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A novel mutation at a splice acceptor site of *WDR11* in a patient with combined pituitary hormone deficiency.

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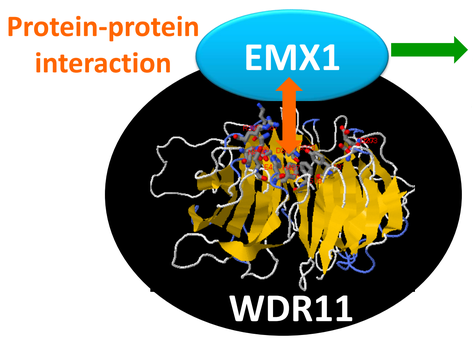
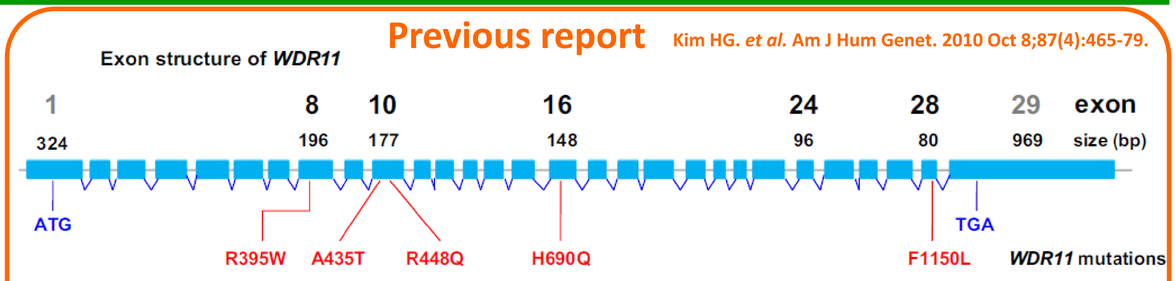
WDR11 is involved in the development of olfactory neurons by interacting with EMX1.

- ***WDR11*** **has recently been reported as one of the causative genes of isolated hypogonadotropic hypogonadism (IHH).**
- **To date, five missense mutations in *WDR11* have been identified in six patients with normosmic isolated HH (nIHH) or Kallmann syndrome (KS).**



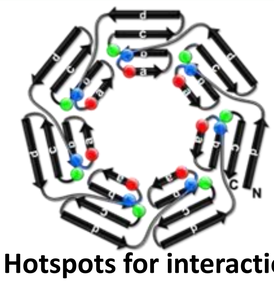
Previous report

Kim HG. *et al.* Am J Hum Genet. 2010 Oct 8;87(4):465-79.



Gender	Phenotype	Nucleotide change	Amino acid change
Male	Complete IHH	c.1183C>T	R395W
Male	Complete IHH	c.1303G>A	A435T
Male	IHH	c.1343G>A	R448Q
Female	KS	c.2070T>A	H690Q
Male	Incomplete IHH	c.3450T>G	F1150L
Female	Incomplete IHH	c.3450T>G	F1150L

Complete IHH: Complete absense of sexual development
Incomplete IHH partial pubertal development



CASE

Clinical information

【Patient】7 years old boy
【Perinatal course】Birth at 37w3d weight 3460 g (+1.9 SD) ,Caesarean delivery
Matarnal complications: PIH and GDM.
【Clinical course】
He showed apparent growth failure from 1.5 y.o. Endocrine evaluation revealed severe GHD. GH supplementation therapy from 1.11 y.o. significantly improved his growth.
At 7 years of age, he presented with micropenis.
【Physical findings】
Height 111.1 cm (-1.7 SD) Weight 30.4 kg (+1.8 SD)
Penile length 3.0 cm (-2.6 SD) Testicular volume 2.0 ml
Mild mental retardation
【Brain MRI】Pituitary malformation

