

Transcriptional and epigenetic analysis indicates *ESX1L* gene as a diagnostic marker for Sertoli cell-only syndrome

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Despite a number of loci have been implicated in defective spermatogenesis, the genetic cause in over 40% of sterile males remains unknown. Not only OA (obstructive azoospermia), but also NOA (non-obstructive azoospermia) patients benefit from intracytoplasmic sperm injection (ICSI), because multiple testicular sperm extraction (TESE) can retrieve the rare spermatozoa in selected NOA cases. Identifying new spermatogenic phase-specific markers, predictive of a successful sperm recovery, is therefore a valuable goal.

ESX1L (Xq 22.2) is a human homeobox gene expressed in testis, placenta, brain and lung. The mouse homologue, *esx1*, is expressed in placenta and testis, specifically in pre- and post-meiotic germ cells. In humans, *ESX1L* role has not been defined as yet. We have investigated genomic sequence, expression, and epigenetic status of *ESX1L* in testicular tissue samples from 72 infertile subjects (histologically both OA and NOA), to check a possible association between *ESX1L* alterations and impaired spermatogenesis. The gene was transcribed in OA as well as those NOA cases showing residual spermatogenesis (maturation arrest or severe hypospermatogenesis), whereas in Sertoli cell-only syndrome (SCO) cases it was predominantly (>80% of samples) not expressed. Accordingly, the pyrosequencing of *ESX1L* promoter CpG island revealed methylation levels that were significantly lower in *ESX1L* expressors as compared to *ESX1L* non expressors (expressed 4.30% and non-expressed 7.31%).

Based on these results, concordant *ESX1L* transcription and methylation patterns can be proposed as a novel, accurate spermatogenesis phase marker in testicular biopsies, useful for differentiating SCO cases from the other NOA subtypes.