

# Polygenic Risk Scores for Cervical HPV Infection in Ghanaian Women

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# INTRODUCTION

- Cervical cancer is the fourth most frequently diagnosed cancer and the fourth leading cause of cancer death among women, with an estimated 604,000 new cases and 342,000 deaths worldwide in 2020.
- In Ghana, an estimated 3,072 new cases are diagnosed, with 1,815 deaths attributed to the disease annually.
- The age-standardized incidence and mortality rates are 27.0 and 16.9 per 100,000, respectively.

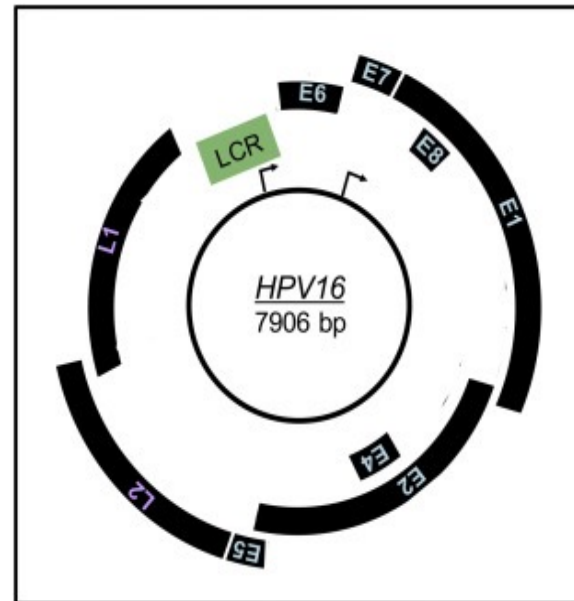


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# HPV BIOLOGY

Genotype	Risk	Disease
HPV 16	High risk	Cervical cancer Penile cancer Oropharyngeal cancer
HPV 18	High risk	Cervical cancer Oropharyngeal cancer
HPV 31, 33, 35, 39, 45, 51, 52, 56, 58, 59	Low risk	Cervical squamous cell carcinoma Oropharyngeal cancer
HPV 6, 11	Low risk	Benign genital warts Oral hyperplasia
HPV 13, 32	Low risk	Benign genital warts Oral hyperplasia



