IT’S ALL IN THE GENES

Wessex Nephro-urology Regional Study Day
Rachel Day and John Tolliday
15 year old girl

- Attended GP due to tiredness and fatigue
- **Lethargy**
  - Present for 8 weeks before admission
- **Menorrhagia**
- **Skin rash**
  - Facial rash for 1/52
  - Erythematous papules over shins
• Referred to local DGH
  – Impaired renal function
  – Hypertension
  – Oedema
  – Proteinuria
• PMH: Obesity
• DH: nil
• FH:
  – Lives with Parents and older brother
  – Mum and Grandma diagnosed with long term medical problem
• **Tertiary nephrology referral**
  – Nephrotic syndrome with features of nephritis

• **OE:** hypertensive with BP 150-160 systolic
  – Raised BMI 41, weight 121kg
  – Facial erythema over cheeks with nasolabial sparing. Some pustules
  – Non-specific erythematous blanching papules lower legs
  – Pitting oedema to legs and sacrum

• **Normal heart sounds, chest clear, abdo SNT**
Initial investigations

<table>
<thead>
<tr>
<th>Test</th>
<th>Initial</th>
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<tbody>
<tr>
<td>Hb</td>
<td>104</td>
</tr>
<tr>
<td>ESR</td>
<td>60</td>
</tr>
<tr>
<td>Albumin</td>
<td>21</td>
</tr>
<tr>
<td>Potassium</td>
<td>5.1</td>
</tr>
<tr>
<td>Urea</td>
<td>19.5</td>
</tr>
<tr>
<td>Creatinine</td>
<td>116</td>
</tr>
<tr>
<td>TSH</td>
<td>16.31 (↑)</td>
</tr>
<tr>
<td>Protein:creatinine ratio</td>
<td>1023 (↑)</td>
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</tbody>
</table>

**Echo:**
Mild LVH but good function

**US abdomen:**
Normal kidneys, splenomegaly and fatty liver
Making the diagnosis

• Features that led to the underlying diagnosis
  – Nephrotic syndrome
  – Obesity
  – Hypothyroidism
  – FH

<table>
<thead>
<tr>
<th>Test</th>
<th>Status</th>
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<tbody>
<tr>
<td>Lupus anticoagulant</td>
<td>Positive</td>
</tr>
<tr>
<td>dsDNA</td>
<td>82 (high)</td>
</tr>
<tr>
<td>C3 / C4</td>
<td>0.49 / &lt;0.08</td>
</tr>
<tr>
<td>DAT</td>
<td>Positive</td>
</tr>
<tr>
<td>ENA RNP and SM, CTD</td>
<td>Positive</td>
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</tbody>
</table>

• Renal biopsy: lupus nephritis class IV and V
### SLICC Classification Criteria for Systemic Lupus Erythematosus

**Requirements:** ≥ 4 criteria (at least 1 clinical and 1 laboratory criteria)

- OR biopsy-proven lupus nephritis with positive ANA or Anti-DNA

#### Clinical Criteria

<table>
<thead>
<tr>
<th>1. Acute Cutaneous Lupus*</th>
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<tbody>
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<td>2. Chronic Cutaneous Lupus*</td>
</tr>
<tr>
<td>3. Oral or nasal ulcers*</td>
</tr>
<tr>
<td>4. Non-scarring alopecia</td>
</tr>
<tr>
<td>5. Arthritis*</td>
</tr>
<tr>
<td>6. Serositis*</td>
</tr>
<tr>
<td>7. Renal*</td>
</tr>
<tr>
<td>8. Neurologic*</td>
</tr>
<tr>
<td>9. Hemolytic anemia</td>
</tr>
<tr>
<td>10. Leukopenia*</td>
</tr>
<tr>
<td>11. Thrombocytopenia (&lt;100,000/mm³)</td>
</tr>
</tbody>
</table>

#### Immunologic Criteria

| 1. ANA |
| 2. Anti-DNA |
| 3. Anti-Sm |
| 4. Antiphospholipid Ab* |
| 5. Low complement (C3, C4, CH50) |
| 6. Direct Coombs’ test (do not count in the presence of hemolytic anemia) |

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†SLICC: Systemic Lupus International Collaborating Clinics

* See notes for criteria details

Initial management

• Renal:
  – Pulse methylprednisolone for 3/7
  – High dose prednisolone 60mg OD
  – Mycophenolate mofetil 500mg QDS
  – Hydroxychloroxine 400mg OD
  – Amlodipine 10mg OD
  – Atenolol 50mg OD
  – Enalapril 5mg OD
Initial management

• Skin:
  – Sun protection SPF 50 daily
  – Positive Ro antibodies suggest photosensitivity
  – Will be followed up in clinic

