

MRC Epidemiology Unit

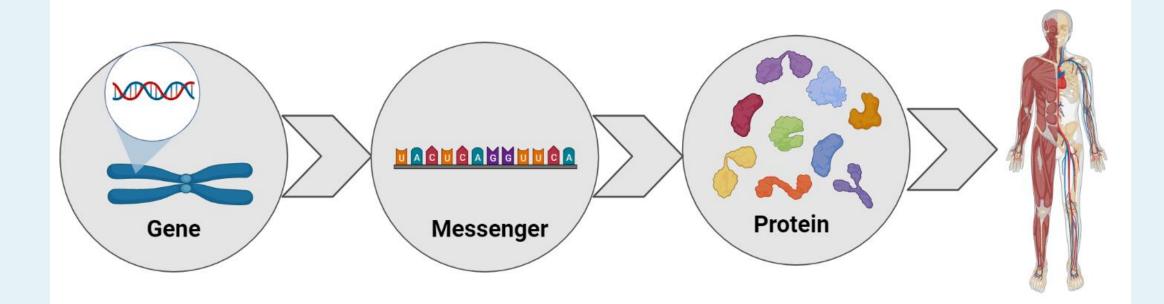
Connecting the dots: Unravelling human diseases through genetics and blood protein levels

Mine Koprulu, Julia Carrasco-Zanini

Introduction

Our genes and proteins

- Every cell in our body has a DNA that is unique to US.
- This code contains our genes, which are like instruction manuals for creating proteins.
- Proteins are important for many things in our body ranging from their role in fighting infections to carrying out various functions that keep us healthy.
- Proteins are the majority (>95%) of drug targets.



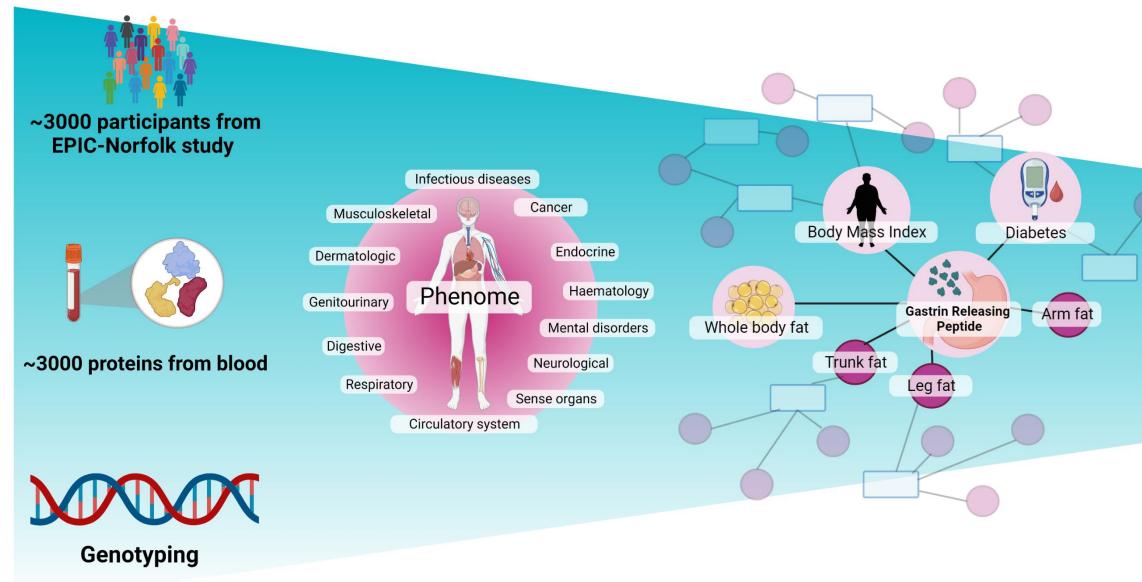
Why should we study genes or proteins?

- Changes in our genetic code or blood protein levels can impact our risk for disease such as diabetes.
- Studying genetic changes, blood protein levels and other biological data help us:
 - Better understand disease mechanisms, in other words, how diseases act in our body.
 - Identify disease-causing proteins, which can be targeted for more effective therapies.
 - Identify markers that might indicate you are at high risk of a specific disease.

