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Original Research

CCDC149: a novel gene associated with hypopituitarism and neurodevelopmental impairment

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Abstract

Objective & Design **Congenital Hypopituitarism (CH) is a complex developmental disorder characterized by variable pituitary dysfunction that is often associated with midline structural abnormalities that affect the brain, eyes and face. To date, only ∼10%-15% of patients have an underlying molecular basis.**

Methods **Next generation sequencing was conducted on a subset of CH patients with no known genetic aetiology. Human embryonic brain tissue sections were used to generate an expression profile, and a knock-out mouse model was generated using CRISPR-Cas9 gene editing and phenotypically analysed.**

Results **Two novel homozygous frameshifts in *CCDC149*, p.Gly278* and p.Leu222*, were identified in two unrelated CH pedigrees (three patients), respectively. Patient phenotypes included growth hormone deficiency (GHD), hypogonadotropic hypogonadism, and developmental delay/autism. Severe scoliosis was present in one pedigree, with a small anterior pituitary on MRI in the other. Human embryonic *CCDC149* was localized to the developing hypothalamo-pituitary region at Carnegie stages 16-23, and *Ccdc149*-null mice recapitulated patient phenotypes, including growth impairment and reduced fertility compared with wild-type littermates.**

Conclusions **Our study is the first to report *CCDC149* variants in association with CH. Previous studies in *C.elegans* report *CCDC149* orthologue expression in the basal bodies of ciliated neurons, supporting the possibility of impaired ciliary function as an underlying mechanism in this complex disorder.**

Keywords congenital hypopituitarism, neurodevelopment, neuroendocrinology, growth, *CCDC149*

Significance

We have identified recessive truncations in the *CCDC149* gene in two unrelated families with congenital hypopituitarism and neurological defects. Human expression and murine functional studies highlight the critical role of CCDC149 in hypothalamo-pituitary development and function, regulating growth, fertility and neurodevelopment. We report the first association of *CCDC149* with the phenotype of Congenital Hypopituitarism (CH), suggesting a novel ciliary-related mechanism in the pathogenicity of the disease with associated neurodevelopmental impairment. We suggest that this gene should be considered for sequencing in patients with CH, especially in those with growth hormone deficiency associated with hypogonadotropic hypogonadism.

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Introduction

Congenital hypopituitarism (CH) is a highly variable, debilitating, life-threatening disorder requiring extensive evaluation and rapid, often life-long, treatment.[1] CH is characterized by deficiencies of one (classically Isolated Growth Hormone Deficiency; IGHD) or more (Multiple Pituitary Hormone Deficiencies; MPHD) pituitary hormones. The disorder results from abnormal development of the hypothalamus and pituitary. CH may be associated with a spectrum of complex disorders associated with significant morbidity/mortality, such as septo-optic dysplasia (SOD), holoprosencephaly and pituitary stalk interruption syndrome, amongst others.[2]

Studies performed over the last 35 years have partially unravelled the molecular mechanisms underlying CH.[2-4] Much of the evidence for human hypothalamo-pituitary development has been transposed from animal models, given that the process is highly conserved across all vertebrates. The pituitary gland derives from the oral ectoderm (early anterior pituitary) and the overlying neural ectoderm (early posterior pituitary). In humans, the pituitary placode thickens around 4-6 weeks of gestation, to form the oral ectoderm, which invaginates to form Rathke's pouch (the primordium of the anterior pituitary). Sequentially, temporal and spatial expression of a cascade of signalling molecules and transcription factors give rise to the cell proliferation, patterning, and differentiation of anterior pituitary hormone secreting cells.[3,5]

Whilst the initial genetic variants associated with MPHD were identified in classical transcription factors including *POU1F1*, *PROP1*, *HESX1*, *SOX2*, *SOX3*, *LHX3*, and *LHX4,*[6] several studies have identified perturbations in multiple molecular pathways in rare forms of CH.[7] These include translation initiation, spliceosome formation, ciliogenesis, and fatty acid metabolism.[8-12] Nevertheless, pathogenic variants have been identified in only 10%-15% of CH patients,[13] in spite of the advent of next generation sequencing (NGS).

Over 50% of known CH genes are dominant, with incomplete penetrance and variable expressivity giving rise to highly variable phenotypes within families, suggesting interactions between genetic and environmental factors. Furthermore, oligogenicity is described in some cases, where more than one gene is implicated in the aetiology.[13] The majority of CH cases remain unsolved,[3] largely due to genetic heterogeneity and a lack of funding for NGS in a large number of patients, that may identify novel genetic causes.

