ABSTRACTS

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to test result), robust (accommodating tens of samples per batch), and highly cost -effective with respect to aCGH.

Reference list: Hou Y, Fan W, Yan L, Li R, Lian Y, Huang J, Li J, Xu L, Tang F, Xie XS, Qiao J. (2013)

PGD for variants of unknown significance (VUS) ; perform or not to perform ?

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Introduction: Whole Exom Sequencing (WES) has become an effective tool for delineating the mutations to enable PGD application for families without previous diagnosis of their affected child. A family was referred to our clinic who had two deceased children with phen otypes resembling a complex metabolic disorder. Due to lack of clinical diagnosis WES was performed and two disorders (Menkes, Joubert Syndrome) were highlighted in results.

Menkes syndrome is a disorder that affects copper levels in the body. Joubert sy ndrome is a disorder that affects many parts of the body. The signs and symptoms of this condition vary among affected individuals. Combination of these disorders may lead to an unexpected phenotype making diagnosis quite difficult for clinicians who face cases with overlappping phetoypes of multiple disorders.

Material & methods: The couple referred to our center for genetic counseling. Family history reported 2 deceased male siblings with similar phenotype . Whole exome sequencing (WES) was performed for the healthy son and parents. After couple's consent, PGD was designed specificly for three variants of unknown significance.

Results: WES analysis performed on a healty child and parents revealed three VUS . The WES results of the trio analysis, concl uded that several disorders might partially account for the deceased children phenotypes including X-linked Menkes disease and autosomal recessive ciliopathies. In the light of this assumption, PGD application was designed for these variants. We have perfo rmed two IVF/PGD cycles for this family. In their first attempt only one embryo was appropriate for transfer . Due to failure in achieving succesful pregnancy, second IVF/PGD cycle was performed. Eight embryos were evaluated and two normal embryos were transferred. The rest of the embryos were vitrified for future considerations.

Conclusions: WES results reveal vast amount of data and it is not always straight forward to filter out the mutation responsible for the disorder. Unusal phenotypes also turns a nalysis stage into a difficult one. In cases where a published mutation can not be delineated variants of unknown significance (VUS) comes into the scenario. It is not always easy to report VUS and it is even harder to interperete them If you are planning to perform PGD for the familiy. The families need need to be informed about the risk of PGD applications based on VUS elimination may not related with the phenotype of the affected child.
WES results revealed three VUS in our case with each disorder h aving an overlapping phenotype with the index cases. We have decided to try and exclude all three VUS with the PGD since none of them could be excluded due to complexity of the pheotype. Frequent use of WES for families demanding PGD may change our approa ch towards PGD cases. We may have to consider performing new techniques like karyomapping enabling us to investigate multiple target regions but the more we try to exclude the less likely we will find an appropriate embryo for transfer. In these cases the families should be informed of this possibility before consenting to PGD applications.