**Rapid-onset obesity, hypoventilation, hypothalamic dysfunction, autonomic dysregulation, and neural tumour (ROHHADNET) syndrome in two Italian patients: clinical characterization and exome sequencing analysis.**

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ROHHADNET syndrome is often misdiagnosed. Early diagnosis and correct multi-disciplinary management improve patient outcome and life expectancy. Finding the gene responsible for ROHHADNET pathogenesis will help to disentangle the genetics of this disorder, allowing molecular diagnosis and genetic counselling.

We present our preliminary results regarding exome sequencing analysis in two patients with ROHHADNET syndrome

VSM, female, 5th child of unrelated parents, was born full term after an uneventful pregnancy and had no neonatal complications. Birth weight was normal. History was not significant until 3 years of age; then she developed rapid weight gain (6Kg in 3 months), fatigue, polydipsia, nocturnal enuresis, syncope episodes, strabismus, behavioral problems. She was admitted at 3.5 years for suspect pneumonia; mechanical ventilation was performed for severe hypoxia and hypercapnia, followed by NIV. Polysomnography showed sleep hypopnea and apnea. Blood tests showed normal thyroid function, low cortisol, high prolactin levels. Low dose and standard dose ACTH tests confirmed adrenal insufficiency and steroid therapy was started. A gradual reduction of height velocity was observed; GH deficiency was diagnosed at 4.5 years, and rhGH therapy was started.

PA, female, 1st child of unrelated parents, was born full term; pregnancy was complicated by miscarriage threat; perinatal asphyxia was present. Birth weight was normal. History was not significant until 3 years of age (growth impairment was noticed between 1 and 3 years), when she developed rapid weight gain (6Kg in 3 months), polyuria, central and obstructive apnea. NIV was started at 4 years. Blood tests showed hyperprolactinemia, normal thyroid and adrenal function. She developed central precocious puberty at 6.5 years. GH deficiency was diagnosed at 7.5 years, and rhGH therapy was started.

Brain MRI was normal in both patients. No evidence of neural tumor has been found in either patient yet.

After excluding mutations of the PHOX2B gene in DNA samples from the two patients, an exome sequencing approach has been undertaken by ©Genomnia srl ([www.genomnia.it](http://www.genomnia.it)). A list of all the single nucleotide, indels and copy number changes found in the two patients was provided to us, including a total of 13822 and 14085 single nucleotide substitutions in the two DNA samples respectively. Of these, 409 and 388 are resulted to be still unreported in the dbSNP nor in in-house controls and around 100 from each patient are potentially damaging (www.ensembl.org). After checking 14 genes carrying variants in both patients, and verifying whether these had been inherited from one of the parents, we have started to test different hypothesis, among which 1) the recessive inheritance of homozygous variants for different genes in the two patients and 2) the possible presence of severe mutations affecting a same pathway. The analysis and validation of results is in progress.