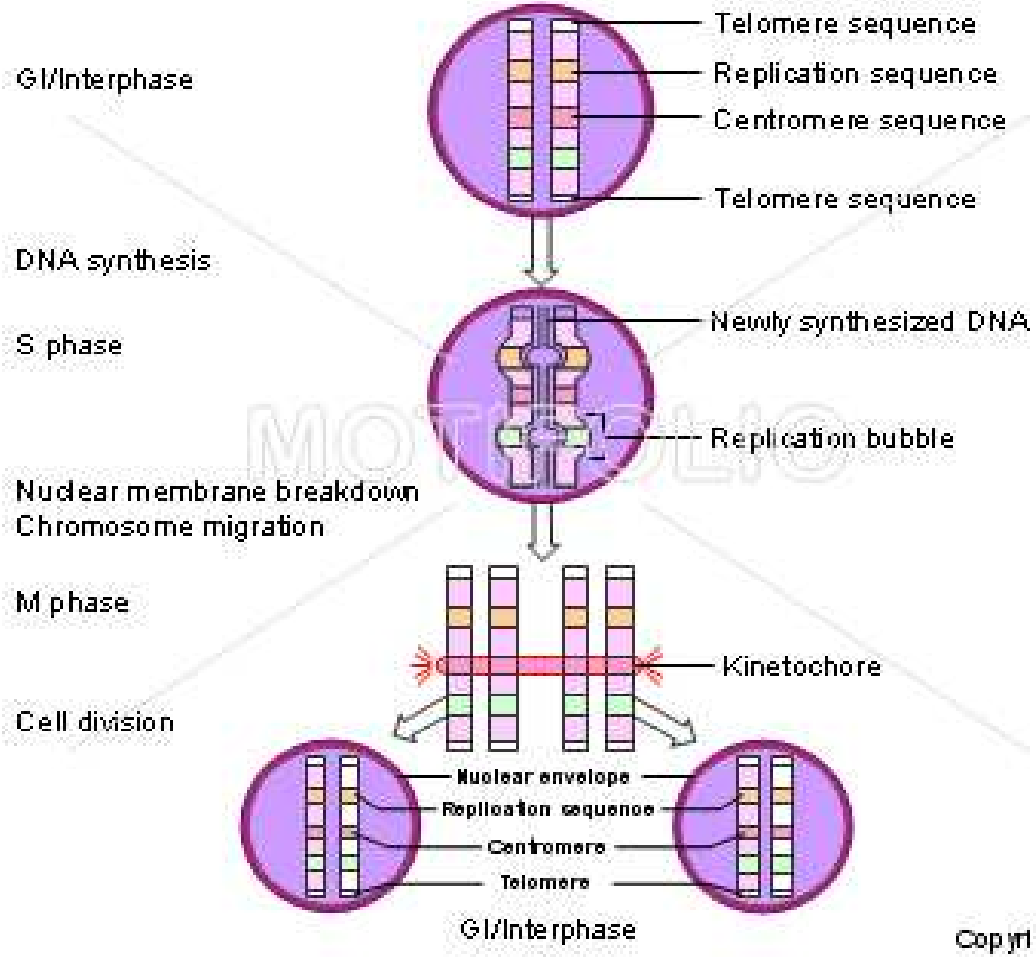
Sequence elements of chromosomes



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VENTAJAS DE LA MEDICINA
Y
TRATAMIENTO PERSONALIZADOS

- Se pueden tomar decisiones mas adaptadas a la biología del paciente
- Mayor probabilidad de obtener mejores resultados
- En tratamientos farmacológicos mayor eficacia con dosis ajustadas y menos secundarismos
- Mejor y mas precoz planificación de la prevención
- Posiblemente un importante ahorro en el gasto sanitario

FENOTIPOS CLINICOS DE EPOC

(actualmente en investigación genética)

- Descenso de la función pulmonar
- Bronquitis crónica
- Exacerbaciones
- Enfisema
- Respuesta broncodilatadora
- IMC y pérdida de peso
- Capacidad de ejercicio
- Disnea
- Calidad de vida
- Hipoxemia
- Hipercapnia
- Hipertensión pulmonar
- Comorbilidades

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Pharmacogenetics of chronic obstructive pulmonary disease: challenges and opportunities

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Genes associated with potential phenotypes for chronic obstructive pulmonary disease pharmacogenetics studies

