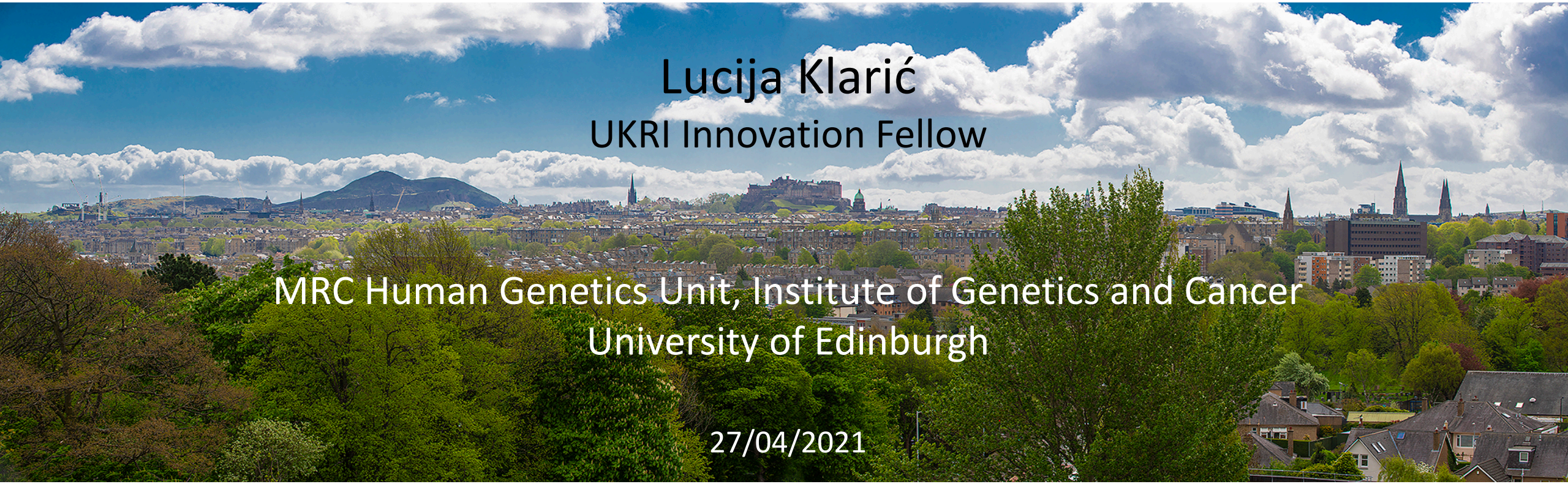
Genomski čimbenici u patogenezi COVID-19



Lucija Klarić
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27/04/2021

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Genomski čimbenici u patogenezi COVID-19

Article | Published: 11 December 2020

Genetic mechanisms of critical illness in COVID-19

Erola Pairo-Castineira, Sara Clohisey, Lucija Klaric, Andrew D. Bretherick, Konrad Rawlik, Dorota Pasko, Susan Walker, Nick Parkinson, Max Head Fourman, Clark D. Russell, James Furniss, Anne Richmond, Elvina Gountouna, Nicola Wrobel, David Harrison, Bo Wang, Yang Wu, Alison Meynert, Fiona Griffiths, Wilna Oosthuyzen, Athanasios Kousathanas, Loukas Moutsianas, Zhijian Yang, Ranran Zhai, Chenqing Zheng, Graeme Grimes, Rupert Beale, Jonathan Millar, Barbara Shih, Sean Keating, Marie Zechner, Chris Haley, David J. Porteous, Caroline Hayward, Jian Yang, Julian Knight, Charlotte Summers, Manu Shankar-Hari, Paul Klenerman, Lance Turtle, Antonia Ho, Shona C. Moore, Charles Hinds, Peter Horby, Alistair Nichol, David Maslove, Lowell Ling, Danny McAuley, Hugh Montgomery, Timothy Walsh, Alexandre C. Pereira, Alessandra Renieri, The GenOMICC Investigators, The ISARIC4C Investigators, The COVID-19 Human Genetics Initiative, 23andMe Investigators, BRACOVID Investigators, Gen-COVID Investigators, Xia Shen, Chris P. Ponting, Angie Fawkes, Albert Tenesa, Mark Caulfield, Richard Scott, Kathy Rowan, Lee Murphy, Peter J. M. Openshaw, Malcolm G. Semple, Andrew Law, Veronique Vitart, James F. Wilson & J. Kenneth Baillie ✉ -Show fewer authors