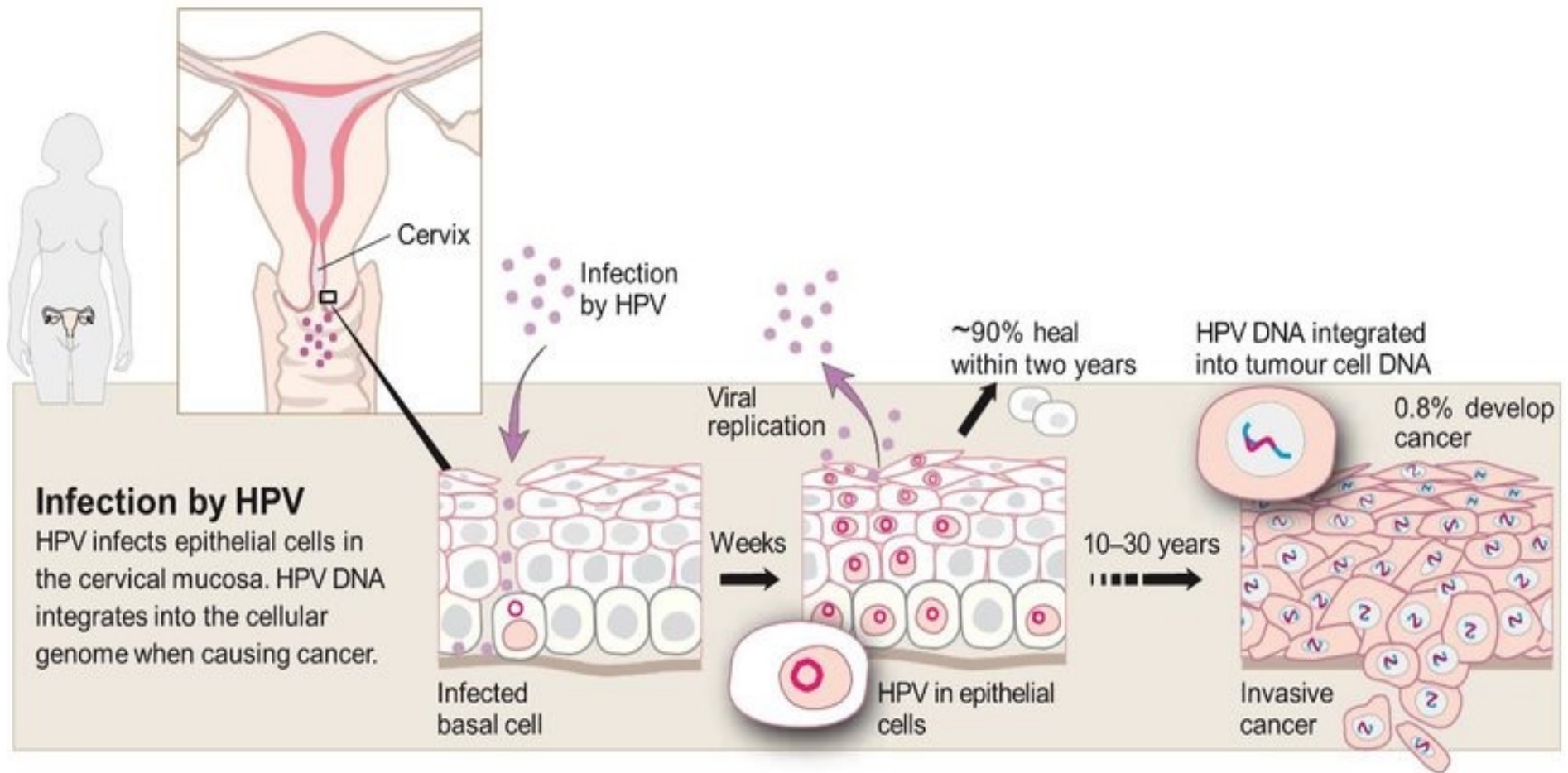
EARLY REGION: proteins necessary for viral replication

