The role of CD4+T cell expression profiles in colorectal cancer development

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wellcome

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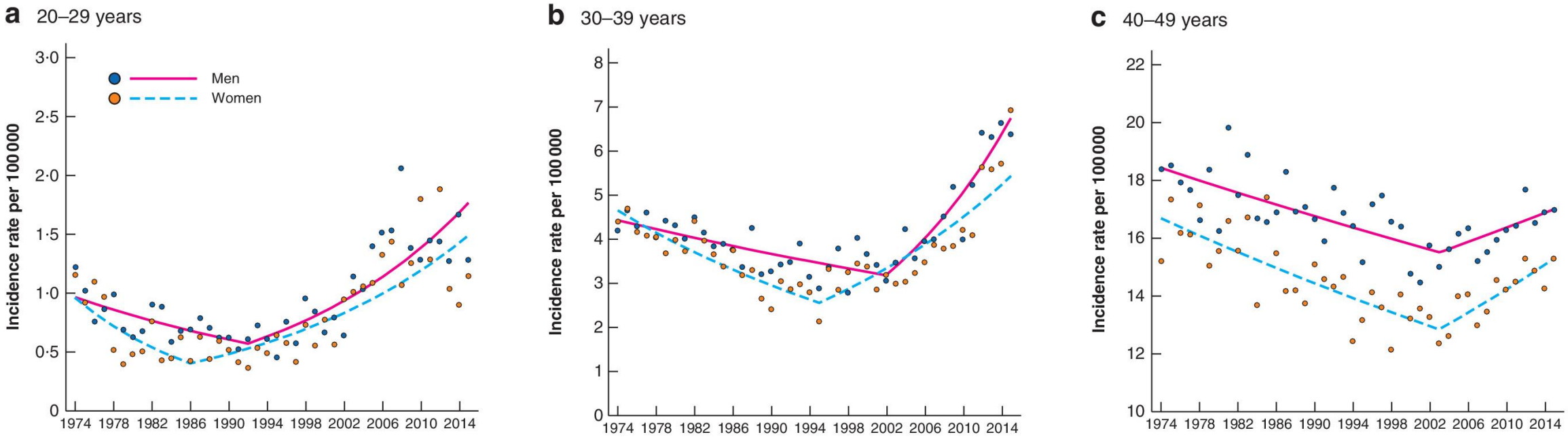
Colorectal cancer

- Colorectal cancer (CRC) is the **4th most common** cancer in the UK
- 54% cases are estimated to be **preventable**



Chambers et al. (2020)

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RESEARCH ARTICLE
Cancer Epidemiology

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Circulating white blood cell traits and colorectal cancer risk: A Mendelian randomisation study

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Immune disease risk variants regulate gene expression dynamics during CD4$^+$ T cell activation

Blagoje Soskic, Eddie Cano-Gamez, Deborah J. Smyth, Kirsty Ambridge, Ziying Ke, Julie C. Matte, Lara Bossini-Castillo, Joanna Kaplanis, Lucia Ramirez-Navarro, Anna Lorenc, Nikolina Nakic, Jorge Esparza-Gordillo, Wendy Rowan, David Wille, David F. Tough, Paola G. Bronson & Gosia Trynka