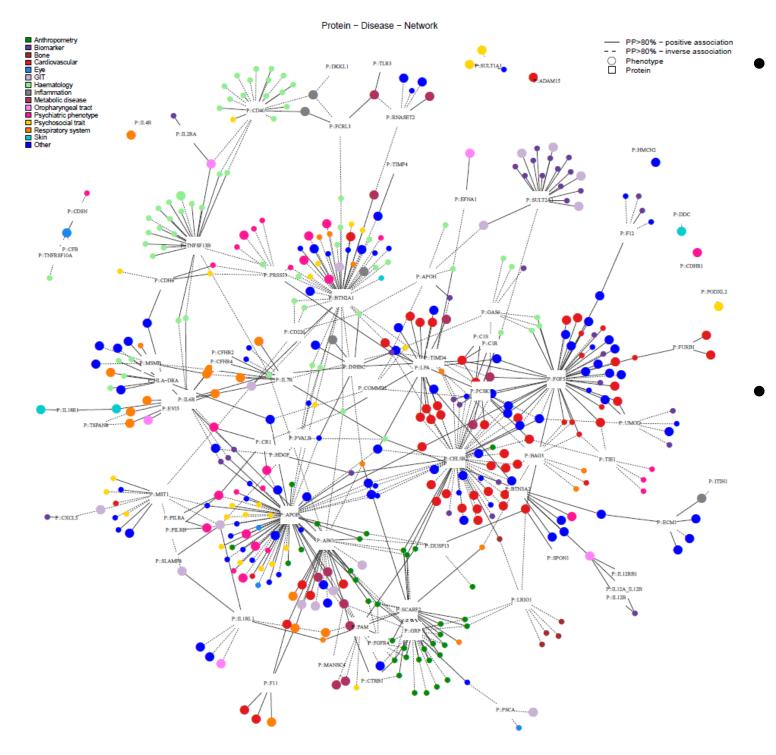


Identifying disease-causing proteins

Genetic sequencing and measurement of blood protein levels of ~3.000 proteins was performed in ~3,000 EPIC-Norfolk participants.



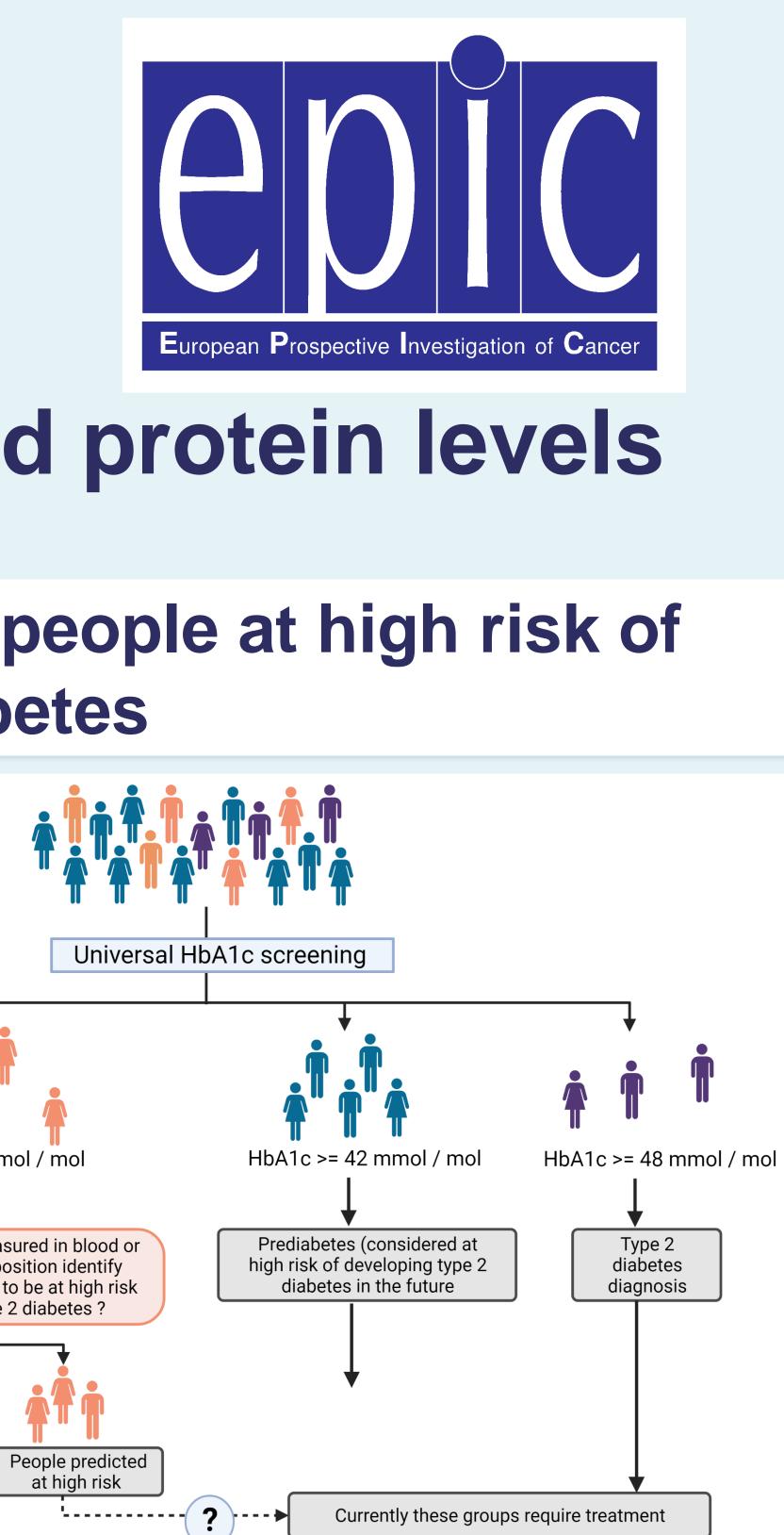
Combining these different layers of biological data allowed us to identify disease-causing proteins, such as gastrin releasing peptide (GRP) for diabetes.