LATE REGION: viral capsid proteins

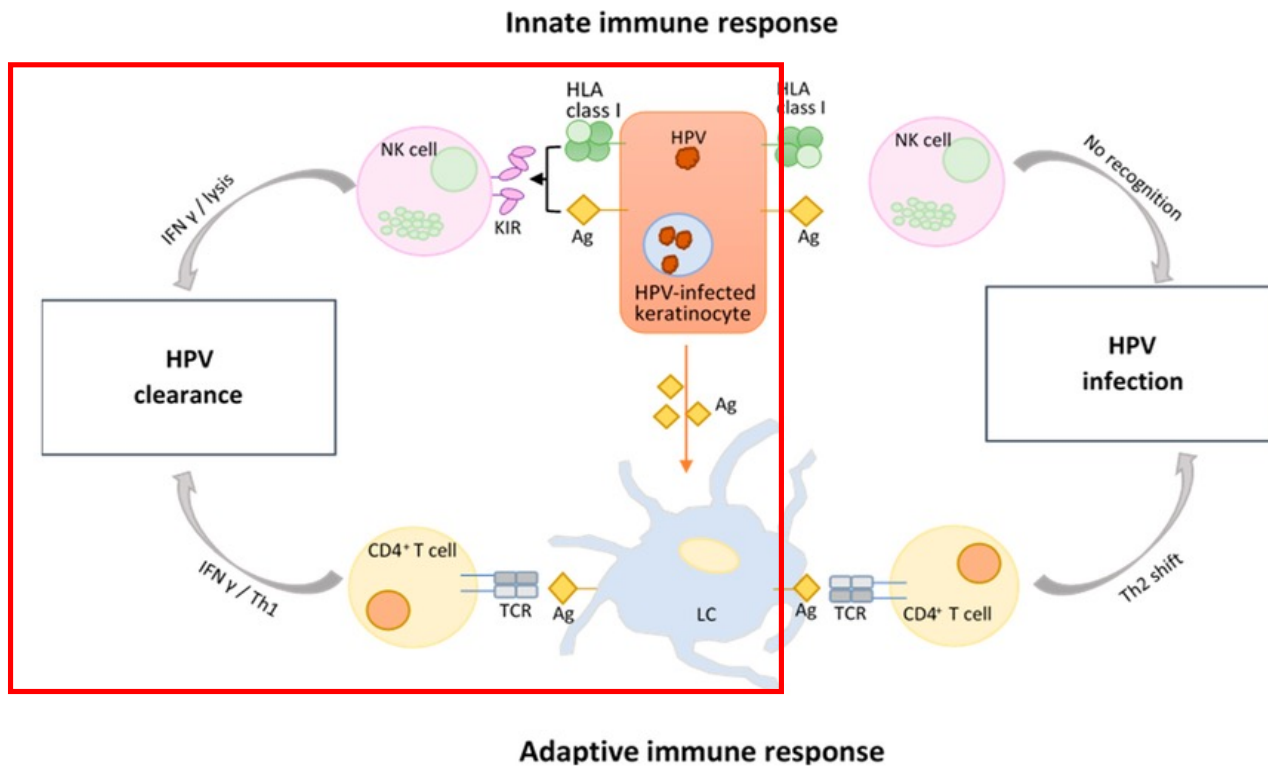
LONG CONTROL REGION: sequences controlling viral replication & transcription

ORF	HPV16 PROTEIN FUNCTION
E1	origin binding protein, ATPase-dependent helicase involved in genome replication
E2	regulator of viral gene transcription, association with E1 (origin binding), viral genome partitioning
E4	expressed abundantly as E1 <sup>+</sup> E4 fusion protein, cyokeratin network destabilization, virus release and transmission
E5	small transmembrane protein, interacts with EGF receptor activating mitogenic pathways
E6	drives cell cycle allowing genome amplification in upper epithelial layers, association with E6AP and degradation of p53, PDZ-protein binding, hTert activation
E7	drives cell cycle allowing genome amplification in upper epithelial layers, association with and degradation of pRB, mitotic mutator
E8	expressed as E8 <sup>+</sup> E2 fusion protein, acts as a repressor of transcription and replication during the viral life cycle
L1	major capsid protein, assembles into pentameric capsids forming the icosahedral virion (prophylactic vaccines)
L2	minor capsid protein, involved in viral DNA encapsidation, facilitates viral entry and trafficking