Phenotype	Genes with significant association
Lung function decline in chronic obstructive pulmonary disease	*SERPINA1*[*] [37] *EPHX1* [37] *IL1B, IL1RN*[‡] [91] *GSTP1, GSTT1, GSTM1*[§] [92] *MMP1* [93] *IL4RA* [94] *ADRB2* [68] *GC* [95] *HMOX1* [96] *IL6* [36] *CDC6* [97] *LEPR* [98]

Chronic obstructive pulmonary exacerbations	*SERPINA1** [56]
	MBL2 [52]
	CCL1 [53]
	SFTPB [54]
	SOD3 [55]
Exercise capacity	*EPHX1* [58]
	LTBP4 [58]
	SFTPB [58]

Symptoms (e.g., dyspnea)	*TGFB1* [58]
Emphysema on quantitative chest CT scan analysis	*GC* [95]
	MMP9 [21]
	EPHX1 [20]
	GSTP1 [20]
	ADRB2 [22]
	TGFBR3 [99]

*Studies of α1-antitrypsin heterozygous carriers (PI MZ).

†Combination of variants in multiple genes associated with lung function decline, but not each gene individually.

AAT (SERPINA 1)

- Glicoproteina que pertenece al grupo de las antiproteasas. Inhibe la elastasa de los neutrofilos y la mayoría de serinproteasas
- El gen se localiza en el cromosoma 14 y se transmite por herencia mendeliana
- El alelo Z se produce por sustitución de guanina por adenina en el exón 5 cambiando GLUT x LIS en el aa. final
- Los homocigotos ZZ tienen unos niveles séricos de AAT ≈ 10%

GST y mEPHX

- Las dos actúan como antioxidantes
- El grupo de GST tiene varios polimorfismos siendo el mas relevante el que condiciona la sustitución de ISOL x VAL en posición 105
- El déficit de GSTT1+GSTM1 se asocia con caída de función pulmonar.
- La mEPHX tiene dos polimorfismos

  - exon 3 HIS x TIR
  - exon 4 ARG x HIST

  se asocian a enfisema

METALOPROTEINASAS

- Enzimas proteoliticos
- MMP1 MMP9 y MMP12
- Su sobreexpresión esta relacionada con el enfisema
- Tendencia a la asociación entre los genotipos MMP1 y una función pulmonar disminuida
- Se sugiere que los polimorfismos de los genes de MMP1 y MMP12 pero no MMP9 son factores predisponentes del daño pulmonar causado por el tabaco
- Inhibidores tisulares de las metaloproteinasas (TIMP)

Am J Respir Crit Care Med Vol 163. pp 469–473, 2001
Internet address: www.atsjournals.org

Susceptibility Genes for Rapid Decline of Lung Function in the Lung Health Study

ANDREW J. SANDFORD, TABASSUM CHAGANI, TRACEY D. WEIR, JOHN E. CONNETT, NICHOLAS R. ANTHONISEN, and PETER D. PARÉ

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Arch Bronconeumol. 2006;42(12):645-59

NORMATIVA SEPAR

Diagnóstico y tratamiento del déficit de alfa-1-antitripsina

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Am J Respir Crit Care Med Vol 165. pp 795–799, 2002
DOI: 10.1164/rccm.2102057

Genetic Loci Influencing Lung Function

A Genomewide Scan in the Framingham Study

OSCAR JOOST, JEMMA B. WILK, L. ADRIENNE CUPPLES, MICHAEL HARMON, AMANDA M. SHEARMAN, CLINTON T. BALDWIN, GEORGE T. O'CONNOR, RICHARD H. MYERS, and DANIEL J. GOTTLIEB

Boston University School of Medicine and Boston University School of Public Health; Research Service, Boston VAMC, Boston; and Center for Cancer Research, Massachusetts Institute of Technology, Cambridge, Massachusetts

Eur Respir J 2004; 23: 818–824
DOI: 10.1183/09031936.04.00104904

European Respiratory Journal
ISSN 0903-1936

Genetic polymorphism of epoxide hydrolase and glutathione S-transferase in COPD

S-L. Cheng*,#, C-J. Yu#, C-J. Chen¶, P-C. Yang#

Genetic polymorphism of epoxide hydrolase and glutathione S-transferase in COPD. S-L. Cheng, C-J. Yu, C-J. Chen, P-C. Yang. ©ERS Journals Ltd 2004.

