Reasoning of dissertation topic and competency of potential supervisor for admission into LSU biology doctoral studies with a participation of Tartu university 2023

Area of research (title and code)	**Biomedicine**
Field of research (title and code)	**Biology**
Topic of research	**Physiology**
Institution	**LSU**

Potential supervisor

Pedagogical and scientific degree	Name, surname	Academic position
dr.	Tomas Venckunas	prof.

Short reasoning of proposed dissertation topic

Title

The role of *ACTN3* loss-of-function R577X polymorphism in regulation of metabolism

Short research description (max 1500 characters).

Skeletal muscles comprise ~50% of a healthy adults body mass (PMID: 22232606) and is a primary site for energy storage and use. Even for basal metabolic rate muscles use ~30% of energy (PMID: 2243122). Innert weight gain as with over-eating or under-exercising leads to cardiovascular disease, type 2 diabetes mellitus, cancer and metabolic syndrome (PMID: 18200017). Despite exercise being the most commonly prescribed therapeutic treatment of obesity, most of the research until now has focused on the significance of increased adiposity on overall health but not on skeletal muscle function and metabolism. It also remains a significant gap in our understanding of an individual's genetic predisposition to the development of obesity. This study will address this need and improve our understanding to define how skeletal muscle and whole body metabolism is affected by *ACTN3* genotype and how this is modified by cold stimulus.

We will explore the effects of *ACTN3* genotype on skeletal muscle size and function as well as skeletal muscle, adipose tissue and whole body metabolism and their response to acute and chronic cold exposure using a cohort of healthy untrained individuals (n=20 per genotype (RR and XX) group per gender, total n=80; age 40-60 years, BMI 25-30). Volunteers for the study will be genotyped on DNA extracted from peripheral venous blood samples, and then included according to their determined *ACTN3* R577X genotype (as in our studies PMID: 22891846, 33600773).

Relevance of the problem, its novelty (max 1500 characters).

~18% of people worldwide do not express the fast skeletal muscle protein α-actinin-3 because of a loss of function polymorphism in the *ACTN3* gene (577XX, rs1815739). Interestingly, the *ACTN3* X-allele has undergone strong and recent positive selection during modern human evolution, with the frequency of the X-allele increasing as modern humans migrated out of Africa into the colder Eurasian climates. The reasons for this increase remained unclear until now.

Our recent study has shown that in α-actinin-3 deficiency (i.e. 577XX carrier status) the organism can maintain a higher core temperature when exposed to cold. These data strongly suggest that the loss of α-actinin-3 have been beneficial to modern humans migrating out of Africa into the colder Eurasian climates, but how far the α-actinin-3 deficiency is beneficial or perhaps disadvantageous today?

By the study proposed here we therefore further hypothesize that *ACTN3* genotype is a modifier of the whole-body metabolic response (lower increase in metabolic rate and less reliance on fat exidation), which is detrimental in modern society posed to a significant calorie surplus and therefore weight gain. This proposal will characterise how our skeletal muscle influences whole-

body metabolism and energy expenditure in prie-obese healthy individuals and explore the potential role of *ACTN3* genotype as a modifier of an individual's predisposition to weigh gain and obesity.
Research methods and possibilities for conducting these studies (maximum 1500 characters). Genotyping conducted at LSU – we have all the equipment to test the extracted DNA, running PCR and visualizing the gels. Transcriptomics and proteomics of the samples will be performed in collaboration with Thomas Chaillou (Orebro University), Hans Degens (Manchester Metropolitan University) and Hakan Westerblad (Karolinska Institutet). Phenotyping subjects conducted at LSU as within other similar projects.
Is the proposed topic for the doctoral thesis related to currently funded research projects? Please indicate the links between the proposed topic for the doctoral thesis and funded research projects **1.** "The role of ACTN3 loss-of-function R577X polymorphism in regulation of metabolism with cold exposure" (LMT funded project, 2023-2025; 149.000 Eu). **2.** "Role of ACTN3 loss-of-function R577X polymorphism in regulation of metabolism" (2022-2026; Ideas grant in collaboration with Murdoch Children's Research Institute (Australia, led by Peter Howeling) and Karolinska Institutet (Sweden, led by Hakan Westerblad) (LSU share – 56.000 Eu).
Is the proposed topic for the doctoral thesis related to joint research with a foreign institution? Please indicate the links between the proposed topic for the doctoral thesis and research with a foreign institution. Orebro University (Sweden): Thomas Chaillou (project on ACTN3) Manchester Metropolitan University (UK): Hans Degens (project on ACTN3) Murdoch Children's Research Institute (Australia): Peter Houweling (project on ACTN3)

Currently I am supervisor of 2 doctoral students.

Supervisor _____ (signature) TOMAS VENCKŪNAS (Name, surname)

Date