# HPV Pathogenesis

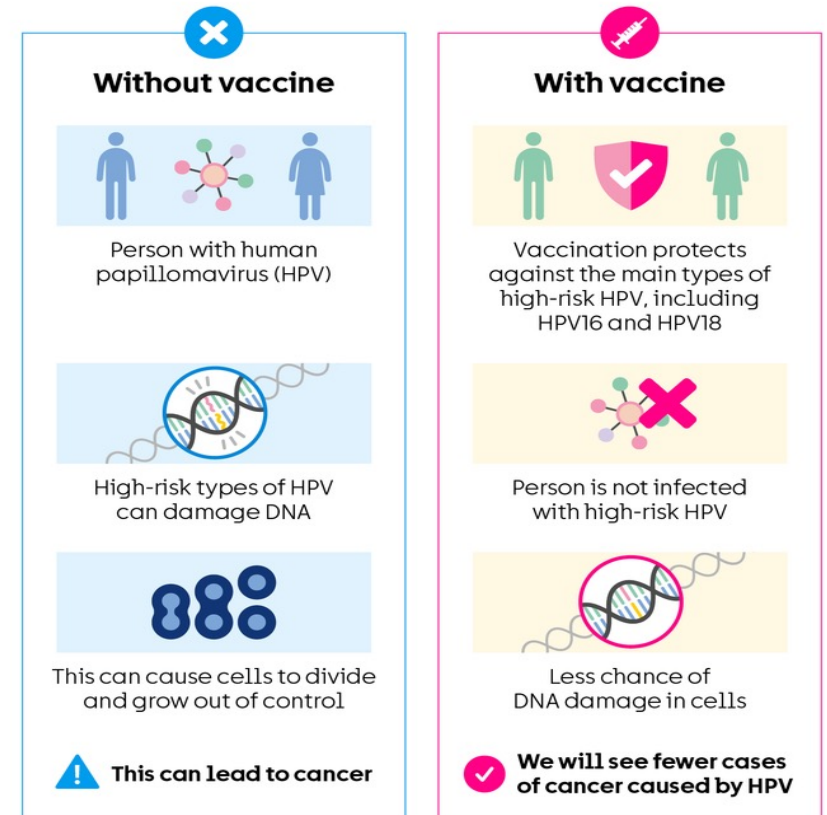


# Immune Response to HPV



Why is clearance effective in some women than others?

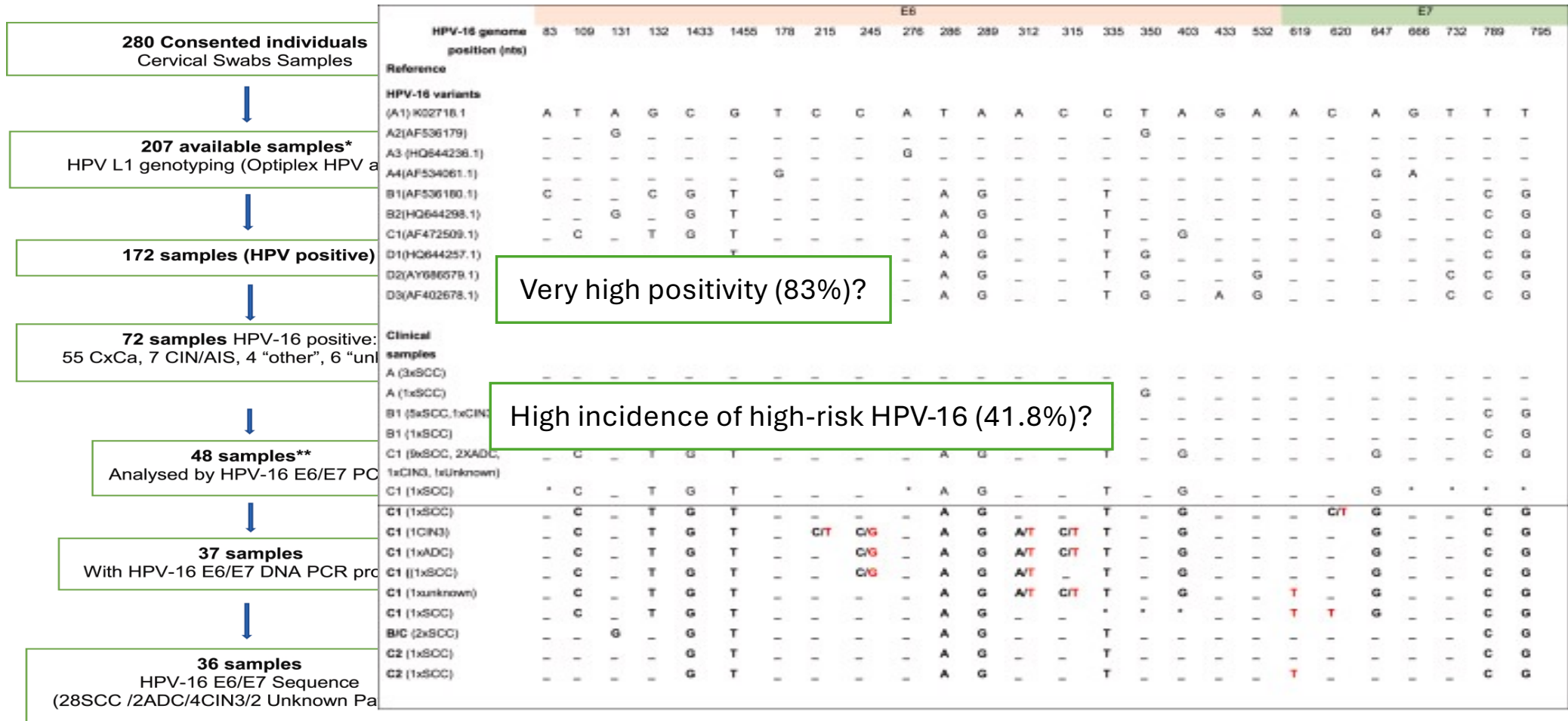
## How does the HPV vaccine work?