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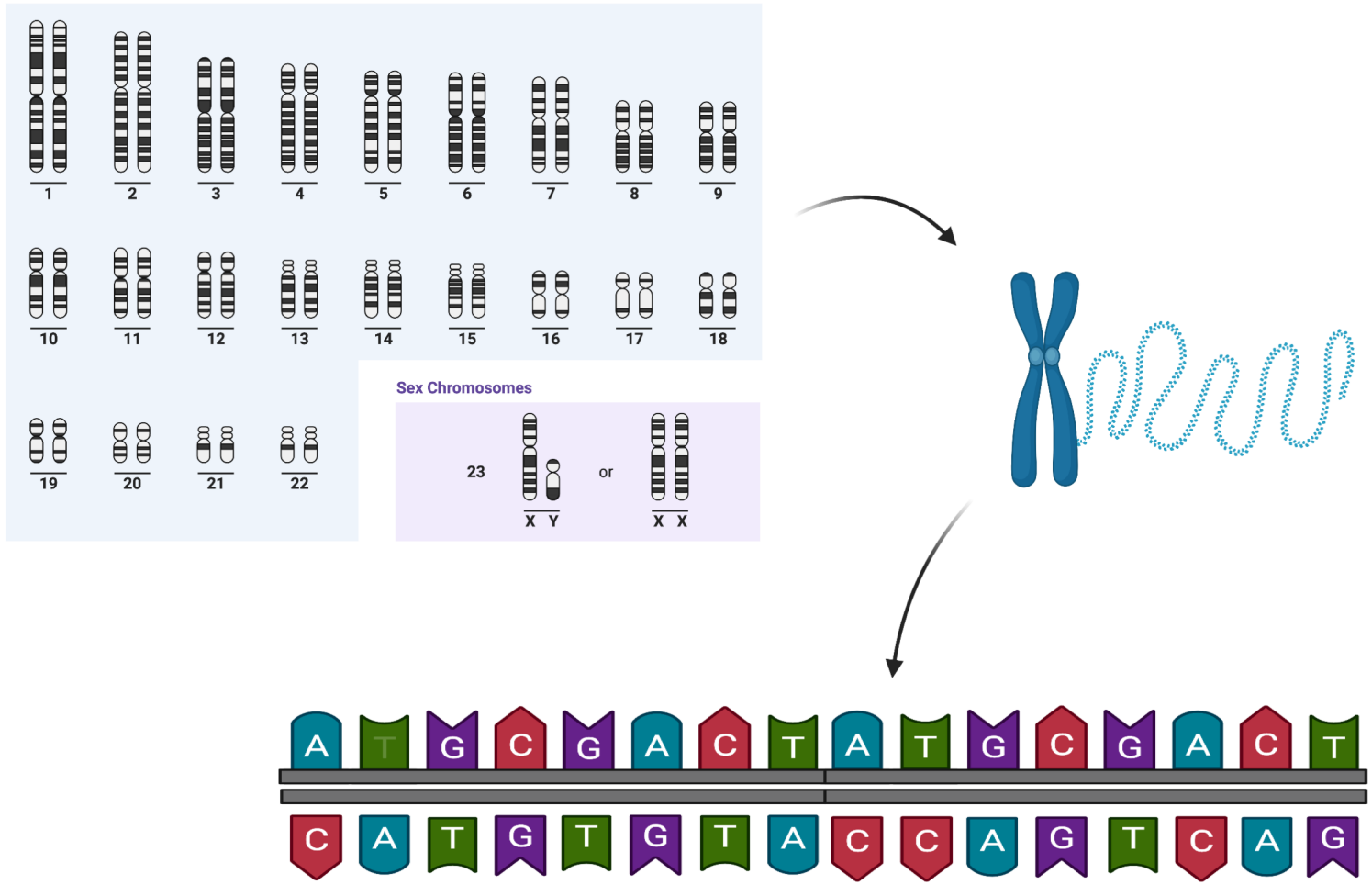
Cjelogenomske studije asocijacija (*engl* GWAS)

- *engl Genome-wide Association Study – GWAS*



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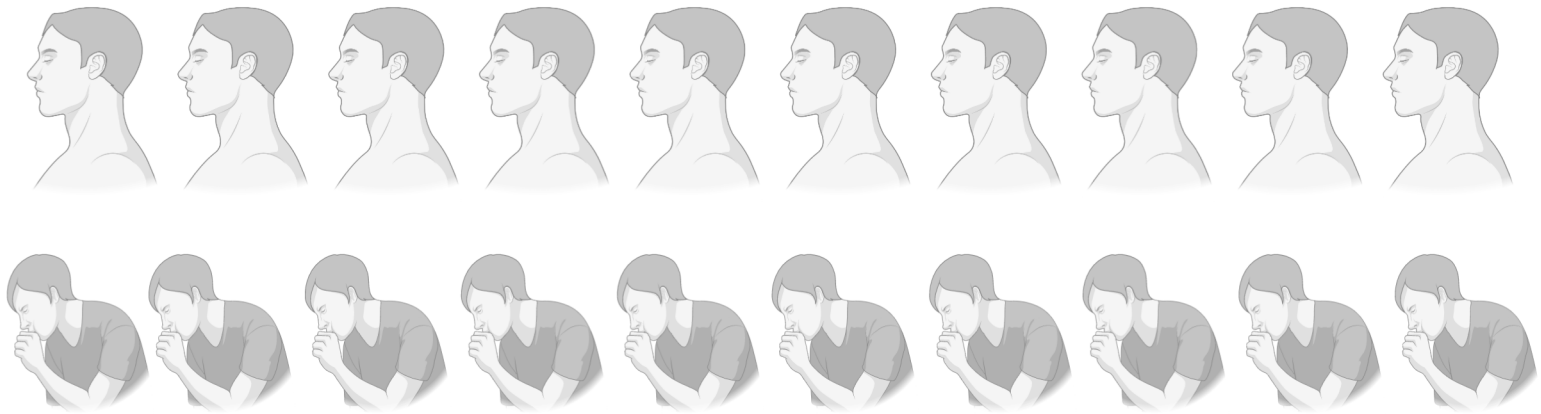

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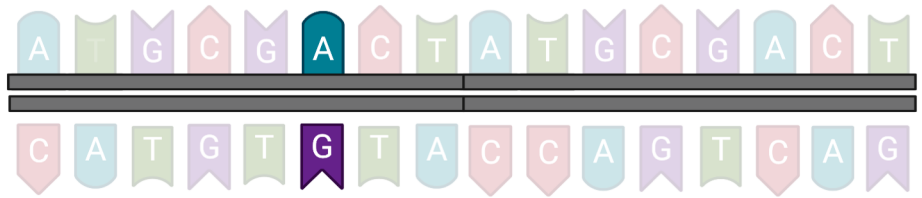

