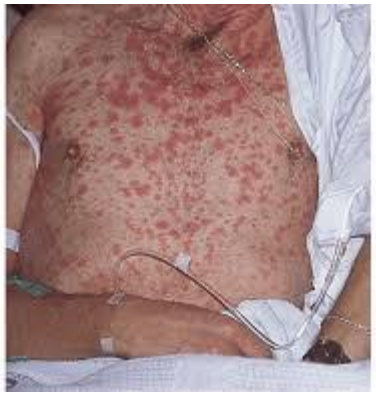
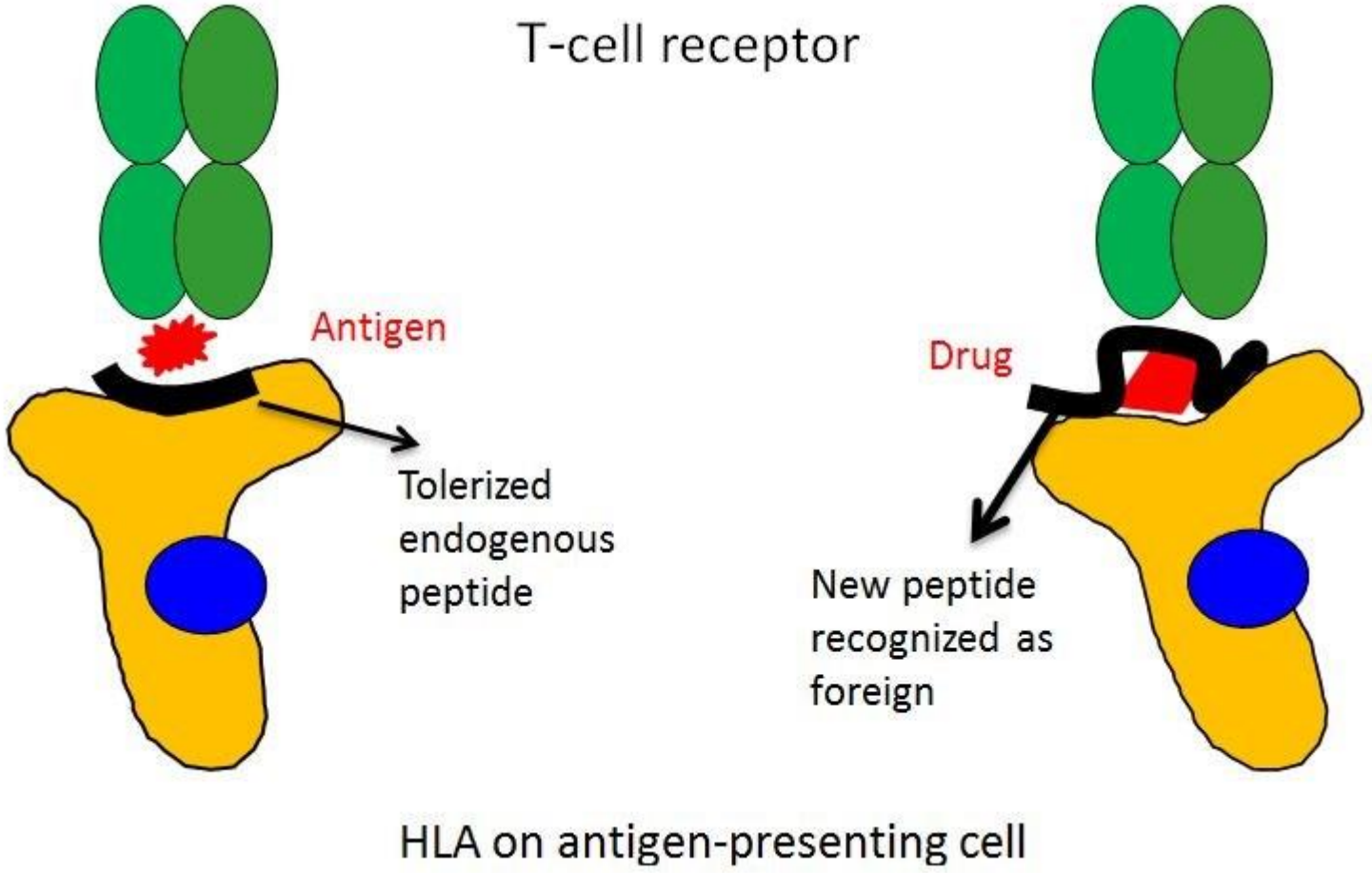
Example – HLA-B and abacavir





Roujeau 2014

FDA requires testing for abacavir

- Treatment with abacavir is generally well tolerated, but 5% of the patients experience hypersensitivity reactions that can be life threatening and warrant immediate discontinuation of the drug.
- Presence of at least one copy of the HLA-B*5701 allele has a very high odds ratio for developing hypersensitivity with abacavir. 6.7% of people have at least one copy of a HLA-B*5701 allele.
- 50% of the hypersensitivity is attributed to the effects of the HLA-B*5701 allele.
  - This equals the maximum percentage of cases that can be prevented if individuals who test positive for HLA-B*5701 are not treated with abacavir but receive alternative treatment.

