

Clinical Genomics in Infectious Disease

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2025 Conti Symposium on Veterinary Continuing Education
Current Concepts and Controversies in Clinical Genomics

Outcomes in infectious disease are dependent on multiple factors – including host and organism genetics

Recommended reading: Infectious disease diagnostics

The Journal of Clinical Investigation VIEWPOINT

Status check: next-generation sequencing for infectious-disease diagnostics


Kyle G. Redino¹ and Patricia J. Simmer²

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Review: **From Tradition to Innovation: Diverse Molecular Techniques in the Fight Against Infectious Diseases**


Ahmed Nouri Abharksi ¹, Serhat Sirekbasan ^{2*}, Tuğba Gürkök-Tan ³ and Adam Mustapha ⁴


Tools for infectious disease testing include





- > Culture (and sensitivity)
- > Viral antigen testing (including SNAP / lateral flow)
- > Immunohistochemistry or Immunofluorescence on biopsies or cells
- > Secondary evidence testing e.g. rising titre of antibodies
- > Molecular genetic testing


 TIME


 SPECIFICITY


 COST


 SENSITIVITY


 PRIOR
 KNOWLEDGE OF
 ORGANISM

What role does clinical genetics play in infectious disease?

> PART 1: Using genetics in diagnosis and management of infectious diseases

- > PCR based technologies
- > NGS based technologies
- > Nanopore and rapid clinical sequencing

- > PART 2: Using genetics to investigate different host responses to viruses (with the example of coronavirus)
- > Can we predict who will become severely ill?
- > Can the genes involved in susceptibility point us to new treatments?
- > Can genetics help us design and test new vaccines?

Diagnostic PCR-based technologies are in widespread use

- > e.g. for Virus, Fungus, Parasite, Bacteria, Mycobacteria, Protozoa
- > **Primary purpose** is diagnostic testing (eg COVID-19 outbreak, Leptospirosis) - but you do need to know the organism sequence to design the PCR primers
- > Can be a very **sensitive** technique – detecting early and low level infections
- > Can test many different samples including blood, urine, bone marrow, tissue biopsies, CSF, oronasal swabs, eye swabs
- > **Quicker** than traditional culture techniques (eg in sepsis, TB, fungal disease)
- > However it does not detect viral proteins (unlike lateral flow), only nucleic acid (RNA / DNA), so can give false positive for active infection

Diagnostic Quantitative PCR-based technologies are in widespread use

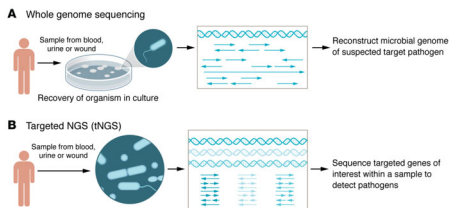
- Secondary features of PCR tests include:
 - Tracking of new variants in the organism by sequencing the PCR product
 - Quantitation of number of viral copies to give an indication of viral load (eg HIV)

Currently PCR tests have to be performed in specialist laboratories, so are not an "in-house" veterinary diagnostic

The LAMP (Loop-mediate isothermal amplification) assay is a new alternative technique, gaining popularity especially in resource-limited settings – tracking malaria, dengue, Zika.

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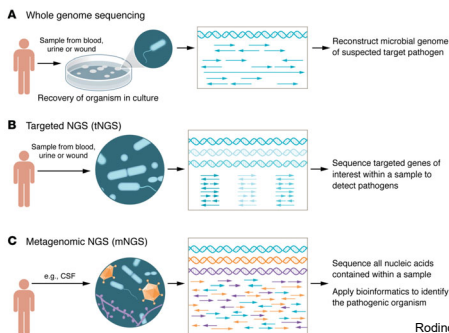
Diagnostic NGS-Sequencing-based technologies



Rodino and Simner 2021

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Diagnostic NGS-Sequencing-based technologies



Rodino and Simner 2021

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What about detecting anti-microbial resistance (AMR) genes?

- > This is possible but requires "deep" coverage sequencing and improvements in technology – typically culture and sensitivity are still needed in parallel
- > A 'negative' result does not always mean that AMR genes are not present – ie genetics has a poor negative predictive value
- > Not all AMR genes are known and present in the databases used for detection
- > When detecting multiple organisms, it is challenging to associate the AMR gene with the particular pathogen
- > Other techniques – e.g. Mass spectrometry, biomarker analysis, bacterial culture and sensitivity are required alongside genetics for this purpose

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What are the targets in targeted sequencing?

