Visioon

Kus oleme 100 aasta pärast?

Kaur Alasoo

Ehk kuidas geeniteaduse avastustes ravimid saavad ning miks see nii kaua aega võtab

Uudsete ravimite mehhanismid

- Ensüümide inhibiitorid (väiksed molekulid)
- Transkriptsiooni inhibiitorid (antisense oligonukleotiidid)
- Monoklonaalsed antikehad
- Geeniravi (geenivektorid ja CRISPR)
- PROTAC (https://en.wikipedia.org/wiki/Proteolysis_targeting_chimera)
- Vaktsiinid

Monogeensed haigused

Sirprakuline aneemia

BlueBird Bio / Vertex / CRISPR Therapeutics

- Geen: HBB

Illustration by Ibrahim Rayintakath

ANNALS OF MEDICINE

ARE WE ABOUT TO CURE SICKLE-CELL DISEASE?

https://www.newyorker.com/science/annals-of-medicine/are-we-about-to-cure-sickle-cell-disease

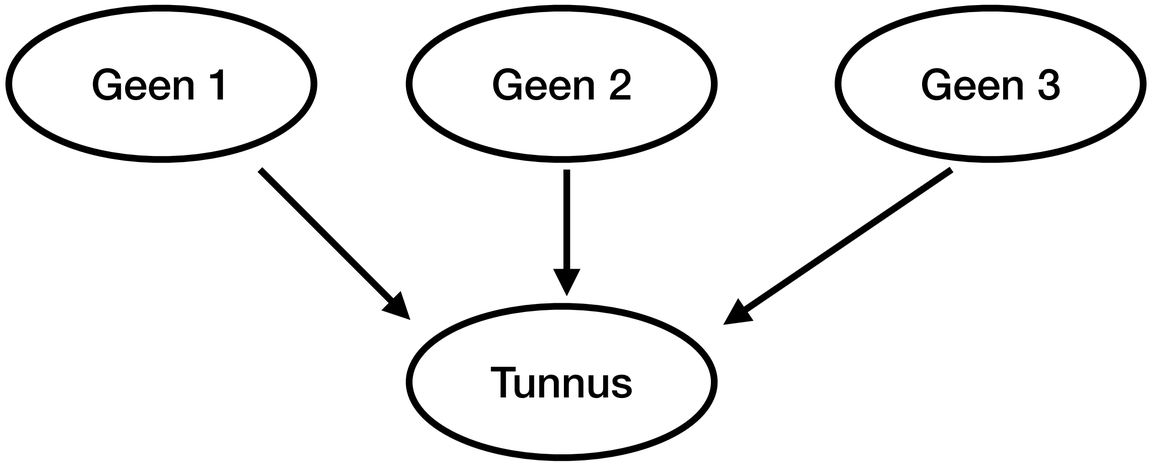
Tsüstiline fibroos

Vertex Pharmaceuticals

- Geen: CFTR
- Rakumudel 2005: https://journals.physiology.org/doi/full/10.1152/ajplung.00169.2005
- Esimene ravim 2012, järgmine 2015: https://www.statnews.com/2019/10/23/we-conquered-a-disease-how-vertex-delivered-a-transformative-medicine-for-cystic-fibrosis/
- 2021 kliiniline uuring: https://www.nejm.org/doi/full/10.1056/NEJMoa2100665