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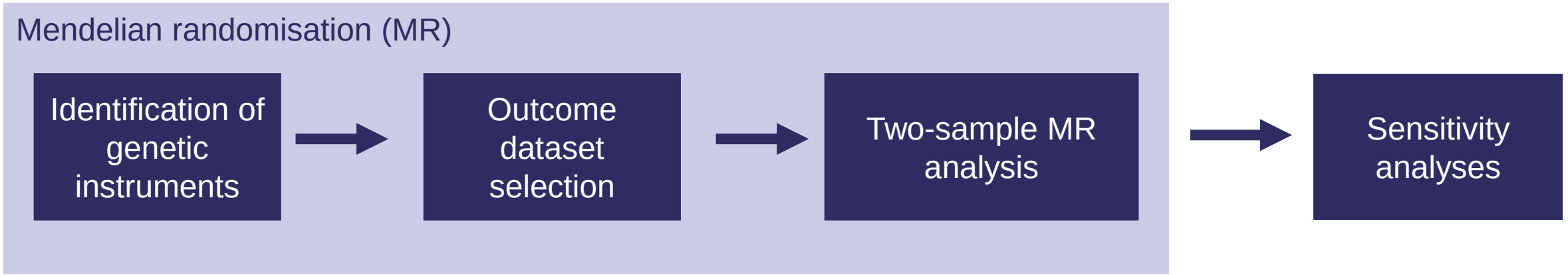
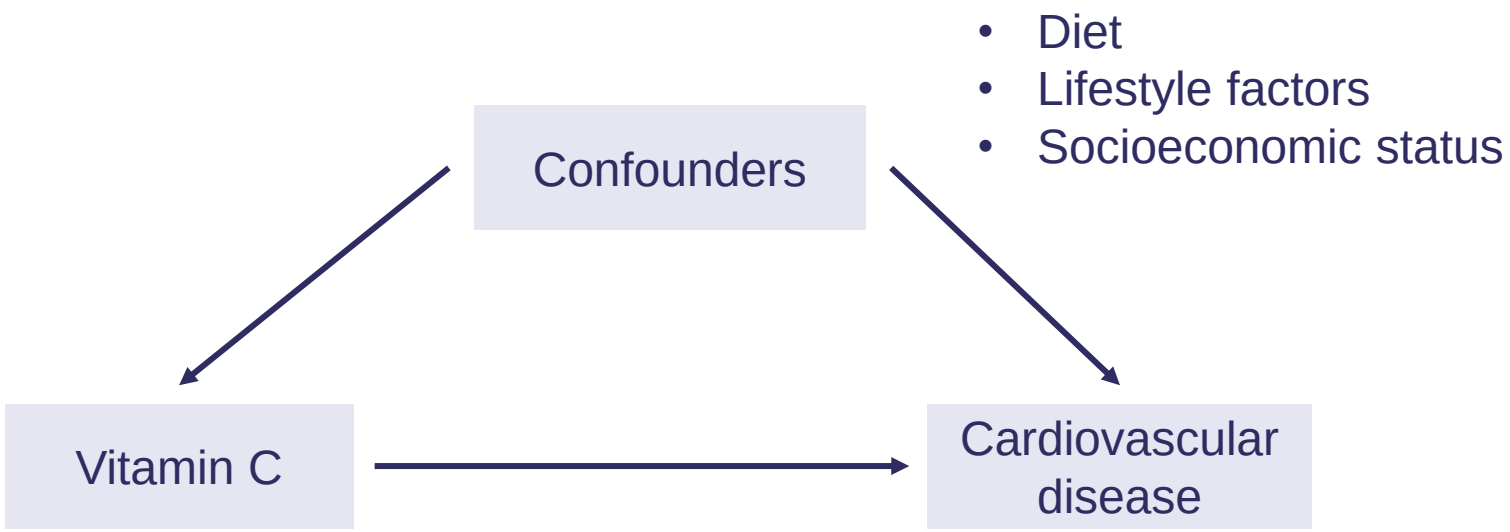
Aim: to investigate the role of CD4+T cell expression profiles on colorectal cancer development.

Methods


Mendelian randomisation (MR)
Identification of genetic instruments
Outcome dataset selection
