PEDIGREE ANALYSIS IS ESSENTIAL FOR CLARIFYING OLIGOGENIC TRANSMISSION IN A FAMILY WITH CONGENITAL HYPOGONADOTROPIC HYPOGONADISM (CHH)

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INTRODUCTION

- CHH is a rare disease with a complex clinical picture and genetic background.
- In up to 50% genetic mutations are found.

CASE PRESENTATION

- At the age of 16 years a boy presented at our clinics with delayed puberty.
- By LHRH and HCG testing hypogonadotropic hypogonadism was diagnosed.
- The patient's personal and family history showed many **symptoms of complex CHH:**

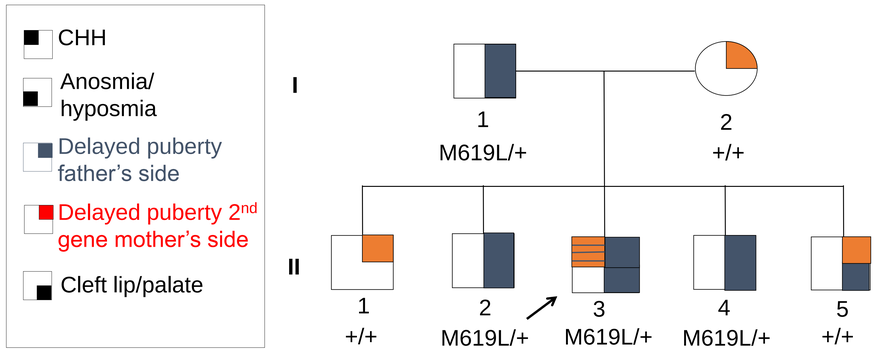

Figure 1: Two-generations' pedigree

Son	II 1	II 2	II 3	II 4	II 5
Year of birth	1989	1991	1994	1997	2005
Hearing loss	?	?	**deafness**	?	(+)
Testes	Normal	Retractile testes	Retractile testes	Sliding testis	Normal
Oligodontia	Normal	Normal	**+**	+	+
Kidneys	?	?	?	Renal duplication	?
Hypertelorism	?	?	+	?	+
Skeletal	?	?	Short L 4th finger	?	Brachydactyly

Table 1 : Symptoms of the five sons

RESULTS

- Genetic tests showed a **monoallelic loss-of-function *NOS1* mutation (M619L/+)** in the father and the three middle sons (fig. 1), consistent with an **autosomal dominant mode of inheritance.** No genetic mutation was found in the other sons and in the mother with delayed puberty**.** Caused by the **oligogenic mode of inheritance** only our patient had CHH.
- NOS1 codes for the neuronal nitric oxide synthase and stimulates GnRH release via the sGC-cGMP pathway by NO production in a dose-dependent manner. nNOS neurons regulate beside other central nervous functions the reproduction. [1]
- In mice, during minipuberty, nNOS reduces the transcription of GnRH expression at the level of the promoter. [2]
- Total loss of nNOS catalytic activity (i.e. deletion of the heme-binding domain of nNOS) results in hypogonadotropic hypogonadism. [3]

CONCLUSIONS

- Next to a detailed history and physical examination pedigree drawing is essential for determining the likely mode of transmission. [4]
- NOS1 mutation has been suggested to be pathogenic if oligogenic. [5]
- Studies are underway to causally treat gonadal insufficiency with the NOS inhibitor, in a cryptorchid mouse model [6], so that knowledge of this mutation found is important for offspring of this family.

METHODS

- Segregation analysis of the family
- Whole exome sequencing
- Assessment of NOS1 mutants' activity by their ability to promote nitrite and cGMP in vitro.

CONTACT INFORMATION

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