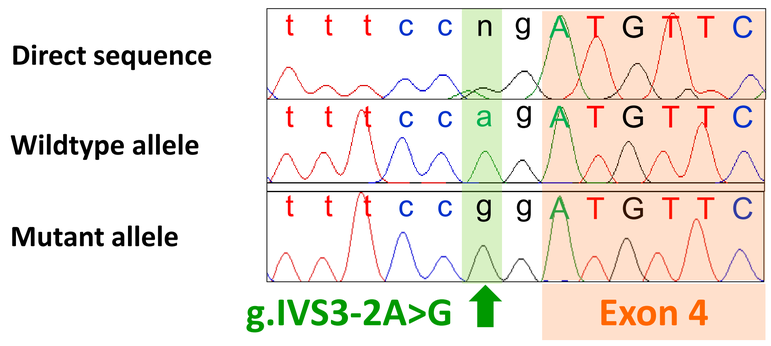
【Endocrine data】

		Stimulation	Basal	Peak	Unit
1.5 y.o	GH	Arginine		1.42	ng/ml
		Clonidine		0.62	ng/ml
7.0 y.o	IGF-1		<4.0		ng/ml
	LH	GnRH	<0.2	0.2	mU/ml
	FSH	GnRH	<0.5	2	mU/ml
	Testosterone		undetectable		ng/ml
	TSH	TRH	2.7	8.6	μU/ml
	fT_4	TRH	1.15		ng/ml
	Prolactin	TRH	4	4.9	ng/ml
	ACTH	CRH	11	28.7	pg/ml
	Cortisol	CRH	7	20.8	μ g /dl

Molecular Analysis

- The mutation was detected by systematic mutation screening of 29 known causative genes by next-generation sequencing
- Pedigree analysis
- mRNA/cDNA analyses of the mutants/variants
- *In silico* functional assessment
  WD40-repeat protein Structure Predictor
  http://wu.scbb.pkusz.edu.cn/wdsp/
- *WDR11* expression analysis in human tissues

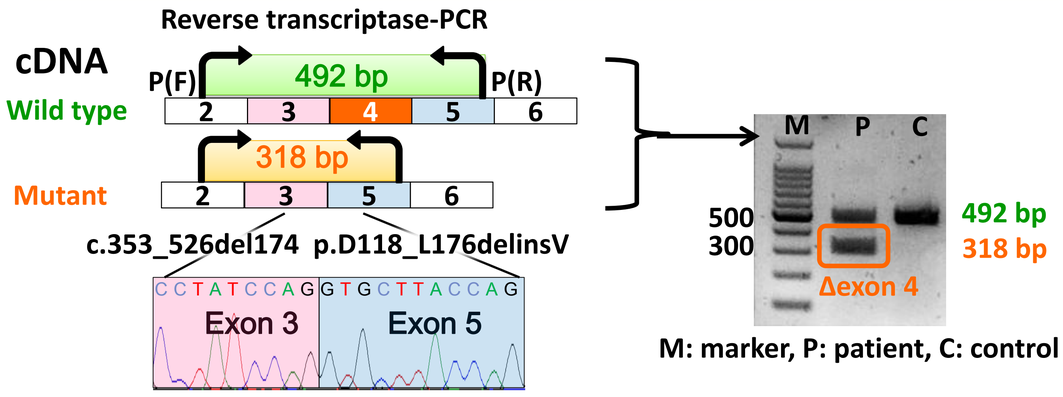
WDR11 gene sequence



- No pathogenic copy number change nor mutation in the other 28 candidate genes.

A heterozygous mutation at a splice acceptor site of *WDR11* (g.IVS3-2A>G) was identified in a male CPHD patient.

