NIMBL NEWS

EDITION 3: DECEMBER 2012

NIMBL PROJECT ONLINE: WWW.NIMBL.EU

WELCOME...

Welcome to the third edition of NIMBL News. If you would like any further details about any of the information here, please don't hesitate to get in touch. New families are still being identified and invited to join the study, so please contact us directly if you are interested in taking part: nimbl@manchester.ac.uk.

NIMBL/AGS NEWS AND EVENTS

AGS Family Conference, 30th April 2011, Washington D.C.

A video was made of this conference and the links are given below:

1. Interview with Jonah, an AGS patient, Dr Adeline Vandever: https://stream.manchester.ac.uk/Play.aspx?VideoId=12566
2. "Immunology of AGS", Dr Dan Stetson: https://stream.manchester.ac.uk/Play.aspx?VideoId=12569
3. "An update on research since 2009", Dr Adeline Vanderver: https://stream.manchester.ac.uk/Play.aspx?VideoId=12568
4. "DNA Testing Strategies in AGS", Dr Gunter Scharer: https://stream.manchester.ac.uk/Play.aspx?VideoId=12572
5. Video link with Prof Yanick Crow: https://stream.manchester.ac.uk/Play.aspx?VideoId=12573

AGS Family Conference, 3rd July 2012, Pavia

A successful Family Conference Day was held at the Italian National Institute of Neurology in July. Topics covered included the NIMBL study, its progress and related research activities in Italy, the USA, and throughout Europe, and whether the time is right to start carrying out clinical trials in AGS.

AGS Family Conference, 6th October 2012, Washington D.C.

This conference day in Washington D.C. provided families with updates on the work of IAGSA (the International Aicardi-Goutières Syndrome Association), and the NIMBL study. Yanick Crow contributed to the meeting via video link, and discussed the future of treatments in AGS. Speakers also presented on setting up family support groups for rare conditions, and how laboratory-based research might result in future treatments.

If you are interested in hearing more on these topics, follow these links for the recordings of the Conference:
AGS Family Conference 6/10/2012 (Morning session— duration: 2 hours)
https://cnmc.webex.com/cnmc/ldr.php?AT=pb&SP=MC&rID=13191317&rKey=8e9c9a39ae098da9
AGS Family Conference 6/10/12 (Afternoon session— duration: 1 hour)
https://cnmc.webex.com/cnmc/ldr.php?AT=pb&SP=MC&rID=13191327&rKey=6a5dd026d177c34d

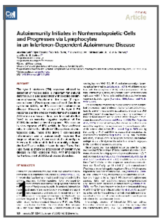
NIMBL Study Clinic & Family Conference Day, 5-6th March 2013, Manchester

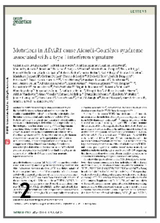
The NIMBL researchers invite AGS families to join them at this event in Manchester early next year. There will be the opportunity to meet other families affected by AGS, talk to the NIMBL study team, learn about the latest findings related to AGS, and hear about the first steps towards future treatments in the condition. A research clinic will be held the day before the conference (5th March), and there will be a social event that evening.

Please contact Professor Yanick Crow(yanickcrow@mac.com), or Kate Strong (kate.strong@cmft.nhs.uk) for further information, and to register your interest.

NIMBL PUBLICATIONS

Several new papers have been published recently, adding to the literature on Aicardi-Goutières syndrome.