ABSTRACT: Genetic susceptibility to the development of chronic obstructive pulmonary disease (COPD) might depend on variation in the activities of enzymes that detoxify cigarette smoke products, such as microsomal epoxide hydrolase (mEPHX) and glutathione *S*-transferase (GST). It was investigated whether polymorphisms in these genes had any association with susceptibility to COPD and COPD severity.

The genotypes of 184 patients with COPD and 212 control subjects were determined by polymerase chain reaction followed by restriction fragment length polymorphism analysis of the mEPHX, GSTM1, GSTT1 and GSTP1 genes. All subjects were smokers or exsmokers.

The proportion of GSTM1-null genotypes was significantly higher in patients with COPD than in control subjects (61.4 *versus* 42.5%). No differences were observed in the frequency of polymorphic genotypes for mEPHX, GSTT1 and GSTP1. During combined analysis of genetic polymorphisms for mEPHX, GSTM1 and GSTP1, it was found that there are strong indicators for susceptibility to COPD (genotype combination with at least one mutant mEPHX exon-3 allele (histidine 113), GSTM1 null and homozygous for the GSTP1 isoleucine 105 allele). The frequencies of homozygous mutant alleles of mEPHX exon 3 and the GSTM1-null genotype were significantly higher in patients with severe COPD (forced expiratory volume in one second or <35% of the predicted value).

It is proposed that the combination of genetic variants including at least one mutant microsomal epoxide hydrolase exon-3 allele and glutathione *S*-transferase M1-null and homozygous isoleucine 105 glutathione *S*-transferase P1 genotypes are significant indicators of susceptibility to chronic obstructive pulmonary disease in the Taiwanese population. In addition, the homozygous variant of microsomal epoxide hydrolase exon 3 and the glutathione *S*-transferase M1-null genotype are independent risk factors for developing severe chronic obstructive pulmonary disease.

Eur Respir J 2004; 23: 818–824.

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Keywords: Chronic obstructive pulmonary disease
epoxide hydrolase
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polymorphism

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Tumour necrosis factor-α gene promoter polymorphism in chronic obstructive pulmonary disease

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Tumour necrosis factor-a gene promoter polymorphism in chronic obstructive pulmonary disease. M.A. Higham, N.B. Pride, A. Alikhan, N.W. Morrell. ©ERS Journals Ltd 2000.

ABSTRACT: Tumour necrosis factor(TNF)-α levels are elevated in airways of patients with chronic obstructive pulmonary disease (COPD) and may contribute to its pathogenesis. A guanine to adenine substitution at position -308 of the TNF-α gene promoter (TNF1/2) has been associated with chronic bronchitis of various aetiologies in a Taiwanese population. The authors performed a study investigating association of the polymorphism with smoking-related COPD in Caucasians.

Frequencies of TNF1/2 alleles in 86 Caucasians (52 males) with COPD were compared with 63 (52 males) asymptomatic smoker/exsmoker control subjects and a population control of 199 (99 males) blood donors. Genotyping was performed by the polymerase chain reaction-restriction fragment length polymorphism technique on genomic deoxyribonucleic acid (DNA) obtained from peripheral blood.

There were no significant differences in TNF1/2 allele frequencies between groups: 0.85/0.15 in COPD, 0.85/0.15 in smoker control subjects, 0.83/0.17 in population control subjects. Within the COPD group there was no association of TNF1/2 alleles with indices of airflow obstruction (% predicted forced expiratory volume in one second (FEV_1) and % predicted FEV_1/vital capacity ratio) nor gas transfer (% predicted carbon monoxide transfer coefficient and % predicted carbon monoxide diffusing capacity of the lung).

It is concluded that: 1) the tumour necrosis factor gene promoter allele does not influence the risk of developing chronic obstructive pulmonary disease in a Caucasian population of smokers; and 2) there is no association of the tumour necrosis factor gene promoter genotype with severity of airflow obstruction nor degree of emphysema in chronic obstructive pulmonary disease.

Eur Respir J 2000; 15: 281–284.

