Genetic Testing in Primary Care

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Genetic testing in primary care

• Haemochromatosis (HFE 282 mutation)

• Factor V Leiden (Arg 506 Gln)

Not recommended for population screening

Done for work up of clinical events (iron overload or VTE or family history of a VTE)
Genetic testing in primary care

- Haemochromatosis (HFE 282 mutation)

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Done for work up of clinical events (iron overload or VTE or family history)
Basis of genetic variation: SNP/polymorphism

- Naturally occurring genetic variants
- Prevalence 1-90%
- Easily identified by high throughput technology
- Many have functional effects on protein amount or function
- SNP variant may confer protection (higher in controls) or susceptibility (higher in cases)
Structure of a gene

Transcription unit

m-RNA start +1
Exon 1  Exon 2  Exon 3  Exon 4
Promoter
Intron 1  Intron 2  Intron 3
m-RNA end

5’
3’

Regulatory regions above
5’ leader
Internal regulatory regions

3’ trailer
Regulatory regions below

3’
5’
Genetic testing in primary care

Haemochromatosis (HFE 282 mutation)

- HFE testing to establish Haemochromatosis diagnosis in iron overload (↑Fe Satn)
- Poor specificity (25-50% of gene test (+) are affected by iron overload)
- Reduced sensitivity (explains only some patients with idiopathic iron overload)
- Prompts venesection to treat overload
Genetic testing in primary care

Factor V Leiden (Arg 506 Gln mutation)

- Part of thrombophilia screen (↑ risk of VTE)
- Mutation occurs in 5% of the general population
- May prompt secondary prevention in those with a history of VTE
- May prompt secondary prevention in those with risk of recurrent fetal loss
- Risk of DVT multiplicative with OCP use
Lung Cancer & Tobacco Mortality

About 438,000 U.S. Deaths Attributable Each Year to Cigarette Smoking*

- Lung cancer: 123,800 (31%)
- Chronic lung disease: 90,600 (21%)
- Coronary heart disease: 86,800 (20%)
- Other diagnoses: 84,600
- Stroke: 17,400
- Other cancers: 34,700

* Average annual number of deaths, 1997–2001.
Gene test for lung cancer
NZ scientists develop way to predict smoking risk

Couple win big: $250,000 plus a baby

Slain girl’s dad on sex charges
Genetic susceptibility to lung cancer (COPD)

- Environmental factor known and measurable
- Preventable with smoking cessation
- Lifestyle intervention (quitting) has many benefits (health, financial, social)
- Smoking cessation is very cost effective
- Risk assessment has been shown to both trigger and improve smoking cessation rates
- Many available treatments to assist with quitting
- Potential benefits of statins in reducing COPD complications and risk of lung cancer (Booth 60A)
Smokers attitudes to smoking: literature review

- Smokers want to know their risk for smoking related complications (>80%)
- Smokers generally under-estimate their personal risk for lung cancer (>50% of smokers with lung cancer did not think they were at risk)
- Smokers state fear of lung cancer as their greatest concern and that fear of future poor health motivates them to quit (older smokers)
- Recognition that risk information has inherent value to patients above that of what doctors might act on
Changes in smoking prevalence since 1950

- **UK Men**
- **Finnish Men**

The link between smoking and lung cancer was made public in the 1950s and 1960s.

Public health initiatives continued to reduce smoking rates.

Smoking prevalence has levelled out over the last 20 years.

**Link made between smoking and lung cancer**

**Introduction of public health measures**
- eg taxes, advertising bans and health warnings
Epidemiology of lung cancer

- Smoking (90%)
  - Duration over 30 years or over 30 pk years

- Age (over 50 yo)

- Other factors
  - Asbestos, radon, radiation, cooking fuels
  - Low consumption of fruit and vegetables (antioxidants)
  - Lower risk in atopics

- Lung function

- Family history
Lung Cancer Risk climbs steeply with age

10 Year Mortality for Lung Cancer by Smoking Status

Deaths per 100 Men

- Smoker-life long
- Smokers-quit aged 50 yo
- Smokers-quit aged 60 yo
- Smokers-quit aged 70 yo
- Nonsmokers

Incidence ≈ Mortality

Age (Years)
Epidemiology of lung cancer

• Smoking (90%)
  – Duration over 30 years or over 30 pk years

• Age (over 50 yo)