Two-sample MR analysis
Sensitivity analyses

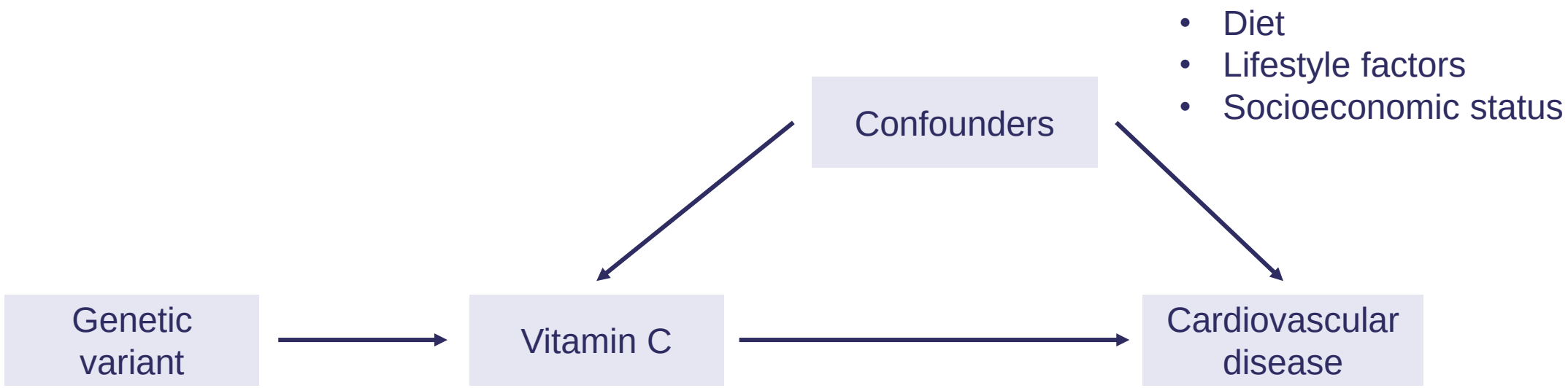
Mendelian randomisation

Mendelian randomisation



- Diet
- Lifestyle factors
- Socioeconomic status

Mendelian randomisation



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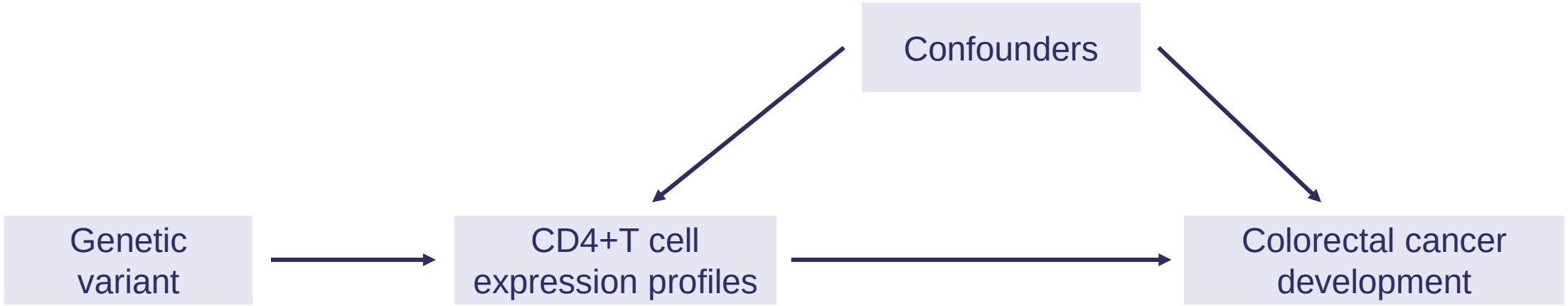