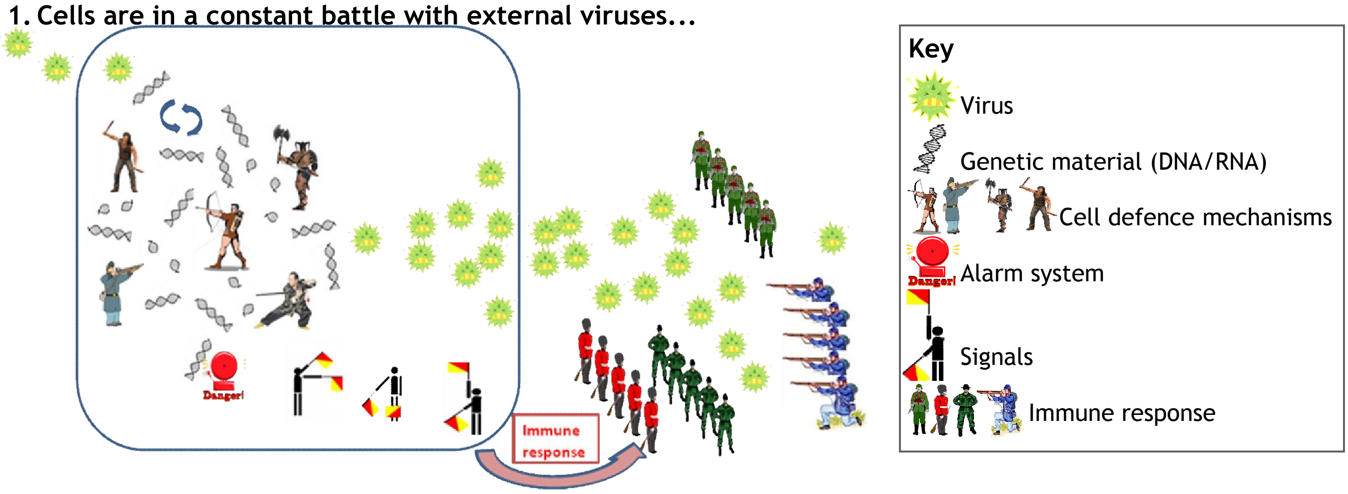
1. Dan Stetson in Seattle has published evidence of TREX1's involvement in the cell's anti-viral response (www.ncbi.nlm.nih.gov/pubmed/22284419)
2. The Manchester group has identified a sixth gene that causes AGS (ADAR1) (published in *Nature Genetics*) (www.ncbi.nlm.nih.gov/pubmed/23001123)
3. The Italian AGS group has published a review article on the condition (www.ncbi.nlm.nih.gov/pubmed/22940555)

4. Yanick Crow has co-authored a paper on how patterns of intracranial calcification might be defined for certain conditions including AGS, and used as a diagnostic aid in future (www.ncbi.nlm.nih.gov/pubmed/23121296)

AICARDI GOUTIÈRES SYNDROME – AN UPDATE

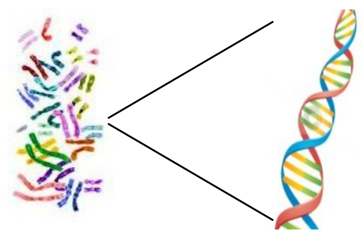
- The physical features of AGS (e.g. irritability, high temperatures) are similar to a viral infection.
- AGS is like a viral infection at a biochemical level too, as it causes an increased number of white blood cells in the cerebrospinal fluid, and raised levels of interferon alpha.
- **AGS is a mimic of infection. Why? Recent research suggests it might be explained like this…**

1. Cells are in a constant battle with external viruses...

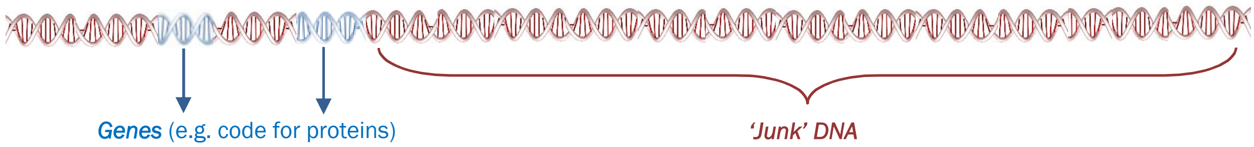


Viruses such as e.g. cold or 'flu, enter cells and highjack the cell's machinery to make more copies of themselves by duplicating their genetic material (either DNA or RNA). The cell's defence mechanisms detect and destroy this foreign DNA/RNA. However, if the infection takes hold, the viral DNA/RNA is multiplied to produce more viruses. This sets off an alarm system and signals are sent to other cells in the body indicating "Help - I've been invaded! Send in the troops!" This triggers an ***immune response***, which enables the body to fight the infection, by attacking and destroying the cells that are infected by the virus.