Tonk 2017

Let’s calculate the odds ratio (n=100)

		Hypersensitivity		
		Yes	No	Total
HLA-B	5701+	a	b	a+b
	5701-	c	d	c+d
Total		a+c	b+d	100

What we know:
Hypersensitivity occurs in 5% of people.
50% of hypersensivity (cases) occurs in 5701+ individuals.
The 5701+ allele is found in 6.7% of people.

Let’s calculate these values (n=100)

ODDS RATIO

		Hypersensitivity		
		Cases	Controls	Total
HLA-B	5701+	**2.5**	b	a+b
	5701-	**2.5**	d	c+d
Total		**a+c=5**	b+d=95	100

What we know:
Hypersensitivity occurs in 5% of people.
50% of hypersensivity (cases) occurs in 5701+ individuals.
The 5701+ allele is found in 6.7% of people.

Let’s calculate these values (n=100)

ODDS RATIO

		Hypersensitivity		
		Cases	Controls	**Total**
HLA-B	5701+	2.5	b	**6.7**
	5701-	2.5	d	**93.3**
Total		a+c=5	b+d=95	**100**

What we know:
Hypersensitivity occurs in 5% of people.
50% of hypersensivity (cases) occurs in 5701+ individuals.
The 5701+ allele is found in 6.7%

Let’s calculate these values (n=100)

ODDS RATIO

		Hypersensitivity		
		Cases	**Controls**	Total
HLA-B	5701+	2.5	**4.2**	6.7
	5701-	2.5	**90.8**	93.3
Total		a+c=5	**b+d=95**	100

What we know:
Hypersensitivity occurs in 5% of people.
50% of hypersensivity (cases) occurs in 5701+ individuals.
The 5701+ allele is found at a frequency of 6.7%

Let’s calculate these values (n=100)

		Hypersensitivity		
		Yes	No	Total
HLA-B	5701+	2.5	4.2	6.7
	5701-	2.5	90.8	93.3
Total		a+c=5	b+d=95	100

$$\text{OR}= \frac{a/b}{c/d} = \frac{ad}{bc}$$

(2.5 *90.8) / (4.2*2.5) = 21.6

$$\ln\left(\frac{p}{1-p}\right) = a + B*(5701+ = 0 \text{ or } 1)$$

log odds hypersensitivity= ln(2.5/90.8) + ln(21.6)X_{5701+}

Odds in 5701- = 2.5/90.8

Odds in 5701+ = 2.5/4.2

B = ln(21.6) = 3.07

Intercept = ln(2.5/90.8) = -3.59

Y = -3.59 + 3.07(X_{5701+})

Let’s calculate screening parameters

		Hypersensitivity		
		Cases	Controls	Total
HLA-B	5701+	2.5	4.2	6.7
	5701-	2.5	90.8	93.3
Total		5	95	100

Sensitivity = a/(a+c) = test + who will develop hypersensitivity
Specificity = d/(b+d) = test – who won’t develop hypersensitivity
Positive predictive value = a/(a+b) = develop hypersensitivity who test +
Negative predictive value = d(c+d) = don’t develop hypersensitivity who test -

Let’s calculate screening parameters

		Hypersensitivity		
		Cases	Controls	Total
HLA-B	5701+	2.5	4.2	6.7
	5701-	2.5	90.8	93.3
Total		5	95	100

Sensitivity = a/(a+c) = 2.5/5= 50%
Specificity = d/(b+d) = 90.8/95 = 96%
Positive predictive value = a/(a+b) = 2.5/6.7 = 37%
Negative predictive value = d(c+d) = 90.8/93.3 = 97%

Number needed to treat

- (1/frequency of allele * 1/PPV)
- (1/0.067) * 1/(0.37) = 40.3
- How many people do we need to genotype to get one person with a 5701 allele (and then we give those people a different medication)
- How many of those people would have developed hypersensitivity if they did not receive a different medication (1 out of 3).

What we learned

- Why we study genetic epidemiology.
- The types of genetic variation and their effect on phenotypes.
- How population genetics principles can help us and hurt us in genetic epidemiology, especially related to population substructure (ancestry patterns) and linkage disequilibrium.
- How family studies can pinpoint loci linked to outcomes.
- Types of genetic data available and their pros and cons.
- How we conduct association studies and calculate odds ratios using 2x2 table and logistic regression.
- How to conduct genome wide association studies and consider rare variants.

What we learned

- Bioethical principles and public health screening parameters to help us decide whether and how to conduct studies and implement results.
- The principles in conducting gene-environment interaction studies including practical issues that need to be taken into account.
- Pharmacogenetics and precision medicine leverages many of the principles of genetic epidemiology to tailor medications for individual patients.
- Mendelian Randomization studies use genetics as proxies for modifiable risk factors to study associations between risk factor and outcome while overcoming some of the common pitfalls in observational epidemiology.
- There is an increasing interest in leveraging GWAS results to generate risk prediction models in the general population.