IPWSO Leadership ECHO Q&A November 30, 2021: How basic science research is advancing our understanding of PWS

"I found the presentation from Professor Anthony most informative and I was able to understand the concepts. Excellent! Thankyou"

~Leadership ECHO survey response

We were pleased to hold another fantastic Leadership ECHO session on November 30, 2021. In this session we welcomed Anthony Isles, Professor of Molecular and Behavioural Neuroscience, Cardiff University, UK. Anthony presented *"How Basic Science Research is Advancing our Understanding of PWS".*

His presentation gave us an understanding of what basic research with cell or animal models can tell us about PWS, and how this can help inform therapeutic developments, and gave us an appreciation of the limitations of cell or animal research into PWS.

In summary, Tony Holland commented that us a very nice example given by Anthony, on how the study of one particular gene in PWS showed how it could be connected to a different syndrome, and that that syndrome had symptoms in common to PWS, highlighted not only the excitement of this research and how connections are made, but also the complexity of this method of trying to study all different genes and their effects.

This talk was a great illustration for us on how basic science research could then identify some of the key pathways which then might allow some new interventions and take us a step further to new treatments.

We hope you enjoyed the presentation; if you would like to revisit it or if you weren't able to join us on the day, here is the video link so you can view in your own time.

Anthony Isles: How basic science research is advancing our understanding of PWS

You can read a transcript of the Q&A with Anthony which followed the discussion below and the PDF is available here.

Please note this document is abridged from audio transcription of the Zoom session. Some errors resulting from the transcription process may be present.

Q: I know that when the research started, 20% was mothers deletion, 70% fathers. Is it still the same today or have they come to some other conclusion?

AI: In terms of the genetic, my understanding is that Prader Willi syndrome is caused by disruption of paternal gene expression, but that can be got out by a number of different mechanisms. So you can have a deletion, like you mentioned on the paternal chromosome, so that schematic I showed, that's literally gone in the paternal chromosome. You can get the equivalent effect on paternal gene expression by having 2 copies of a maternal chromosome 15. So rather than having a paternal and a maternal chromosome 15, there's a mutation that's occurred that means that you have a duplication of one of those chromosomes. The maternal derived chromosome and the paternal 1 used to get spat out really early in development, so that leads to the mutation, and of course the consequence of that is that you have no paternal gene expression because you've got 2 copies of paternal. So the pattern is about is about the same. About 70-75% of PWS is caused by deletions and then about 20 to 25% I think is caused by these maternal duplications.

Q: My question is where do you see it going in the future? What are the upcoming research or in what way in which direction do you see the research going?

AI: That research that I just highlighted is really fascinating. That's a really exciting new finding that that has great relevance, and PWS is in there of course. A lot of what people are hoping to do is to understand the molecular basis, so there's a lot of these studies where we can look at that kind of global changes in gene expression, like we did with our mouse model, where you can look at thousands and thousands of genes and then you can take that list and just as we did, get a kind of biological insight, look at the patterns of the groups of genes, and so I think those kind of studies done in animal models and also in the cell line models would give us insight into general patterns of change, which could then be targeted by drugs, not necessarily specifically for those genes that are changed, but for the kind of biological pathways.

There's a really good example of the mouse model looking at oxytocin. You probably know about the oxytocin potential therapies that are coming through. That was originally an observation in mouse models, they were looking at Global changes in gene expression and they found that oxytocin receptors and things like that would change. And they looked at the oxytocin neurons, and they found that they were reduced in this mouse model. And then they tried to rescue some of the physiology that the animal model was displaying using oxytocin, and that has of course gone on to start to begin trials, and I think is maybe even used in in therapies in the States, particularly for Prader Willi syndrome.

I think for the Prader Willi research, that's the kind of area that people want to get insight from. These biological models, and get insight from converging biological models, cells and mouse and pig, possibly, and rat, because there are rat models as

well. Now and then try to move forward in terms of understanding the biology and look at therapies.

Q: When you were when you were talking Anthony, you mentioned deletion and vulnerability, but not necessarily disomy. Had does vulnerability relate?

AI: So the question is right, one of the main vulnerable genotypes for psychotic illness, is this disomy. This maternal having 2 copies of a maternal chromosome 15 and that is the main vulnerable genotype. However, there is also vulnerability in what's called an imprinting center deletion genotype. Lots of very rare genotype and what that does is it's a small deletion, but it affects a regulatory region of the DNA and that has the same consequences as disomy in that you get loss of paternal gene expression, like you do in all Prader Willi syndrome and you get overexpression of maternal gene expression, so UB3A in particular. So the reason why I talked about vulnerable is because our mouse model was an imprinting centre deletion model. It wasn't a dysomy model.

There are some dysomy models, I think, but I don't, think they've been studied in this context. Certainly, when we started, many years ago now with Tony, there was no dysomy model, so we used the imprinting centre deletion model. The mechanism by which you get to the same route is slightly more complex, so I just thought I'd call it the vulnerable model rather than talk about *(audio unclear)* printing sensors, but effectively genetically it does the same thing, but it's mimicking the very rare mutations that occur in less than 5% of individuals with PWS.

Comment: I'm so glad that there will now become I hope more focus on the cerebellum because you know in PWS the motor problems they have, they have a poor balance and this is also related to abnormal cerebellum function. And also about speech, cerebellum is very important for our development of normal speech so it has always been my dream to focus a bit more on cerebellum and now in a way it comes so I hope. I do not know at all if what you found here has something to do with the motor performance but perhaps it could.

AI: So that that wasn't my work, it's just some work that came out recently, but it is really interesting and we have never looked at the cerebellum and we probably should, because this now gives us not just the motor problems, but they could all be related to a very similar thing. You're absolutely right, and I think the fact that part of the feeding circuitry is related to the cerebellum, it gives it much more impetus and it's really an interesting an interesting angle. It could be that the genetic lesion that occurs in Prader Willi syndrome has consequences for cerebellar development, or something like that, which has both feeding and consequences for speech and motor function. It's really interesting. And we've never looked at the cerebellum in in our model and maybe we should.

Comment: We have all we have always just stated that the cerebellum function is not good and they have the balance problems and also this is great variety, for example,

someone may learn to ride a bike and others do not learn, and it has also to do with the differences in their balance problems.

Q: A question relating to a previous one, what about environmental and epigenetic?

AI: So, the Prader Willi mutation occurs in an area where there's a lot of epigenetic control in terms of genomic imprinting. And as I mentioned about the DNA methylation and how those changes can occur in in vitro culture, for instance, in cell culture, so there is evidence that some adverse environments can have consequences for epigenetic regulation of genes later on in life, but as far as I'm aware there's no link between epigenetic disturbance and the Prader Willi interval. Of course the environment always has an impact on how individuals develop, but whether it's mediated via changes in DNA methylation, I'm not massively convinced, and I certainly don't think there's any evidence for it having an effect on the Prader Willi gene locus in particular.

There have been a number of studies of how assisted reproductive technologies, which is an environment of a sort, whether they can lead to increases in Prader Willi Syndrome, Angelman Syndrome, Beckwith-Wiedemann syndrome, all these syndromes which are related to imprinted genes, so I know that there was an increased incidence in Angelman syndrome, but I don't think there's ever been a demonstration of an increased incidence of Prader Willi syndrome following assisted reproductive technologies, as far as I'm aware.

JOB: Thank you once again and thank you Anthony for your presentation this morning.

AI: You're welcome.

Thank you very much to everyone who attended the session and participated. We look forward to seeing you again at the next session on the 11th of January.

Ends.