Why Genetics



Plenge Science Translational Medicine (2016)

Human genetics helps kick-start drug discovery



Many genes influence cholesterol levels and risk of heart disease

PCSK9 mutations associated with high and low LDL cholesterol levels (and heart disease risk)



PCSK9 binds to LDL receptor outside of cells to reduce LDLR on cells

drugs that mimic the mutation & lower LDL and protect from heart disease



Genetic support for FDA approved drugs in 2018

36 approved new new molecular entities so far in 2018 (Sept. 25)

FDA website

- Of these, 22 are for non-oncology / non-ID indications
- Most have some degree of genetic support for the targets:
 - tezacaftor / ivacaftor for CF -> strong prospective evidence (CFTR)
 - burosumab for hypophosphatemia -> strong prospective evidence (FGF23)
 - tildrakizumab for psoriasis -> strong retrospective evidence (IL23A)
 - avatrombopag for thrombocytopenia –> strong prospective evidence (MPL)
 - pegvaliase for PKU deficiency -> strong prospective evidence (PAH)
 - baricitinib for rheumatoid arthritis -> weak prospective evidence (JAK1)
 - patisirin for polyneuropathy of amyloidosis -> strong prospective evidence (TTR)
 - elagolix for pain with endometriosis -> strong prospective evidence (GNRH1)
 - Iusutrombopag for thrombocytopenia –> strong prospective evidence (MPL)
 - migalastat for Fabry -> strong prospective evidence (GLA)
 - cenegermin for neurotrophic keratitis –> strong prospective evidence (NGF)
 - lanadelumab for hereditary angioedema –> strong prospective evidence (KLKB1)

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O'Shea and Plenge Immunity (2012)

Lessons learned from the fate of AstraZeneca's drug pipeline: a five-dimensional framework

David Cook, Dearg Brown, Robert Alexander, Ruth March, Paul Morgan, Gemma Satterthwaite and Menelas N. Pangalos





The support of human genetic evidence for approved drug indications

Matthew R Nelson¹, Hannah Tipney², Jeffery L Painter¹, Judong Shen¹, Paola Nicoletti³, Yufeng Shen^{3,4}, Aris Floratos^{3,4}, Pak Chung Sham^{5,6}, Mulin Jun Li^{6,7}, Junwen Wang^{6,7}, Lon R Cardon⁸, John C Whittaker² & Philippe Sanseau²

~2-fold increase in success for genetic targets



Rare genetic diseases have >2-fold higher success rate

