conference review; translating genetics to phenotype...

Translating Genetics to Phenotype: the Society for the Study for Behavioural Phenotypes Research Symposium, Brisbane Oct 2011

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This was an intimate meeting of 70 international clinicians in the Riverside Centre designed by Harry Seidler, overlooking the Brisbane river. Drinks at the Powerhouse was especially memorable, where Bill Shorten Federal Minister for Finance, sponsor of the National Disability Insurance Scheme, opened a photographic exhibition by an eminent American fashion photographer Rick Guidotti. Rick presented work to challenge the stigma of people with genetic disorders and disability, capturing moments of their joy and beauty in photographs and thereby *celebrating diversity*. Intellectual diversity in bringing science to our understanding of the mind best describes this stimulating meeting organised by Honey Heussler Paediatrician at the Mater Children's Hospital.

The last decade has seen so much invested in genetics research. 'Gene Wide Association Studies' may have identified numerous genes of interest, but together they explain very little, such as 1% of the causes of schizophrenia or autism. Prof John Mattick, Director of the Centre of the Centre for the Molecular Biology and Technology at University of Queensland said the human genome project has failed to unlock the function of the brain. All the 'silent' DNA in our chromosomes is involved in the coding of small 'non coding' RNA molecules which are involved in regulatory feedback systems. There are 180,000 exons where the active DNA areas creates functional proteins (1% of the genome), but we are starting to discover that the rest of the genome is there for a purpose. Exploring the functional roles of these previously unrecognised RNAs has made understanding the regulation of the brain so much more complicated. Professor Frank Bowling a biochemist and Director of Inherited Metabolic Diseases at the Mater Children's Hospital described how individuals with every neurotransmitter/biochemical metabolic disorder have been described. Some of these are found in certain genetic phenotypes, such as abnormalities of the glutamate transporter system found in 5/6 families with OCD; Tourettes is a presentation of histamine decarboxylase deficiency. But genetic diseases do not represent dysfunction of a single gene, but a disruption of a function from several genes (disease polymorphism) and no single biochemical mechanism is the cause of a mental illness. Mental illness must be the consequence of parallel processes coming together to create such disorders. The gene revolution has led to amazing complexity in understanding intracellular metabolic pathways and some of the differences in function in different cells and different brain locations, what is called epigenomes. The European Union has just invested 30 Million Euros in 41 institutions studying this variation of epigenomes. The current technical challenge requires a new discipline of "informatics" ie high powered computer analysis to unravel the patterns in 2 terabytes of information from identifying different proteins and other chemicals through mass spectrometry in a single experiment.

This level of complexity creates scientific uncertainty and a significant error margin. Prof James Harris, Neuropsychiatrist from Harvard illustrated this with his talk on Oxytocin. Oxytocin is currently the fad explanation for a whole range of situations and can be bought by salesmen in the internet in the hope of making their victims socially compliant. Oxytocin certainly contributes to sociability and social cohesion of the prairie vole and a dose at a developmentally sensitive time leads to consistent long term pairing. There are several types of oxytocin receptor. Increased methylation of oxytocin gene leads to reduced activity with increased fear and reduced trust. Oxytocin administration has led to short term reduced repetitive behaviour in Prader Willi Syndrome, increased eye gaze in Williams Syndrome, reduced eye gaze aversion in Fragile X Syndrome, it may help self injurious behaviour in Lesch Nyhan Syndrome and there are now 7 current studies on its use in autism and 8 in schizophrenia!

There is no doubt that the animal models of genetic conditions are an important part of the process of unravelling biological and neurotransmitter systems in certain conditions. Prof Bruce Tonge gave an elegant presentation on the extreme male brain theory of autism, as promoted by Simon Baron Cohen, with a 'knock out' mouse deficient in estrogen aromatase, which leads to increased formation of testosterone. These Spiny Arko mice have increased sexual activity, increased ritualistic grooming behaviour rubbing hair off their face, increased running, cerebellar problems with variability of stride length and toes turned in (also found in autism), reduced social interaction and increased withdrawal, reduced (ultra sonic) communication, bigger brains and increased abnormal purkinje cells in the cerebellum. Darren Hocking made a case for using gait analysis for studying these sorts of coordination problems in Autism and other behavioural phenotypes as a core clinical feature.

Mouse models of Fragile X have identified a number of complex biochemical and neurotransmitter details of this disorder. The number of repeats (copy number variants) on the X chromosomes correlates to increase in the FMR1 RNA which inhibits the production of FMRP and other proteins, and affects many regulatory mRNAs and in turn synaptic formation and plasticity. There is

enhanced metobotropic glutamate receptor 5 activity leading to long term depression in the hippocampus. Glutamate is the final common pathway of neurone energy metabolism. Anti oxidants reduce these effects and smoking increases them. Randi Hagerman, Director of UC Davis MIND Institute, summarised the science and the forays into treatment with mGlucR5 antagonists which is a form of targeted treatment to reverse these abnormalities. Fenobam, RO491723, AFQ 056, Racemic Baclofen (Arbaclofen) and STX209 are all mGlucR5 antagonists and a number of international phase 3 drug trials are under way. In randomised cross over trials, Arbaclofen reduces aggression and anxiety, increases language. Those under 8 years do better especially with enhanced education but the effects are not large compared to placebo, emphasising the importance of early intervention. Aminocycline can tighten up floppy muscle tone and has also been look at in Autism. Lithium down regulates these mRNAs. GABAa and glutamate imbalance are also found in both Downs Syndrome and Autism and GABAa down regulation is being studied with Ganaxolone a neurosteroid, used in Infantile Spasms, and Allopregnalone which has been used in PTSD, as they are found to be neuroprotective and stimulate neurogenesis. Winari reported on the use of small doses of sertraline in children 12-50 months age with Fragile X and found improved receptive and expressive language. Sertraline affects increased neurogenesis and brain neurotrophic factor.