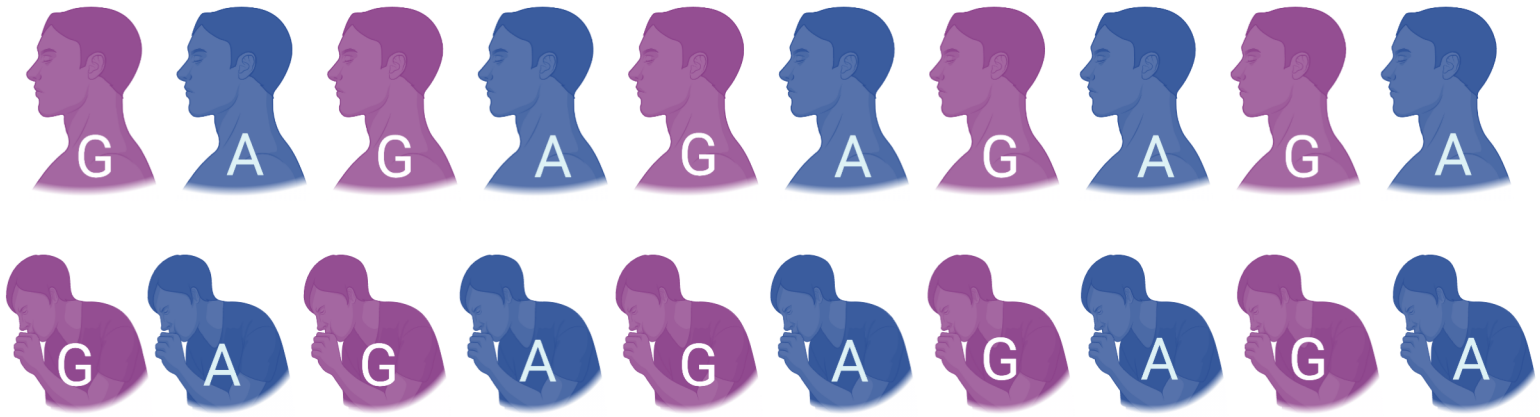

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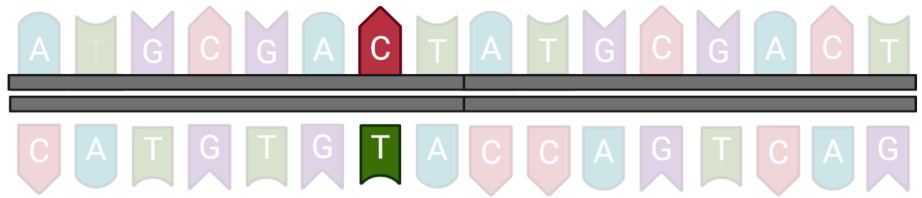

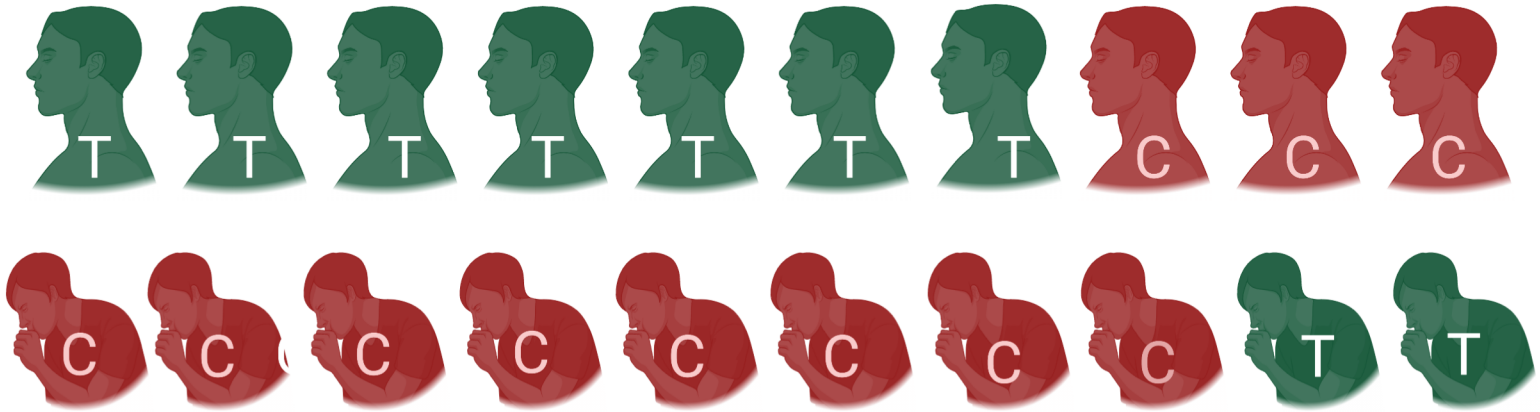

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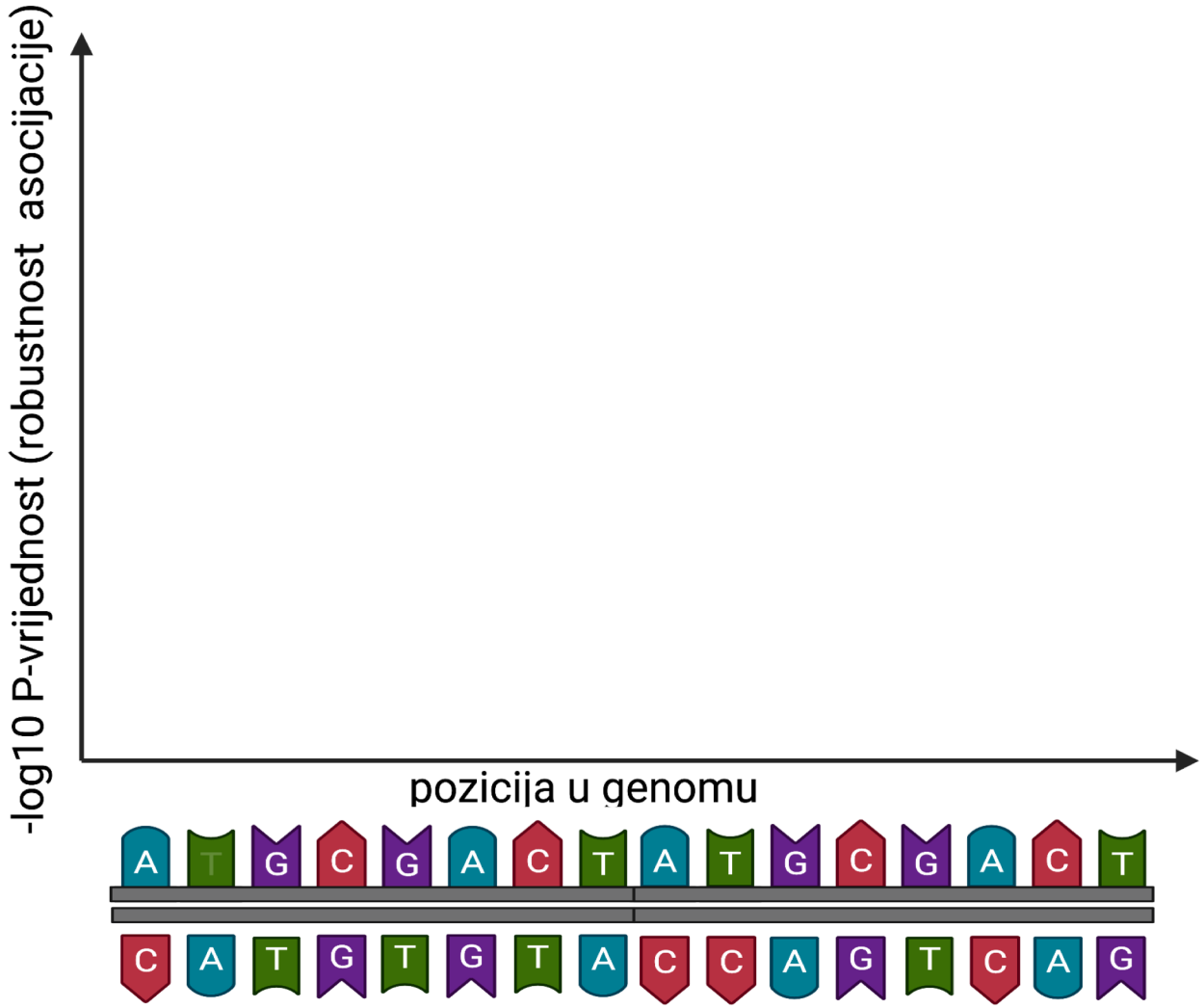

