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A De Novo Heterozygous Nonsense Variant In The SEC31A Gene Associated With Pituitary Hormone Deficiency And Disorders Of Sex Development.

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Introduction: XYdisorders of sex development (DSD) result from variants in many different human genes but frequently have no detectable molecular cause. In approximately 25% of cases of XY DSD, the index case may have associated malformations. Genetic disorders of endoplasmic reticulum (ER) function are increasingly being recognised but have not been associated with DSD or pituitary disorders.

Clinical case: Three siblings (with unaffected non-consanguineous parents) were reviewed at the tertiary endocrine clinic. Child I was noted at birth to have cliteromegaly. Imaging and examination under anaesthetic revealed a normal vagina and uterus but gonads of

indeterminate origin. She was 46,XY and basal endocrine investigations at the age of 4 years showed a low AMH for male but otherwise normal gonadal and thyroid function and normal IGF-1. She had a laparoscopic bilateral gonadectomy aged 5 years. Pathology demonstrated bilateral testicular tissue, with substantial fibrotic atrophic change and occasional placental alkaline phosphatase (PLAP) positive cells, suggestive of germ cell tumours. Aged 8 years she developed obesity and later hypertension. Child II was reviewed due to short stature and diagnosed with GH deficiency aged 2 years. She has normal adrenal and thyroid function and gonadotrophins. MRI demonstrated an ectopic posterior pituitary. Child III presented with perineal hypospadias, a small phallus, bilateral undescended testes and craniofacial abnormalities. Endocrine investigations revealed hypogonadotrophic hypogonadism, with no testosterone response to hCG stimulation, a low normal AMH and no response of LH or FSH on LHRH stimulation. He has panhypopituitarism with an ectopic posterior pituitary gland on MRI and is currently on treatment with GH, hydrocortisone and levothyroxine. His BP is on the 98th centile for age and height. Child I and Child III have mild developmental delay but are in mainstream school with additional educational support. High-throughput DNA sequencing revealed, in all three siblings, a heterozygous truncating variant in the SEC31A gene that encodes a component of the COPII-complex that coats the vesicles mediating ER to Golgi transport. CRISPR-Cas9 targeted knockout of the corresponding Sec31a region resulted in embryonic lethality in homozygous mice. mRNA phenotyping of ER-related genes demonstrated increased mRNA expression of ATF4 and CHOP in the affected children, genes encoding key ER stress-related proteins, associated with defective protein transport.

Conclusions: Dysregulation ofanterograde and retrograde COPII-coated-vesicle ER-Golgi transport is increasingly recognised to underlie human developmental disorders, including Craniolenticulosutural dysplasia (OMIM 607812) and Saul-Wilson syndrome (OMIM 618150). The de novo SEC31A nonsense variant in all three affected siblings, the ER stress response, plus reported developmental syndromes with dysfunction of this transport mechanism and evidence from the preclinical mouse model suggest that SEC31A might underlie a previously unrecognised clinical syndrome comprising DSD, endocrine abnormalities, dysmorphic features and developmental delay.

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