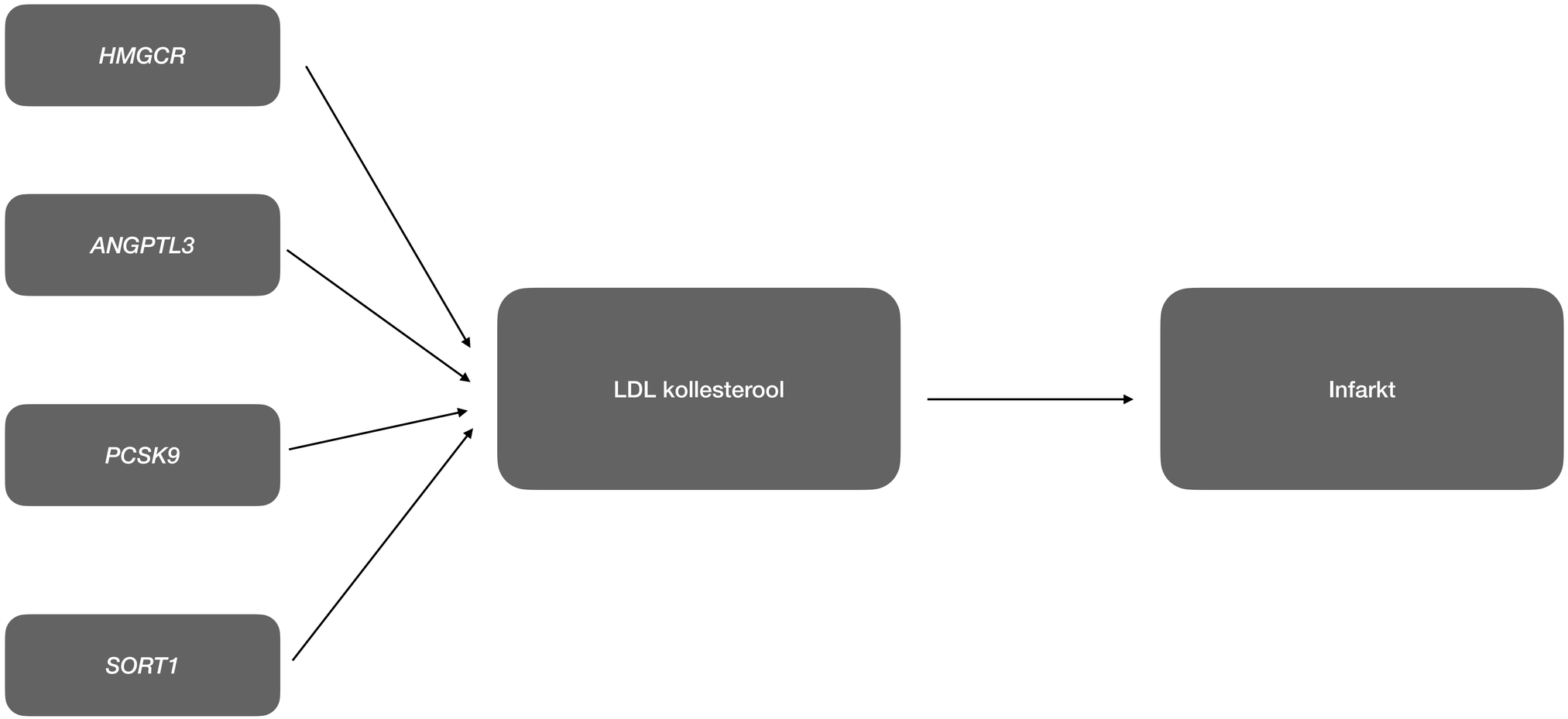
Polügeensed haigused

Polügeensus

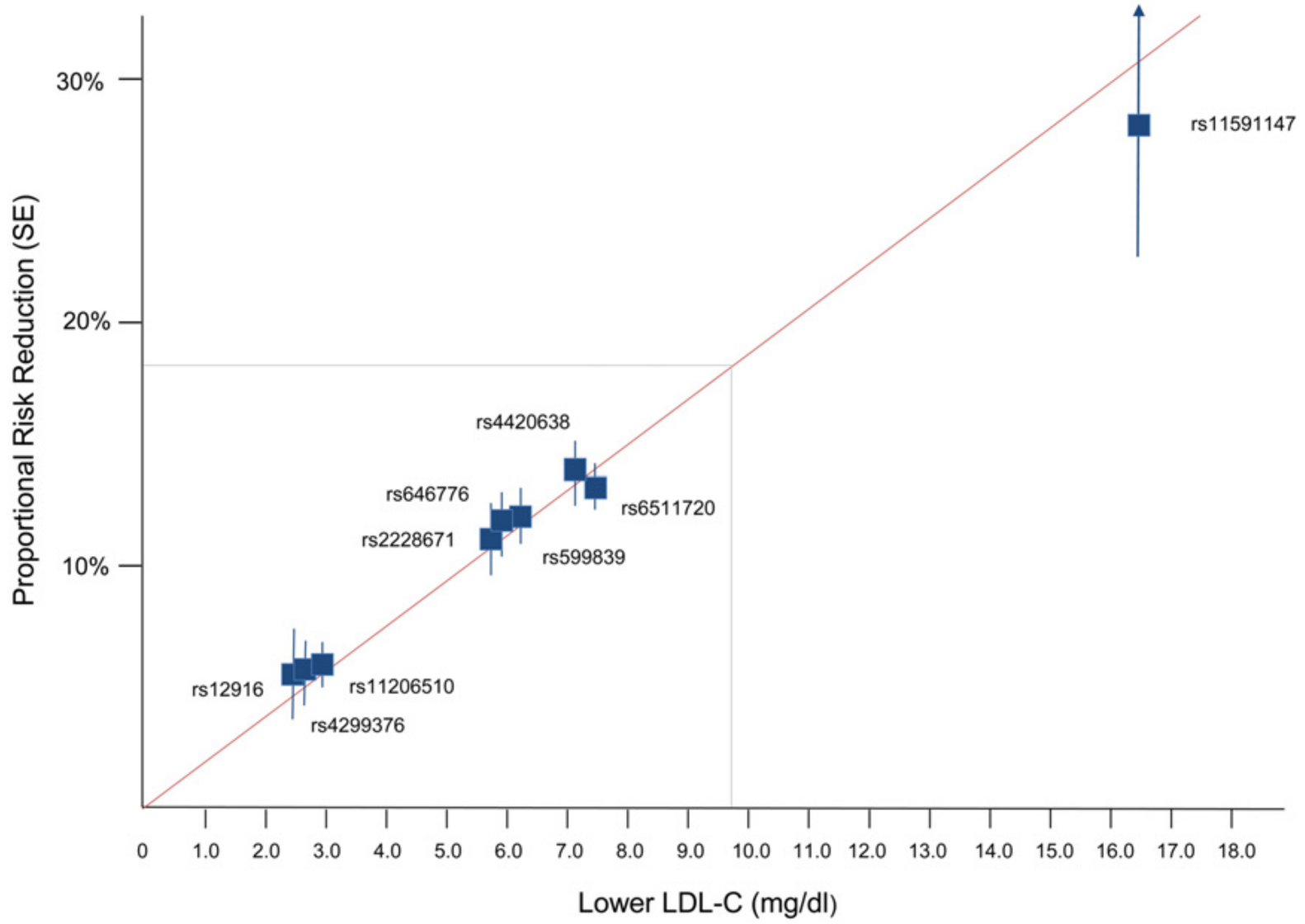


(Perekondlik) hüperkolesteroleemia

- Geenid: APOB, LDLR, LDLRAP1, PCSK9, ANGPTL3, ….
- https://www.youtube.com/watch?v=2ALbhPdRoyU


HMGCR
ANGPTL3
PCSK9
SORT1
LDL kollesterool
Infarkt

Geneetilise variandi mõju infarktiriski vähenemisele



Geneetilise variandi mõju LDL-kollesterooli langetamisele

Ference, Brian A., et al. "Effect of long-term exposure to lower low-density lipoprotein cholesterol beginning early in life on the risk of coronary heart disease: a Mendelian randomization analysis." *Journal of the American College of Cardiology* 60.25 (2012): 2631-2639.

2010: geneetiline avastus

The NEW ENGLAND JOURNAL of MEDICINE

BRIEF REPORT

Exome Sequencing, *ANGPTL3* Mutations, and Familial Combined Hypolipidemia

Kiran Musunuru, M.D., Ph.D., M.P.H., James P. Pirruccello, B.S., Ron Do, M.S., Gina M. Peloso, M.S., Candace Guiducci, B.S., Carrie Sougnez, B.S., Kiran V. Garimella, M.S., Sheila Fisher, M.L.A., Justin Abreu, M.S., Andrew J. Barry, B.S., Tim Fennell, B.S., Eric Banks, Ph.D., Lauren Ambrogio, B.S., Kristian Cibulskis, B.S., Andrew Kernytsky, Ph.D., Elena Gonzalez, B.S., Nicholas Rudzicz, M.S., James C. Engert, Ph.D., Mark A. DePristo, Ph.D., Mark J. Daly, Ph.D., Jonathan C. Cohen, Ph.D., Helen H. Hobbs, M.D., David Altshuler, M.D., Ph.D., Gustav Schonfeld, M.D., Stacey B. Gabriel, Ph.D., Pin Yue, Ph.D., and Sekar Kathiresan, M.D.