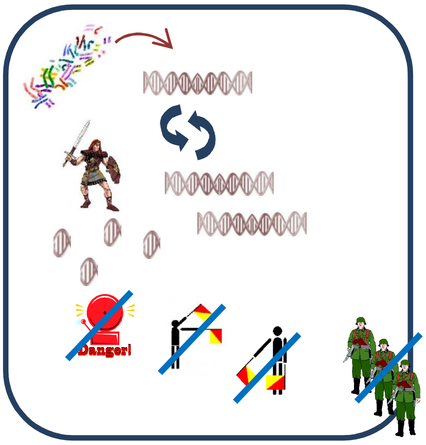
2. Chromosomes, genes and "junk" DNA...



Within chromosomes there are stretches of DNA that code for proteins, which have many different functions. This coding DNA (genes) only accounts for a very small proportion (about 1%) of the total DNA. A large amount of the remaining DNA (sometimes referred to as 'junk' DNA, because it has no known function) is thought to be made up from the remnants of ancient viruses, which have integrated into our chromosomes' DNA during evolution over many millions of years.



3. One probable function of the AGS proteins…



Ancient viruses, that have been integrated into our chromosomal DNA, sometimes escape from this confinement, and highjack the cell's mechanisms to replicate themselves, in a similar way to external viruses, but the cell has developed devices to keep these 'viruses' under control. The same mechanisms that identify and destroy external viruses (like cold and 'flu), detect these pieces of DNA as being 'foreign'. TREX1 is one of the mechanisms that chews up this 'viral' DNA. This means that the alarm is not triggered and signals are not sent out to 'mobilise the troops' - there is no immune response.

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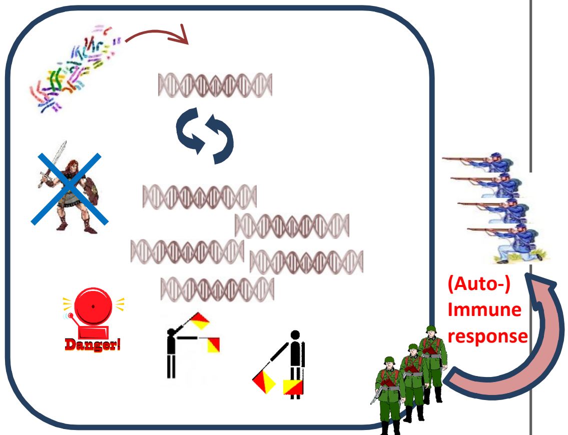
AICARDI GOUTIÈRES SYNDROME – AN UPDATE (continued...)

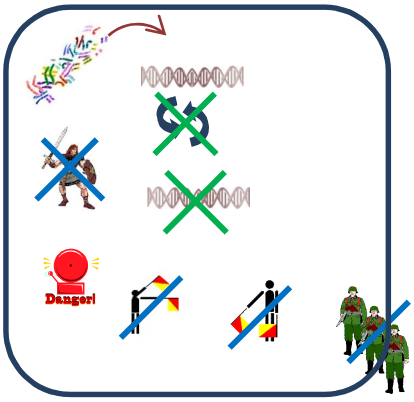
However, in the absence of TREX1, this 'viral' DNA isn't destroyed and it accumulates in the cell like a viral infection, the alarm is raised, and signals are sent out to 'send in the troops'.

This sets off an immune response, similar to when the body experiences a viral attack. However, since the foreign DNA comes from the body's own cells, this is considered an auto-immune ('against self') response. Recent research indicates that the other AGS proteins (RNASEH2 [A, B and C], SAMHD1 and ADAR1), may also be involved in this process, in a similar way to TREX1. This might explain why AGS mimics viral infections.