- > Selected genes in pathogens are selected that are constant between variant strains
- > In bacteria the 16s rRNA gene is commonly used as this allows differentiation of organisms at the genus level across all major phyla of bacteria
- > This is dependent on there being a database of organism gene sequences that is accessible to the person doing the analysis



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Can infectious disease sequencing in humans be prompt enough to have a clinical impact?

- > MinION has been used in the field in real time outbreaks for diagnosis, contract tracing and mutation tracking (e.g. influenza, Ebola, Zika)
- > Nanopore workflows have also been used in hospital settings



eBioMedicine
2025;314: 105633
Published Online 17 March 2025
<https://doi.org/10.1016/j.ebiom.2025.105633>

Next-generation diagnostics of bloodstream infections enabled by rapid whole-genome sequencing of bacterial cells purified from blood cultures

Wang Y, Chen Y, Wang Y, et al. *Cell* 2025;183:1-12. doi:10.1016/j.cell.2025.02.012

bio-protocol

bioRxiv

Direct RNA Sequencing of Foot-and-mouth Disease Virus Genome Using a Flongle on MinION

Wang Y, Chen Y, Wang Y, et al. *Cell* 2025;183:1-12. doi:10.1016/j.cell.2025.02.012

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How can genetic variants contribute to risk in a complex disease?

- 1. High-frequency & fixed variants in a breed**
 - providing an overall increased susceptibility of the whole breed to the disease (may or may not be exclusive to the breed)
- 2. Variants in a subset of individuals with the breed**
 - modifying susceptibility to the disease within a breed (i.e. seen in more cases than controls within a breed)
- 3. Low-frequency or unique variants**
 - modifying risk of the disease in individual dogs or cats

Genome-wide association study (GWAS) – using a “SNP Chip”

DNA from Cases
n=20 to several thousand

DNA from Controls
n=20 to several thousand

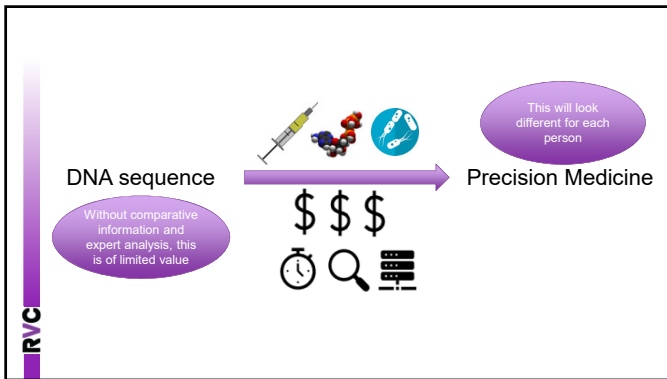
Manhattan plot shows significant SNPs differing in frequency between the two populations

How do genetic variants contribute to the risk of disease?

>Association ≠ Causation

- Most genetic variants identified to date are **SNPs (single nucleotide polymorphisms)** but other types include insertions, deletions, copy number variants, inversions and translocations
- Some SNPs are **non-synonymous** – coding sequence / amino acid change
- Synonymous SNPs** - do not change the amino acids, but can still affect gene function e.g. through mRNA transcript stability or splicing
- Other SNPs in **introns or untranslated regions** and can have a regulatory effect on gene function
- Some SNPs lie **outside genes** altogether but can still have a regulatory function e.g. through transcription factor binding or chromatin accessibility







Infectious disease research interests: Where will the next veterinary infectious disease diagnostic test come from?

> Canine Respiratory Coronavirus

- Host genetics
- MHC associations
- RNA-sequencing
- *In vitro* mechanistic work
- (Vaccination strategies – historic)

> Feline Infectious Peritonitis

- Host genetics
- RNA-sequencing
- Virus sequencing
- Feline MHC
- Feline immune repertoire
- Clinical / therapy studies
- Functional studies / genome annotation

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Acknowledgements


MASCOT team (alphabetical order):

- Dr Emi Barker (Veterinary clinician / FIP phenotypes / archive) – Bristol
- Prof Lucy Davison – PI (RVC / Oxford)
- Dr Sara Falcone (Post-doc / Sample processing / Canine MHC) – Oxford
- Dr Tom Hiron (Bioinformatics / Transcriptomics) – RVC / Oxford
- Dr Kate Hughes – (Veterinary pathologist) Cambridge
- Dr Lorna Kennedy – (MHC expertise) Manchester
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- Dr Sophie Binks – (Human medic) Oxford
- Dr Androniki Pafidi – (Complex disease genetics) RVC
- Dr Rachael Tarlinton – (Virus genomics) Nottingham
- Dr Marsha Wallace (Bioinformatics / WGS) – RVC / Oxford