SUMMARY

We sequenced all protein-coding regions of the genome (the "exome") in two family members with combined hypolipidemia, marked by extremely low plasma levels of low-density lipoprotein (LDL) cholesterol, high-density lipoprotein (HDL) cholesterol, and triglycerides. These two participants were compound heterozygotes for two distinct nonsense mutations in *ANGPTL3* (encoding the angiopoietin-like 3 protein). ANGPTL3 has been reported to inhibit lipoprotein lipase and endothelial lipase, thereby increasing plasma triglyceride and HDL cholesterol levels in rodents. Our finding of *ANGPTL3* mutations highlights a role for the gene in LDL cholesterol metabolism in humans and shows the usefulness of exome sequencing for identification of novel genetic causes of inherited disorders. (Funded by the National Human Genome Research Institute and others.)

2020: uus ravim

The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 AUGUST 20, 2020 VOL. 383 NO. 8

Evinacumab for Homozygous Familial Hypercholesterolemia

Frederick J. Raal, M.D., Ph.D., Robert S. Rosenson, M.D., Laurens F. Reeskamp, M.D., G. Kees Hovingh, M.D., Ph.D., John J.P. Kastelein, M.D., Ph.D., Paolo Rubba, M.D., Shazia Ali, Pharm.D., Poulabi Banerjee, Ph.D., Kuo-Chen Chan, Ph.D., Daniel A. Gipe, M.D., Nagwa Khilla, M.S., Robert Pordy, M.D., David M. Weinreich, M.D., George D. Yancopoulos, M.D., Ph.D., Yi Zhang, Ph.D., and Daniel Gaudet, M.D., Ph.D., for the ELIPSE HoFH Investigators*