Here we report two novel homozygous frameshifts in *CCDC149* in two unrelated pedigrees with hypogonadotropic hypogonadism (HH), growth hormone deficiency (GHD), and neurodevelopmental delay. Previous limited studies of the *CCDC149* orthologue in *C.elegans* have shown expression in ciliary basal bodies and along the dendrite of ciliated neurons.[14]

Methods

Whole exome sequencing

Whole exome analysis was performed on DNA samples extracted from whole blood taken from Pedigree I. Exonic sequences from DNA were enriched with the xGen Exome Research Panel v2.0 with or without the xGen Human mtDNA Research Panel v1.0 (IDT). Analysis of FASTQ files was performed by Genoox, against the human genome assembly hg19 (GRCh37) reference sequence. The results of both siblings and their father were confirmed by Sanger sequencing. This pedigree attended an endocrine clinic (Poria, Israel) and was not part of a distinctive CH cohort.

Research targeted gene panel

The DNA from Patient 3 was analysed on our established targeted CH-gene panel at UCL GOS ICH (unpublished). Library preparation, sequencing and bioinformatic analysis generating VCF files, were performed by our in-house service "UCL Genomics". The variant calling was performed using Qiagen Clinical Insights, with strict filtering criteria, eg, variants with a $<0.01\%$ frequency in the control gnomAD database (https://gnomad.broadinstitute.org). The whole exome of 135 genes was sequenced in 140 patients (~10% were consanguineous) with variable CH phenotypes including IGHD, hypogonadotropic hypogonadism (HH), SOD and MPHD.

Human embryonic gene expression analysis

In situ hybridization was performed as previously described[15] on human embryonic brain tissue sectioned through the hypothalamo-pituitary region, from Carnegie stages (CS) 16, 19, 20, and 23 respectively. A purified pBluescriptR vector containing full-length human wild-type *CCDC149* cDNA (IMAGE ID: 4792817) (Source Bioscience) was used to make antisense and sense digoxigenin-labelled RNA probes. Restriction enzymes (XhoI and ApaI) were used for linearizing plasmids, and RNA probes were purified using Chroma Spin + TE −100 DEPC- H_2O columns (Clontech) with1 µL of RNA inhibitor added.

Single-cell transcriptomics of developing human hypothalamus and adult mouse hypothalamus

Single-cell RNA sequencing (scRNA-seq) analysis of *CCDC149/Ccdc149* and ciliary genes was performed using publicly available single-cell datasets on developing human hypothalamus[16] (GSE169109) and pituitary,[17] and adult mouse hypothalamus[18] (GSE87544) and pituitary[19] (GSE146619). Briefly, single-cell clusters and gene expression plots (Uniform Manifold Approximation and Projection (UMAP), and DotPlot) were generated using the standard Seurat single-cell analysis package (v5.1.0)[20] in R. A human pituitary dataset was analysed using the R shiny webpage.

Body weight phenotyping

Animals were weighed weekly from post-weaning from 4 weeks (P28) to adults (P70) using an analytical balance.

Reproductive phenotyping

Adult mice over 2-3 months of age were bred for ~6 months to assess sex-specific fertility. Mutants were bred with

heterozygotes as they exhibited a normal reproductive phenotype and wild-type by wild-type mating was used as controls. The number of litters, pups born, and pups that survived were recorded to assess the overall fertility phenotype. See material for additional information on the generation of *Ccdc149*$^{-/-}$ mutants.

Results

CCDC149 variants cause congenital hypopituitarism and developmental delay

Pedigree I: patients 1 and 2

A novel homozygous frameshift variant in *CCDC149* (ENST00000635206.3), Chr 4 :24,831,624 (GRCh38) c.832G > T, p.Gly278*, absent from the gnomAD database (ACMG: PM2) and predicted to be pathogenic (CADD score = 40), was identified in two siblings, a female (Patient 1) and male (Patient 2), of Israeli Arab origin born to consanguineous parents with HH, neurodevelopmental delay and severe scoliosis (Figure 1). No additional genetic variants were documented in the WES analysis of Pedigree I that segregated or were considered as contributing towards the phenotype.

At 19 months of age, Patient 1 presented with global developmental delay, with a neurodevelopmental age of 14-15 months, manifesting both motor and speech delay. Despite a recommendation for endocrine review following this initial assessment, Patient 1 first presented in clinic at 15.5 years of age with short stature (Height −5.21SDS, Weight −3.23 SDS) and delayed puberty (Table 1). She was diagnosed with GHD [peak GH 2 mcg/L and 0.2 mcg/L on Arginine and Clonidine stimulation tests respectively, IGF1 57.1 ng/mL (NR 117-323)] and commenced GH (0.033 mg/kg/day) treatment at 16.5 years of age. She was prepubertal and diagnosed with HH following a GnRH test (FSH <0.3 IU/L, LH <0.07 IU/L, Estradiol <11.8 pg/mL) and was commenced on a low dose of oestrogen (0.125 of a 50 mcg Evorel patch). Other endocrine values were within the normal range (Table 1). The GH dose was gradually increased to 0.037 mg/kg/day with close monitoring of growth and IGF1 concentrations.

