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Analysis of the *WDR11* gene in patients with isolated hypogonadotropic hypogonadism with and without olfactory abnormalities

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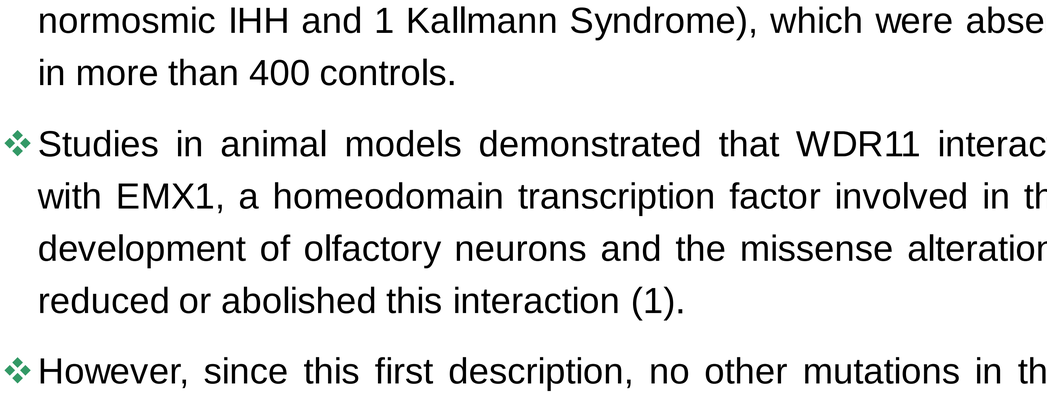
INTRODUCTION

- The *WDR11* gene was recently involved in the pathogenesis of isolated hypogonadotropic hypogonadism (IHH).
- In 2010, Kim *et al*. (1) identified five different heterozygous missense *WDR11* rare variants in 6 of 201 IHH patients (5 normosmic IHH and 1 Kallmann Syndrome), which were absent in more than 400 controls.
- Studies in animal models demonstrated that WDR11 interacts with EMX1, a homeodomain transcription factor involved in the development of olfactory neurons and the missense alterations reduced or abolished this interaction (1).
- However, since this first description, no other mutations in this gene were associated with the IHH phenotype (2-4).

OBJECTIVE

- To investigate the presence of *WDR11* rare variants in patients with isolated hypogonadotropic hypogonadism (IHH) with and without olfactory defects.

PATIENTS



- 28 patients (21.7%) had familial IHH
- All patients have been previously screened for variants in the following IHH associated genes:
  - *KAL1* in Kallmann syndrome
  - *GnRH1/GnRHR, KISS1/KISS1R* and *TAC3/TAC3R* in normosmic IHH
  - *FGF8/FGFR1* and *PROK2/PROKR2* in both conditions.
- 32% of the patients had an identified defect in one of these genes.

METHODS

Genomic DNA extraction from peripheral leukocytes

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PCR amplification of the 29 exons and intron-exon boundary regions of the *WDR11*, using specific intronic primers pairs

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Sanger sequencing and comparison to the reference DNA sequence available at NCBI: NM_018117.11

RESULTS

- No rare variants were identified in the patients studied.
- Only the following known polymorphisms were identified:

rs35692153	COSM147066	rs151162552
rs7899928	COSM147068	rs34567350
rs1652727	rs34567350	COSM147069
rs149486212	rs117848117	COSM1346180
rs12268298		

CONCLUSIONS

- These results suggest that *WDR11* rare variants are not a common cause of IHH.
- The role of this gene in the pathogenesis needs to be further investigated.

REFERENCES

1. Kim HG, Ahn JW, Kurth I, et al. *WDR11, a WD protein that interacts with transcription factor EMX1, is mutated in idiopathic hypogonadotropic hypogonadism and Kallmann syndrome.* Am J Hum Genet, 2010. 87(4): 465-79.
2. Laitinen EM, Vaaralahti K, Tommiska J, et al. Incidence, phenotypic features and molecular genetics of Kallmann syndrome in Finland.Orphanet J Rare Dis. 2011;6:41.
3. Quaynor SD, Kim HG, Cappello EM, et al. The prevalence of digenic mutations in patients with normosmic hypogonadotropic hypogonadism and Kallmann syndrome. Fertil Steril. 2011;96(6):1424-1430.
4. Izumi Y, Suzuki E, Kanzaki S, et al. Genome-wide copy number analysis and systematic mutation screening in 58 patients with hypogonadotropichypogonadism. Fertil Steril. 2014 pii: S0015-0282(14)00563-9.

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