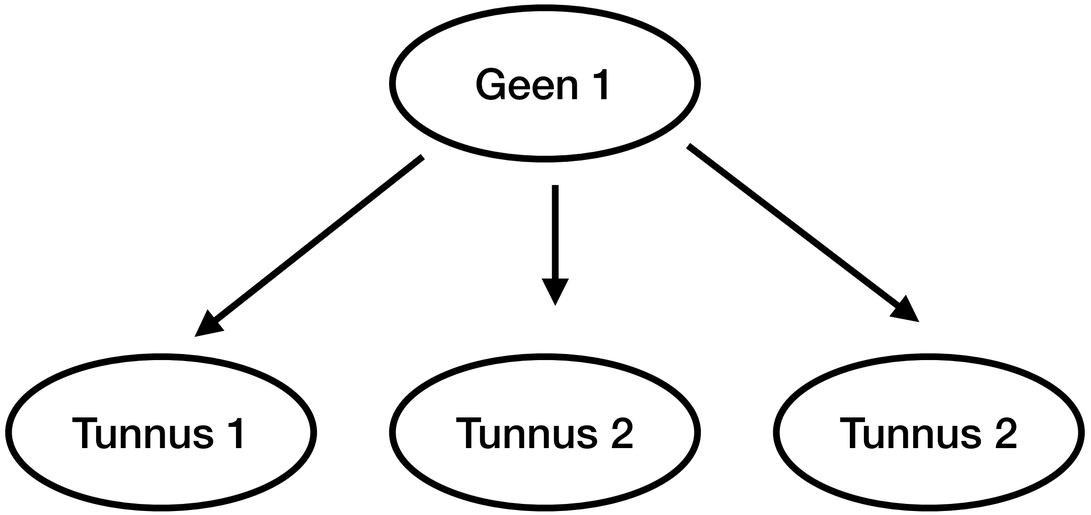
ABSTRACT

RESULTS

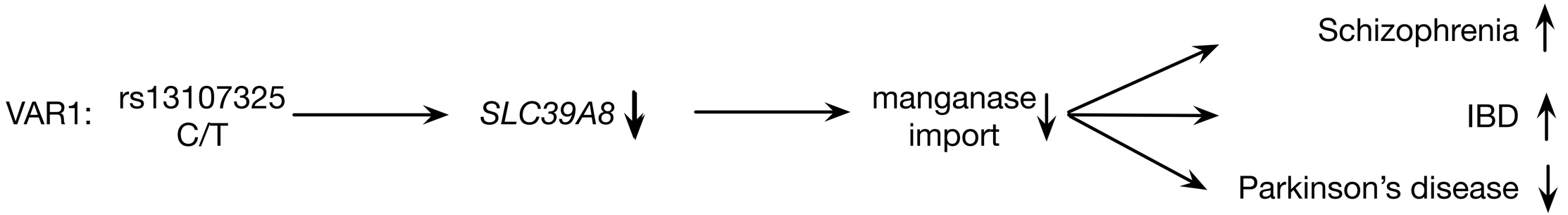
The mean baseline LDL cholesterol level in the two groups was 255.1 mg per deciliter, despite the receipt of maximum doses of background lipid-lowering therapy. At week 24, patients in the evinacumab group had a relative reduction from baseline in the LDL cholesterol level of 47.1%, as compared with an increase of 1.9% in the placebo group, for a between-group least-squares mean difference of –49.0 percentage points (95% confidence interval [CI], –65.0 to –33.1; P<0.001); the between-group least-squares mean absolute difference in the LDL cholesterol level was –132.1 mg per deciliter (95% CI, –175.3 to –88.9; P<0.001). The LDL cholesterol level was lower in the evinacumab group than in the placebo group in patients with null–null variants (–43.4% vs. +16.2%) and in those with non-null variants (–49.1% vs. –3.8%). Adverse events were similar in the two groups.

