Appendix I
(Oral Free Paper Session)

ORAL PRESENTATION 8:

Mutation in PIK3CA leading to developmental mosaic disorders

Yeung KS,[1] Leung GKC,[1] Wong WL,[1] Li CH,[2] Choi KY,[3] Kuong E,[4] Chow W,[4] To M,[4] Ip J,[5] Chow CP,[6] Chan GCF,[1] Chung BHY[1]

[1]Department of Paediatrics & Adolescent Medicine, Li Ka Shing Faculty of Medicine, The University of Hong Kong; [2]Department of Paediatrics & Adolescent Medicine, Tuen Mun Hospital; [3]Department of Orthopaedics & Traumatology, Tuen Mun Hospital; [4]Department of Orthopaedics & Traumatology, Queen Mary Hospital; [5]Department of Radiology, Queen Mary Hospital; [6]Child Assessment Service, Department of Health, Hong Kong

Background and aims

Mutation in phosphatidylinositol-4, 5-bisphosphate 3-kinase (PIK3CA), one of the genes involved in the PI3K/AKT/mTOR pathway, is associated with developmental mosaic disorders which are now collectively termed as PIK3CA-Related Overgrowth Spectrum (PROS). PROS can be further divided into two subgroups based on the affected body systems, which are body asymmetrical overgrowth and central nervous system (CNS) overgrowth respectively. Body asymmetrical overgrowth includes diseases such as CLOVES Syndrome, Klippel-Trenaunay Syndrome, Cystic Hygroma and Fibroadipose Hyperplasia. More than 90% of these patients have somatic mutations in one of the 4 mutation hotspots in PIK3CA. CNS overgrowth includes diseases such as Megalencephaly Polymicrogyria Polydactyly Hydrocephalus Syndrome (MPPH) and Megalencephaly Capillary Malformation Syndromes (MCAP). Patients who have CNS overgrowth have megalencephaly and at the same time developmental delay and/or autistic spectrum disorder. We have ten patients that are suspected to have PROS, and we aim to identify the diseasing causing mutation in each patient.

Methods

For patients who have body asymmetrical overgrowth, somatic mutations can only be detected on affected tissues. Since there are mutation hotspots, digital PCR was used to identify low level somatic mosaicism. For the 2 patients with CNS overgrowth, mutation can be detected on blood, saliva and buccal tissues. Whole exome sequencing was used to identify the diseasing causing mutation.

Results

In 7 out of 8 patients with asymmetrical overgrowth, somatic mutations in PIK3CA have been identified. The percentage of mutant in these patients ranged from 3.3% to 31.6%. For the 2 remaining patients with CNS overgrowth, 1 reported somatic mutation with 4.5% mutant and 1 novel germline mutation in PIK3CA have been identified.

Conclusion

In order to obtain a molecular diagnosis of PROS, the correct choices of affected tissues and sequencing technology are important. Surgical debulking is now the only option for treatment for PROS. With the identification of mutations in PIK3CA, inhibitors that inhibit PI3K/AKT/mTOR pathway may be used in controlling the progressive overgrowth in patients.

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