• Ophthalmology:
  – Normal orthoptics
  – Still awaiting further screening

• Endocrine:
  – TFTs to be rechecked in 1 month
  – Referral to obesity clinic

For no live vaccines

Other meds:
Levothyroxine 25mcg OD
Omeprazole 20mg OD
Colecalciferol 1000 units OD
Gaviscon PRN
The story continues

• Clinic review at 3/52
  – ESR now 12, urine dip protein 3+
  – Renal function showed improvement (creat 86)
  – However, remained oedematous and not in clinical remission

• First rituximab infusion on 20/05
  – Subcutaneous clexane started
  – BP 128/60 so enalapril increased to 10mg
  – Has noted change in mood/behaviour – CAMHS nurse RV
  – Education with online resources
Genomics and lupus nephritis

What do we know about heritability?
Is there a role for genetic testing?
How can genetics help us?
AUG UUG CAU GUA UUG AUA GGG UAU UAG

DNA HAS ALL YOU CAN ASK FOR normal
DNA HAS ALL YOU CAN ASK FOR silent
DNA HAS ALL YOU CAN ASK FOR missense
DNA HAS ALL YOU CAN ASK FOR nonsense
DNA HAS ALL YOU CAN ASK FOR frameshift
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<th>Chr</th>
<th>SNP</th>
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<td></td>
<td>P*</td>
<td></td>
<td></td>
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<td>OR (95% CI)*Padj</td>
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<td>OR (95% CI)*Padj</td>
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<td>OR (95% CI)*Padj</td>
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<td>P*</td>
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<td>2.44 (1.75–3.40)</td>
<td>7.6×10^{-6}</td>
<td>3.61 (2.09–6.23)</td>
<td>4.05 (2.12–7.73)</td>
<td>1.5×10^{-11}</td>
<td>1.95 (1.60–2.37)</td>
<td>1.1×10^{-8}</td>
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<td>2.27 (1.63–3.17)</td>
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<td>3.52 (2.04–6.08)</td>
<td>3.93 (2.07–7.47)</td>
<td>1.0×10^{-9}</td>
<td>2.03 (1.61–2.56)</td>
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<td>2.14 (1.52–3.01)</td>
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<td>P*</td>
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<td>1.53 (1.19–1.95)</td>
<td>P*</td>
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<td>rs13277113</td>
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<td>1.51 (1.18–1.95)</td>
<td>P*</td>
<td>1.51 (1.13–2.01)</td>
<td>8.2×10^{-3}</td>
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<td>1.48 (0.67–3.24)</td>
<td>0.36</td>
<td>1.48 (0.67–3.24)</td>
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</table>

The best SNP in each gene is shown and for STAT4, IRF5, TNIP1 and BLK also the SNPs used for meta-analysis, marked in bold; STAT4 rs11889341, rs7582694 r²=0.98, IRF5 rs2070197, rs10488631 r²=1.00, TNIP1 rs7708392, rs6889239 r²=1.00 and BLK rs922483, rs13277113 r²=0.87 calculated in SLE Swedish controls. OR: odds ratio, CI: confidence interval, NA: not available.

*Uppsala, Stockholm and Lund, Sweden, n = 567 SLE cases, n = 512 controls

WHO class III or IV on renal biopsy, according to the 1995 WHO classification system [2].

Glomerular filtration rate <30 mL/min/1.73 m² [22].

rs3135394 has an r² = 0.87 with the HLA-DR3 (DRB1*0301) allele [6].

Unadjusted p-value and OR for differences in allele frequencies between patients and controls.

Adjusted p-value and OR from logistic regression analysis including age and gender as covariates. Number of cases and controls; lupus nephritis, n = 194, proliferative nephritis, n = 91, severe renal insufficiency, n = 28, SLE, n = 566, controls, n = 504.

doi:10.1371/journal.pone.0084450.t002
Specify a genotype for specific annotations

Pick alleles for TPMT

*4  *2

Alleles not present in the above pull-down menus have no CPIC recommendation.

Implications
Extremely high concentrations of TGN metabolites; fatal toxicity possible without dose decrease; no methylTIMP metabolites

Metabolizer Status
Poor Metabolizer

Phenotype (Genotype)
Homozygous variant, mutant, low, or deficient activity (two nonfunctional (no function) alleles - *2, *3A, *3B, *3C, or *4)

Recommendations
Consider alternative agents. If using azathioprine start with drastically reduced doses (reduce daily dose by 10-fold and dose thrice weekly instead of daily) and adjust doses of azathioprine based on degree of myelosuppression and disease-specific guidelines. Allow 4–6 weeks to reach steady state after each dose adjustment. Azathioprine is the likely cause of myelosuppression.

Guideline Strength
Strong

Summary
Consider an alternate agent or extreme dose reduction of azathioprine for patients with low or deficient TPMT activity. Start at 30–70% of target dose for patients with intermediate enzyme activity.
Any questions?