Title	**Molecular Diagnosis for Paediatric Genetic Disorders Using Whole Exome Sequencing of the Next Generation Sequencing Technology**
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minutes; Post-call day median sleep duration: 229 minutes; p-value 0.001). Lower standard global score in Beery's Visual-Motor Integration (VMI) test was noted on post-call day (p-value 0.025) with a consistent association of poorer performance with increasing age on post-call day. No difference in simulated clinical scenario performance was detected despite the differences in neurocognitive outcomes.

Conclusion: Acute sleep deprivation adversely affects neurocognitive outcomes including visual perception and motor coordination in paediatric residents. This adverse effect is more prominent with increasing age.

Molecular Diagnosis for Paediatric Genetic Disorders Using Whole Exome Sequencing of the Next Generation Sequencing Technology

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Molecular diagnosis for paediatric genetic diseases is important for targeted or tailored treatment, more informative genetic counselling and guiding the families for prenatal or pre-implantation diagnosis. Traditionally, linkage analysis using large multiplex families or multiple families with the same molecular cause is essential and the process could take years before a diagnosis can be reached. Candidate gene screening is usually the only method available for clinical laboratories for genetic diseases in Hong Kong.

Next generation sequencing technology has virtually revolutionised the way genetic studies are conducted and provides opportunities for molecular diagnosis for genetic disorders that were never available before. With the possibility of sequencing the whole genome or almost all the coding exons of the genome, the method does not require the availability of large, multiple affected families and prior knowledge of candidate causal genes. It can be applied to a single patient or, as a usual practice, whole genome or whole exome sequencing for the patient plus parents. For whole exome sequencing (WES), it usually produces up to 100 million short sequencing reads of usually 100bp long. These short reads were firstly compared with sequences of a reference human genome and mapped to genomic regions from which they were generated. Each position (base pair) of a coding exon is usually covered with dozens to hundreds of sequencing reads. Analysing the sequences of these reads allows for identification of mutations that are different from the reference sequences.

For WES for a single individual, up to 100,000 variants can be identified, with some of which are common variants in a population and some of which rare or private. The population frequencies of these variants are looked up in public databases such as those from the 1000 Genome Project or ESP6500, a project that sequenced 6500 individuals in the US. An internal database is also established with WES data from 200 samples from the local population. For rare, severe genetic disorders that are likely to be caused by mutations from a single gene, we can safely rule out the common (>1% in a population) variants and only focus on the rare or private variants. The nature of the mutations, such as with or without amino acid changes, changes in the open reading frame of the protein, the nature of the amino acid changes (similarity of the amino acid changed to), the conservation of this amino acid in different species, and the function of the gene in relationship to the disease phenotype, are considered to help pinpoint the causal mutations.

We will present examples on using WES for molecular diagnosis for paediatric genetic disorders in our Department. These include detection of de novo mutations (mutations that are not detected in parents), somatic mutations and compound heterozygous mutations, and mutations missed by traditional laboratory testing, which demonstrated the power of this new technology in providing accurate molecular diagnosis.