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Keywords: Chronic obstructive pulmonary disease
gene promoter polymorphism
tumour necrosis factor-α

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ISSN 0903-1936

Gene polymorphism for microsomal epoxide hydrolase and susceptibility to emphysema in a Japanese population

K. Takeyabu, E. Yamaguchi, I. Suzuki, M. Nishimura, N. Hizawa, Y. Kamakami

Eur Respir J 2001; 18: 748–752
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ISSN 0903-1936

Tissue inhibitor of metalloproteinases-2 gene polymorphisms in chronic obstructive pulmonary disease

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Tissue inhibitor of metalloproteinases-2 gene polymorphisms in chronic obstructive pulmonary disease. K. Hirano, T. Sakamoto, Y. Uchida, Y. Morishima, K. Masuyama, Y. Ishii, A. Nomura, M. Ohtsuka, K. Sekizawa. ©ERS Journals Ltd 2001.

ABSTRACT: Proteinase/antiproteinase imbalance is the most widely accepted theory for development of chronic obstructive pulmonary disease (COPD). Mutations of tissue inhibitor of metalloproteinases-2 (TIMP-2) that downregulate its activity may increase the activities of matrix metalloproteinases and result in the degradation of the lung matrix.

Polymorphisms of the TIMP-2 gene were investigated in 88 COPD patients and 40 control subjects. The variations were examined by single-strand conformational polymorphism analysis followed by sequencing.

Two polymorphisms were identified, −853 G/A and -418 G/C nucleotide substitutions. There was a significant deviation in the genotypic frequencies at −853 and the allele frequencies for G were significantly higher in the COPD patient group than in the control group. For locus -418, the allele frequencies for C in the COPD patient group also tended to be higher than those in the control group. The −853 G/A nucleotide substitution was a silent variant. The -418 G/C substitution was located in the consensus sequence for the Sp1 binding site.

These polymorphisms may be associated with the development of chronic obstructive pulmonary disease, decreasing the transcription and stability of the messenger ribonucleic acid, and available as genetic markers of susceptibility to the disease.
Eur Respir J 2001; 18: 748–752.

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Fax: 81 298533144

Keywords: Chronic obstructive pulmonary disease
polymorphism
tissue inhibitors of metalloproteinases

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CHRONIC OBSTRUCTIVE PULMONARY DISEASE

Transforming growth factor-β_1 genotype and susceptibility to chronic obstructive pulmonary disease

L Wu, J Chau, R P Young, V Pokorny, G D Mills, R Hopkins, L McLean, P N Black

Thorax 2004;**59**:126–129. doi: 10.1136/thorax.2003.005769

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Accepted 15 October 2003

Background: Only a few long term smokers develop symptomatic chronic obstructive pulmonary disease (COPD) and this may be due, at least in part, to genetic susceptibility to the disease. Transforming growth factor β_1 (TGF-β_1) has a number of actions that make it a candidate for a role in the pathogenesis of COPD. We have investigated a single nucleotide polymorphism at exon 1 nucleotide position 29 (T→C) of the TGF-β_1 gene that produces a substitution at codon 10 (Leu→Pro).

Methods: The frequency of this polymorphism was determined in 165 subjects with COPD, 140 healthy blood donors, and 76 smokers with normal lung function (resistant smokers) using the polymerase chain reaction and restriction enzyme fragment length polymorphism.

Results: The distribution of genotypes was Leu-Leu (41.8%), Leu-Pro (50.3%), and Pro-Pro (7.9%) for subjects with COPD, which was significantly different from the control subjects (blood donors: Leu-Leu (29.3%), Leu-Pro (52.1%) and Pro-Pro (18.6%), $p=0.006$; resistant smokers: Leu-Leu (28.9%), Leu-Pro (51.3%) and Pro-Pro (19.7%), $p=0.02$). The Pro^{10} allele was less common in subjects with COPD (33%) than in blood donors (45%; OR=0.62, 95% CI 0.45 to 0.86, $p=0.005$) and resistant smokers (45%; OR=0.59, 95% CI 0.40 to 0.88, $p=0.01$).

Conclusions: The proline allele at codon 10 of the TGF-β_1 gene occurs more commonly in control subjects than in individuals with COPD. This allele is associated with increased production of TGF-β_1 which raises the possibility that TGF-β_1 has a protective role in COPD.

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Pharmacogenetics of chronic obstructive pulmonary disease: challenges and opportunities

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Abstract

Similar to other common chronic diseases, chronic obstructive pulmonary disease (COPD) is a heterogeneous disorder with multiple disease subtypes. Candidate gene studies have found genetic associations for COPD-related phenotypes that may be relevant for pharmacogenetics studies, including lung function decline and COPD exacerbations. However, few COPD pharmacogenetics studies have been completed. Most studies have focused on the role of variants in the β2-adrenergic receptor gene on bronchodilator response, but the findings have been inconclusive. Candidate gene studies highlight the concept that genes for COPD susceptibility may also be relevant in COPD pharmacogenetics. Currently, there are no clinical applications of pharmacogenetics to COPD therapy, but the use of pharmacogenetics to determine initial smoking cessation therapy may be closer to clinical application.