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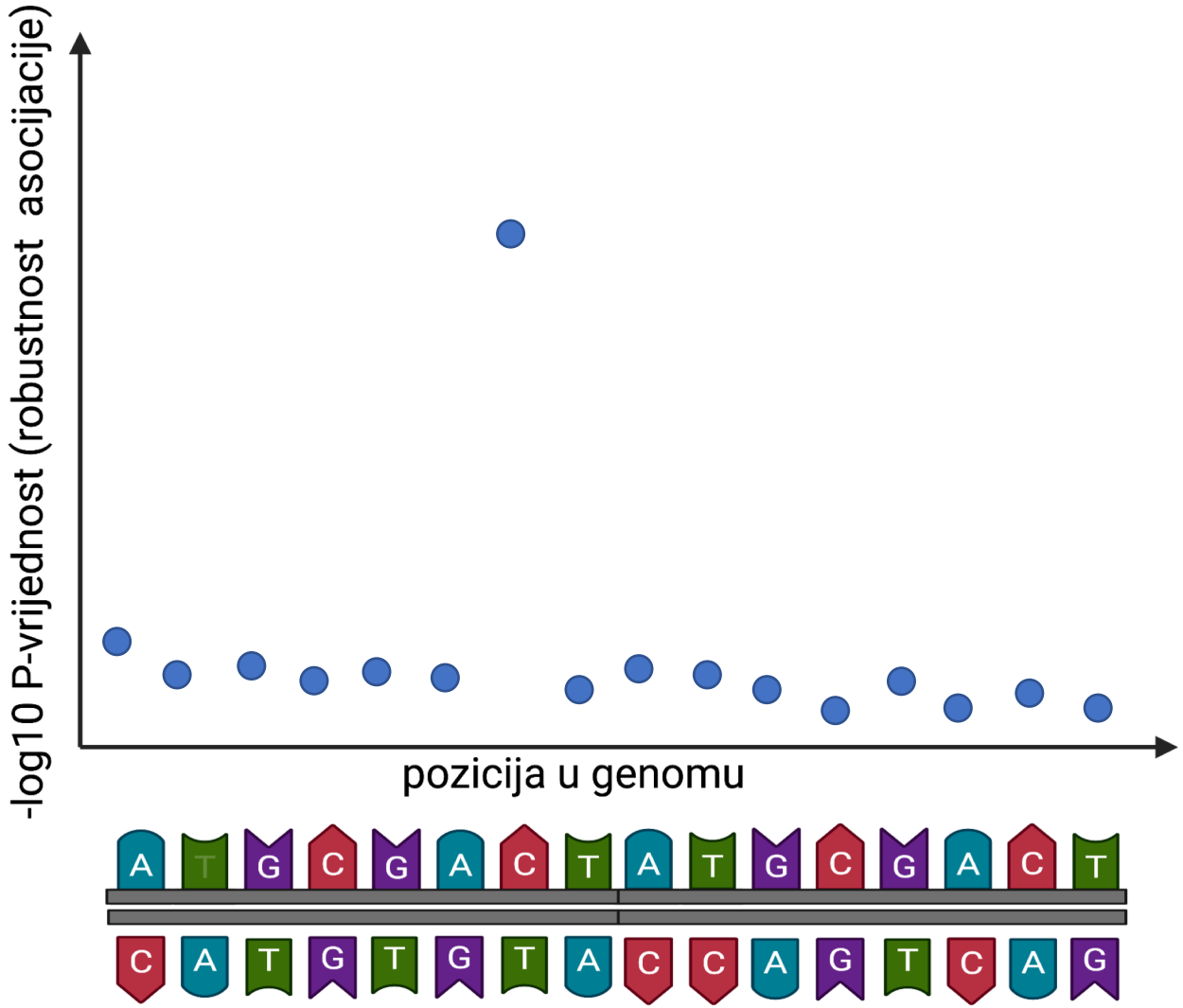

