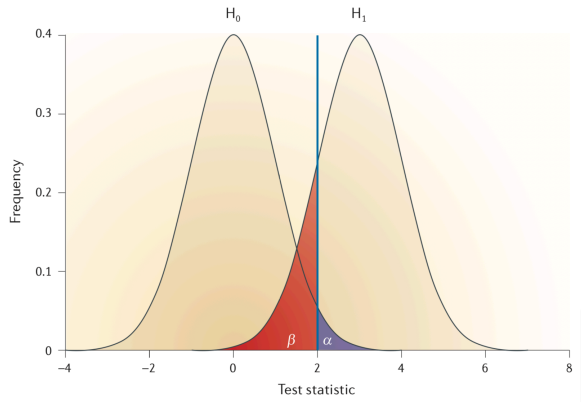
Power Calculation

Definition of Power



Power = P(reject Null I Alternative True)

Power is defined as the probability of rejecting the null when the alternative hypothesis is true.

If we want to limit the type 1 error (\alpha), we can choose the rejection threshold so that the area under the null hypothesis density to the right of the threshold is \alpha.

Given the alternative, H1, that will determine the type 2 error = β.

Power is the area under the H_1 density to the right of the rejection threshold. 1 - \beta

Why Do We Need to Compute Power?

- To design study as to not miss a real effect
  - typically determine sample size so that power > 80% at significance level \alpha
- To improve reproducibility
- When no significant results are found, to estimate a upper bound of effect sizes
- Risch & Merikangas laid out the vision for the future of genetic studies by comparing the power of linkage vs association studies

Risch and Merikangas call for Transitioning to Association Analysis

The Future of Genetic Studies of Complex Human Diseases

Geneticists identifying t diseases, at le minants. The disease, Alzh breast cance netic factors schizophreni has been far

the method that has been used successfully (linkage analysis) to find major genes has limited power to detect genes of modest effect, but that a different approach (association studies) that utilizes candidate genes has far greater power, even if one needs to test every gene in the genome. Thus, the future of the genetics of complex diseases is likely to require large-scale testing by association analysis.

Risch & Merikangas, Science 1996

4

In this extremely influential paper, Risch and Merikangas conclude that a GWAS approach would be much more powerful than linkage analysis.

Based on these results, they advocated for the need to switch from linkage analysis to GWAS approach. At the time measuring 100K markers was a mere thought experiment. This was before the human genome project and thus the technology to interrogate the genome was not available.

Association more powerful than linkage for small effects

		Linkage			Association	
					Singletons	Sib pairs
Genotypic risk ratio (γ)	Frequency of disease allele A (p)	Probability of allele sharing (Y)	No. of families required (N)	Probability of transmitting disease allele A P(tr-A)	Proportion of heterozygous parents (Het)	(N)	(Het)	(N)
4.0	0.01	0.520	4260	0.800	0.048	1098	0.112	235
	0.10	0.597	185	0.800	0.346	150	0.537	48
	0.50	0.576	297	0.800	0.500	103	0.424	61
	0.80	0.529	2013	0.800	0.235	222	0.163	161
2.0	0.01	0.502	296,710	0.667	0.029	5823	0.043	1970
	0.10	0.518	5382	0.667	0.245	695	0.323	264
	0.50	0.526	2486	0.667	0.500	340	0.474	180
	0.80	0.512	11,917	0.667	0.267	640	0.217	394
1.5	0.01	0.501	4,620,807	0.600	0.025	19,320	0.031	7776
	0.10	0.505	67,816	0.600	0.197	2218	0.253	941
	0.50	0.510	17,997	0.600	0.500	949	0.490	484
	0.80	0.505	67,816	0.600	0.286	1663	0.253	941

Comparison of linkage and association studies. Number of families needed for identification of a disease gene.

SCIENCE • VOL. 273 • 13 SEPTEMBER 1996 Risch & Merikangas

5

The number of samples needed to map disease genes were much larger with association approach than linkage. These power calculations provided the evidence for Risch and Merikangas to advocate for genome wide association approach.

Whole Genome Sequence of Pedigrees Powered to Detect Large Rare Variant Effect

Evaluating the contribution of rare variants to typ 2 diabetes and related traits using pedigrees

Goo Jun[a,b,c,1,2], Alisa Manning[d,1], Marcio Almeida[e,1], Matthew Zawistowski[a,b,1], Andrew R. Wood[f,1], Tanya M. Teslovic
Christian Fu
Han Chen[c]
Stephen E.
Alison Heat
Adam E. Lo
Manuel A.
Joanne E. C
Craig L. Ha
Jennifer E.
David Altsh
Gonçalo R.

