OXFORD BROOKES UNIVERSITY

Professor Ragge Update for Health Professionals - MACS

Around 1 in 3,500 children are born with one or both of their eyes not fully developed. This represents a major cause (25%) of childhood blindness. These conditions include Anophthalmia (missing eye), Microphthalmia (small eye) and Coloboma (gap in one or more layers of the eye structures), (AMC). The eye anomalies are associated with other systemic findings in over 50% of individuals. The impact on the families cannot be underestimated since there may be a combination of visual impairment, cosmetic issues and other major health issues, including developmental delay, autistic spectrum disorder, heart, kidney and limb anomalies. The majority of these conditions are thought to be caused by alterations in one of the many genes that underlie human eye development.

Professor Nicola Ragge, who is a Consultant Clinical Geneticist at the West Midlands Regional Genetics Service, and is also an experienced ophthalmologist, has been conducting research into the genetics of developmental eye anomalies since 1999. She played a key role in identification of the two genes most frequently altered in AMC, *SOX2* and *OTX2,* thus changing the whole perception of the genetic basis for eye anomalies. Since this time through her key role and through a worldwide effort, she has continued to identify new genes and syndromes associated with these conditions, and was integral in defining a new field of research and clinical practice, that of developmental ocular genetics. By inspiring other groups to take on work in their own centres worldwide, over 103 genes linked directly to conditions with AMC have been described repeatedly, and there are at least another 40 genes implicated in publications describing findings from 1 or 2 families.

With therapeutic trials for the genetic treatment for inherited retinal diseases, similar treatment may become available for AMC in the foreseeable future. As eye development is complete within the first two years of life, with most of it occurring in the first few months of life, any treatment should be started soon after birth. For best management of a new baby or affected individual, rapid genetic diagnosis is of paramount importance. This will also allow accurate estimate of recurrence risk and genetic counselling. To enable genetic diagnosis, Professor Ragge has pioneered two diagnostic methods testing over 350 genes involved in eye development, in collaboration with the NHS West Midlands Regional Genetics Service based at Birmingham Women's and Children's Foundation Hospital Trust. These tests include the customised eye array – which detects structural changes of the chromosomes or the eye development genes (down to the level of the exons), and the eye gene panel or whole exome (testing all the genes) – which detects sequence variants in these 350 genes. These tests are currently available through the West Midlands Regional Genetics Service and will form the basis of standardised, genetic testing for structural eye disorders that will be implemented by NHS England in 2020.

As AMC has a highly complex genetic aetiology, it is advisable for families to be seen by a geneticist specialising in structural eye anomalies. With over 20 years experience, Professor Ragge is one of the few specialists in the UK. She accepts referrals from throughout the United Kingdom and offers access to the AMC-specific diagnostic tests at the West Midlands Regional Genetics Service. For families that do not receive a diagnosis through these diagnostic methods, Professor Ragge offers further state-of-the-art testing through her research programme in Oxford.

For families the impact of receiving a genetic diagnosis is immense, as an explanation may provide reassurance regarding any factors that families had thought might have led to this during pregnancy. The diagnosis will also enable them to understand the features and the prognosis of the condition, and access appropriate screening and management of associated problem, for instance, over 50% AMC conditions are associated with systemic anomalies e.g. kidney, growth, developmental delay, autism. Some of these conditions e.g. kidney, heart, growth development can be screened for and early detection can be life-saving. For families wishing to extend their families, having already had an affected child, a diagnosis provides accurate information on recurrence risk, and allows prenatal and pre-implantation diagnosis to be offered. Most importantly, having a diagnosis, and the knowledge that the AMC and potential other health problems are part of a known syndrome may aid in accessing health, visual impairment, school, social and financial support and will allow them to be in contact with families affected by the same condition as well as support groups.

Professor Ragge is happy to accept referrals from any part of the United Kindom. Referrals should be sent through the NHS E-RS system.

Details for Professor Ragge:

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If you have any further questions you are most welcome to contact Professor Ragge through ragge.eye.study@me.com or speak to her research co-ordinator in Oxford, dr. Dorine Bax (01865 484413, dbax@brookes.ac.uk).