Chronic obstructive pulmonary disease pharmacogenetics studies of the β_2-adrenergic receptor (*ADRB2*)

Study	Treatment	Result	Ref.
Studies showing association			
Hizawa *et al.* (2007)	SABA	Arg16 allele was associated with lower BDR	[69]
Umeda *et al.* (2008)	LAMA	Arg16 homozygotes had significant increase in FEV_1 at 12 weeks	[72]
Kim *et al.* (2009)	SABA	Two synonymous coding SNPs were associated with BDR in NETT, but not in the family-based study	[28]
Studies showing no association			
Joos *et al.* (2003)	SABA	No association between codon 16 or 27 variants and BDR	[68]
Kim *et al.* (2008)	SABA, LABA/ICS	No association between codon 16 or 27 variants and either acute BDR or 12-week change in FEV_1	[71]
Mokry *et al.* (2008)	SABA	Haplotypes of codon 16 and 27 variants were not associated with BDR	[70]

BDR: Bronchodilator responsiveness; FEV_1: Forced expiratory volume in 1 s; ICS: Inhaled corticosteroid; LABA: Long-acting β-agonist; LAMA: Long-acting muscarinic antagonist; NETT: National Emphysema Treatment Trial; SABA: Short-acting β-agonist.

Other genes with significant chronic obstructive pulmonary disease pharmacogenetic associations

Study	Gene	Treatment	Outcome	Ref.
Zhang *et al.* (2007)	Hemopoietic cell kinase (*HCK*)	SABA	BDR	[75]
Hersh *et al.* (2007)	Microsomal epoxide hydrolase (*EPHX1*) Glutathione *S*-transferase pi 1 (*GSTP1*)	LVRS	Change in BODE score at 6 months	[78]
Kim *et al.* (2009)	Corticotropin-releasing hormone receptor 1 (*CRHR1*)	LABA/ICS	Change in FEV_1 at 12 weeks	[77]
Kim *et al.* (2009)	Microsomal epoxide hydrolase (*EPHX1*) Serpin peptidase inhibitor E2 (*SERPINE2*)	SABA	BDR	[28]

BDR: Bronchodilator responsiveness; BODE: BMI, airflow obstruction, dyspnea and exercise capacity; FEV_1: Forced expiratory volume in 1 s; IC Inhaled corticosteroid; LABA: Long-acting β-agonist; LVRS: Lung volume-reduction surgery; SABA: Short-acting β-agonist