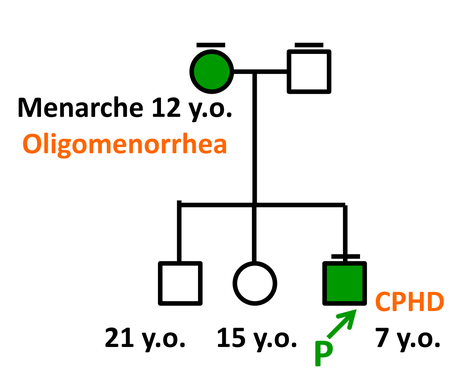
mRNA/cDNA analyses



M: marker, P: patient, C: control

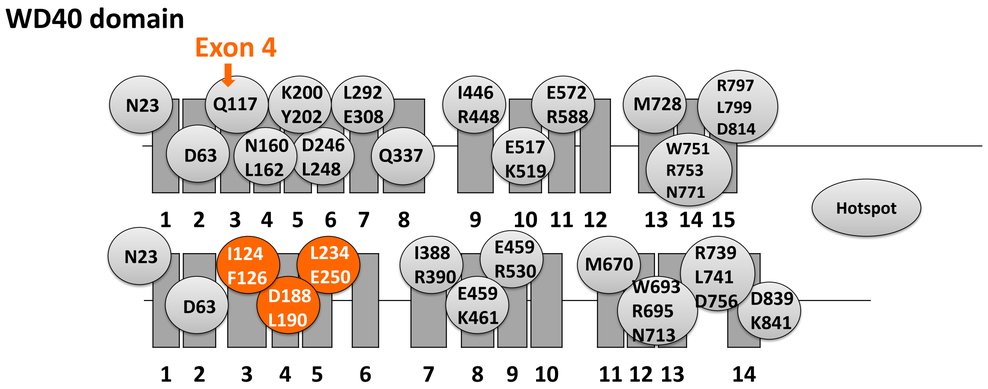
The mutation led to an inframe deletion of the entire exon 4 of *WDR11*.

Pedigree analysis



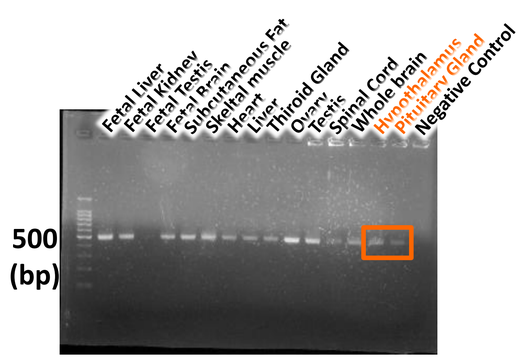
Mutation positive mother demonstrated oligomenorrhea.

Prediction of the WDR11 structures



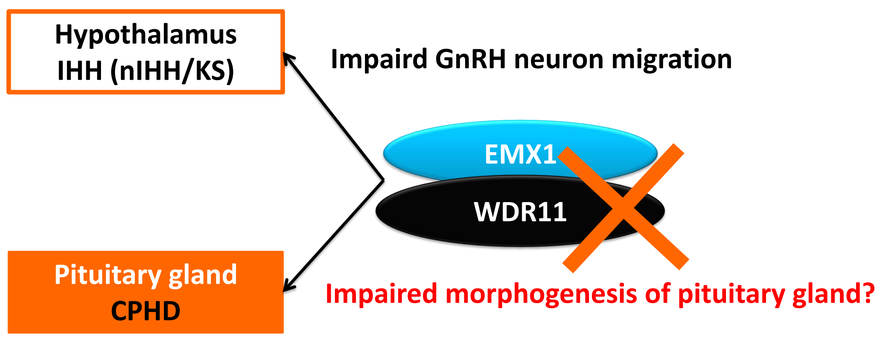
The mutant allele was predicted to encode an aberrant protein that disrupts the functionally-important WD40 domain.

WDR11 expression in human tissues



***WDR11* is expressed in not only hypothalamus but also pituitary gland.**

Discussion



Loss of function mutation in *WDR11* can impair not only hypothalamic neuron migration but also pituitary morphogenesis.

Conclusion

***WDR11* mutations can result in variable phenotypes of HH, not only IHH but also CPHD.**