**By protecting against HPV infection, we can help prevent cell changes and reduce the risk of cancer**



# Diversity of cervicovaginal human papillomavirus (HPV) genotypes and naturally occurring E6/E7 DNA polymorphisms of HPV-16 in Ghana



Very high positivity (83%)?

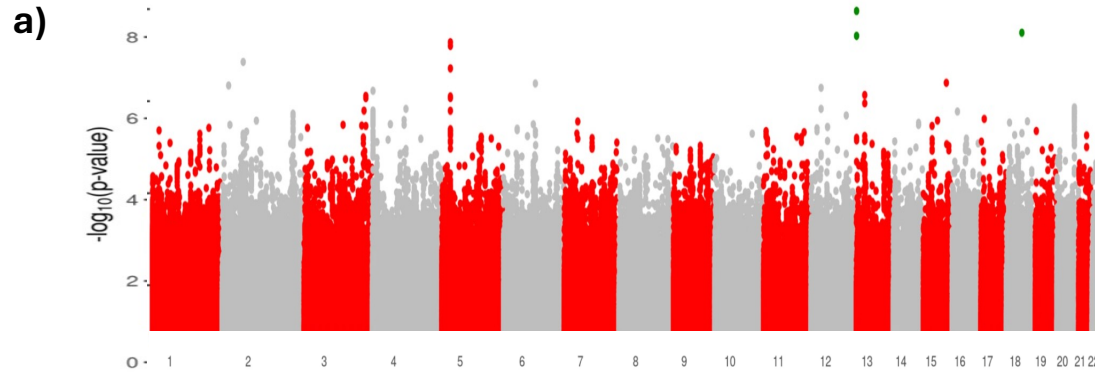
High incidence of high-risk HPV-16 (41.8%)?

SCC = Squamous Cell Carcinoma; ADC = Adenocarcinoma; CIN3 = Cervical Intraepithelial Neoplasia Grade 3. SNP = Single Nucleotide Polymorphism; HPV-16 A lineages SNPs = (145G/286T/289A), HPV-16 B/C lineages SNPs = (C143G/G145T/T286A/A289G/C335T); HPV-16 D lineage SNPs = G145T/T286A/A289G/C335T/T350G. Novel SNPs discovered in the samples are indicated in red text.

# Can PRS help predict immune clearance?

- Recruit approximately 500 women, (aged matched cervical cancer+ vs cervical cancer negative) – 2022 - 2024
- Aged 40 – 60 years
- Detailed Demographic information (for environmental component)
- Serological IgG for HPV16/18 infection and HPV testing
- Genotype participants using Illumina H3Africa\_2017\_20021485 Array (HLA alleles)
- Imputation of all samples was performed into the TOPMed reference panel.
- The resulting imputation dataset of all samples was filtered for variants with  $MAF \geq 0.01$  and information score (info)  $\geq 0.3$  for association analysis.

