

# Invited speakers

## Comunicações por convite

### CC-01

#### **MECHANISMS OF PRIMARY OVARIAN INSUFFICIENCY**

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Primary ovarian insufficiency (POI) affects 1-2% of the general population. Patients have primary or secondary amenorrhea, lasting more than 4 months, occurring before the age of 40. Their plasma gonadotropins, measured twice, are elevated (FSH > 20 IU/L) with low estradiol levels.

In the absence of previous chemotherapy, radiotherapy and ovarian surgery, genetic causes of POI need to be investigated. Many of them are linked to X chromosomal abnormalities, such as Turner syndrome with 45,X karyotype or 45,X/46,XX mosaicism. Two copies of two different regions located on Xq, named POF1 and POF2, are necessary for the maintenance of ovarian follicles. As those regions escape X inactivation, due to their haploinsufficiency in Turner syndrome, ovarian follicle loss is accelerated. Apart from Turner syndrome, the patient's karyotype can reveal Xq deletions as well as X autosomal translocations. In rare cases gene disruption is involved. However, those Xq regions are poor in gene and a position effect on autosomal gene might be responsible for follicle depletion. Taken together, X chromosome abnormalities represent around 10 -15% of POI.

Mental retardation in males from the family, related to fragile X syndrome, should be searched for, as *FMR1* premutations are identified in 3% and 13% of sporadic cases and familial cases of POI, respectively. The main mechanism involved is an increased mRNA inducing ovarian toxicity.

In patients with blepharophimosis, POI can be related to *FOXL2* mutations. POI may also be linked to autoimmunity. It may rarely belong to Autoimmune Polyendocrinopathy Ectodermal Dystrophy (APECED) due to *AIRE* mutations. More frequently, it is associated with type 1 diabetes, adrenal insufficiency, hypothyroidism as well as vitiligo, lupus.... As the genes involved in APS2 and APS4 have not been identified so far, the autoimmune origin of POI is often difficult to prove. In less than 2% of cases, POI is due to *SF1* mutations.

Many genetic causes of POI are non syndromic. The main one is *NOBOX* gene mutations, coding for a protein expressed

in the oocyte, identified in 6% of POI cases. Other genes such as *eIF4ENIF1*, *STAG 3*, *HFM1*, *MCM8* and *MCM9* have been identified recently.

More than 30 candidate genes have been identified so far in POI. They can be tested by Next Generation Sequencing. However, the cause of POI is identified in less than 30% of cases. Studying familial cases of POI should increase our knowledge in the near future.