Alport Syndrome is the second most common inherited cause of kidney failure. It is caused by mutations (mistakes) in the DNA of one of three genes that generate proteins in the filtration barrier in the kidney, the glomerular basement membrane (GBM).

The 2014 International Workshop on Alport Syndrome was held in Oxford, UK from January 3-5, through the concerted efforts of patient groups from four continents. The Workshop brought together scientists, physicians and geneticists to discuss the latest findings and possible ways to improve treatment.

An important aspect that scientists working in laboratories were able to meet individuals and families affected by Alport syndrome, and to hear first-hand their perspective about what it is like to live with the disease.

Genetics/Diagnosis

Genetic testing is developing very quickly and is becoming available in more countries and for more families. It is likely that costs of testing will continue to come down. To speed progress there is huge benefit from sharing experience and knowledge. Information is currently stored in six different databases for the major gene COL4A5. This is the gene that is responsible for 80%+ of cases. It is on the X chromosome and usually affects men and boys more severely than women and girls. The labs represented at the Workshop all agreed to use the same database in future, the Leiden Open Variant Database system (www.lovd.nl/3.0/home), which will speed progress in accuracy of testing, and knowledge about what different mutations mean.

Different methods for finding mutations were described, with many labs testing “next generation sequencing” (NGS) methods that are just moving from research labs into clinical services. Detection is not yet 100% and reasons for this are being investigated. Most families have new mutations, but in some places (including Britain and Cyprus) some particular mutations can be found quite widely.

It can be predicted that some kinds of mutation will lead to more severe disease, but the disease is very variable in severity in some families, and particularly in some of those carrying one of the less common COL4A3 or COL4A4 mutations. Why some people who carry these mutations get severe disease, while others remain OK, is an important question as it could reveal ways to prevent disease from getting worse.

Alport Syndrome caused by mutations in the COL4A3 or COL4A4 genes, which aren’t on the X chromosome, accounts for only about 15% of patients with severe disease and is usually described as Autosomal Recessive. However some carriers do get disease, usually much later in life than in ‘usual’ Alport Syndrome, and this seems to be more common in some families. There are particularly clear examples of this in Cyprus. There was a lively debate about whether these families should be described as ‘autosomal dominant’ type inheritance. Most thought not, as even in these families it is only a minority of carriers who get severe disease. It also turns out that this kind of mutation is sometimes behind some genetic kidney disease that doesn’t immediately seem to be Alport’s – we’re just learning what that means.

Basic science

Scientific discussions focused initially on the collagen proteins that are abnormal in Alport’s. The reason that the filtration membrane is split and altered in Alport syndrome is not fully proven. Some favour that it’s just weak, others believe that other things are involved, but work to investigate this is important as it suggests that different treatments will be best.

Recent studies in genetically engineered mice showed an important point. Restoring production of normal collagen protein could stop the progress of kidney loss even quite long after the deterioration had been started. So if gene therapy does become possible for this protein in the human kidney (unfortunately that’s a challenging problem), it suggests that it will work.

An important question was whether the loss of kidney function in Alport’s is just down to the genetic problem, or whether this slow loss of kidney function, with protein leaking into the urine, was similar to
the process that can be triggered by other kinds of kidney damage. The fact that a protein leak comes before the tests start to fail, and that ACE inhibitors slow it, suggests that it might have a lot more in common than we used to think. That will be useful because it means that it is worth testing a whole different range of treatments in Alport Syndrome, and it means that what is learnt in Alport Syndrome may also be important for many other types of kidney disease.

**Treatment**

Two major areas were discussed. The first was to fix the underlying problem. Most agreed that gene repair, gene replacement, protein replacement, or podocyte replacement (podocytes are the cells that produce the basement membrane collagen proteins that are abnormal) should be effective if applied early enough during the course of disease. However all of these are technically very difficult.

The second target was the things occur as a later result of the genetic problem. Different types of mice with the same mutation can have highly variable rates of progression to kidney failure, indicating that other genes might be important. Next generation sequencing could be beneficial in identifying the modifier genes responsible and hopefully reveal additional targets for drugs. We know that ACE inhibitors are effective – it seems likely that they work through preventing later consequences, but there are at least two different ways they could be doing that.

‘Alport mice’ have already taught us a lot, and with them we can learn much more and discover things we never could in humans. We were reminded that there are some other animals that develop Alport Syndrome naturally, but it seemed likely that new mouse techniques had the best possibility to speed things along. There was serious discussion about how to collaborate to best achieve this.

**Registries and Clinical Trials**

The European Registry has shown the value of getting patient information into one place – this made it possible to show that treatment with ACE inhibitors seems to slow down the disease quite powerfully. To test further treatments and learn more, bigger and better registries will be needed. Because Alport’s is rare, this will need international collaboration. Currently there are 6 registries of patients with Alport Syndrome in different countries, including around 3000 registrants, but there is scope to get many more.

If these are to be utilised to support drug trials and other studies, a problem is that most do not get regular follow-up information. An exception is the UK RaDaR registry, which links to “Renal Patient View” (RPV). RPV incorporates laboratory results from participating UK renal clinics, so follow up information can be fed automatically to the Registry.

**Patient Organizations**

Patient representatives at the meeting came from Australia, China, France, Germany, Italy, The Netherlands, Spain, United Kingdom and the United States. All wanted to discuss ways of working together to support research that will result in the improvements for individuals and families living with Alport Syndrome.

**Conclusion**

It was an outstanding meeting that revived hopes that collaboration could one day Alport syndrome can be prevented in most patients by multimodal therapy. Future objectives to build upon the success of this Workshop include:

- Strengthen the patient communities by recruiting more patients and working with local clinicians, geneticists, and registries (or starting or joining an existing registry)
- Expand patient organizations to additional countries
- Develop national meetings with patients, clinicians and scientists to foster collaboration, communication, and education
- Support future international workshops that bring together all stakeholders in the Alport Syndrome community (patients, clinicians, geneticists, scientists, and industry).
Links to images

Graphic summaries
https://www.dropbox.com/s/86x61aor59w7xv1/illustn_1IntlAlportmtg.jpg
https://www.dropbox.com/s/sku6200336n6uel/illustn_2IntlAlportmtg.jpg

Participants
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Report written by the organising committee. alportuk.org