Instrument selection

- Summary-level dynamic eQTL data extracted from Soskic et al. (2022)
- 119 healthy individuals of British ancestry
- Rest and four activation states
- *cis*-eQTLs (+-500kb) strongly associated with gene expression ($P<5x10^{-8}$), independent ($r^2<0.001$) and *F*-statistic >10

eQTL = expression quantitative trait loci

Outcome data selection

1

Fernandez-Rozadilla et al. (2023)

78,473 CRC cases and 107,143 controls

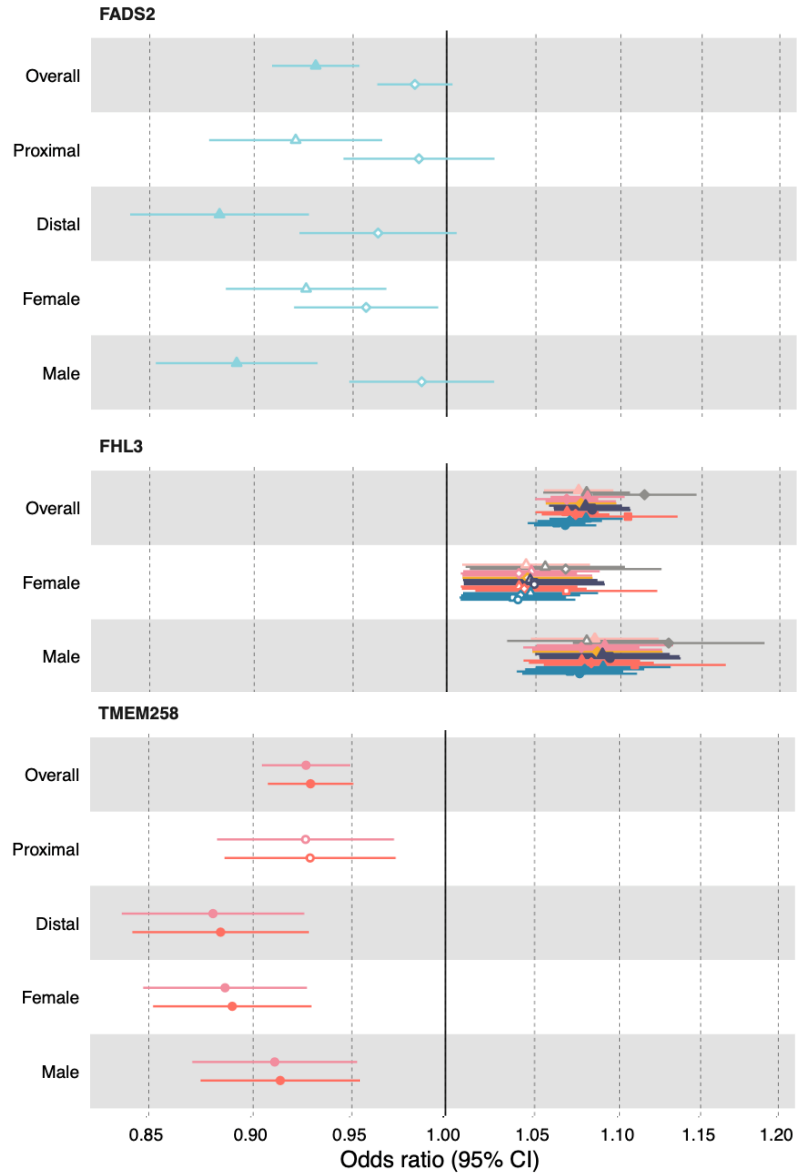
2

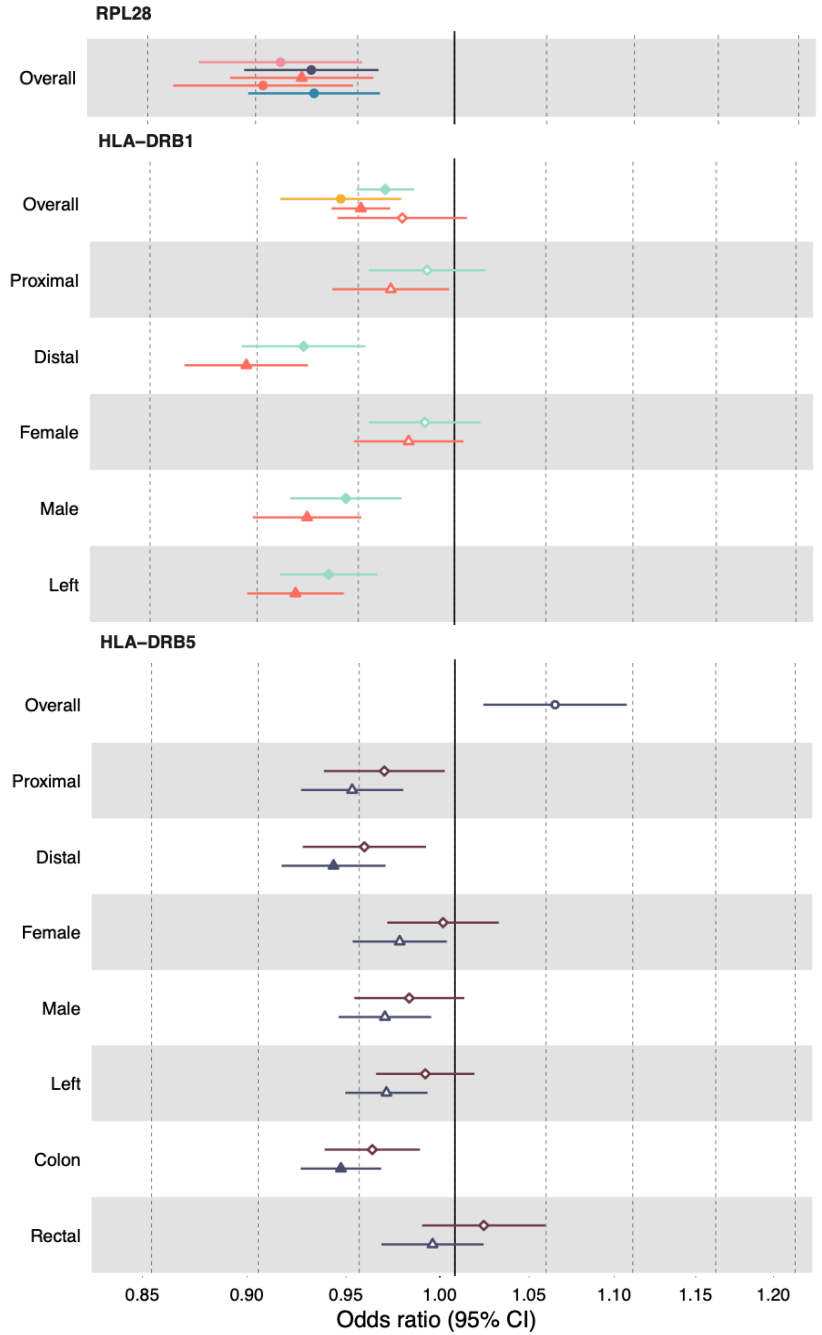
Huyghe et al. (2021) (GECCO)

Site- and sex-specific CRC cases

Proximal, distal, rectal, left-sided, colon, female, male

Results





Results are given for every SD increase in expression of a gene in activated CD4+T cells at a specific activation timepoint.

TMEM258

- Located in endoplasmic reticulum (ER)
- Part of the OST complex
- Involved in N-linked glycosylation