Wood *et al.*: *Genome Medicine* 2009, **1**:112

Review

Chronic obstructive pulmonary disease: towards pharmacogenetics

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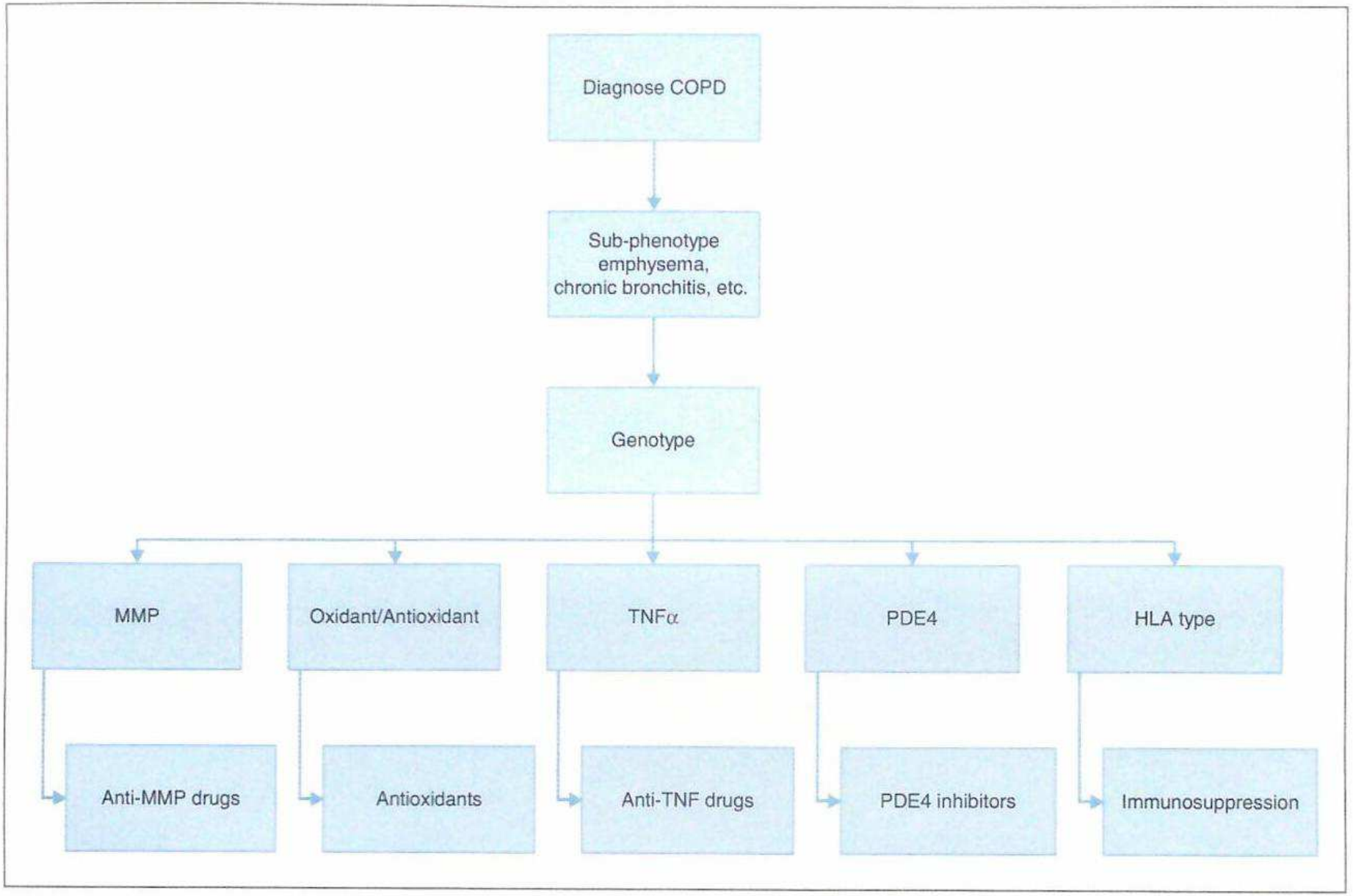
Diagnose COPD
Sub-phenotype
emphysema,
chronic bronchitis, etc.
Genotype
MMP
Oxidant/Antioxidant
TNFα
PDE4
HLA type
Anti-MMP drugs
Antioxidants
Anti-TNF drugs
PDE4 inhibitors
Immunosuppression

Table 3

Potential new medical treatments for COPD, their mechanisms of action and reported clinical effects

Treatment	Mechanism	Clinical effects	Genes associated with response to therapy*	Genes associated with COPD†	References‡
Cilomilast	PDE4 inhibitor	Improvement in FEV1 and quality of life; reduced FEV1 decline; fewer exacerbations	-	*PDE4*	[72,73,75]
Roflumilast	PDE4 inhibitor	Improvement in FEV1	-	*PDE4*	[74]
BAYx1005	LTB4 synthesis inhibitor	Reduced bronchial inflammation	-	-	[111]
ABX-IL8	Monoclonal antibody specific to IL8	Improvement in dyspnoea and FEV1 early in treatment, but no sustained improvement in lung function by the end of the trial	-	-	[112]
N-acetylcysteine	Antioxidant	No improvement in lung function or exacerbation frequency	-	*GSTP1*, *GSTM1*, *EPHX1*, *SOD3* and *HMOX1*	[113]
Infliximab	Anti-TNFα	No benefit except in cachectic participants, whose 6MWT distance and frequency of hospital admissions improved	*TNFA*	*TNFA*	[53,79]
Marimastat	MMP inhibitor	Tested in asthma; reduced airway hyper-responsiveness	-	*MMP1* and *MMP9*	[114]
All-*trans*-retinoic acid	Repairs elastase/smoke induced lung damage	Clinical trials in progress; pilot studies confirm safety	-	-	[115]
Montelukast	Leukotriene receptor antagonist	Improved FEV1 and quality of life; observational study suggested reduced hospital admissions and medication usage	LTC4 synthase	-	[59,116,117]

*Refers to all studies of the drug class, which may have been carried out on other diseases. †Refers to genes relevant to the pathways on which each listed drug acts. ‡Refers to publications reporting clinical drug trials, studies of pharmacogenetics, and those genetic association studies not listed in Table 2. Further details can be found in the text. Abbreviations: LTB4, leukotriene B4; 6MWT, 6 minute walk test.

