Successful treatment of male congenital hypogonadotropic hypogonadism with rFSH pretreatment followed by GnRH

Haruo Mizuno[1]; Kohei Aoyama[1]; Shinji Saitoh[1]

[1]*Nagoya City University Graduate School of Medical Sciences, Department of Pediatrics and Neonatology, Nagoya, Japan*

【Background 】 Congenital hypogonadotropic hypogonadism (CHH) is a group of rare disorders responsible for insufficient secretion of the pituitary gonadotropins LH and FSH. We have observed CHH in men with poorer responses to human chorionic gonadotropin (hCG), or combined FSH and hCG for testicular maturation and fertility after adolescence. Dwyer AA et al. rFSH pretreatment followed by GnRH is successful in inducing testicular growth and fertility in men with CHH with prepubertal testes (J Clin Endocrinol Metab. 2013 Nov;98(11):E1790-5.). However, they could not divide the subgroup according to genotype.

【Objective 】The purpose of this research is to clarify how best to tailor-make treatment according to the genotype by retrospectively analyzing the results of a treatment method based on exact gene diagnosis. rFSH pretreatment may become a successful means of treatment for men with CHH.

【Method】We investigated the clinical course of 11 male patients (aged 4-25 years) with CHH, including eight patients with Kallmann syndrome and two patients with CHARGE syndrome. All male patients with CHH were subjected to mutation assessment in 48 CHH-associated genes, using Ion Torrent next-generation sequencing. We then confirmed these mutations using Sanger sequencing.

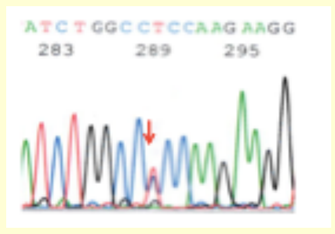
【Patients】

Patients	Age (years)	Clinical diagnosis
1	25	CHARGE syndrome
2	21	Kallmann syndrome
3	20	Kallmann syndrome
4	19	Kallmann syndrome
5	19	Kallmann syndrome
6	17	Kallmann syndrome
7	15	Kallmann syndrome
8	13	CHARGE syndrome
9	7	Kallmann syndrome
10	4	Idiopathic CHH
11	4	Kallmann syndrome

【next-generation sequencing】

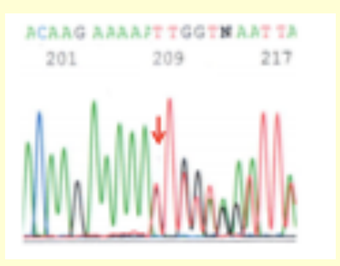
Patients	gene	mutation	In silico evaluation
4	*FGFR 1*	c.1846T>C; p.Ser616Pro	Polyphen2 : possibly damaging, SIFT : deleterious
7	*CHD7*	c.5192T>C; p.Leu1731Pro	Polyphen2 : possibly damaging, SIFT : deleterious
8	*CHD7*	c.7321delG; p.Val2441fs	
9	*KAL1*	c.1449+1G>A	Human Splicing Finder : Broken WT Donor Site
11	*KAL1*	Xp22.31(8501017-8507861) :Copy Number 0	

4

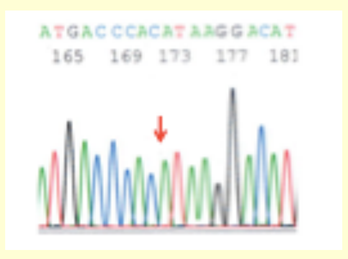


7

8



9



【Results】Seven of the patients had bilateral cryptorchidism and micropenis, and three patients had micropenis only. All patients had no olfactory blub. Abnormal delay of secondary sexual characteristics was noted in the seven patients older than 15 years, who revealed no response in the hCG test. We discovered *KAL1, FGF1R* and *CHD7* mutations during the study. In one adolescence man (Patient 4) with Kallmann syndrome and *FGF1R* mutation, testicular maturation was absent during continuous hCG injections for 6 months. His testes volume was <1 ml. We administered rFSH 75 IU sc daily for 2 months, following which hCG 1000 IU sc and rFSH 75 IU sc were administered every other day. Consequently, his testes became larger and his serum testosterone value reached a normal range.

【Conclusions】rFSH pretreatment followed by GnRH may be useful in enhancing testicular growth in men with CHH including Kallmann syndrome. However, further studies are needed to clarify whether rFSH pretreatment results in fertility.