The first Belgian series of 56 patients with congenital hypogonadotropic hypogonadism(CHH): genetics and brain abnormalities.

Valdes-Socin H [1*], Libioulle C, [1] Harvengt J. [1], Pintiaux A [1], Jonas C [1], Parent AS [1], Geenen V [1], Corman V [1], Debray FG. [1], Dideberg V. [1], T'Sjoen G [2], De Leerner A [5], Beckers D [4], Destree A [6], Roland D [6], Lederer D [7], Boscolo M [3], Bours V [1], Maiter D [4] and Beckers A [1].

GP1277
Monday13-14h

1-CHU de Liège, Liège, Belgium, 2-CHU Gand,Belgium 3-Université libre de Bruxelles,Belgium 4-Cliniques Saint Luc (UCL), Belgium, 5-UZ Leuven 6-CHC, Belgium 6-Génétique,Gosselies 7-Genetique, Namur, Belgium
* hg.valdessocin@chu.ulg.ac.be

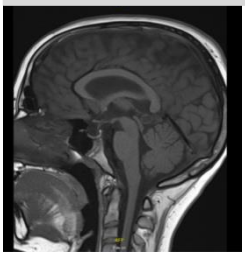
Introduction : CHH is a genetic syndrome that combines reproductive and brain abnormalities. The brain phenotype has been incompletely characterized. We aimed to study neuroradiological and genetic features in this first Belgian cohort of patients with CHH.

Patients and methods:.
A series of 56 adult patients (48 males, 8 females) presenting with CHH was investigated for a panel of 16 genes related to hypogonadotropic hypogonadism by next generation sequencing on a MiSeq® Instrument (Illumina) and by using a validated targeted approach with xGen® Lockdown® Probes (IDT). We then reviewed cerebral or hypothalamic-pituitary abnormalities in 32 patients using magnetic resonance image (MRI).

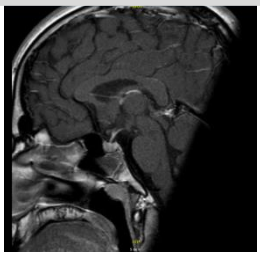
Results. Among the 56 patients, we found, until now, some 26 genetic variants including FGFR1, GnRHR, CHDT, TAC3, WDR11, HS6ST1, PROKR2 and KISSR genes.
In this series, five new variants (class3 to 5) were present in the following genes: TAC3 gene (c.238+1 G>A, class 5), FGFR1 gene (c.169C>A, p.Leu57Met, class 3), CDH7 gene (c.7212_7214del,p.Arg2405del, class 3), KISS1R (c.502G>A, p.Val168Ile, class 3) and a deletion of KISSR.

Brain Imaging Studies

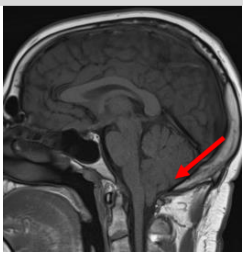
No MRI= **24** | Normal MRI= **23** | Abnormal MRI= **11**



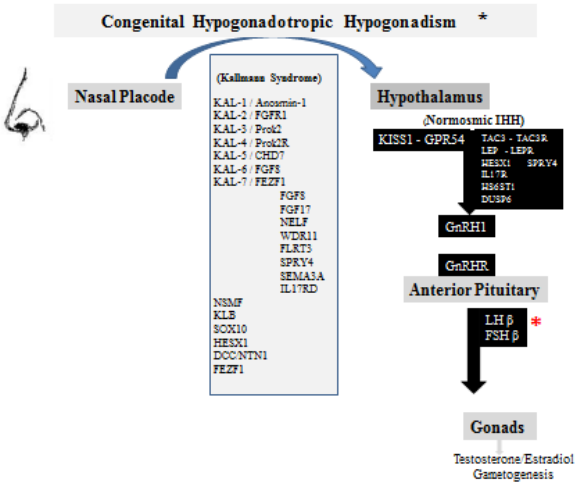
Anterior pituitary hypoplasia n=3



Rathke Pouch kyst n=1



Chiari Malformation type 1 n=3



Discussion: In our cohort, CM1 was found in three of the 32 patients (9.3%) who performed a brain MRI. In the general population, incidence of CM1 is estimated at 0,7%. CM1 and CHH have not been previously reported, although CM1 and cerebellar herniation were seen in GHD or in multiple hormone deficiency patients. We found a new FGFR1 mutation for one of our patients with CM1. Common variants in genes involved in somitogenesis and fetal vascular development may confer a susceptibility for CM1: the contribution of FGFR1 to these defects deserve more investigations.
Conclusions: In this largest Belgian series of CHH, we describe for the first time five new pathogenic variants. Moreover, we suggest a new syndromic association between CHH and CM1. Multicenter studies and systematic brain MRI may be required to extend the phenotype and the genotype of CHH patients.

References
Valdes-Socin & al. New England Journal of Medicine 2004
Valdes-Socin & al. J Clin Endocrinol Metabol 2009
Valdes-Socin & al Frontiers in Endocrinology 2014