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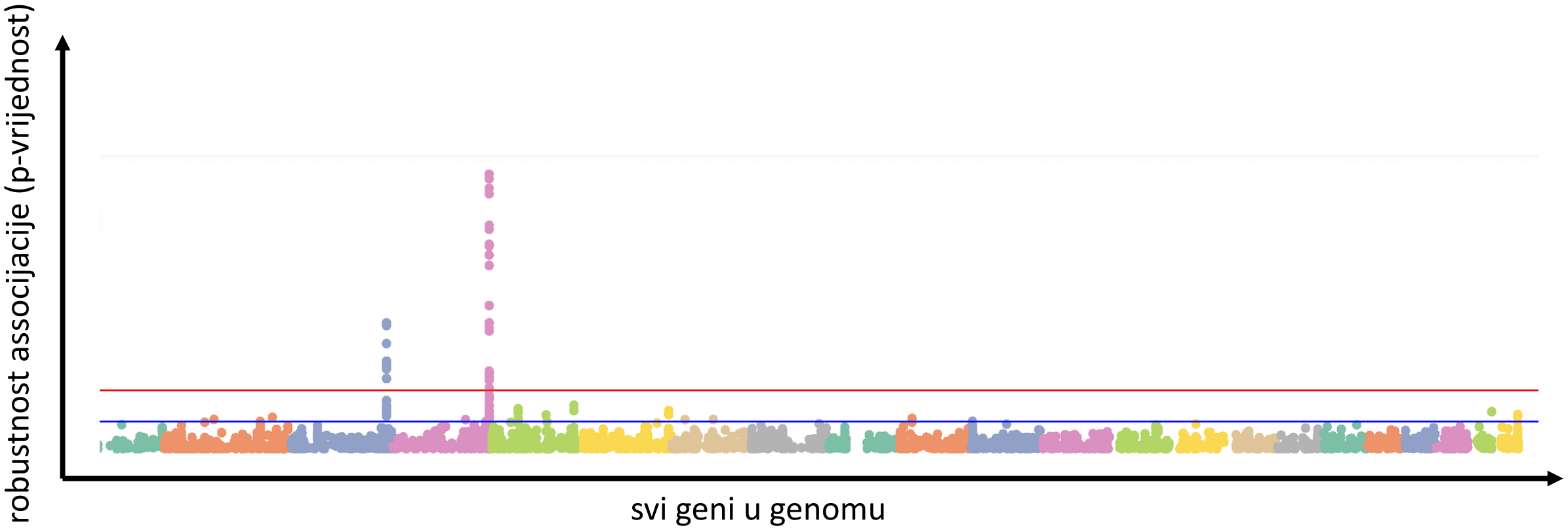
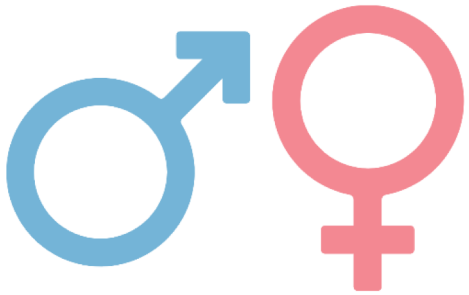


Cjelogenomske studije asocijacija (*engl* GWAS)

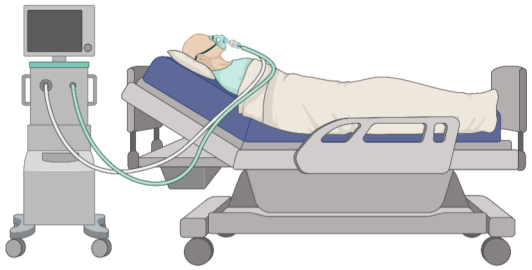
Genetska predispozicija za teški oblik COVID-19

- pacijenti sa intenzivnih jedinica diljem Ujedinjenog Kraljevstva (206)
- 1,676 pacijenata Europskog podrijetla

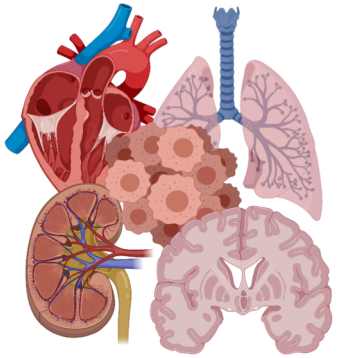
57 ± 12 godina



70% 30%



74% (1,152)



20% (335)

22% (369)

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Genetska predispozicija za teški oblik COVID-19

- UK biobanka
  - biomedicinska baza (500,000 sudionika)
  - genetika, klinički fenotipovi, elektronički medicinski zapisi, razni upitnici

- 8,380 “zdravih” sudionika
  - odgovarajuće karakteristike: spol, tjelesni indeks mase (*engl. BMI*), socio-ekonomski status

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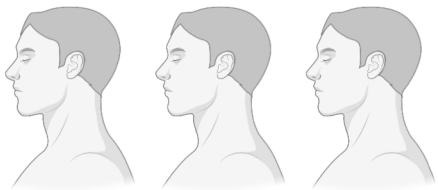
biobank uk



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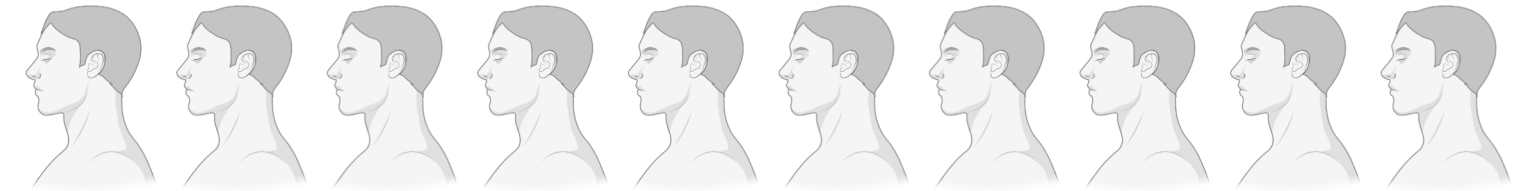
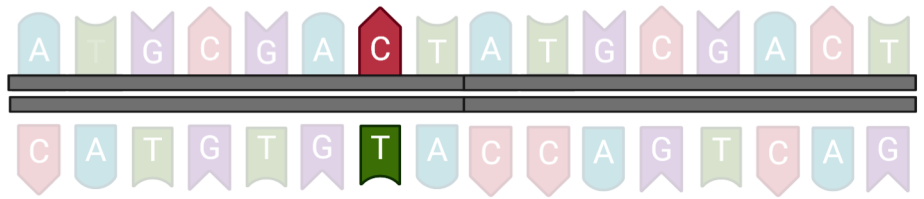


