COMMON ELEMENTS IN UNCOMMON KIDNEY DISEASES
TRANSLATION FROM RESEARCH TO CLINICAL CARE

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Newcastle University
Disclosure of Interests

- Alexion Pharmaceuticals - consultancy
- Akari Therapeutics - consultancy
- Omeros - consultancy
Translation from Research to Clinical Care

1. What are the positive practical outcomes for patients from improved translation from research to clinical care?
2. How to set up a clinical research collaborative network?
3. How to allow for successful trials in rare renal diseases?
4. How to ensure an optimal use of genetic services/genomics for the patients?
5. What is the best organization of care to ensure that clinical research develops and leads to clinical practice recommendations to the benefit of all?
6. What initiatives can boost drug development?
7. How to disseminate good practices for translational medicine?
Translation from Research to Clinical Care Lessons from aHUS

1. Studying families has been pivotal in understanding the molecular mechanisms responsible for the disease.

2. You need some luck.
Rare condition strikes eight family members
Helen Rae, *Evening Chronicle*, July 23rd 2009

“Dad Shaun McCowie is living with a rare genetic condition that has killed seven members of his family. The 47-year-old has atypical hemolytic uremic syndrome (HUS), a form of kidney failure, and the genetic defect his family has been plagued with is believed to be one of only 10 cases in the world…… “
Newcastle Family 2016
Translation from Research to Clinical Care Lessons from aHUS

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2. You need some luck.

3. Data sharing is essential for unsolved families.
Familial aHUS – Newcastle cohort

- CFH: 27%
- MCP: 18%
- CFI: 4%
- C3: 9%
- Unknown: 30%
- DGKE genes: 5%
- 3 Novel genes: 7%

56 families in total
Translation from Research to Clinical Care
Lessons from aHUS

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Database of complement gene variants

aHUS, C3G and AMD associated genetic variants

Since the first reports in 1998 by Warwicker et al., predisposition to aHUS is due to variants in the genes that code for proteins of the alternative pathway (AP) of complement. There are currently 1019 unique genetic variants (438 literature sourced, 617 laboratory sourced, and 190 with no patient associated) compiled within this database, corresponding to 832 literature sourced and 1143 laboratory sourced cases.

What can you do in this database?

You can search for genetic variants reported in the ADAMTS13, C9, C1Q, CFH, CFB, CFHR1, CFHR2, CFHR3, CFHR5, CFHR6, CFI, C4BP, C4BPA, DGKE, FHL1, THBD and THBD genes which may have an association with aHUS, AMD, C3G. Usually, DNA and TTP by using the Simple Search tools on the right hand side or by clicking Advanced Search on the menu bar. The search result will display variant sequence, phenotype, structural, functional and allele frequency information.

Citing us


HGVS numbering ▼

Transcript and protein IDs ▼

Have you or someone you know been diagnosed with aHUS, C3G or AMD? ▼

Acknowledgements ▼

News and updates; latest release: Version 3.0 ▼
<table>
<thead>
<tr>
<th>ID</th>
<th>FH level</th>
<th>C3 level</th>
<th>F1 level</th>
<th>MCH level</th>
<th>AntiFH Ab</th>
<th>Zygosity</th>
<th>Disease inheritance</th>
<th>Other Variants</th>
<th>Condition</th>
<th>Reference</th>
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<td>1.76</td>
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**Allele Frequency**

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<tr>
<th>Allele Count (AC)</th>
<th>No. of patients screened for CFTN</th>
<th>Allele Number (AN)</th>
<th>Allele Frequency (AF) estimate</th>
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<td>aHUS population</td>
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**C3G population**

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<th>No. of patients screened for CFTN</th>
<th>Allele Number (AN)</th>
<th>Allele Frequency (AF) estimate</th>
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**Control population**

dbSNP: rs146973787

The 1000 Genomes Project:

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<th>1000 GP Alleles</th>
<th>1000 QP Allele</th>
<th>1000 QP Allele Frequency (AF)</th>
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**ExAC:**

<table>
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<th>ExAC Allele Frequency (AF)</th>
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<td>121400</td>
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<td>South Asian</td>
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**Exome Variant Server (EVS):**

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<tr>
<th>EVS Allele</th>
<th>EVS Allele Count (AC)</th>
<th>EVS Allele Number (AN)</th>
<th>EVS Allele Frequency (AF)</th>
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<tbody>
<tr>
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<td>African-American</td>
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**Structure and Function**

No functional or structural studies for this variant (c.2867C>T) currently exist in the database.

