

Summary of the BBS conference 26 April 2008 in Northampton, UK.

***Disclaimer :** these are notes taken during the conference by Francis Lestel. As the author is not a doctor, it does not mean that these notes are exactly what the speakers said, it is only what the author has understood.*

This BBS meeting is the 21st. The first one was organised in 1987 with 30 persons, and this number is increasing almost every year, so that the record of 225 persons was reached this year !

It includes medical representatives of UK, USA, Uruguay, Germany, and Spanish biologists working temporarily in the British hospitals. Other participants were as a majority British, with some coming from Ireland one from France.

1) Introduction by Professor Phil Beales, president of British LMBBS association.

Since 2003, there was an exponential raise of the number of publications about BBS. The first BBS gene was discovered (localized) by Jim Lupski in 1993, then identified some years later. As of today, 14 genes have been published.

2 years ago, a campaign of 3D face photography was made with BBS patients and non-BBS volunteers. So the database now comprises more than 200 BBS and non-BBS profiles, and can define what is the “average BBS face” and “average non-BBS face”

So that the computer can now predict with a reliability >90% if the photographed person has BBS or not.

This is also rather accurate for mice and zebra-fish to check whether they have BBS by studying their craniofacial distortions.

This is probably due to incorrect trajectories of neural crests when doing their migration during the embryo development.

Since 2003, beating cilia disturbances have been recognized as having a paramount effect for BBS. Professor H.Omran of the Clinical University of Freiburg will make a presentation showing that beating cilia might also be involved in the chest infections.

2) Presentation by Professor Nicholas Katsanis, John Hopkins School of Medicine, Baltimore, USA.

We thank Dr Nico for coming again, after his last visit in 2004.

We proceed in 4 steps :

1. molecular prognosis of the disorder
2. clinical prognosis of the progression
3. identification of the cellular defect
4. selective intervention : blindness / kidney problem / weight management

In other words :

1. get the genes
2. understand the relationship between mutations and disease
3. understand the normal function of the genes/proteins
4. correlate mutation with cellular dysfunction
5. develop therapeutic targets

BBS13 & 14 were published in 2007. We estimate the maximum number of genes at about 30, and there is a clear acceleration of discovery rate.

Up to 2001, we thought that BBS was monogenic. Now we know that it takes 2 or more genes which affect the severity of the problem.

Cilia affect all 5 senses :

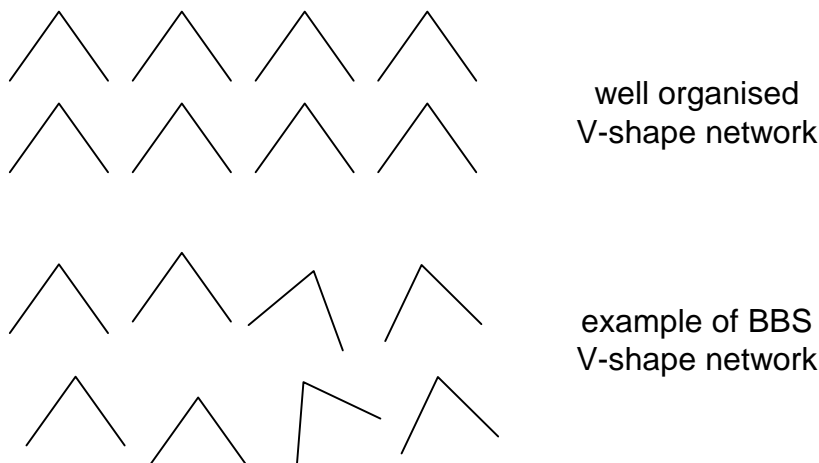
Sight : in fact, the complete “light sensing scenery” of the retina is a big modified cilia !

So there is a progressive thinning of the retina thickness with time.

Smell : a cascade of chemical reactions from cell receptors to olfactory nerves; as well there is a thinning of the olfactory neurones area.

Taste : very linked with smell. If you eat an apple while smelling an orange, you might get the impression of eating an orange ! Some BBS are less reactive to spicy tastes, some are over reactive.

Hearing : some BBS kids have hearing spectrum degraded as an old adult, while some are hearing “too well”. The ear receptors are organised into a geometrical V-shape network:



Touch sense : there are different types of sensors (temperature, mechanical pressure, pain, acidity,...) below the epidermis (derma). For BBS case, they can be affected in different manners :

- higher hot/cold threshold to get a reaction,
- lower or higher pain threshold (lower reaction or hyper reaction)
- longer reaction time to remove finger (human) or tail (mouse) when too hot,
- higher threshold to mechanical pressure (more force is required to get the same reaction)

All these sensors are connected to proprioceptor sensors, then to the brain.

The brain is normal in the majority of BBS persons, but due to altered sensors, they have a different perception of the outer world.

This probably explains a different behaviour, that can sometimes be compared as an “autistic-like reaction*” (* : these words are not from Nico, but he did not deny them). And most of the BBS kids do not like to be touched, so their sensation must be different...