• Other factors
  – Exposure to asbestos, radon, radiation and cooking fuels
  – Low consumption of fruit and vegetables (antioxidants)
  – Lower risk in atopics

• Lung function

• Family history

Genetic factors
Lung Function and Lung Cancer

Consistently reported risk of 3-6x for lung cancer in smokers with impaired lung function

<table>
<thead>
<tr>
<th>Lung cancer</th>
<th>Age</th>
<th>RR 2.8</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>↓FEV1</td>
<td>RR 6.4</td>
</tr>
<tr>
<td></td>
<td>Pk yrs</td>
<td>RR 3.1</td>
</tr>
</tbody>
</table>

Lung Cancer

downarrow FEV1

Age

↓FEV1 RR 6.4

Pack Yrs

1.8

2.2

1.4

1.8

5.3

2.4

16
Smoking, lung function and lung cancer

Smoking

20-30% of smokers develop impaired lung function (COPD)

COPD

65-75% of lung cancer patients have COPD

Lung Cancer

Parallel:
Obesity predisposes to diabetes
Segmentation of Lung Function Decline

A 0-20 Pack Years

B 50-60 Pack Years

C 50-60 Pack Years

D COPD

Resistant Smokers

% of Population

% FEV1

% of Population

% FEV1

% of Population

% FEV1

% of Population

% FEV1
Case association study – novel approach

**Initial Study**
446 smokers with lung cancer
484 resistant smokers

**Now screened 160 candidate SNPs from 157 different genes……..**
….. Matrix remodeling
….. Inflammation & innate immunity
….. Anti-oxidant response
….. Apoptosis, DNA repair

**Resistant smokers** = smokers with normal lung function recruited from the community & no history of lung cancer

**Lung cancer** = histologically confirmed lung cancer
Pool of many SNPs each conferring a modest effect through modifying the body’s response to smoke in the lungs

- Genes altering metabolism of the smoke derived toxins
- Anti-oxidant response genes
- Genes controlling DNA repair
- Genes controlling apoptosis and/or inflammation *
- Genes controlling matrix remodeling
- Genes controlling airway fibrosis
- Genes controlling nicotine addiction *

Genetic susceptibility to lung cancer

- Many genetic variants
- Interaction with smoking
- Affect many different pathways

Overlap between genes conferring COPD and lung cancer

nAChR gene* locus associated with lung cancer, COPD and nicotine addiction
Additive model for lung cancer susceptibility

- Age
- FHx of lung cancer
- PHx of COPD
- SNPs
Lung cancer SNP score

• Based on an algorithm developed in COPD case-controls study
• Combines genotypes from protective and susceptible SNPs
• Makes no assumptions about biological pathways
• Not hierarchical
• Modelled on the Gail score - optimised by age, history of COPD and FHx of lung cancer
OR according to Lung Cancer risk score

![Graph showing the relationship between ln(Odds of Lung Cancer) and Lung Cancer Risk Score. The x-axis represents the Lung Cancer Risk Score, while the y-axis represents ln(Odds of Lung Cancer). The graph includes data points corresponding to risk scores of 0.5, 1, 2, 4, 8, 16, 32, 64, 2.1, 4.4, 8.1, and 28.8.](image)
OR according to Lung Cancer risk score

- >80% of all eligible smokers
- >80% of all lung cancers

Sensitivity=90%
Specificity=45%
Lung Cancer Susceptibility Model Based on Age, Family History and Genetic Variants

Robert P. Young¹, Raewyn J. Hopkins¹, Bryan A. Hay¹, Michael J. Epton³, Graham D. Mills⁴, Peter N. Black¹, Heather D. Gardner¹, Richard Sullivan², Gregory D. Gamble¹

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Box plot of LCSS in the case control study (n=930) and prospective study (n=728)

ANOVA P<0.001 ***

Lung Cancer Susceptibility Score

LCSS score ≥ 6
Specificity of 70-80%
Sensitivity of 40-50%
Lung cancer susceptibility score

