1. Background

Childhood disintegrative disorder (CDD) is a rare and severe neurodevelopmental disorder, characterised by a normal development up to the age of at least 2 years, followed by a rapid and significant loss of previously acquired skills, such as receptive or expressive language, play, social skills, bowel or bladder control and, sometimes, motor skills. This severe regression results in significant long-term impairments in social and communication skills, similar to features of autism spectrum disorder (ASD) with intellectual disability. Interestingly, CDD presents also a strong comorbidity with epilepsy. The estimated prevalence of CDD is about 1/100,000 (Fombonne, 2009) and its etiology is still poorly understood. Given the rarity of this condition, the research on CDD has been carried out mainly on small numbers of patients, whereas few families are available, and the recruitment of new cases is limited by the low prevalence of the disorder. In this context, genetic studies are essential to identify the genetic factors contributing to CDD.

2. Clinical Examination

In the family presented in this study, two individuals (III.1 and III.2) were diagnosed with Childhood Disintegrative Disorder. Both children were born after a normal pregnancy and a normal delivery. Patient III.1 is the elder of two children. He started to walk at 22 months. He was referred for speech and language delay when he was about 18 months old. At the age of 3½ he became a sociable child, showed rather basic play, said single words, learnt his numbers, liked music. At the age of 3 months he became noise sensitive, socially avoidant and showed less eye contact. This period of regression lasted about 6 or 7 months. Currently, he talks well, uses sentences, he can read and he is curious about the world. Fine motor skills remain particularly problematic for him. Full investigations have shown that the screening tests for inherited metabolic diseases are non-contributory. No seizures were reported.

Patient III.2 walked at 14 months and there were no concerns about her early development. She experienced several episodes of floppiness lasting between 2 and 5 minutes, and was subsequently put on Epilim for a year. Investigations including repeat EEGs were entirely normal. The regression started at age of 2 years 4 months and lasted for 16 months. She gradually lost her language, and became unable to accurately carry out the coordinated motor skills she previously exhibited. Generally, she became more lethargic, stressed, less interested in food, toys and playing. She then had a phase of more intensive sound sensitivity. After that, she has become physically more stable and has begun to use a few more words. However, her mother reports that she is still gaining skills but then losing them again. Currently, she is 6 years old and her behaviour is very variable. However, our social interactions remain very poor and she shows stereotypical behaviours.

3. Whole Exome Sequencing

Six family members were subject to whole exome sequencing (WES). Samples were sequenced in a single lane on the Illumina HiSeq 2500. 100 bp paired-end sequence reads were mapped to the Human Reference Genome (UCSC hg19, NCBI build 37). Single nucleotide variants (SNVs) were called using the Platypus algorithm (v0.5.1) and annotated with ANNOVAR. After quality control (goodness of fit > 30, variant quality > 200, minimum variant coverage > 50, no flanking homopolymer, read depth <10), 831,214 variants were detected in the quartet (cases-unaffected parents). Candidate variants were then confirmed by Sanger sequencing.

4. Network analyses

AED and neuropsychiatric disorders have been shown to have a complex genetic architecture with multiple variants contributing to the susceptibility and it is possible that variants affecting different genes, but involved in the same pathway or cellular function, could interact to increase the risk. In order to identify such variants, a list of genes harbouring rare and potentially damaging variants had been imported into WebGestalt (WEB-based Gene SeT Analysis Toolkit) to test for enrichment within specific pathways, and into the STRING database (v10) to identify protein-protein interaction networks.

5. Complex compound heterozygosity?

A child patient was observed to have a severe developmental delay, and autism-like behaviors, associated with seizures. Whole-exome sequencing uncovered two novel compound heterozygous mutations in two different genes.

6. Conclusions

WES was performed on a family with two individuals affected by Childhood Disintegrative Disorder, but none of the rare and potentially damaging SNVs affecting coding genes could explain the disorder with a de novo or recessive complex compound heterozygosity model of inheritance.

Both children carry a maternally derived stop codon in PCM1 and a paternally derived novel stop codon in ALMS1, which likely cause in-frame truncation of the proteins.

HYPOTHESIS: the stop codon (E1912X) might cause nonsense-mediated decay or a truncation of the protein with the complete lack of the 8543-binding domain, which would affect the correct localisation of PCM1 and, consequently, other centrosomal proteins.

HYPOTHESIS: the missense mutation S763N falls in a large tandem repeat domain (34 imperfect repetitions of 47 aa, function unknown). The impact of missense mutations in ALMS1 is still unclear. The substitution of the Serine could affect phosphorylation, stability, protein-protein interactions...

Preliminary results: coexpression of HX-ALMS1/S763N and Mys-ALMS1-wt in MRC5 cells shows an identical localisation pattern of the two proteins, including at the centrosome (reported endogenous localisation), indicating that the missense mutation does not lead to any evident mislocalisation of ALMS1.

References

Kaput E, et al. Recruitment of PCM1 to the centrosome by the cooperative action of DISC1 and BDNF as a candidate for psychostimulant action. Arch Gen Psychiatry. 2005 Sep;62(9):969-76.

Case report: exome sequencing of a family with childhood disintegrative disorder

Ceroni F1, Absoud M. 2, Baird G, Velayos-Baeza A.1, Newbury D.1

1 Wellcome Trust Centre for Human Genetics, Roosevelt Drive, Oxford OX3 7BN, UK.
2 Guy’s & St Thomas’ NHS Foundation Trust, Kings Health Partners Academic Health Science Centre, London, England

Any questions contact: fabiola@well.ox.ac.uk
You can read more about our research at www.well.ox.ac.uk/newbury
Follow us on Twitter @DIanneNewbury

The Newbury Lab is funded by the Medical Research Council.