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Pharmacogenetics of chronic obstructive pulmonary disease.

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Abstract

Chronic obstructive pulmonary disease (COPD) is a complex genetic disease that develops as a result of the interaction of multiple susceptibility genes and environmental factors. Major therapeutic approaches include smoking cessation, treatment with bronchodilators and corticosteroid therapy. The goal of understanding the genetic defects in patients with COPD will be not only to redefine thedisease phenotypes based on the genetic information, but also to alternatively approach patients based on the understanding of COPD pathogenesis, which will lead to improved clinical outcomes. Although there is no single ideal phenotype for COPD pharmacogenetic studies, thus far, most pharmacogenetics studies have focused on the role of variants in the β2-adrenergic receptor gene on bronchodilator response. The inconclusive results yielded by these studies highlight many of the difficulties researchers face in assessing the influence of genetic variants and in translating this to clinically relevant outcomes.

PMID: 23859575 [PubMed - in process]

Heterogeneity of chronic obstructive pulmonary disease: variable treatment response according to chronic obstructive pulmonary disease subphenotype

- Chronic obstructive pulmonary disease (COPD) is a complex condition with pulmonary and extrapulmonary manifestations.
- Several phenotypes are associated with different responses to currently available therapies.
- These phenotypes include the exacerbator phenotype, the overlap phenotype with asthma, the emphysema phenotype and a subset of COPD patients with persistent systemic inflammation.

Pharmacogenetic studies in COPD

- Most pharmacogenetic studies have focused on the role played by variants in the *ADRB2* gene on bronchodilator response.
- *ADRB2* has at least four functional polymorphisms (Cys19Arg, Arg16Gly, Gln27Glu and Thr164Ile).
- These *ADRB2* polymorphisms may be determinants of preferential bronchodilator response to either β2-agonists or anticholinergics in COPD patients.
- Overall, the evidence for *ADRB2* polymorphisms as pharmacogenetic determinants of response to COPD therapies is conflicting, a common finding in diseases with complex trait genetics.

Pharmacogenetics of smoking cessation

- Cigarette smoking is the major environmental risk factor for COPD, and smoking cessation reduces the rate of lung function decline and mortality in COPD.
- Multiple studies, including a genome-wide association study, have demonstrated genetic effects on smoking behaviors and cessation.
- To date, the most promising results were obtained for polymorphisms in the *CYP2A6* gene.

Conclusion & future perspective

- We need to focus more attention on unraveling the heterogeneous pathobiology of COPD so as to be able to effectively deliver the right treatment to the right patient.
- Efforts to identify new targets and pathways related to COPD will provide a basis for refining individual predictors of the disease and drug response.

FARMACOGENETICA EN EPOC

- La mayoría de los estudios de farmacogenética se han centrado en el papel del polimorfismo del gen que codifica el receptor de β2-adrenérgicos en respuesta broncodilatadora (ADRB2)
- ADRB2 tiene al menos cuatro polimorfismos funcionales Cys19Arg, Arg16Gly, Gin27Glu y Thr164Ile
- Estos polimorfismos pueden ser determinantes en la respuesta broncodilatadora a cualquiera de los agonistas β2
- En general la evidencia de polimorfismos ADRB2 en la respuesta al tratamiento de la EPOC no es concluyente, situación frecuente en enfermedades genéticas de rasgo complejo

LA INTEGRACION DE LA GENETICA, LA BIOLOGIA, FACTORES AMBIENTALES Y LOS FENOTIPOS CLINICOS DEBE CONTRIBUIR A MEJORAR LAS EXPECTATIVAS Y EL TRATAMIENTO PERSONALIZADO CENTRADO EN EL PACIENTE CON EPOC

El genotipo indica qué es lo que puede suceder, pero no predice exactamente que sucederá

C. Karlson (1913 – 1997)

Allí donde no hay visión de futuro el pueblo desaparece.

proverbio

Salomón