Contributions of rare variants to common and complex traits such as type 2 diabetes (T2D) are difficult to measure. This paper describes our results from deep whole-genome analysis of large Mexican-American pedigrees to understand the role of rare-sequence variations in T2D and related traits through enriched allele counts in pedigrees. Our study design was well-powered to detect association of rare variants if rare variants with large effects collectively accounted for large portions of risk variability, but our results did not identify such variants in this sample. We further quantified the contributions of common and rare variants in gene expression profiles and concluded that rare expression quantitative trait loci explain a substantive, but minor, portion of expression heritability.

Jun et al PNAS 2018

6

Despite the large effort in whole genome sequencing of large pedigrees expected to be enriched in diabetes causing rare variants, no large effect genes or mutations were found. Based on power calculations, the lack of significance results define an upper bound to the contribution of rare variation to type 2 diabetes.

Power Calculation Software

- CaTS Power (Skol)/GAS Power Calculator
  - http://csg.sph.umich.edu/abecasis/cats/gas_power_calculator/index.html
- PLINK
- Quanto (Windows only)
- PS Power (http://biostat.mc.vanderbilt.edu/wiki/Main/PowerSampleSize)
- G*Power (http://www.gpower.hhu.de)
- Genetic power calculator (Purcell, Cherny and Sham, Bioinformatics, 2003)
  - http://pngu.mgh.harvard.edu/~purcell/gpc/

There are a few software packages that calculate power.

How Can We Increase Power

- Increasing sample size
- Increasing acceptable type 1 error (α)
- Increasing effect size
  - reducing error in Y for example
  - (not under our control but) more common variants (higher allele frequencies) yield higher power
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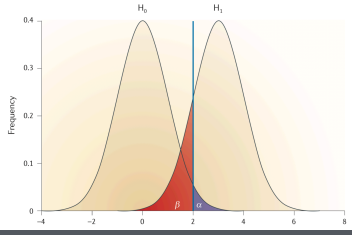


Power increases if we increase the sample size, are willing to accept a large type 1 error (α,FPR), reduce the noise, (not under our control) increase the effect size or the allele frequency. We have more power to detect common variants than rare variants.

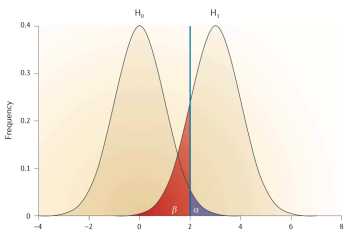
What Determines Power?

$1-\beta$: power

α : significance level, i.e. the acceptable type I error

n : sample size

Δ : standardized effect size



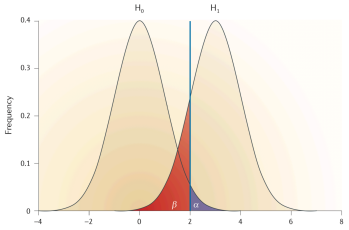
Power is Function of α, n, Δ

```
> library(pwr)
> pwr.norm.test(d = NULL, n=100, sig.level = 0.05, power = 0.8)

     Mean power calculation for normal distribution with known variance

              d = 0.2801491
              n = 100
      sig.level = 0.05
          power = 0.8
    alternative = two.sided
```

$1-\beta$: power
α : significance level
n : sample size
Δ : standardized effect size



10

Given three of the four variables, the fourth one is determined. In the example, we calculate power for to detect whether the mean of a normally distributed random variable is != 0. The test statistics in this case is the sample mean. We assume the standard deviation is known and standardize X dividing by the sd.

Calculating Power via Simulation

https://hakyimlab.github.io/hgen471/L4-power.html

Find code here
https://github.com/hakyimlab/hgen471/blob/master/analysis/L4-power.Rmd

11

We illustrate the power calculation by simulating a phenotype Y and genotype X associations with 1000 individuals.
The null model was Y ~ normal(0,1)
Under the alternative, Y = beta * X + epsilon, where epsilon ~ N(0,sig2epsilon)
I run the association between Y and X for both null and alternative hypothesis, repeating this 10K times.
The Zscore = estimated beta / standard error of beta is used as the test statistic.
-[ ] copy figures into the slides
