

Supplementary

β_2 -Adrenergic Genotypes and Risk of Severe Exacerbations

in COPD: a prospective cohort study

Truls Sylan Ingebrigtsen, Jørgen Vestbo, Line Rode, Jacob Louis Marott, Peter Lange, and

Børge Grønne Nordestgaard

Table S1. Baseline characteristics across the Gly16Arg (rs1042713, c.46G>A) polymorphism. Upper part shows Copenhagen General Population Study and lower part shows Copenhagen City Heart Study.

Characteristic	rs1042713			p-value
	16Gly homozygotes N=36,768	16Gly/Arg heterozygotes N=44,860	16Arg homozygotes N=13,575	
FEV ₁ - liters	2.98 ±0.88	2.97 ±0.89	2.98 ±0.89	0.14
FEV ₁ - % of predicted value	97.0 ±16.9	96.7 ±16.8	96.4 ±16.8	0.0003
FEV ₁ /FVC	0.77 ±0.08	0.77 ±0.08	0.77 ±0.08	0.37
Male sex - no. (%)	16,695 (45.1)	20,148 (44.6)	6,245 (45.6)	0.08
Age - yr	57.9 ±13.1	58.0 ±13.1	57.8 ±13.0	0.36
Current smoking - no. (%)	6,544 (18.4)	7,999 (18.4)	2,480 (18.9)	
Former smoking - no. (%)	14,661 (41.2)	17,869 (41.2)	5,411 (41.1)	0.79†
Never smoking - no. (%)	14,374 (40.4)	17,532 (40.4)	5,259 (40.0)	
Frequent Previous Respiratory Infections* - no. (%)	8,640 (23.7)	10,441 (23.4)	3,110 (23.0)	0.31
Copenhagen City Heart Study	16Gly homozygotes N=3,970	16Gly/Arg heterozygotes N=4,751	16Arg homozygotes N=1,516	
FEV ₁ - liters	2.79 ±1.03	2.79 ±1.03	2.81 ±1.06	0.74
FEV ₁ - % of predicted value	92.2 ±20.1	92.0 ±20.3	92.3 ±20.3	0.87
FEV ₁ /VC	0.77 ±0.09	0.77 ±0.09	0.77 ±0.10	0.94
Male sex - no. (%)	1754 (43.7)	2196 (45.7)	687 (44.8)	0.18
Age - yr	56.6 ±16.1	56.6 ±16.3	56.2 ±16.4	0.62
Current smoking - no. (%)	1887 (47.3)	2233 (46.7)	723 (47.5)	
Former smoking - no. (%)	1069 (26.8)	1226 (25.6)	388 (25.5)	0.39†
Never smoking - no. (%)	1033 (25.9)	1322 (27.7)	411 (27.0)	
Frequent Previous Respiratory Infections* - no. (%)	859 (21.7)	1062 (22.4)	347 (22.9)	0.57

*At least five respiratory infections during the preceding ten years requiring consulting a doctor and/or staying home from work.
†Compares current, former and never smoking.
Plus-minus values are mean ±SD

Table S2. Baseline characteristics across the Gly16Arg (rs1042713, c.46G>A) polymorphism. Upper part shows individuals with COPD in the Copenhagen General Population Study and lower part shows individuals with COPD in the Copenhagen City Heart Study.