Petrus de Vries, child psychiatrist from Cambridge, presented on Tuberose Sclerosis. TSC is caused by two different genes; TSCI is at chromosome 9p34 and TSCII at 16p13.3. There are differences in patterns of severity for example in IQ between TSCI and II genes, although considerable overlap. Drosophila fly research identifies that TSCI and II protein inhibits intracellular signalling, upregulating the mTOR (mammalian target of Rapamycin) leading to dysregulation and proliferation of cell growth. Rapamycin is an antibiotic found in a streptococcus on Easter Island. Rapamycin can significantly shrink subependymal giant cell astrocytomas, angiomyolipomas and the hamartomas in many difference tissues. Petrus has been working on identifying the neuropsychological deficits in those with TSC and finding deficits such as reduced attentional skills, becoming easily stressed by demands and lack of patience in those with the gene but not obviously affected. Phase II Rapamycin studies have shown improved memory and in now licensed as Envolimus.

Helen Leonard from the Telethon Institute in Perth presented on the differences of severity and symptom pattern in Retts Syndrome according to which of the different genetic deletions is involved. She has published clinical guidelines for management of their scoliosis. Retts Syndrome suffer apneustic breathing when they seem to forget to breath. This is a feature that leads to placement on a respirator and is a cause of death. Robert Delamont, a neurologist, has done a study on Buspirone, a 5HT1a agonist, and shown improved breathing patterns.

Prof Mark Bellegrove of the Queensland Brain Institute and the school of psychology presented on ADHD attentional studies suggesting that ADHD was equivalent to a parietal lobe deficit which causes left 'visual neglect' or lack of attentional responsiveness in the left space (as found in stroke victims), whereas normals have a left sided attention preference. This is related to reduced right sided cerebral, cerebellar and caudate nucleus size, reduced right sided activity on functional MRI and the up regulation of the dopamine transporter gene (one of the genes implicated in ADHD).

What is clear is that identification of biological correlates requires good definition of behavioural phenotypes and psychiatric syndromes and symptoms. Lucy Wilde from the Cerebra Institute in Birmingham, UK, presented on the impulsivity and lack of inhibition in Smith Magenis Syndrome on a number of neuropsychometric tests compared with Downs Syndrome. These features correlated to lack of emotional regulation in SMS and may involve the amygdala and frontal cortical processes. These studies suggest that different symptoms of ADHD such as impulsivity and concentration may have different biological mechanisms. These 'hot' executive function skills may respond to biofeedback. Greg O'Brien mentioned that Modafranil has been used to promote wakefulness in SMS. Phil Ray from our department presented on specific executive function deficits in Autism in cognitive flexibility, complex planning and self monitoring.

Chris Oliver Director of the Cerebra Institute presented on the phenomenology of 1p36 syndrome which has self injurious behaviour, profound intellectual disability and autism. They have early feeding difficulties followed by increased appetite and obesity. Their eating problems proved to be less severe than the eating problems in Prader Willi Syndrome who are distinguished by a tendency to hoard food, but will accept a delay in food gratification. Angelman's Syndrome in contrast will eat inedible objects.

Beth Williams reported on the evaluation of computer learned affect recognition in autism using the Transporters Program where trains are the vehicle of affect expression. Although the kids did better on the computer skills, this did not generalise to any clinical improvement, emphasizing that such programs do not lead to improvement without teaching the implementation of the social pragmatics.

Alexander von Gontard reported on the high rates of elimination disorders in Prader Willi Syndrome of both bowel and bladder, day and night time in children and in adults, totalling 30%.These are often ignored but need investigation sometimes with a sonagraph, pelvic floor EMG, and fluid studies in order to properly classified. They are then readily treatable.

Prof Tomy de Ravel from the Centre for Human Genetics in Leuven drew attention to the growing minefield of ethic issues in genetics. Whose information is it and for what purpose?

Prof Tony Holland, psychiatrist in intellectual disability, Cambridge UK, summarised the conference in the Tom Oppe Lecture presenting on the evolving nature of research in intellectual disability. While inborn errors of metabolism and twins genetic studies have contributed to a boom in research, what has had more influence on people with intellectual disability is legislative and social changes with recognition of their rights for example to marry, access to education and normalisation in community living. People with intellectual disability still lack access to health care as demonstrated by the reports in premature death. None the less the dramatic increase in longevity has revealed different problems including the early presentation of dementia. The clinician is attuned to the range of experience and presentation and incorporates what scientific information can be used in the complex process of formulation the understanding of a problem and an individualised approach to intervention. We are along way from standardised approaches to helping people with intellectual disability, but clinical expertise based on scientific method, despite growing scientific complexity, provides real opportunity for improving their health and mental health care.●