Additional collaborators:

- ▶ J Jiang
- ▶ A Kpar
- ▶ R Shipley, T Hanson, K Anonwsmith, AH Seekings, LM McElhinney, S Jones, G Tyson, MJ Hoole
- ▶ Prof Leslie Lyons and Feline 99 Lives Consortium



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Canine Respiratory Coronavirus

- > First discovered in the UK in 2003¹
- > It is a beta coronavirus
- > It is present worldwide, with 50% of USA / Canada dogs having antibodies
- > It is very contagious (aerosol) with >99% dogs in affected shelters seroconverting within 3 weeks
- > There is a spectrum of severity – from asymptomatic to pneumonia – especially if additional pathogens are present (CIRD complex – **Kennel Cough**)
- > No specific anti-viral therapy or vaccine but up to 3 weeks isolation is recommended, and supportive care for severely affected dogs

¹Ertas K, Toomey C, Brooks HW, Brownlie J. Detection of a group 2 coronavirus in dogs with canine infectious respiratory disease. *Virology* 2003; 310:216–223.

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How long does immunity last?

Is a vaccine required?

Which dogs are most susceptible and why?

Will anti-virals help in CIRDc?

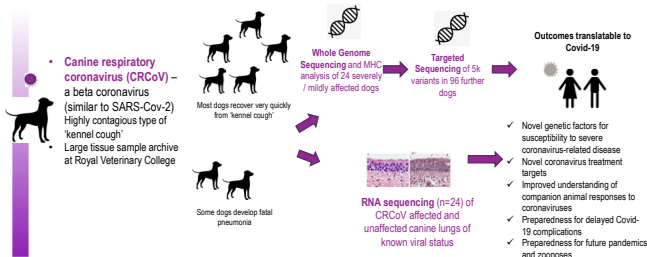
Can we design immunological interventions to limit disease?

Is CRCoV an appropriate model for SARS-CoV2 studies?

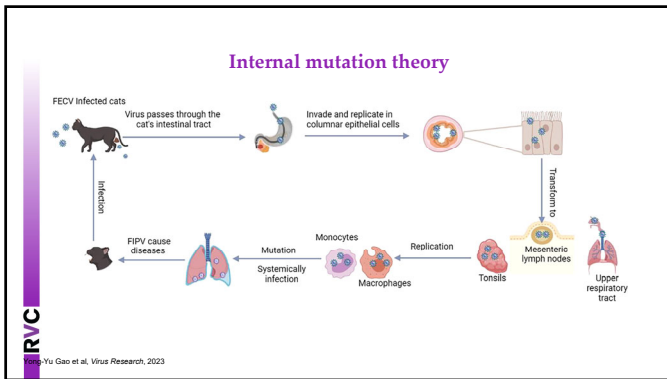
HOW CAN MOLECULAR GENETICS HELP DIAGNOSE, MANAGE AND PREVENT KENNEL COUGH?

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UKRI funded project: COVID 19: LESSONS FROM FATAL CORONAVIRUS INFECTIONS IN COMPANION ANIMALS



MASCOT Mapping Animal Susceptibility to Coronaviruses: Outcomes and Transcriptomics



What is the dysregulated immune response against?

Is a vaccine possible?

Which cats are most susceptible and why?

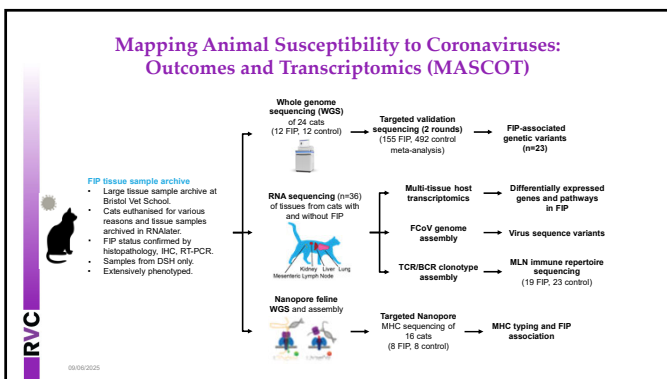
Does the virus always persist in tissues?

Can we design immunological interventions to limit disease?

Are humans at risk of an FIP-like illness?

WHAT KIND OF QUESTIONS CAN WE ASK WITH GENETIC TECHNIQUES APPLIED TO CLINICAL SAMPLES?