OST = oligosaccharyltransferase

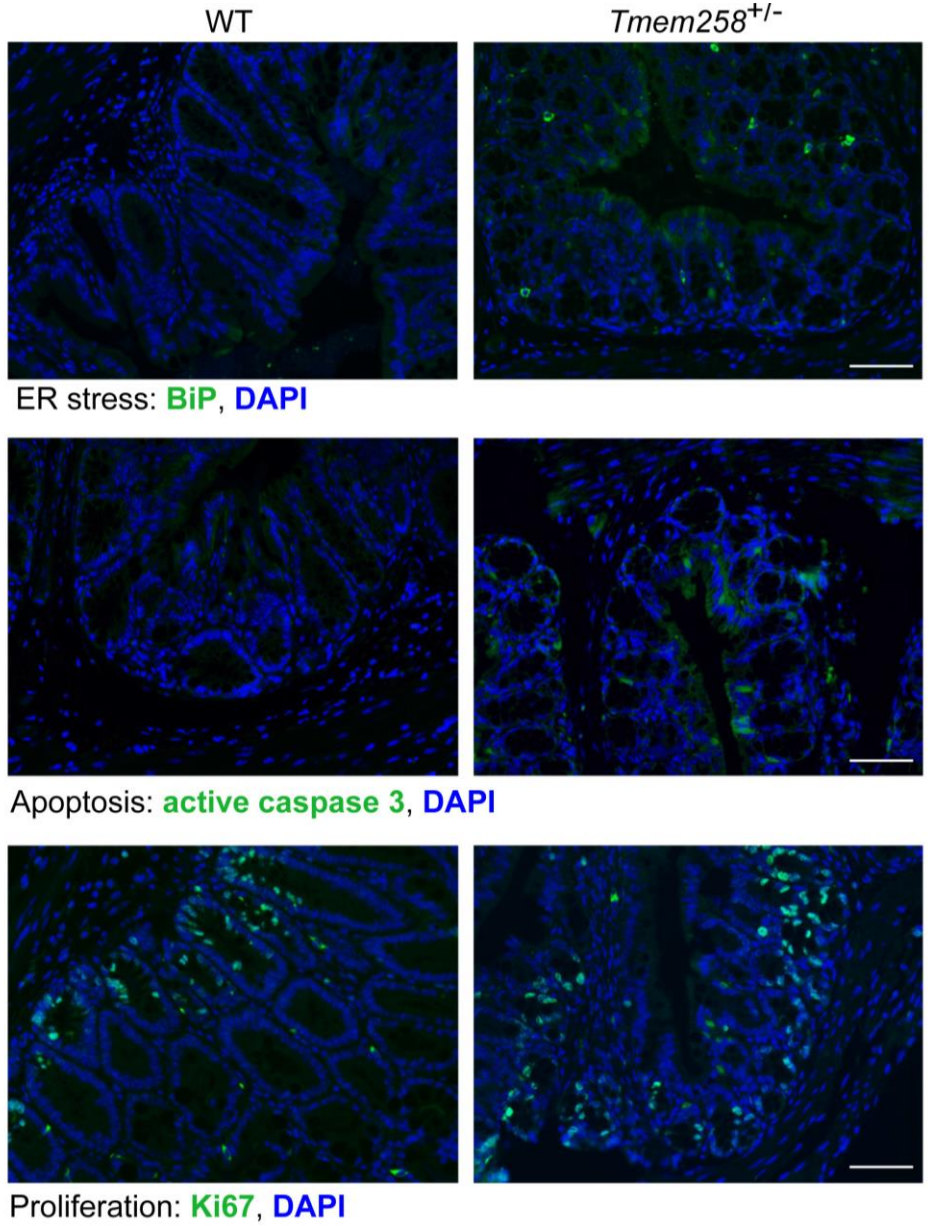
TMEM258

- Located in endoplasmic reticulum (ER)
- Part of the OST complex
- Involved in N-linked glycosylation

- Increased *TMEM258* expression in inflammatory bowel disease
- Mouse model: *TMEM258+/-* greater intestinal inflammation
- Hypothesis: differential *TMEM258* expression may alter OST complex stoichiometry and impair its catalytic assembly / activity

Graham et al. (2016)

OST = oligosaccharyltransferase



TMEM258 - ?

Results: increased *TMEM258* expression in CD4 naïve cells at 0h is protective of CRC development

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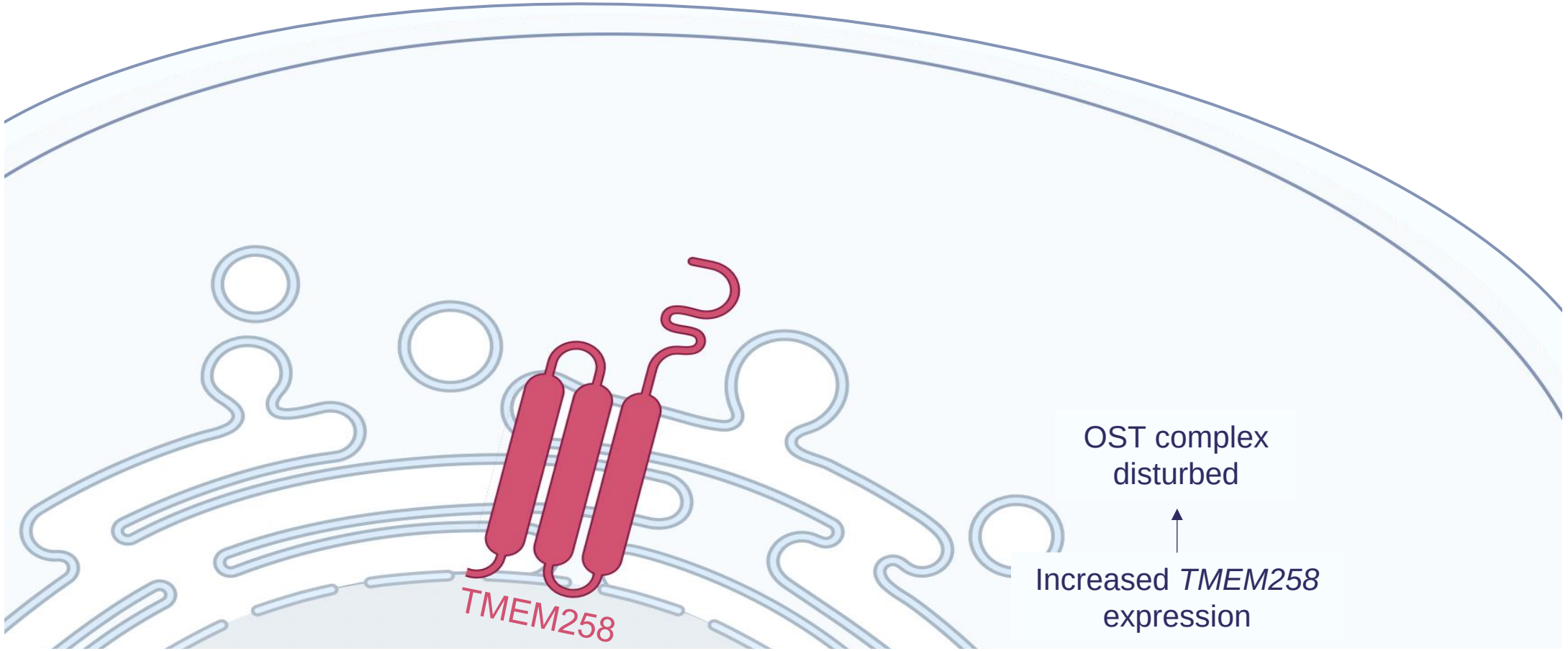