# SNPs in Epithelial Cell Morphology and Signaling Pathway Associated with Persistent HPV infections



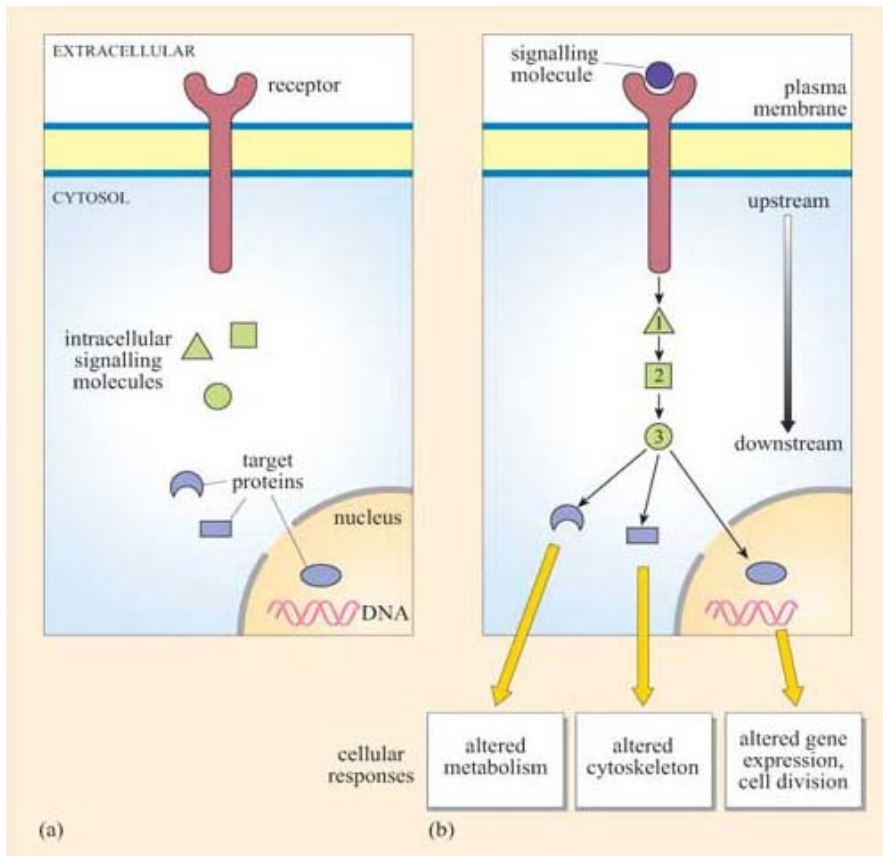
b) **Table 1.** Top Associations with Persistent Cervical HPV Infections

SNP	Chr	Base Position	Near gene	Ref. allele	Discovery Cohort			
					MAF	OR	SE	P-value
Persistent hrHPV								
rs2342234	13	19385993	TPTE2	C	0.01	0.35	0.18	1.50 x 10 <sup>-8</sup>
rs115537401	18	47802812	SMAD2	A	0.01	2.50	0.17	3.26 x 10 <sup>-8</sup>
rs1879062	5	23044423	CDH12	G	0.05	1.79	0.10	3.81 x 10 <sup>-8</sup>
rs1028206	5	23046022	CDH12	G	0.05	1.78	0.10	4.45 x 10 <sup>-8</sup>
rs2152687	13	19382475	TPTE2	G	0.01	0.38	0.18	5.71 x 10 <sup>-8</sup>
rs2180716	6	87974113	SPACA1	A	0.21	1.41	0.06	1.01 x 10 <sup>-7</sup>
rs72750684	5	23050313	CDH12	A	0.05	1.72	0.10	1.44 x 10 <sup>-7</sup>
rs114789544	13	38085944	TRPC4	T	0.04	1.80	0.11	2.76 x 10 <sup>-7</sup>
rs115982456	13	38122581	UFMI	A	0.04	1.78	0.11	3.39 x 10 <sup>-7</sup>
rs188897338	15	88310779	NTRK3	T	0.01	2.66	0.19	3.99 x 10 <sup>-7</sup>
rs12448674	16	85476219	GSE1	T	0.48	0.75	0.06	4.18 x 10 <sup>-7</sup>
rs143857229	15	61364786	RORA	T	0.02	2.16	0.15	4.81 x 10 <sup>-7</sup>



