16 ﻿ ABSTRACTS OF THE 27TH MEETING OF THE BELGIAN ENDOCRINE SOCIETY

A compound heterozygous mutation in the luteinizing hormone/chorionic

gonadotrophin receptor gene leading to Leydig cell hypoplasia type 1

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**Introduction**: Male sexual differentiation depends on

proper signaling via the luteinizing hormone/chorionic

gonadotrophin receptor (LHCGR). When stimulated

by the human chorionic gonadotrophin (hCG) in early

fetal life and afterwards by LH, the LHCGR will induce

testosterone synthesis, which is necessary for the differentiation

of male internal and external genitalia. An

impaired LHCGR will disturb the normal male sexual

differentiation. This will lead to Leydig cell hypoplasia

type 1 with a female phenotype at birth (46,XY Disorder

of Sex Development - DSD) in case of complete inactivation

of the receptor or to Leydig cell hypoplasia

type 2 presenting with male external genital anomalies

ranging from micropenis to hypospadias for incomplete

inactivations. Inactivating mutations of the *LHCGR* are

very rare and so far, only around 20 cases of Leydig cell

hypoplasia type 1 have been reported.

**Aim of the work**: To study a case of Leydig cell hypoplasia

type 1 caused by a compound heterozygous *LHCGR*

mutation and to reveal the mechanisms by which these

mutations lead to a female phenotype in a 46,XY patient.

**Methods**: Sequencing of the *LHCGR* gene was done.

Functional studies were performed after transfection of

HEK293 and HeLa cells with the mutant and wild-type

(WT) *LHCGR* genes. Generation of cAMP was measured.

Membrane and intracellular localizations of the

mutant receptors were analyzed by flow cytometry and

immunocytochemistry. Endoplasmic reticulum (ER)

stress was also assessed.

**Main results**: A novel compound heterozygous

mutation of the *LHCGR* gene was identified: a 4 amino

acid deletion (delLHCGR) on the paternal allele and a 9

amino acid duplication (dup LHCGR) on the maternal

one. Both mutations were located in the region coding

for the signal peptide of the LHCGR.

cAMP generation was significantly reduced for the

mutant receptors compared to WT. Flow cytometry and

immunocytochemistry studies showed that the dupLHCGR

had reduced membrane expression, though found

intracellularly, whereas the delLHCGR had a very low

both membrane and intracellular expression. ER stress

assays revealed a slightly higher ER stress induced by

the abnormal dupLHCGR, whereas ER stress was significantly

lower than that of the WT LHCGR in the case

of the delLHCGR.

**Conclusions**: We report a novel case of Leydig cell

hypoplasia type 1 in a patient with a compound heterozygous

mutation of the *LHCGR* gene. Our studies

reveal different mechanisms of LHCGR dysfunction for

the two mutants – the delLHCGR is probably barely

translated, whereas the dupLHCGR is most likely synthesized,

but its intracellular trafficking is impaired. This

is of particular interest as both mutations are located in

the region coding for the signal peptide, whose main

function is to target nascent proteins to the ER. Our

study therefore illustrates that different mutations in the

signal peptide of the same protein can impair protein

function by inducing different intracellular anomalies.