4. Working towards possible future therapies for AGS...

Findings from Beck-Engeser *et al*: **An autoimmune disease prevented by anti-retroviral drugs.** *Retrovirology* 2011 **8**:91)

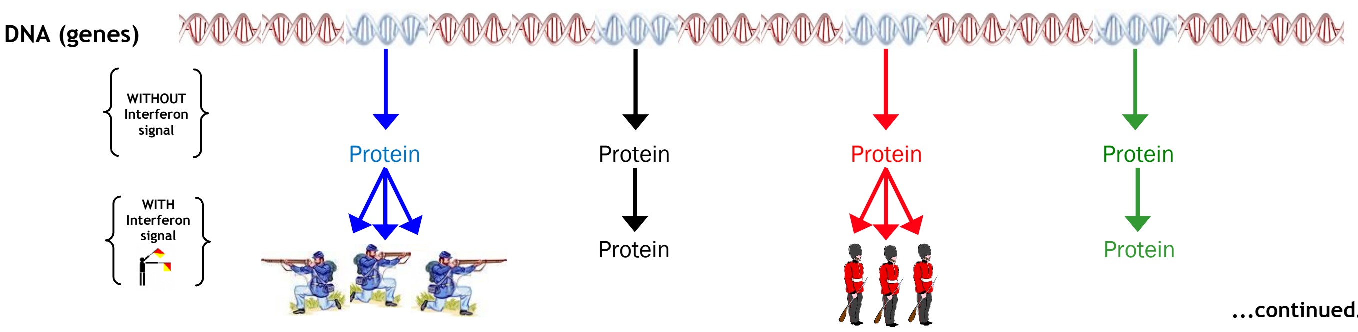


Mice without a functional TREX1 enzyme have been used in this research. These TREX1 knock-out mice develop severe inflammation of the heart muscle, and have a significantly shorter life-span - many of them die very young. The Beck-Engeser research group has reported that treatment with anti-retroviral drugs called Reverse Transcriptase Inhibitors (RTIs) can significantly reduce this heart inflammation and prolong the life of the mice. This is probably because anti-retroviral drugs prevent the replication of the DNA from 'ancient viruses' integrated into our chromosomes. Therefore there is no accumulation of this 'viral' DNA in the cell, so the alarm is not triggered and an immune response is not raised.
The results from mouse models cannot necessarily be directly transferred and applied to humans.

However, the results support the idea that TREX1 (and possibly the other AGS enzymes - RNASEH2, SAMHD1 and ADAR1) are involved in controlling 'ancient viruses', and so antiretroviral therapy might be worth exploring as a treatment in humans.
One of the main aims of a clinical trial is to assess the effectiveness of a particular treatment. This usually involves measuring specific biological indicators or markers, called biomarkers, which may be specific for each medicial condition. Suitable biomarkers will show significantly different levels in affected individuals pre-treatment, compared to the unaffected control 'normal' levels. In a clinical trial these biomarkers are measured before, during and after any treatment, to see if the levels in affected individuals became 'normalised', i.e. if they move towards those found in healthy controls. We are currently investigating potential biomarkers for AGS. One promising possibility is interferon-stimulated genes (ISGs)...

5. Interferon-stimulated genes as biomarkers for AGS...

Human DNA is like an encyclopaedia that contains pages of coded information (genes), divided into a number of volumes (chromosomes). The chromosomes make thousands of different proteins. If a specific protein is required, a copy is made of that particular coding region (gene); like taking a photocopy of a specific page from one volume of the encyclopaedia.



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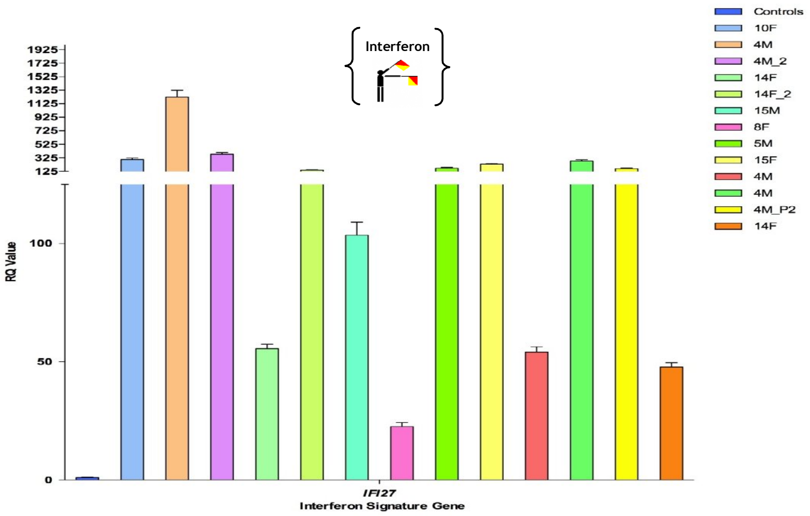
AICARDI GOUTIÈRES SYNDROME – AN UPDATE (continued...)