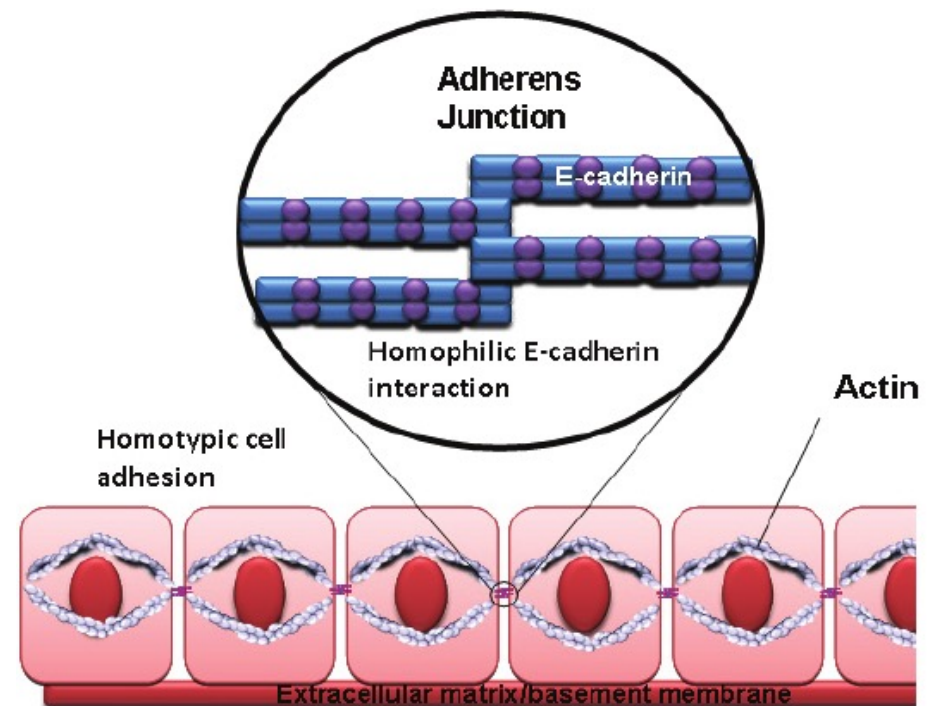
# SNPs in Epithelial Morphology and Signaling Associated with Persistent HPV infections

*TPTE Signalling*



<https://www.open.edu/openlearn/science>

*CDH*



<https://www.tandfonline.com/doi/full/10.1080/19336918.2014.1000072>

## Subset of HLA haplotypes significantly associated with persistence HPV infection

a) A total of 37 haplotypes were significantly associated with persistent HPV, and 46% (17/37) of them were located on DRB1.

b) **Table 2.** Top 10 HLA Haplotypes Associated with Persistent Cervical hrHPV Infections

Haplotype	OR	FDR Adjusted <i>P</i> value
C*07:01 - DQB1*06:02	0.61	<b>2.37 x 10<sup>-04</sup></b>
B*58:02 - DRB1*15:03	0.34	<b>5.91 x 10<sup>-04</sup></b>
C*07:01 - DRB1*15:03	0.62	<b>6.40 x 10<sup>-04</sup></b>
DQB1*05:02 - DRB1*13:02	1.87	<b>7.36 x 10<sup>-04</sup></b>
C*06:02 - DQB1*06:02	0.53	<b>8.43 x 10<sup>-04</sup></b>
A*32:01 - DRB1*15:03	2.5	<b>0.0011</b>
C*06:02 - DRB1*15:03	0.44	<b>0.0011</b>
DQB1*06:02 - DRB1*15:03	0.75	<b>0.0013</b>
B*45:01 - DRB1*03:01	2.63	<b>0.0022</b>
B*45:01 - DQB1*02:01	2.32	<b>0.0027</b>

# Prospective Outcome