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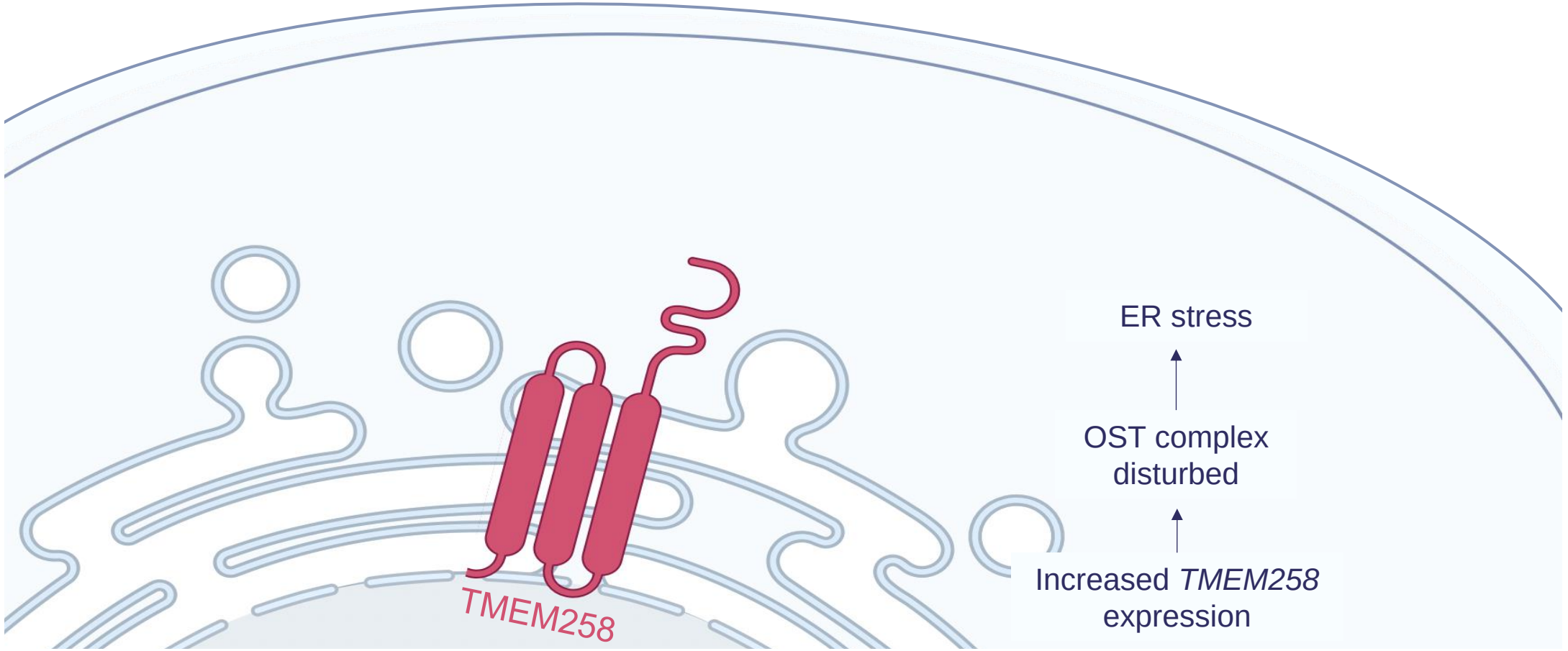