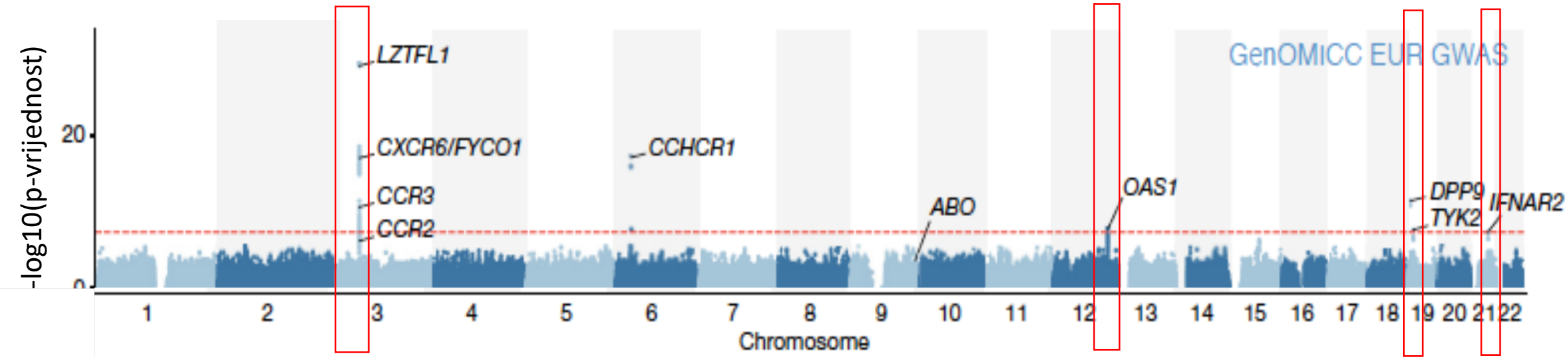
biobank uk

GenOMICC



× 4,500,000

Genetska predispozicija za teški oblik COVID-19



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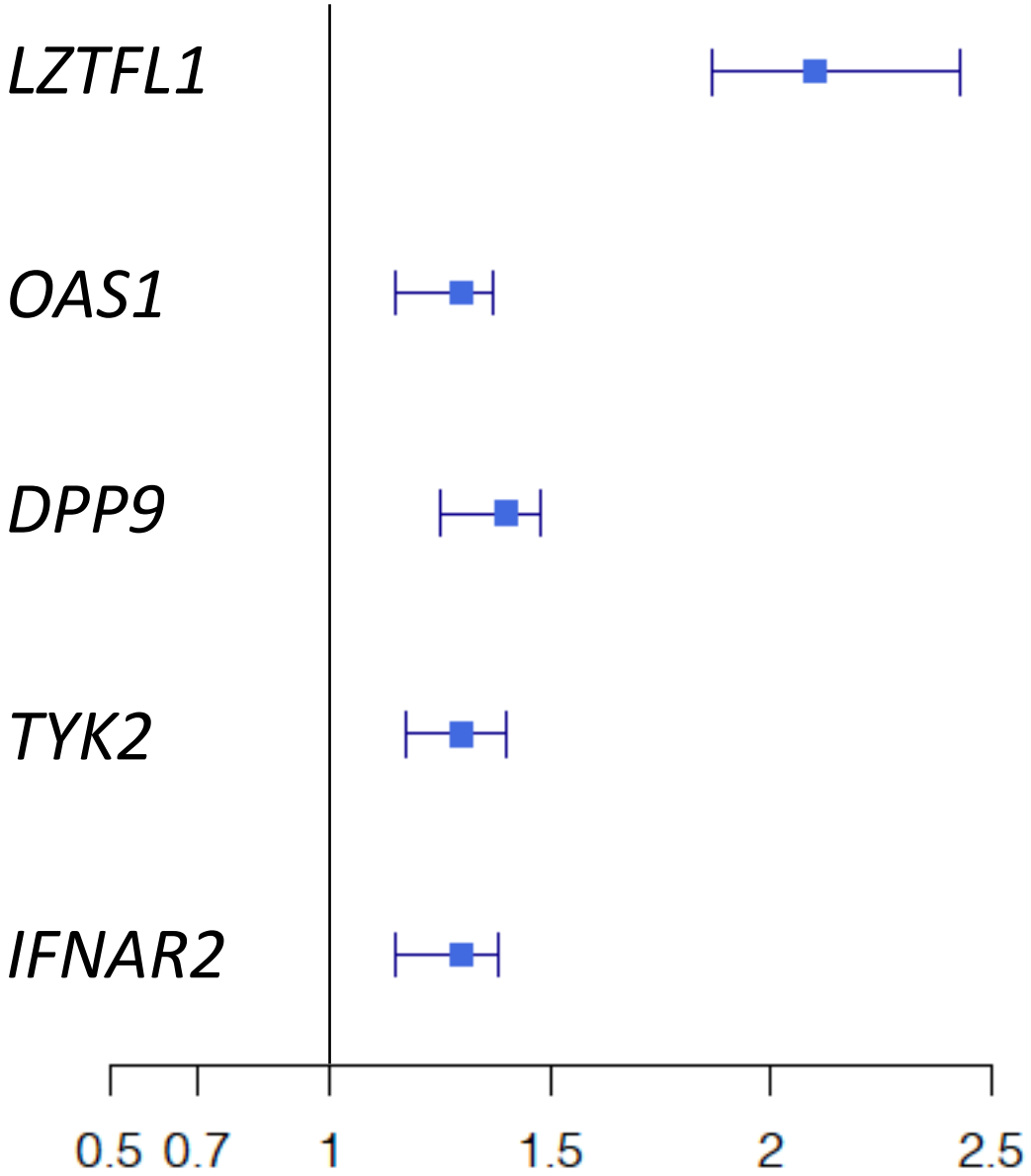
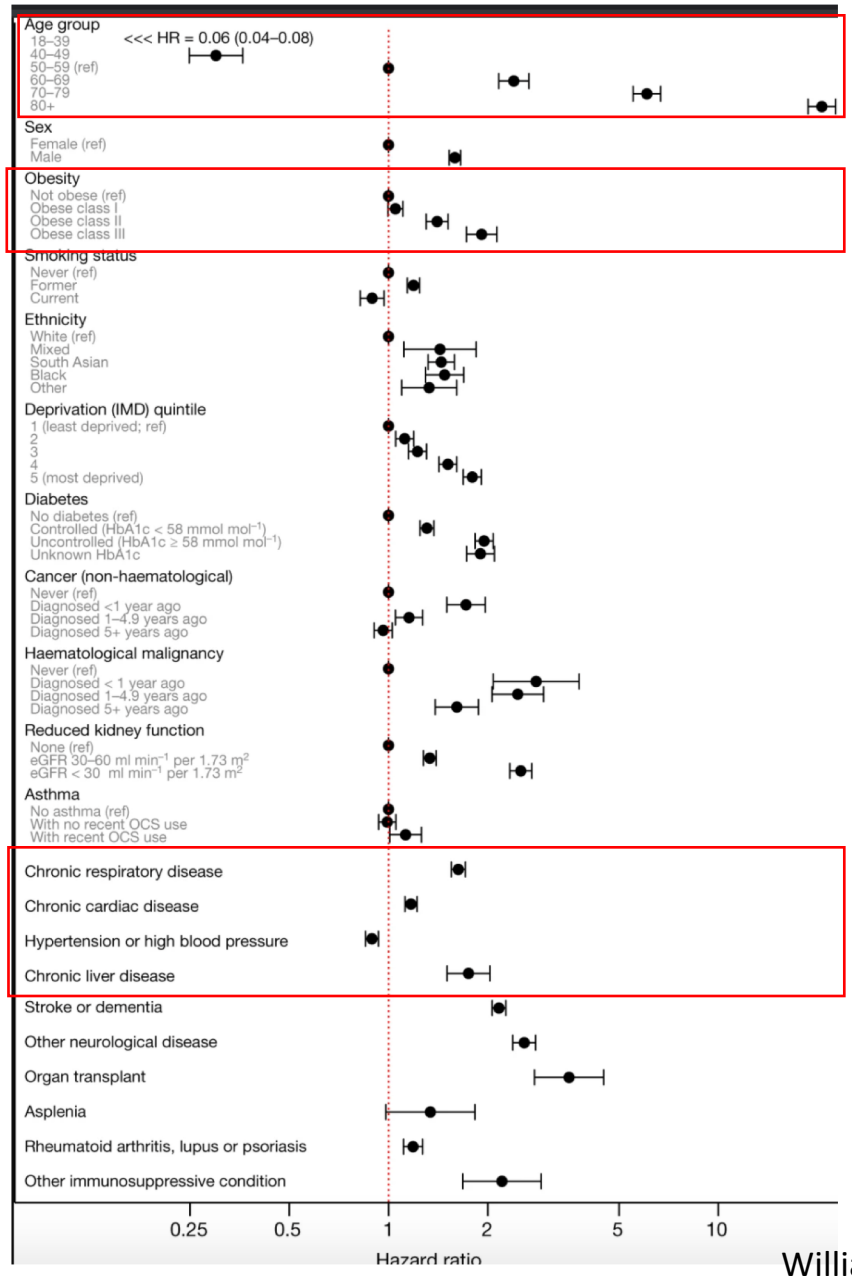
Pairo-Castineira, Clohisey, Klaric, Bretherick, Rawlike *et al*, Nature, 2021

