CC-03

UNRAVELLING THE X FILES: CHALLENGES AND DILEMMAS

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Array-Comparative Genomic Hybridization (array-CGH) has increased the diagnostic yield in patients with intellectual disability (ID), autism spectrum disorders and multiple congenital anomalies due to its improved resolution. X-chromosome has been focus of attention due to the bias in the affected male-to-female ratio and to the knowledge of X-linked genes associated with ID. With array-CGH we can either detect single gene imbalances, chromosomal region imbalances and even aneuploidies.

In a cohort of 1000 patients studied by Agilent 180K oligonucleotide array-CGH several X-chromosome imbalances were detected. Single gene deletions involving ZNF41 or IL1RAPL1 genes were equitably observed in 8 patients; DMD imbalances in 3 females and SHOX gene duplications in 1 female and 9 males. An intragenic deletion in SLC9A6 gene associated with Christianson syndrome that segregated in the family was also detected.

In 6 patients we identified Xp22.31 duplications, 3 females, 1 male with maternal inheritance and 2 males whose inheritance was not yet determined. A chromosome Xq27.1q28 interstitial duplications in 2 males, 1 maternally inherited and the other not yet determined were also identified. We also found other genomic imbalances but in single cases as for example a complex rearrangement with multiple imbalances at Xp22.33p22.2 in a male patient, maternally inherited; an Xp11.3p11.23 duplication in a female with ID whose mother is also affected and a case of triple X in an autistic female.

The challenge with X-chromosome imbalances is to, understand the biological mechanism(s) behind, interpret their impact on the phenotype, due to the presence of some alterations in the normal population and to X-chromosome inactivation in females. Clinical laboratory reporting has to use the correct nomenclature and a clear and objective interpretation of the results.

CC-04

AN INTRODUCTION TO X-LINKED IMDS

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While individually the inherited metabolic diseases are rare or very rare, overall the incidence is around 1:1,400 live births and accounts for about 15% of all single gene disorders. The vast majority of these diseases are inherited in a recessive manner with 3 or 4 being dominant conditions. However, 14 are inherited in an X-linked fashion. By my estimation there are over 200 conditions to consider, most of which are not treatable. My presentation will focus on four diseases—Anderson-Fabry disease (FD); Mucopolysaccharidosis type II (MPS II); Ornithine Transcarbamylase deficiency (OTC); and X-Linked adrenoleucodystrophy (XALD)—that illustrate several points of interest.

FD is a multi-system disease caused by a deficiency of the lysosomal enzyme alpha galactosidase. Accumulation of the substrate globotriaosylceremide (GL3) leads to a sequence of symptoms over time starting with severe neuropathic pain in the peripheries and moving on to proteinuria renal failure, cardiac and cerebrovascular disease. Without treatment death occurs by the 4th or 5th decade. Fortunately, enzyme replacement therapy is available. The clinical and therapeutic aspects of the disease will be discussed as well as the issue of late onset disease and the fact that there is a very high incidence of symptoms in the so called female carriers.

MPS II, or Hunter syndrome, is another multisystem lysosomal storage disorder caused by a deficiency of iduronate-2-sulphatase. The main features are due to skeletal involvement and like FD there is enzyme replacement therapy. However, unlike FD it is exceptionally rare for female carriers to develop symptoms or signs of the disease.

OTC is the commonest of the urea cycle defects. The symptoms are related to the accumulation of ammonia and will be discussed. In most boys the disease presents in the neonatal period. Many do not survive and those that do are usually severely brain damaged and susceptible to destabilization throughout their lives, even with the dietary treatment currently available. Interestingly, as will be discussed, about 15% of females will develop symptoms and require lifelong treatment. One of the times of greatest risk is during pregnancy and delivery.

The presentation will also describe the various manifestations of XALD from the severe childhood presentations to the adrenal and neurological disease of the onset in older boys and young men.

In addition to the clinical aspects of the four diseases, information on diagnosis and genetic counselling implications will be discussed.