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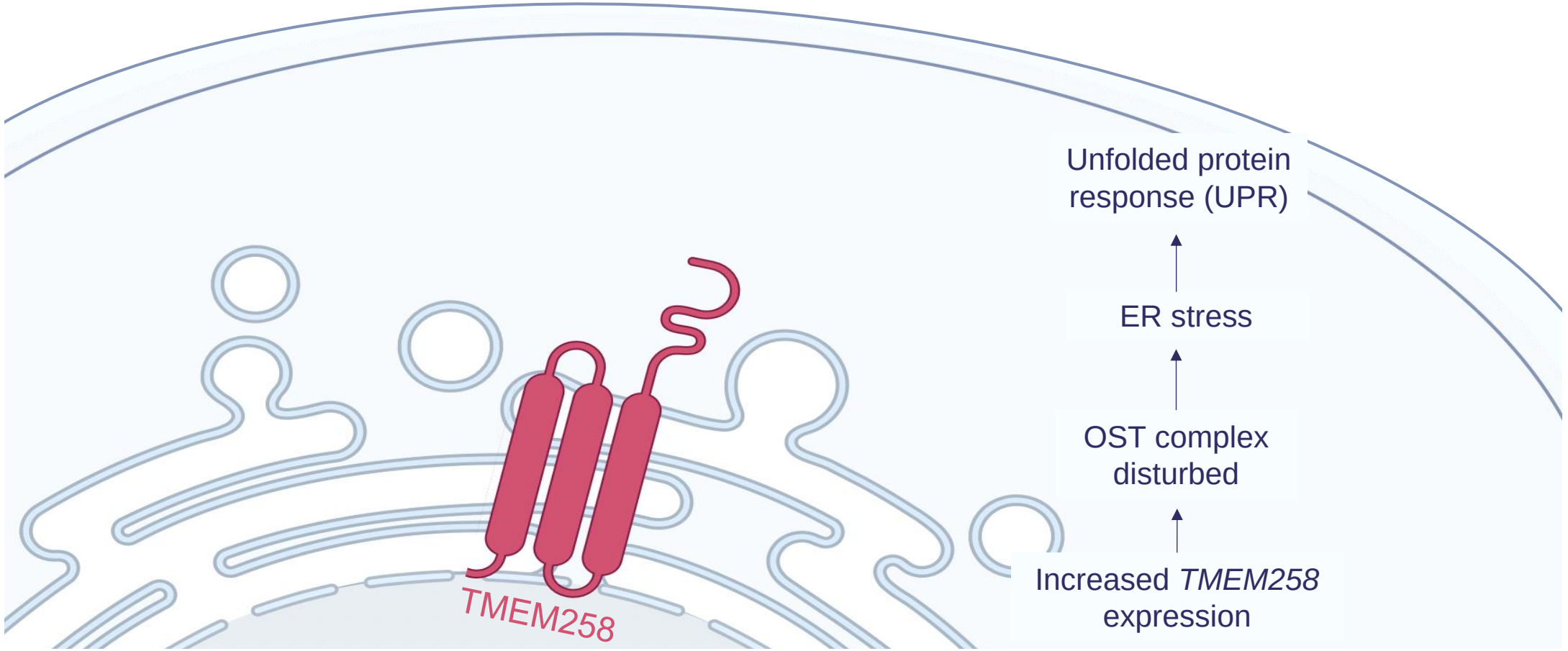

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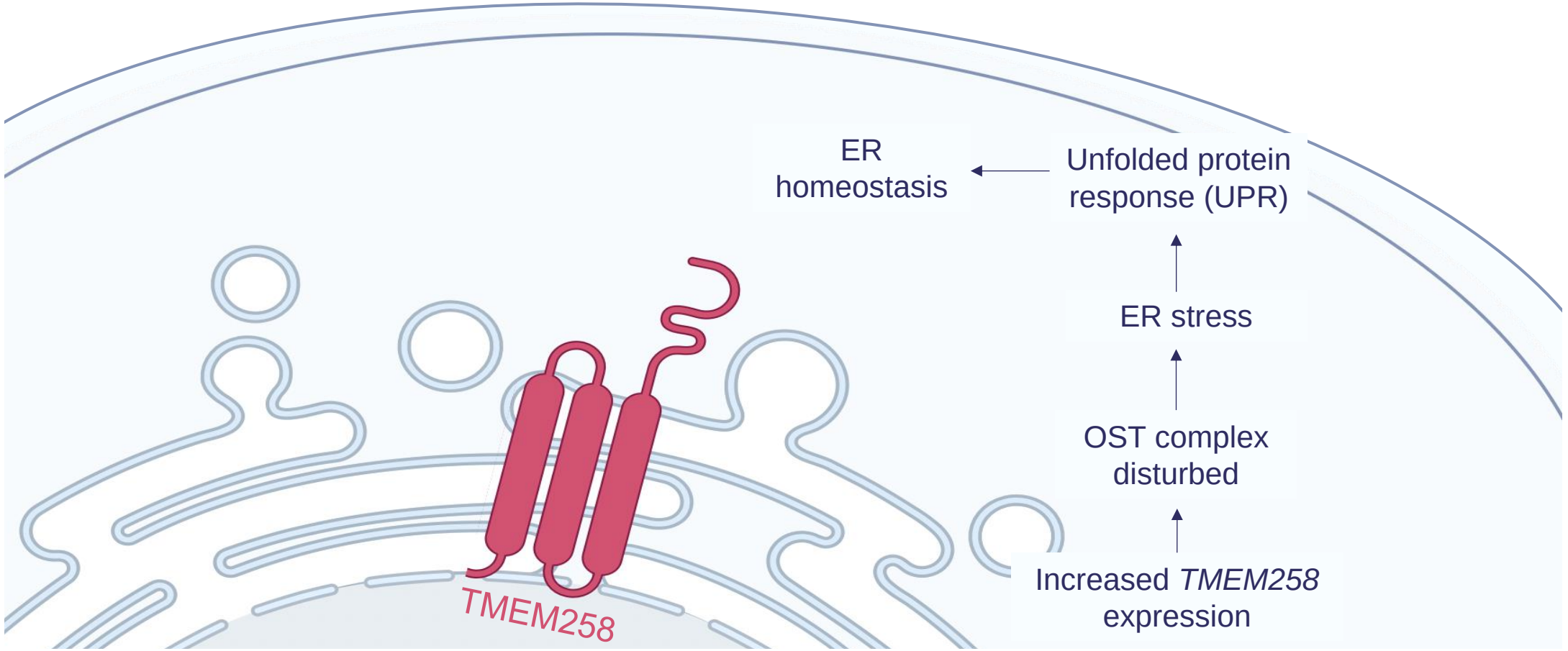