Characteristic	rs1042713			p-value
	16Gly homozygotes N=1,978	16Gly/Arg heterozygotes N=2,488	16Arg homozygotes N=753	
COPD in Copenhagen General Population Study				
FEV ₁ - liters	1.83 ±0.59	1.81 ±0.61	1.83 ±0.60	0.54
FEV ₁ - % of predicted value	65.5 ±11.8	65.1 ±12.3	64.7 ±12.0	0.29
FEV ₁ /FVC	0.61 ±0.08	0.61 ±0.08	0.60 ±0.08	0.46
Male sex - no. (%)	960 (48.5)	1186 (47.7)	398 (52.9)	0.04
Age - yr	66.6 ±10.7	66.9 ±11.0	66.7 ±10.8	0.59
Breathlessness* - no. (%)	373 (18.9)	463 (18.6)	131 (17.4)	0.67
Current smoking - no. (%)	778 (40.4)	985 (40.7)	301 (41.0)	
Former smoking - no. (%)	860 (44.6)	1081 (44.7)	327 (44.6)	0.99 ††
Never smoking - no. (%)	290 (15.0)	355 (14.7)	106 (14.4)	
Frequent Previous Respiratory Infections† - no. (%)	771 (39.9)	948 (38.8)	292 (39.5)	0.76
Any inhalants‡ - no. (%)	301 (15.2)	405 (16.3)	112 (14.9)	0.50
Long-acting β ₂ -agonists - no. (%)	175 (8.8)	264 (10.6)	78 (10.4)	
Long-acting anticholinergics - no. (%)	115 (5.8)	158 (6.4)	38 (5.0)	0.39
COPD in Copenhagen City Heart Study				
	16Gly homozygotes N=344	16Gly/Arg heterozygotes N=414	16Arg Homozygotes N=122	p-value
FEV ₁ - liters	1.67 ±0.61	1.65 ±0.58	1.57 ±0.60	0.30
FEV ₁ - % of predicted value	61.6 ±14.2	61.2 ±14.1	60.0 ±14.3	0.55
FEV ₁ /FVC	0.61 ±0.07	0.61 ±0.08	0.59 ±0.09	0.08
Male sex - no. (%)	187 (54.4)	230 (55.6)	63 (51.6)	0.74
Age - yr	67.2 ±9.1	67.0 ±9.3	67.6 ±9.7	0.81
Breathlessness* - no. (%)	101 (29.6)	114 (27.7)	35 (28.9)	0.85
Current smoking - no. (%)	230 (67.8)	278 (67.6)	78 (65.0)	
Former smoking - no. (%)	83 (24.5)	103 (25.1)	28 (23.3)	0.64 ††
Never smoking - no. (%)	26 (7.7)	30 (7.3)	14 (11.7)	
Frequent Previous Respiratory Infections† - no. (%)	111 (32.8)	137 (33.8)	38 (31.7)	0.90

*A score on the Modified Medical Research Council Scale equal to or larger than two.

†At least five respiratory infections during the preceding ten years requiring consulting a doctor and/or staying home from work

‡Short-acting β₂-agonists, long-acting β₂-agonists with or without inhaled corticosteroids, or long-acting anticholinergics.

†† Compares current, former and never smoking

Plus-minus values are mean ±SD

Table S3. Baseline characteristics across the Gln27Glu (rs1042714, c.79C>G) polymorphism. Upper part shows Copenhagen General Population Study and lower part shows Copenhagen City Heart Study.