Beyond all 5 senses, a lot of systems are affected :

Immune system : it seems also that the immune system is affected (e.g. more sensitivity to diseases, or different reactions to vaccination), but that needs to be studied thoroughly before

getting to a conclusion. For instance, having fever means an infection for a standard person, but for BBS is it partially due to a bad temperature control ?

We have recorded very high fevers for some BBS kids, which seemed not to be very affected. So we don't understand well yet. We also have noted that the recovery from injuries is lower : It takes twice as long to rebuild fibres, this might be extended to wound healing in general, as scars. Regeneration of neurones might be slower as well.

Kidneys :

Of course kidneys are more or less affected in BBS, both in form and function. The function of kidneys uses cilia to sense salts and pressure.

Nervous system :

Nerve cells transport proteins from the centre to their tip like cilia.

Defects in "sensing position" might lead to polydactyly.

Some patients have a lower sense of pain, other on the contrary overreact to pain.

Now back to gene study, we can claim that 70% of BBS patients can have their genes detected. In 2007, BBS13 and 14 were discovered, plus an additional "modifier". What is a modifier ?

This is a gene for which the presence of a mutation gives a worsening factor to the effect of the main mutated gene.

3 DNA diagnosis are being used in the USA, out of them one from John Hopkins Institute, and one from Aspers. About 1000 genes are related to cilia functions, which mutation modify the cilia function. A giant database (www.ciliaproteome.org) has been issued through the co-operation of 12 laboratories.

The limitation is time and money, as the entire sequencing of a human genome costs several thousands of Euros, but we are confident that the price will decrease a lot with time, as this will become more usual.

An important discovery is that BBS genes can also contribute to other disorders like Meckel-Gruber Syndrome (MKS), Joubert Syndrom (JS), or Nephronophytosis (NPH)..., making them even more severe. At least 20 disorders are listed, so that the frontier between BBS and these disorders is decreasing.

The presence of a modifier makes the BBS syndrome more severe; and vice versa, if this modifier is in the MKS or JS loci, that makes BBS even more severe. Example : two sisters having a dual mutation in BBS1, one of the sisters being more severely affected due to the presence of a modifier in BBS6. Knowing the modifying factors, we can predict in advance that a kidney failure is likely to occur in a circa 10 years time span, so that the parents can subscribe to a waiting list for a future transplant.

Now that we know the influence of a "modifier gene" over a "BBS main gene", we start to have a better genotype-phenotype correlation.

Working Plan :

1. screen >150,000 chemical components
2. hit the ciliary pathway(s)
3. improve in fish, then in mice, then on people...

We do not expect any "general healing" of BBS, each tissue must be worked out separately.

We will have to be patient, as we need from 5 to 10 years to get a drug approved for public use (non-toxicity studies).

3) Presentation by Professor Heymut Omram, University Hospital of Freiburg, Germany.

Most of the body cells have cilia. Some cells have a single cilium, some like trachea are fully covered by cilia. Cilia types are motile and unmotile.

Doctor Kartagener reported in 1933 patients with sinus and lungs problems.

They are motile proteins that make the cilia move. If the protein is missing, the cilia become unmotile, explaining that patients cannot clear their airways, like in PCD (Primary Cilia Dyskinesia). Intermediary effect as reduced motility is also expected.

Sometimes the Left/Right symmetry is inverted, partially or totally (e.g. liver in the other side, heart pointing rightwards,...). That is also true for BBS. This is called Situs inversus partial/ or total.

We know that Nephrocystin genes interact with BBS. By checking DNA of respiratory cells, Nephrocystin disease can be diagnosed without the painful biopsy of kidney.

So there is a clear correlation between respiratory diseases and nephrologic diseases.

After his presentation, Dr Omran and his assistant made an interesting test : by scratching out some nasal cells of patients and visualizing them with a microscope equipped with a high speed camera, one can examine the motility of nasal cilia. As long as they are still alive, the result is that they move as well, but the records will be scrutinized later on to check if they motility is slower or with less amplitude.

4) Presentation of Francis Lestel, vice president of French BBS Society.

See annexed Powerpoint charts. Presentation of contacts (doctors and associations) in the World, mainly in Europe

Demonstration of two devices, one enabling enhancement of a camera display onto a laptop (Portanum project), the other one using a high speed camera, an OCR and a real-time processor which transforms the read letters into Braille sensed by the finger. Unfortunately the company that makes that second device only gave a brochure but no demonstration material.

5) Conclusion

Very instructive working day, a lot of progress is being made in the understanding of BBS phenomenon, but we will have to wait several years for any cure, as it must start for each affected organ by progresses on similar individual disturbances (Retinitis Pigmentosa, kidney malfunctions, obesity, nervous system,...).

No feedback was given from the human tests on LCA patients (RPE65) in UK : it might not progress as fast as foreseen 1 year ago ?