Pleiotroopsed geenid

Pleiotroopsus

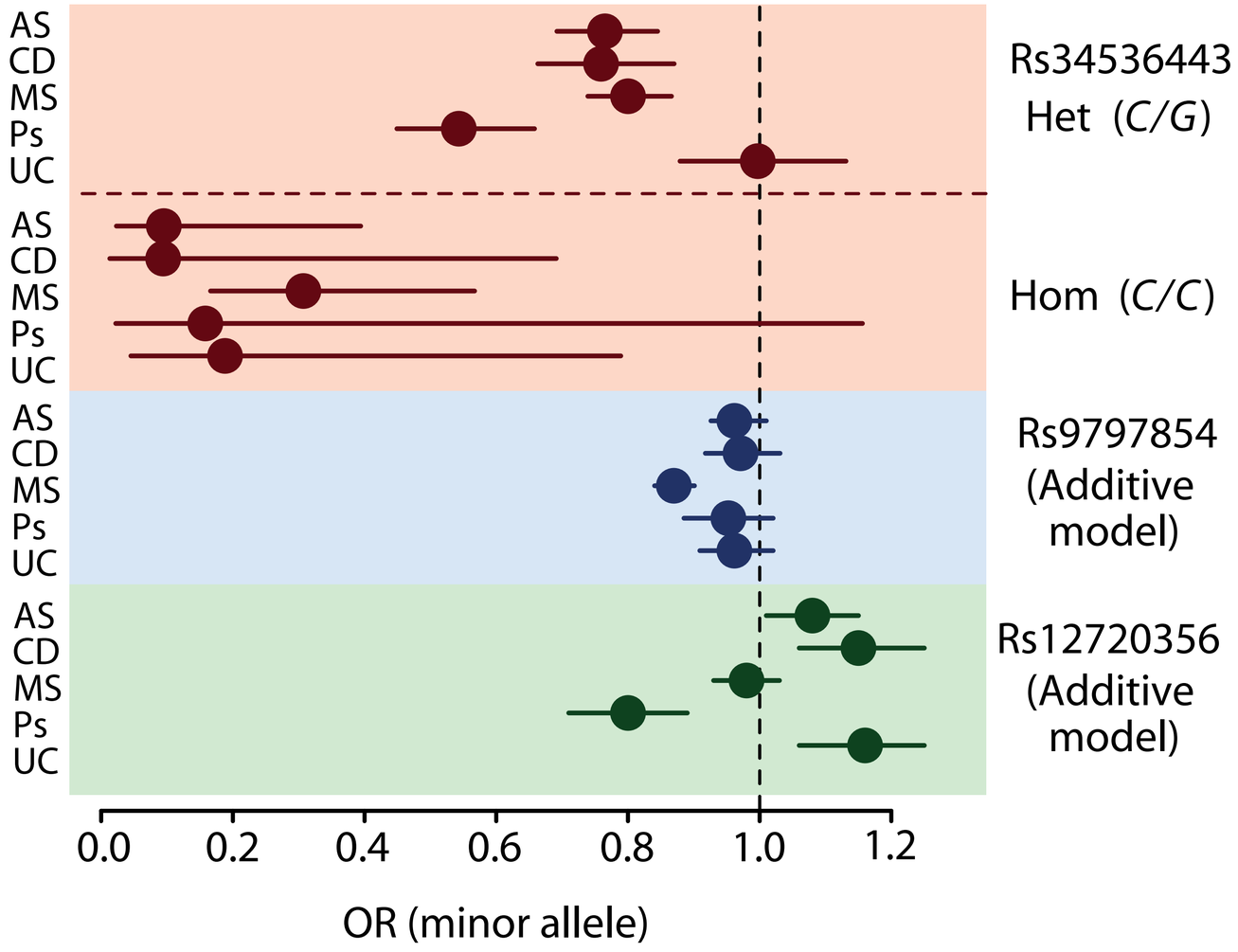


SLC39A8



(Nakata *et al,* 2020, PNAS)

TYK2 (Deucravacitinib)



https://www.dermatologytimes.com/view/deucravacitinib-safe-effective-for-psoriasis

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Phase 2 Trial of Selective Tyrosine Kinase 2 Inhibition in Psoriasis

Kim Papp, M.D., Ph.D., Kenneth Gordon, M.D., Diamant Thaçi, M.D., Ph.D., Akimichi Morita, M.D., Ph.D., Melinda Gooderham, M.D., Peter Foley, M.D., Ihab G. Girgis, Ph.D., Sudeep Kundu, Ph.D., and Subhashis Banerjee, M.D.

ABSTRACT

BACKGROUND

Tyrosine kinase 2 (TYK2) signaling pathways, which mediate cytokine signaling, are implicated in the pathophysiology of psoriasis. Selective inhibitors of TYK2 may be effective in treating psoriasis.

METHODS

We conducted a phase 2, double-blind trial of a TYK2 inhibitor, BMS-986165, in adults with moderate-to-severe psoriasis, excluding patients with a previous lack of response to agents targeting cytokine signaling through the same tyrosine kinase pathway. Patients were randomly assigned to receive the drug orally at a dose of 3 mg every other day, 3 mg daily, 3 mg twice daily, 6 mg twice daily, or 12 mg daily or to receive placebo. The primary end point was a 75% or greater reduction from baseline in the Psoriasis Area and Severity Index (PASI) score at week 12 (higher scores indicate greater severity of psoriasis).

RESULTS

A total of 267 patients received at least one dose in an intervention group of the trial. At week 12, the percentage of patients with a 75% or greater reduction in the PASI score was 7% (3 of 45 patients) with placebo, 9% (4 of 44 patients) with 3 mg of BMS-986165 every other day ($P=0.49$ vs. placebo), 39% (17 of 44 patients) with 3 mg daily ($P<0.001$ vs. placebo), 69% (31 of 45 patients) with 3 mg twice daily ($P<0.001$ vs. placebo), 67% (30 of 45 patients) with 6 mg twice daily ($P<0.001$ vs. placebo), and 75% (33 of 44 patients) with 12 mg daily ($P<0.001$ vs. placebo). There were three serious adverse events in patients receiving the active drug, as well as one case of malignant melanoma 96 days after the start of treatment.

Bristol Myers Squibb Provides Update on Phase 2 Study of Deucravacitinib in Patients With Moderate to Severe Ulcerative Colitis

10/07/2021

CATEGORY: Corporate/Financial News

LATTICE-UC proof of concept study did not meet primary nor secondary endpoints

Safety profile of deucravacitinib consistent with other trials and no new safety signals reported

https://news.bms.com/news/details/2021/Bristol-Myers-Squibb-Provides-Update-on-Phase-2-Study-of-Deucravacitinib-in-Patients-With-Moderate-to-Severe-Ulcerative-Colitis/default.aspx

https://www.evaluate.com/vantage/articles/news/snippets/lattice-miss-grating-bristol-myers

Kokkuvõte

- Katkise valgu parandamine on keerulisem kui terve valgu katki tegemine (HBB)
- Head organoidi- ja rakumudelid kiirendavad ravimiarendust oluliselt (CFTR)
- Polügeensus tähendab, et sama protsessi on võimalik “sihitida” erineva nurga alt (kolesterool)
- Pleiotroopia - sama valk osaleb tihti mitmes erinevas protessis. Suur väljakutse on aru saada, millal ja kus mingit valku sihtida võib, ilma et sellega negatiivsed kõrvalmõjud kaasneksid.