- Applying the same methods, we identifie hundreds of disease causing proteins for many diseases.
- In theory, changing levels of diseasecausing proteins back to what they are in "healthy" people can prevent of treat some diseases.
- Identifying disease-causing proteins can facilitate the development of more effective drugs and therapies for many diseases.

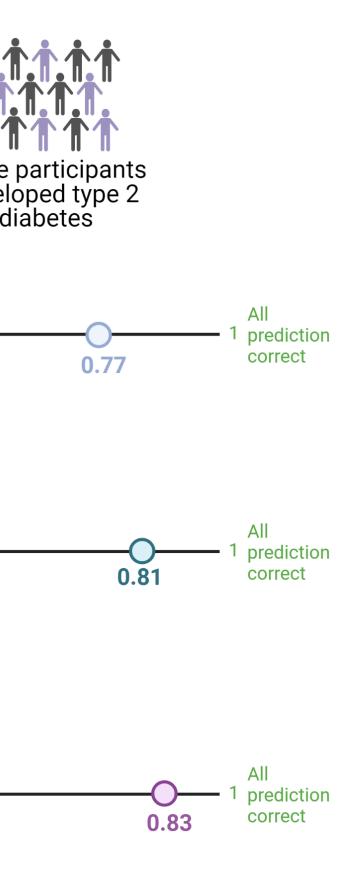
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stuck to red blood cells (called HbA1c or haemoglobin) to identify people at high ri	glycated sk of
 Can blood protein levels or genetics improve identification of people at high risk of diabetes? 	HbA1c < 42 mmo Can proteins measur genetic predisposi people predicted to of future type 2 d
	Pe
 people at high risk of future diabetes, bey Currently, healthcare systems consider p 	ond what is eople with p
10-years of follow-up EPIC-Norfolk (1105 participants) We developed prediction models for future risk of	Some p develo
Clinical risk factors Current clinical prediction model	All prediction 0 wrong
 5,000 proteins We use only the 10 most predictive proteins 	All prediction 0 wrong
<pre>increases risk decreases risk increases risk no change in risk</pre> Combine to generate a Genetic risk score genetic risk	All prediction 0 wrong
	 Currently we use a marker of how much stuck to red blood cells (called HbA1c or haemoglobin) to identify people at high rid developing type 2 diabetes (T2D) in the f Can blood protein levels or genetics improve identification of people at high risk of diabetes? Assessing genetic predisposition (by the people at high risk of future diabetes, bey complete at high risk of future diabetes in the method development of diabetes. Currently, healthcare systems consider people at high risk of future diabetes in the method development of diabetes.

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sk score) can improve the way we identify is currently done by the NHS.

prediabetes are at a sufficiently high risk **rs**) to warrant treatment to prevent



- People with high genetic predisposition are only at about half the risk (~1 in 10 will develop diabetes in the next 20 years) compared to people with prediabetes.
 - Whether intervention is warranted in people with a high genetic predisposition is a political and economic decision.