Please click here to view the mapping of this variant into the latest Pfam structure and view the functional analysis by PolyPhen-2 and SIFT.
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Terminal Complement Inhibitor Eculizumab in Atypical Hemolytic-Uremic Syndrome


BACKGROUND
Atypical hemolytic-uremic syndrome is a genetic, life-threatening, chronic disease of complement-mediated thrombotic microangiopathy. Plasma exchange or infusion may transiently maintain normal levels of hematologic measures but does not treat the underlying systemic disease.

METHODS
We conducted two prospective phase 2 trials in which patients with atypical hemolytic-uremic syndrome who were 12 years of age or older received eculizumab for 26 weeks and during long-term extension phases. Patients with low platelet counts and renal damage (in trial 1) and those with renal damage but no decrease in the platelet count of more than 25% for at least 8 weeks during plasma exchange or infusion (in trial 2) were recruited. The primary end points included a change in the platelet count (in trial 1) and thrombotic microangiopathy event-free status (no decrease in the platelet count of >25%, no plasma exchange or infusion, and no initiation of dialysis) (in trial 2).

RESULTS
A total of 37 patients (17 in trial 1 and 20 in trial 2) received eculizumab for a median of 64 and 62 weeks, respectively. Eculizumab resulted in increases in the platelet count; in trial 1, the mean increase in the count from baseline to week 26 was 73±10 per liter (P<0.001). In trial 2, 80% of the patients had thrombotic microangiopathy event-free status. Eculizumab was associated with significant improvement in all secondary end points, with continuous, time-dependent increases in the estimated glomerular filtration rate (GFR). In trial 1, dialysis was discontinued in 4 of 5 patients. Earlier intervention with eculizumab was associated with significantly greater improvement in the estimated GFR. Eculizumab was also associated with improvement in health-related quality of life. No cumulative toxicity of therapy or serious infection-related adverse events, including meningococcal infections, were observed through the extension period.

CONCLUSIONS
Eculizumab inhibited complement-mediated thrombotic microangiopathy and was associated with significant time-dependent improvement in renal function in patients with atypical hemolytic-uremic syndrome. (Funded by Alexion Pharmaceuticals; O8002 ClinicalTrials.gov numbers, NCT00844545 [adults] and NCT00844444 [adolescents]; O8003 ClinicalTrials.gov numbers, NCT00835813 [adults] and NCT00844428 [adolescents]).
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Eculizumab for treating atypical haemolytic uraemic syndrome

Highly specialised technology guidance
Published: 26 January 2015
nice.org.uk/guidance/hst1
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8. A national expert centre can help to optimise translation from research to clinical care.
Benefits of a national expert centre
Lessons from the aHUS expert centre in England

- 3 year period (April 2013 – March 2016) provided an aHUS expert centre for England
- 119 patients treated with eculizumab, 31 children and 88 adults, 76 incident and 43 prevalent, 81 still receiving treatment
- 28 patients transplanted with prophylactic eculizumab
- 35% mutation detection in incident patients. Mutation negative patients being entered into national WGS study (100,000 genomes)
- Provide all the specialist investigations
- Provide a service for the counselling of family members
- Hopefully a national study of withdrawal of treatment will start in 2017
- A national service for aHUS provides an infrastructure for patients to be treated with eculizumab when they need it for as long as they need it
- A locally delivered national service with oversight from an expert centre provides both local and national accountability
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9. Establish an appropriate, professional relationship with pharma.
Newcastle family 2016