Interferon is a biochemical messenger that is involved in the body's immune response. If the body is being attacked by external viruses, such as cold or 'flu, interferon stimulates certain specific genes (ISGs) to make more anti-viral proteins - it sends a message telling them to 'send in the troops'.

When the infection has cleared and the body is no longer fighting the virus, the interferon signal is switched off, and the ISGs drop back to 'normal' levels. However, AGS mimics infection, so we are trying to find out if these ISGs are constantly activated in AGS patients, by measuring specific chemicals in the blood.

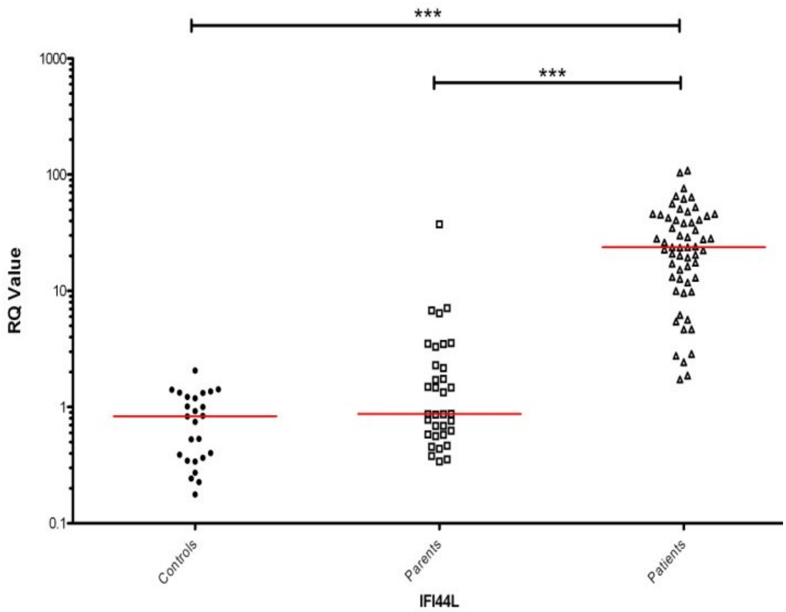
6. Measuring the relative amounts of ISGs …



To begin with, we have focused on fifteen ISGs that are involved in the normal immune response. So far, the results are very interesting. This graph shows the results from one of these interferon-stimulated genes (IF127).

Compared with the pool of controls (relative quantity = 1; small blue bar on the left-hand-side), all the AGS patients had significantly more RNA – from about 20 times to over 1,000 times of each of these ISGs. The affected person's age (4 years to 35 years), gender, or AGS gene carrier status didn't seem to affect these levels (work on-going).

The relative amount of several ISGs has now been measured in blood samples from a number of AGS patients and their parents, and in controls. Each dot represents the amount of ISG from a single individual. In general, patients have very significantly higher levels of RNA compared to controls, with little overlap. We published an example of this kind of result in *Nature Genetics* in September 2012.



The next step is to test serial samples from patients (e.g. samples taken at 6-mothly intervals), to check if there is any variation in their RNA levels over time.

Measuring the levels from several ISGs might provide a 'signature' or pattern, for each patient. This could then be used as an AGS biomarker, and the levels of several ISGs would be measured before, during and after treatment to measure the effectiveness of any therapy.

With the help of many affected families, we are exploring this important possibility in great detail.