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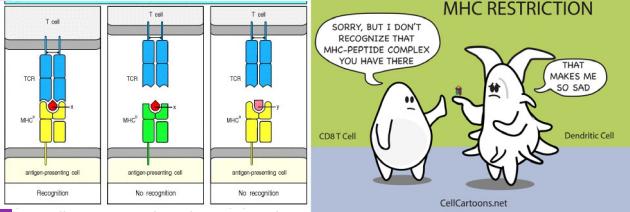
In humans, understanding the MHC type provides insights into the risk and /or outcome of many different diseases including...

- Autoimmune diseases, immune mediated diseases, cancer, infectious diseases e.g.
 - Type 1 diabetes
 - Systemic Lupus Erythematosus
 - Multiple sclerosis
 - Primary biliary sclerosis
 - Autoimmune encephalitis
 - Ankylosing spondylitis
 - Celiac disease
 - Myasthenia gravis
 - Hashimoto's thyroiditis
 - Colorectal cancer
 - Lung cancer
 - Nasopharyngeal carcinoma
 - Leprosy
 - HIV
 - Covid-19
 - Hepatitis B

Could MHC testing eventually become part of veterinary medicine?

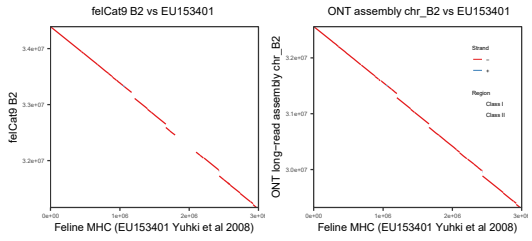


MHC is important in infectious diseases as it presents antigenic (pathogen) peptides to T-cells, shaping the immune response

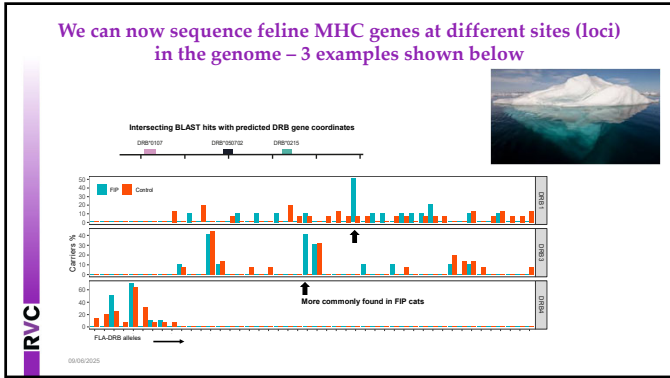


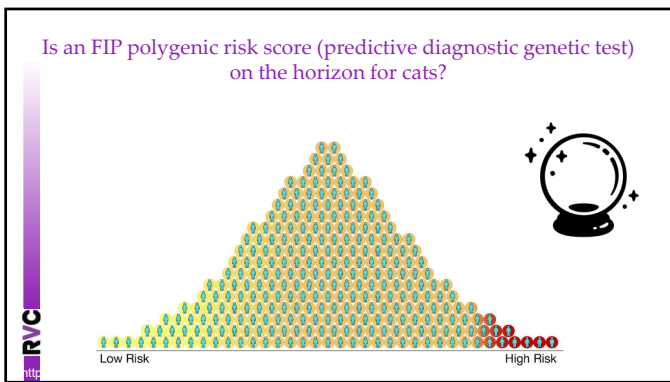
<https://cellcartoons.net/comic/mhc-restriction/>

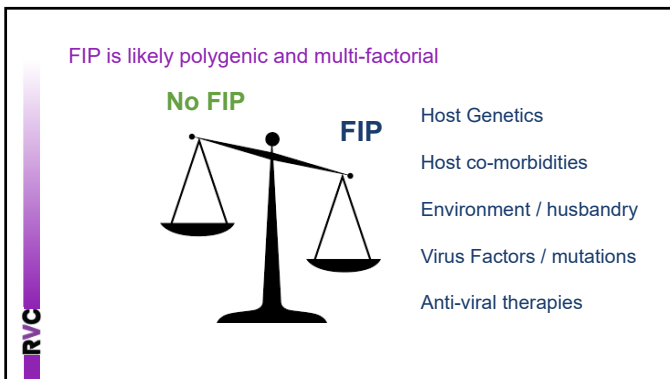
The feline MHC region was very poorly covered until we assembled a new feline genome using Oxford Nanopore technology (long reads)



09/06/2025







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THANK YOU FOR YOUR ATTENTION – QUESTIONS?

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