- Educational tool to personalise risk and raise awareness of lung cancer
- Refines existing risk derived from smoking exposure
- Based on age, FHx of lung cancer, COPD and SNP markers
- Target 40+ yr old who are smokers and ex-smokers (last 10 years)
- Aim to motivate smoker to quit or ex-smoker to avoid relapse
- Referenced against the “average” smoker’s risk
- Shows risk reduction with quitting

No one is lower than average risk for lung cancer

Risk Level

Lung Cancer Susceptibility Score

Score

Risk reduction with quitting

High Risk Smoker

Average Smoker

Ex-Smokers

Non-Smokers

Risk Level

Lung Cancer Risk Score

(Range 0-12)

Risk compared with non-smokers

HIGH Risk = 4 x the Average Smoker Risk

VERY HIGH RISK = 10 x the Average Smoker Risk

Smoking substantially increases the risk

YOU

High Risk

Moderate Risk

Very High Risk

500x

Risk Level

Score

27

No one is lower than average risk for lung cancer
10 year mortality for lung cancer by smoking status

- Smoker-life long
- Nonsmokers
- Smokers-quit aged 50 yo
- Smokers-quit aged 60 yo
- Smokers-quit aged 70 yo

Deaths/100 men

Age (years)

Lung cancer risk and clinical utility

Smoking cessation

?CT screening

?Chemoprevention

Targeted by genetic testing
Genetic risk of lung cancer and quitting smoking.

Genetic testing for risk of lung cancer helps to personalize the risk from continued smoking.

Smokers who underwent genetic testing (blue bars) in a randomized trial had higher quit rates than those in a smoking cessation programme alone (yellow bars).

Personalising the risks of smoking helps people choose healthier lifestyle options (eg quitting smoking and preventing relapse).

Questions?
Smoking cessation

- Most smokers quit using cold turkey

- For older smokers, future poor health is the most cited reason for quitting

- Developing lung cancer and COPD are the most feared complications

- Most smokers continue to smoke on the basis the benefits outweigh the harms

- Most smokers overestimate the general risk of lung cancer but underestimate their own risk (below average risk = optimistic bias)

- Smokers quit when the motivational tension favour quitting (trigger)
Smoking cessation

- Most smokers quit using cold turkey
- For older smokers, future poor health is the most cited reason for quitting
- Developing lung cancer and COPD are the most feared complications
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Intention to quit smoking based on genetic testing for lung cancer risk

- Smokers - average risk for lung cancer
- Smokers - above average risk for lung cancer
Lung Cancer SNP score utility

• Personalise risk to smokers/ex-smokers
  – Bach score – age and smoking history
  – SNP score – age, genetic factors and other factors

• Segment the population into high risk and low risk
  – Motivate people to quit smoking or not relapse
  – Prioritise people for screening (?sputum cytology, serum biomarkers, CT screening)
  – Prioritise people for chemoprevention (statins, NSAID)
Lung cancer SNP score and FEV1

Distribution of the lung cancer SNP score in controls and lung cancer according to FEV1

- Control smokers
- LC-low FEV1%pred
- LC-high FEV1%pred
Poor Prognosis from Late Presentation

Smoker
- New onset
  - Cough
  - Breathlessness
  - Chest pain
- Dx: COPD/bronchitis

Ex-smoker

Persisting symptoms

• See GP
  • X-ray
  • Specialist referral

• CT thorax
  • Nodule biopsy
  • Bronchoscopy
  • Mediastinoscopy

• Staging CT
  • Surgery
  • Chemotherapy
  • Radiotherapy

Current paradigm

Time 0
- 5 mm
- 90%

6 months
- 10 mm
- 70-90%

6-11 months
- 20 mm
- 50%

- 40 mm
- 20%

10 Year Survival

2-3 doubling times
Risk Stratifying with Improved Prognosis from Early CT?

- Smoker
- Ex-smoker

Lung cancer Susceptibility score
Score ≥ 6
Baseline CT

New paradigm

Symptoms Surveillance
- New onset
  - Cough
  - Breathlessness
  - Chest pain

Repeat CT
- Nodule biopsy
- Bronchoscopy
- Mediastinoscopy

- Staging CT
- Surgery
- Chemotherapy
- Radiotherapy

Aim to diagnose more lung cancer in stage 1

5 mm: 90%
1 doubling times

10 mm: 70-90%

5 Year Survival

Time 0
2-3 months