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PPAR-alpha Variants as Modulators of Fenofibrate Cardiovascular Effectiveness in patients with type 2 diabetes

Mario Luca Morieri MD

UNIVERSITÀ DEGLI STUDI DI FERRARA
- EX LABORE FRUCTUS -

Joslin Diabetes Center

HARVARD MEDICAL SCHOOL

OUTLINE

- **Preliminary data: Identification of a PPARA polymorphism as a genetic modulator of fenofibrate CV effectiveness in type 2 diabetes.**

- **On going and future analysis to understand the mechanism behind this genetic heterogeneity**

- **Expected results and future perspectives towards a precision medicine approach of CV prevention in T2D**

Background

CVD is the major cause of morbidity and mortality in T2D

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Use of additional metabolic drugs

→ Fibrates

PPAR-alpha agonist

↓ Triglycerides ↑ HDL-c

↑ LDL size and ↓ Inflammation

↓

Disappointing results on CVD outcomes

↓

Heterogeneity in fibrates effectiveness

↓

Hypothesis

Hypothesis

Hypothesis: the disappointing results of CVD trials of fenofibrate could be accounted for by genetic heterogeneity in the *PPARA* gene

- **A corollary of this hypothesis is that it may be possible to:**

  → **develop genetic tests to identify diabetic patients who would benefit from fibrates from those who would not.**

  → **highlight new possible pathways through which fibrates affects CVD risk**

ACCORD-Lipid genetic study

- **Study Population:** ACCORD-lipid trial
  - 5518 subjects with T2D at high CV risk randomized to fenofibrate + statin or placebo + statin
  - Primary outcome: MACE (CV death, non-fatal MI and stroke)

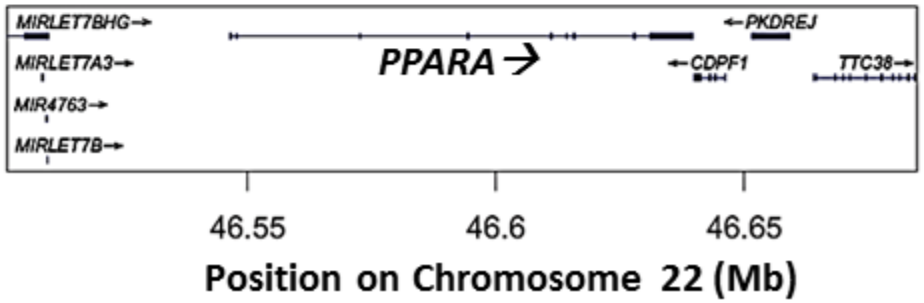
  → non-significant beneficial effect (HR 0.92; 0.79-1.08)

- **Genetic data:** Genome Wide data (80% of the population) obtained at ***Joslin Diabetes Center, Boston USA*** in collaboration with Universities of Virginia and North Carolina.
  - 7 millions of imputed and genotyped common SNPs

A Strong and Ideal Candidate Gene
– PPARA –

DATI NON PUBBLICATI

- 3065 self-reported Whites
- 360 common SNPs tested: "SNP x fenofibrate" interaction.
- Cox Hazard Model → MACE
- Adjustment: age, gender, history of CVD at baseline



On going and future analysis

Objective: to dissect the pathways through which these SNPs exert such modulatory effect

- ***Aim 1:***

  To explore the mechanism – at clinical levels – through which the PPAR-alpha variant modulate the CV effectiveness of fenofibrate

- ***Aim 2:***

  To explore the – transcriptional pathways – influenced by this PPAR-alpha variant

Aim 1 - mechanism behind genetic effects - clinical level -

A. *Explore the genetic modulation of fenofibrate-induced change in:*
   - *Apolipoproteins*
   - *Lipoprotein size and particle number*
   - *Plasma fatty acid*
   - *hsCRP*

B. *Explore the downstream genetic modulation of the relationship between change in this biomarkers and CVD*

C. *Explore the genetic modulation on fenofibrate effectiveness on other micro-vascular outcome*

Aim 2 - mechanism behind genetic effects - molecular level -

A. ***Seek for regulatory* annotations** of this noncoding variant by analysis of public available dataset (e.g. Genome-Tissue Expression Analysis, HaploReg, Encode …).

B. ***Analysis in vitro:***

1) Explore the genetic modulation in the response to fenofibrate stimulation of **human monocyte.**
   - In collaboration with Dott. Juana Sanz (Dott. Angelina Passaro Lab at University of Ferrara – Department of Medical Science)
2) Explore the genetic effects in **human umbilical vein cell (HUVEC).**
   - In collaboration with Prof. Vincenzo Trischitta, Dott. Sabrina Prudente (IRCCS and Sapienza University) and Prof. Assunta Pandolfi (University of Chieti)

Expected results and summary

- If successful, this project will provide further confirmation of the modulatory role of these genetic variants.

➢ allowing us to build genetic prediction models to select T2D patients who are most likely to benefit from fenofibrate

  ➢ Path the way to rescue a cardio-protective therapy that would be otherwise dismissed as ineffective

➢ By dissecting the pathways involved in this genetic effect, this research may also point to other key pharmacological targets to prevent CVD in T2D.

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