**INTRODUCTION**

Congenital hypogonadotrophic hypogonadism (CHH) is a rare condition caused by a dysfunction of the GnRH Axis. The clinical variability of the disease is accompanied by genetic heterogeneity. Indeed, more than 40 genes are implicated in the pathogenesis of this condition. (1, 2)

Classified as a long time as a monogenic disorder, CHH does not show regular Mendelian segregation patterns and syncretic effects between CHH genes have been suspected in CHH individuals with rare variants in more than 1 candidate gene (3).

**AIM**

The main goal of this present study was to characterize genetic defects in a large cohort of French CHH patients using a targeted NGS panel.

**METHOD**

**Patients**

121 patients (77 males/44 females) with CHH diagnosis (94 normosmic CHH, 24 Kallmann syndrome, 1 Woodhouse Latchford Syndrome, 1 Kallmann syndrome and 1 Gordon Holmes Syndrome) were enrolled for this study. Patients were followed in French pediatric and adult endocrinology units. Informed consent was obtained from all patients.

**Variant Analysis**

DNA was extracted from peripheral-blood leukocytes using the kit QiAamp DNA Mini (QiAGEN). A custom SureSelect QT DNA target enrichment panel (Agilent Technologies Inc) was designed to capture 54 CHH candidate genes.

**Alignment**

Variant calling was performed with a homemade Pipeline designed with CLC Genomics Workbench (CLC GWP), then variants were annotated and filtered with Infinium Variant Analysis. Copy number variations (CNVs) were screened using CLC GWP.

**RESULTS**

Variants calling were limited to rare variants of the coding sequence or within acceptor or donor splice sites with a frequency less than 0.5 % in the general population. Variants were annotated in pathogenic, likely pathogenic or "of unknown significance" (based on the ACMG recommendations).

121 unrelated CHH patients were analyzed. A total of 101 rare variants were detected in 28 genes.

32% (39/121) patients were identified with a monogenic variant whereas 23% of patients (28/121) presented at least 2 rare variants in 2 different candidate genes (see Graph1). 54 patients (45%) did not display any rare variant in the 54 candidate genes.

In 31 patients, a molecular diagnosis was reached because of the presence of pathogenic or likely pathogenic variants (class 5 or 4). In 14 of those patients, an additional rare variants were found in at least one additional candidate gene.

A CNV analysis revealed 2 large duplications of ANOS1 gene in 2 patients without rare variant. One large deletion of GNRHR was found in one patient with a missense variant of GNRHR on the other allele.

**CONCLUSIONS**

CHH is a rare condition with an uncovered complex model of genetics (monogenicity and oligogenicity).

Targeted sequencing using selected panel is effective for a molecular diagnostic (clinical diagnostic confirmation or shifting) but still insufficient to explain all cases.

Exome and whole genome sequencing (WGS) will should to overcome the limitation of selected panel.

Reporting more variants with CHH cases will help to make substantial progress in our understanding of CHH.

**REFERENCES**


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