Genetska predispozicija za teški oblik COVID-19





Dob: ~2 -15x

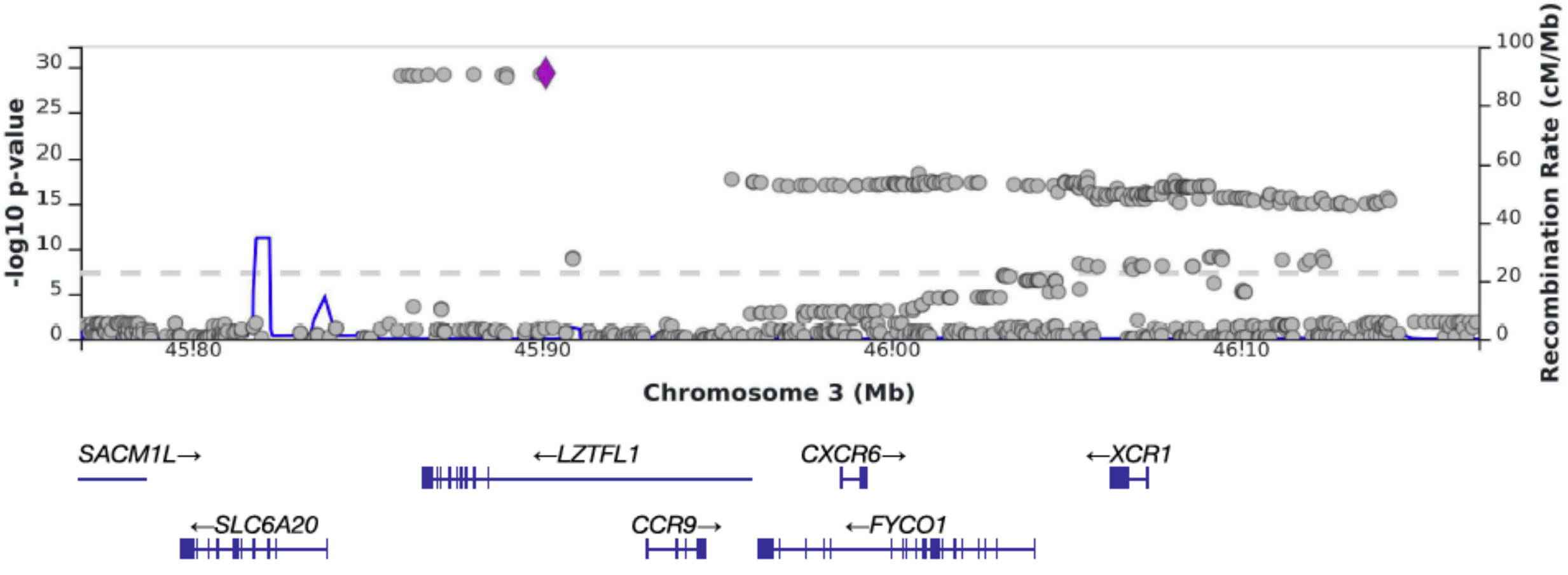
BMI: ~1.5-2.5x

Kronične bolesti pluća, srca i jetre: ~1.3-1.8x

Williamson *et al*, Nature, 07/2020

Genetska predispozicija za teški oblik COVID-19

- *LZTFL1* – interakcija sa Bardet-Biedl Syndrome proteinima
- *FYCO1* – potencijalno povezan sa beta-koronavirusima
- *CXCR6, CCR9, CCR2, CCR3* – kemokinski receptori vezani uz regulaciju upalnih procesa



