Finding Rare Variants of Large Effects Related to Complex Disease

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NHGRI, DC
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Rare Variants

• Who cares?
PCSK9 schematic of nonsense mutations associated with low LDL cholesterol

A

R46L  Y142X  C679X

SP  Pro  Catalytic  P Domain  C Terminal

1  30  143  474  573  692
S127R  F216L  N  D374Y

B

Y142X or C679X variants
African-Americans
N = 3,363 followed 15 years

28% ↓ LDL; 88% ↓ risk
p = 0.008

R46L variant
European-Americans
N = 9,524 followed 15 years

15% ↓ LDL; 47% ↓ risk
p = 0.003
PCSK9 as a Therapeutic

Liver

Hepatocyte

Blocking PCSK9 synthesis:
- ALN-PCS in preclinical development from Alnylam Pharmaceuticals Inc. (NASDAQ:ALNY);
- BMS-PCSK9Rx in preclinical development from Isis Pharmaceuticals Inc. (NASDAQ:ISIS) and Bristol-Myers Squibb Co. (NYSE:BMY)

1. Autocatalysis
2a. Secretion
2b. LDL receptor synthesis

mAbs against PCSK9 in preclinical development from Amgen Inc. (NASDAQ:AMGN)

LDL receptor
LDL cholesterol
PCSK9 (cleaved/uncleaved)

Lysosomal degradation
Rare Variants

• Who cares?
• How many are there?
Rare variation makes a significant contribution to genetic diversity
How many rare variants?
(Predicting n\textsuperscript{th} Genome)

ENCODE 3 Sequence Data
~ 700 samples. 1 Mb each

ARIC:
~ 11,000 samples, ~ 25 kb

~ 10-300 novel ns / genome!
~90% of Predicted Deleterious Alleles are Rare

- 15% of SNVs (77,746) are predicted to be functionally important
Rare Variants

• Who cares?
• How many are there?
• Where did they come from?
Simulation of Variant Data

- Demographic history of European population

- Population genetic model incorporating demographic change (Boyko et al PloS Genet 2008)
Rare Variants

• Who cares?
• How many are there?
• Where did they come from?
• They are not in me, they are only in really sick people.
How Many Deleterious SNVs Do We Carry?

- AA
- EA
Two Preliminary Examples
Rare Variants

• Who cares?
• How many are there?
• Where did they come from?
• They are not in me, they are only in really sick people.
• How do we analyze rare variants?
NS Allele count for top protective gene: *NBEAL1*

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Impact of Non-Causal Variants (tests for detrimental variants)
Detrimental and Protective Variants ("two-sided" tests)
Rare variants

• Who cares
• How many are there?
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• They are not in me, they are only in really sick people.
• How do we analyze rare variants?
• What are we going to do with WGS?
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Annotation and Analysis of Whole Genomes

Trait: HDL
Chr 16, Positions 56,973,913 : 57,039,678

-log_{10}(p)

Position

Nsnps: 30
Nsnps: 0
Thank You

- Who cares?
- How many are there?
- Where did they come from?
- They are not in me, they are only in really sick people.
- How do we analyze rare variants?
- What are we going to do with WGS?