Characteristic	rs1042714			p-value
	27Gln homozygotes N=29,042	27Gln/Glu heterozygotes N=46,450	27Glu homozygotes N=18,366	
Copenhagen General Population Study				
FEV ₁ - liters	2.98 ±0.89	2.98 ±0.88	2.98 ±0.88	0.99
FEV ₁ - % of predicted value	96.7 ±16.8	96.8 ±16.8	96.9 ±17.1	0.52
FEV ₁ /FVC	0.77 ±0.08	0.77 ±0.08	0.77 ±0.08	0.32
Male sex - no. (%)	13,109 (44.8)	21,081 (45.0)	8,307 (44.9)	0.82
Age - yr	57.9 ±13.1	57.9 ±13.1	58.0 ±13.1	0.59
Current smoking - no. (%)	5,202 (18.5)	8,329 (18.5)	3,291 (18.5)	0.86†
Former smoking - no. (%)	11,545 (41.1)	18,471 (41.1)	7,380 (41.5)	
Never smoking - no. (%)	11,351 (40.4)	18,155 (40.4)	7,103 (40.0)	
Frequent Previous Respiratory Infections* - no. (%)	6,750 (23.4)	10,747 (23.3)	4,389 (24.1)	0.10
Copenhagen City Heart Study				
	27Gln homozygotes N=3,296	27Gln/Glu heterozygotes N=4,949	27Glu homozygotes N=1,986	p-value
FEV ₁ - liters	2.81 ±1.04	2.77 ±1.03	2.80 ±1.02	0.25
FEV ₁ - % of predicted value	92.4 ±20.0	91.8 ±20.5	92.4 ±19.8	0.30
FEV ₁ /FVC	0.78 ±0.09	0.77 ±0.10	0.77 ±0.09	0.11
Male sex - no. (%)	1,481 (44.5)	2,261 (45.1)	891 (44.4)	0.80
Age - yr	56.0 ±16.6	56.9 ±16.0	56.6 ±16.2	0.06
Current smoking - no. (%)	1,544 (46.7)	2,340 (47.0)	955 (47.7)	0.33†
Former smoking - no. (%)	838 (25.4)	1,305 (26.2)	539 (27.0)	
Never smoking - no. (%)	921 (27.9)	1,338 (26.9)	506 (25.3)	
Frequent Previous Respiratory Infections* - no. (%)	740 (22.5)	1,111 (22.5)	415 (20.9)	0.29

*At least five respiratory infections during the preceding ten years requiring consulting a doctor and/or staying home from work

†Compares current, former and never smoking.

Plus-minus values are mean ±SD

Table S4. Baseline characteristics across the Gln27Glu (rs1042714, c.79C>G) polymorphism. Upper part shows individuals with COPD in the Copenhagen General Population Study and lower part shows individuals with COPD in the Copenhagen City Heart Study.

Characteristic	rs1042714			p-value
	27Gln homozygotes N=1,553	27Gln/Glu heterozygotes N=2,576	27Glu homozygotes N=1,031	
COPD in Copenhagen General Population Study				
FEV ₁ -liters	1.82 ±0.59	1.83 ±0.62	1.81 ±0.57	0.70
FEV ₁ - % of predicted value	65.0 ±12.1	65.2 ±12.1	65.2 ±12.0	0.86
FEV ₁ /FVC	0.60 ±0.08	0.61 ±0.08	0.61 ±0.08	0.59
Male sex - no. (%)	777 (50.0)	1,256 (48.8)	486 (47.1)	0.35
Age – yr	67.1 ±10.7	66.6 ±11.1	66.6 ±10.6	0.33
Breathlessness* - no. (%)	309 (19.9)	461 (17.9)	186 (18.0)	0.25
Current smoking - no. (%)	643 (42.4)	993 (39.7)	405 (40.2)	0.51 ††
Former smoking - no. (%)	660 (43.6)	1,130 (45.1)	453 (45.0)	
Never smoking - no. (%)	212 (14.0)	380 (15.2)	149 (14.8)	
Frequent Previous Respiratory Infections† - no. (%)	614 (40.2)	978 (38.8)	398 (39.5)	0.69
Any inhalants‡ - no. (%)	250 (16.1)	405 (15.7)	156 (15.1)	0.80
Long-acting β ₂ -agonists - no. (%)	164 (10.6)	253 (9.8)	94 (9.1)	0.48
Long-acting anticholinergics - no. (%)	102 (6.6)	143 (5.6)	61 (5.9)	0.41
COPD in Copenhagen City Heart Study				
	27Gln homozygotes N=256	27Gln/Glu heterozygotes N=456	27Glu homozygotes N=167	p-value
FEV ₁ - liters	1.62 ±0.61	1.63 ±0.56	1.75 ±0.66	0.05
FEV ₁ - % of predicted value	60.3 ±14.8	61.0 ±13.7	63.1 ±14.2	0.13
FEV ₁ /FVC	0.60 ±0.08	0.61 ±0.08	0.62 ±0.07	0.14
Male sex - no. (%)	136 (53.1)	246 (53.9)	97 (58.1)	0.57
Age – yr	67.4 ±9.3	67.3 ±9.2	66.3 ±9.4	0.43
Breathlessness* - no. (%)	78 (30.8)	132 (29.1)	40 (24.1)	0.31
Current smoking - no. (%)	169 (67.1)	299 (66.3)	118 (71.1)	0.50 ††
Former smoking - no. (%)	58 (23.0)	119 (26.4)	36 (21.7)	
Never smoking - no. (%)	25 (9.9)	33 (7.3)	12 (7.2)	
Frequent Previous Respiratory Infections† - no. (%)	78 (31.2)	154 (34.5)	54 (32.5)	0.66