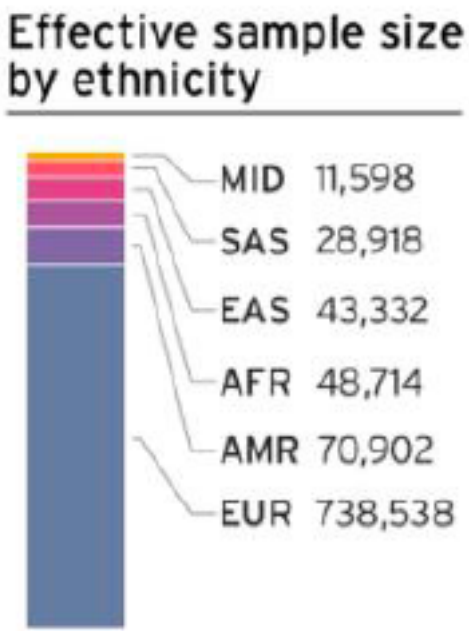
Genetska predispozicija za teški oblik COVID-19

- **Rani odgovor:**
  - ***OAS1*** – RNAza L; degradacije virusne RNA i inhibicija replikacije virusa
  - ***IFNAR2*** – intereferon receptor – aktivacija protuvirusnog odgovora

- **Kasni odgovor (eksesivni upalni odgovor):**
  - ***DPP9*** – serinska proteaza (citokini, uključujući CXCL10); aktivacija ”inflamasoma” (upalni odgovor na infekcije
    - idiopatska fibroza pluća
  - ***TYK2*** – tirozin kinaza (JAK); sudjeluje u interferonskom signalnom putu

Genetska predispozicija za teški oblik COVID-19

- Host Genetics Initiative
  - 46 studija iz 19 zemalja diljem svijeta



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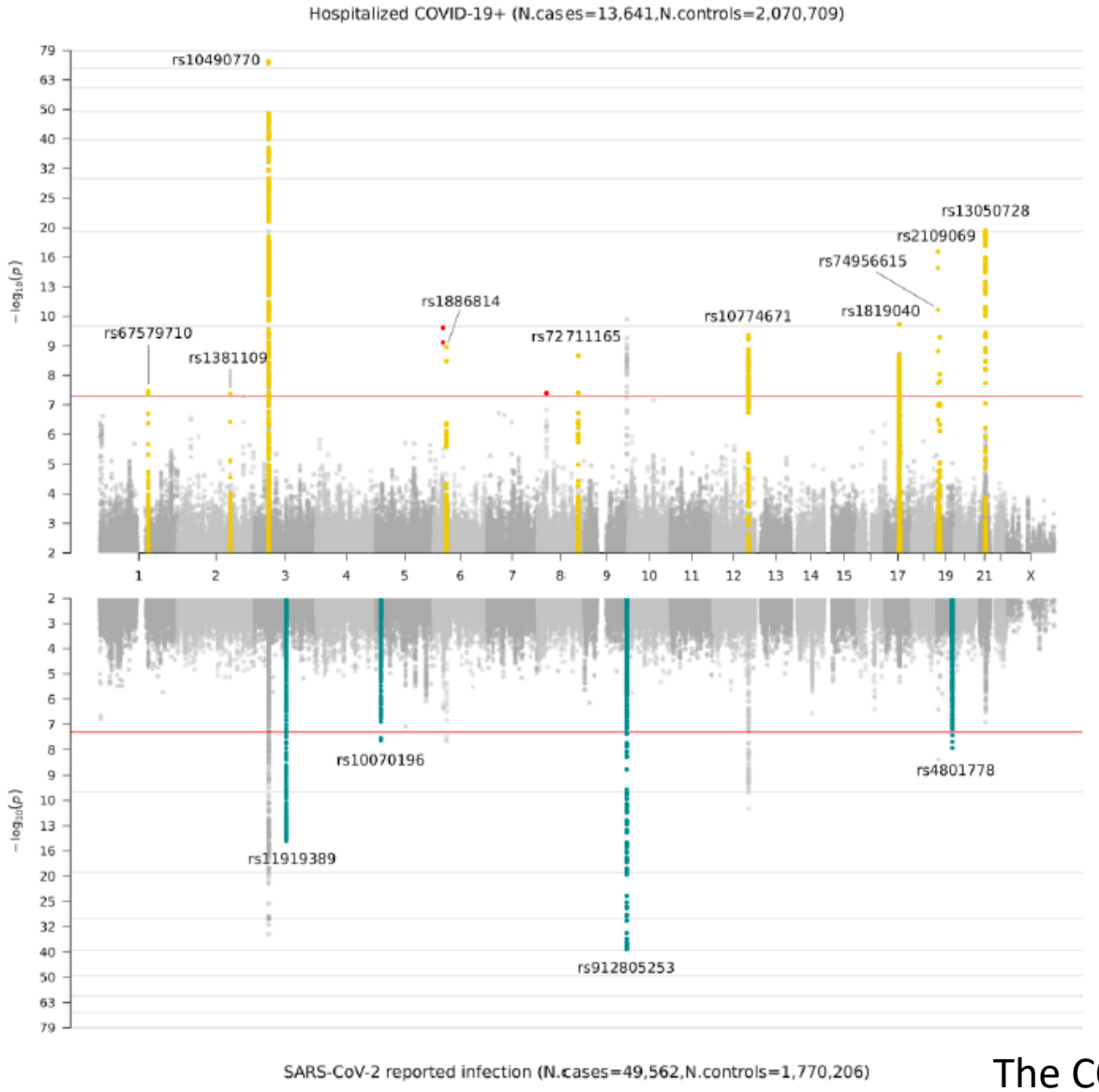
The COVID-19 Host Genetics Initiative, medRxiv, 2021

Genetska predispozicija za teški oblik COVID-19

- Host Genetic Initiative



The COVID-19 Host Genetics Initiative, medRxiv, 2021

Zaključci

- 5 genetskih regija
  - rani odgovor: *IFNAR2, OAS1*
  - oštećenje pluća: *DPP9, TYK2, LZTLF1-CCR2-CCR3-CCR9-CXCR6*

- razumijevanje bioloških procesa -> bolja terapija

- Potencijal za nove terapije:
  - *OAS1* – inhibitori fosfodiesteraze 12
  - *TYK2* – inhibitor JAK kinaze (baricitinib)
  - *IFNAR2* – tretman interferonima – neuspješan

Zahvale

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