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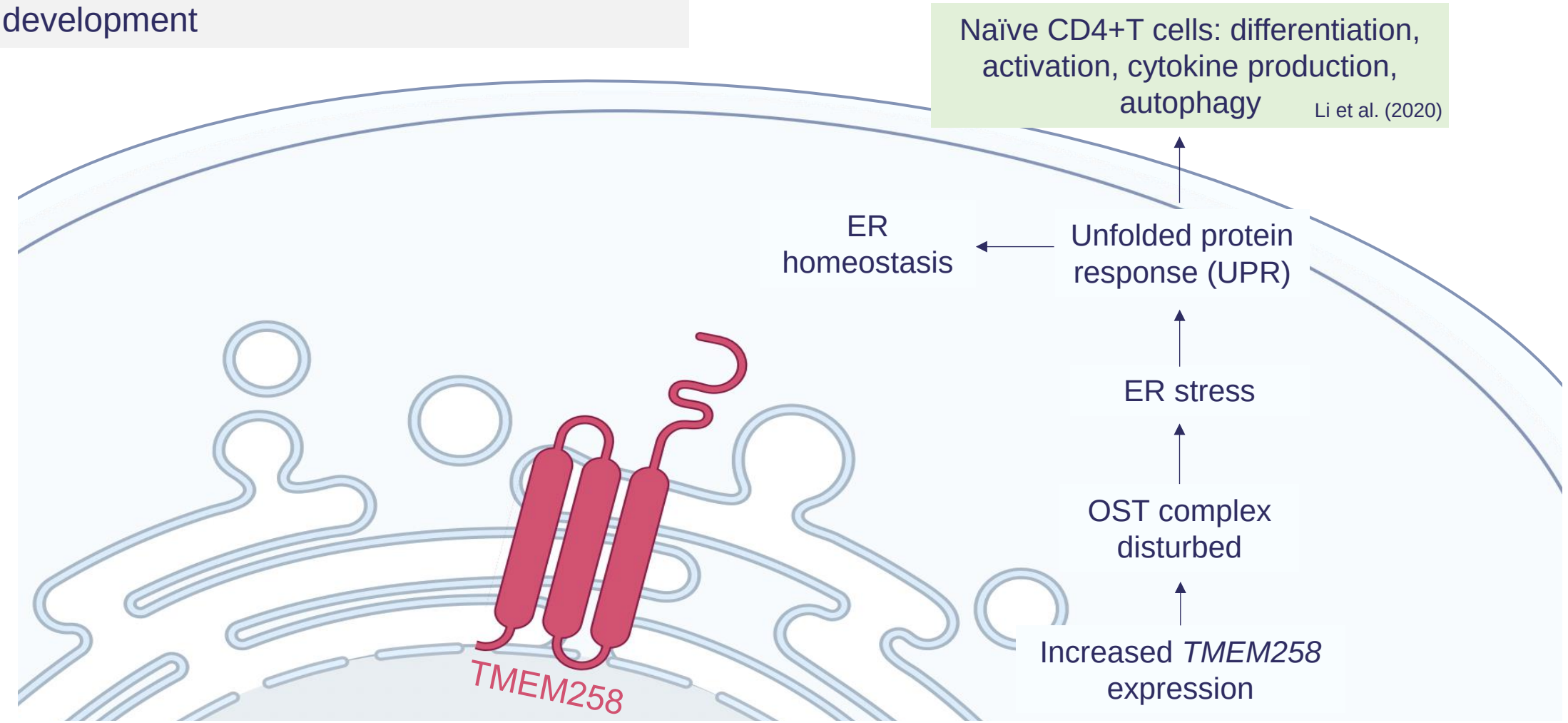

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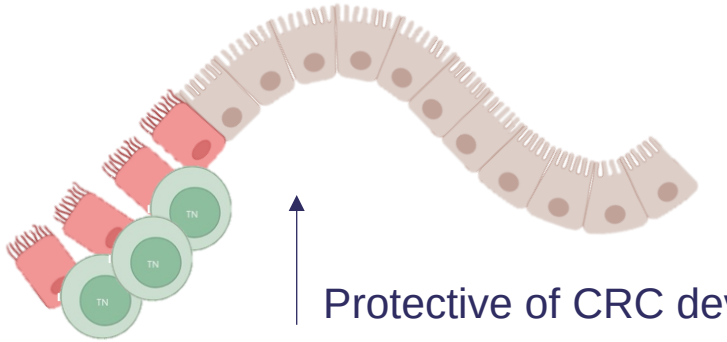

Protective of CRC development

Naïve CD4+T cells: differentiation, activation, cytokine production, autophagy Li et al. (2020)

ER homeostasis

Unfolded protein response (UPR)

ER stress

OST complex disturbed

Increased *TMEM258* expression

TMEM258

CRC = colorectal cancer; ER = endoplasmic reticulum; OST = oligosaccharyltransferase

Graham et al. (2016), Li et al. (2020)

Summary

- **6 genes** with strong evidence with a potential causal role in CRC development.
- Observed differences across different CD4+T cell subtypes, activation timepoints, CRC subsites and sex.
- Demonstrate importance of capturing the **dynamic nature** of CD4+T cells in understanding CRC risk and prevention.

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