*A score on the Modified Medical Research Council Scale equal to or larger than two.

†At least five respiratory infections during the preceding ten years requiring consulting a doctor and/or staying home from work

‡Short-acting β₂-agonists, long-acting β₂-agonists with or without inhaled corticosteroids, or long-acting anticholinergics.

†† Compares current, former and never smoking.

Plus-minus values are mean ±SD

Table S5. Upper part shows unadjusted competing risk regression analyses of the association between the single nucleotide polymorphisms Gly16Arg (rs1042713) and Gln27Glu (rs1042714) and COPD mortality in the Copenhagen General Population Study. Middle part shows competing risk regression analyses of the association between the single nucleotide polymorphisms Gly16Arg (rs1042713) and Gln27Glu (rs1042714) and severe exacerbations in the Copenhagen General Population Study adjusted for smoking status (never/former/current). Lower part shows unadjusted competing risk regression analyses of the association between the rare variant Thr164Ile (rs1800888) and severe exacerbations in the Copenhagen General Population Study

Upper part (COPD mortality, unadjusted)	
Genotype	HR (95% CI, P-value)
Gly16Gly (reference)	Reference
Gly16Arg	0.69 (0.26-1.82, P=0.46)
Arg16Arg	0.58 (0.11-2.96, P=0.52)
Glu27Glu (reference)	Reference
Gln27Glu	1.05 (0.35-3.18, P=0.93)
Gln27Gln	0.69 (0.13-3.57, P=0.65)
Middle part (severe exacerbations, adjusted for smoking)	
Gly16Gly (reference)	Reference
Gly16Arg	1.60 (1.28-2.01, P=0.00004)
Arg16Arg	1.44 (1.06-1.96, P=0.02)
Glu27Glu (reference)	Reference
Gln27Glu	1.39 (1.05-1.85, P=0.02)
Gln27Gln	1.50 (1.12-2.02, P=0.007)
Lower part (rare variant, severe exacerbations, unadjusted)	
Thr164Thr (reference)	Reference
Thr164Ile/Ile164Ile	1.10 (0.65-1.87, p=0.73)

HR=Hazard Ratio. 95% CI=95% Confidence Interval.

Table S6. Distribution of Gly16Arg (rs1042713) and Gln27Glu (rs1042714) genotypes among 94,483 individuals in the Copenhagen General Population Study with successful genotyping of both single nucleotide polymorphisms.

Genotypes*	rs1042713		
	16Gly homozygotes N=36,500	16Gly/Arg heterozygotes N=44,456	16Arg homozygotes N=13,527
rs1042714			
27Gln homozygotes N=29,231	Gly16Gly-Gln27Gln N=3,067 (3.2%)	Gly16Arg-Gln27Gln N=12,717 (13.5%)	Arg16Arg-Gln27Gln N=13,447 (14.2%)
27Gln/Glu heterozygotes N=46,765	Gly16Gly-Gln27Glu N=15,024 (15.9%)	Gly16Arg-Gln27Glu N=31,675 (33.5%)	Arg16Arg-Gln27Glu N=66 (0.1%)
27Glu homozygotes N=18,487	Gly16Gly-Glu27Glu N=18,409 (19.5%)	Gly16Arg-Glu27Glu N=64 (0.1%)	Arg16Arg-Glu27Glu N=14 (0.0%)

*Non-random combinations of Gly16Arg and Gln27Glu reflecting linkage disequilibrium.