During the first year of therapy, her height increased by 5 cm (Figure 2), and her Tanner stage progressed to B3 P4 despite being on a low oestrogen dose, with a bone age of 13 years. Rapidly progressive scoliosis was observed after 18 months of therapy, with increasing shoulder asymmetry noted over a 3-month period (Cobb angle 67 degrees). GH therapy was ceased at 18.3 years and spinal surgery was performed to correct her severe scoliosis at 18.8 years, adding a further 4 cm to her height, with a final height of 143.3 cm (−3.37 SDS). Oestrogen replacement was increased to accommodate ongoing pubertal induction. Ophthalmological evaluation revealed intermittent alternating esotropia with strabismus (at 4 years of age), and hypermetropia. An MRI was performed at the age of 16 years and was reported to show normal brain anatomy, including a normal pituitary gland in size, shape and location, with a centrally located stalk. The posterior pituitary was not demonstrated. Contrast injection revealed a hypointense focus around 2.5 mm in size, possibly consistent with a microadenoma. A neurosurgical review concluded that the study was normal.

At 4 years and 11 months, Patient 2 had a neurodevelopmental assessment which showed moderate global developmental delay, especially in social and language skills. Cognitive abilities were noted as low for age; however no formal cognitive assessment was performed, and he required special education. Physical examination at 4 years of age revealed a micropenis. He first presented in the endocrine clinic at 19 years of age with short stature (Height −4.54 SDS, Weight 0.76 SDS) and a bone age of 15 years. He had no signs of puberty and a GnRH test was consistent with a diagnosis of hypogonadotrophic hypogonadism (LH <0.07 IU/L, FSH <0.3 IU/L, testosterone 0.12 nmol/L) (Table 1), with 2 mL testes present in the scrotal sac bilaterally, a penile length of ∼4 cm, and Tanner stage 3 pubic hair. Other endocrine values were within the normal range (Table 1). He had a similar phenotype to his sister, albeit with obesity and marked acanthosis nigricans (normal OGTT – 2 hr glucose 125 mg/dL). In view of his relatively advanced bone age (15 years), pubertal induction was commenced in Patient 2 with monthly intramuscular low dose (50 mg) Depot Testosterone.

A diagnosis of GHD was made at age 19.8 years (peak GH 2 mcg/L; IGF1 38.8 ng/mL (NR 98.7-289)) and GH therapy commenced in the hope of maximizing remaining growth (Figure 2). After 9 months of therapy, 5 cm of growth had been attained and pubertal stage had progressed to P4 with penile growth. In the following 4 months, no further growth was observed, but scoliosis had developed and progressed, similarly to his sister, and GH therapy was ceased at 21.4 years of age. He reached a final height of 150.2 cm (−3.68 SDS). He underwent spinal surgery to correct his severe scoliosis at 21.7 years. He has left esotropia with strabismus (diagnosed at age 1 year) and hypermetropia. An MRI performed at age 19 revealed a normal pituitary gland with a Chiari type 1 malformation.

Pedigree II: patient 3

A novel homozygous frameshift variant in *CCDC149* (ENST00000635206.3), CHR 4: 24,836,491 (GRCh38), c.665T > A, p.L222*, absent on the gnomAD database (ACMG: PM2) and predicted to be pathogenic (CADD score = 38), was identified in a male patient of Yemeni origin born to 1st degree consanguineous parents, with HH, autism and global developmental delay (Table 1). The patient initially presented with poor feeding, a small phallus, and testes that were at the proximal end of the inguinal canal on ultrasound (R 0.12 mL, L 0.13 mL at 7 months). At the age of 14 months, he had a height of −3.76 SDS, with a weight of −0.08 SDS. A diagnosis of GHD was made on a stimulation test (baseline GH 0.3 mcg/L, peak GH 1.4 mcg/L) with an IGF1 of 17 ng/mL (NR 28.0-156.0). Treatment with Levothyroxine (50 µg once daily (4.5 µg/kg/day)) and GH (32 µg/kg/day) was commenced (see Table 1 for all endocrine values). He underwent a right orchidopexy at 16 months of age. His ophthalmological evaluation was normal apart from astigmatism. He had an MRI at the age of 1.6 years showing a globally small anterior pituitary gland, with an otherwise normal brain appearance (Figure 1B). Eosinophilic oesophagitis was diagnosed at the age of 2 years and resolved at the age of 7. At 11 years, he maintained a small phallus and 2 mL testicular volumes bilaterally, with no evidence of pubic hair. A GnRH stimulation test was performed at 11 years and 5 months, and subsequently at 11 years and 10 months. On administration of Gonadorelin, peak FSH was 2.4 mU/L and 2.2 mU/L, and peak LH was 1.5 mU/L and 1.4 mU/L, respectively. Testosterone was undetectable during both tests (<0.4 nmol/

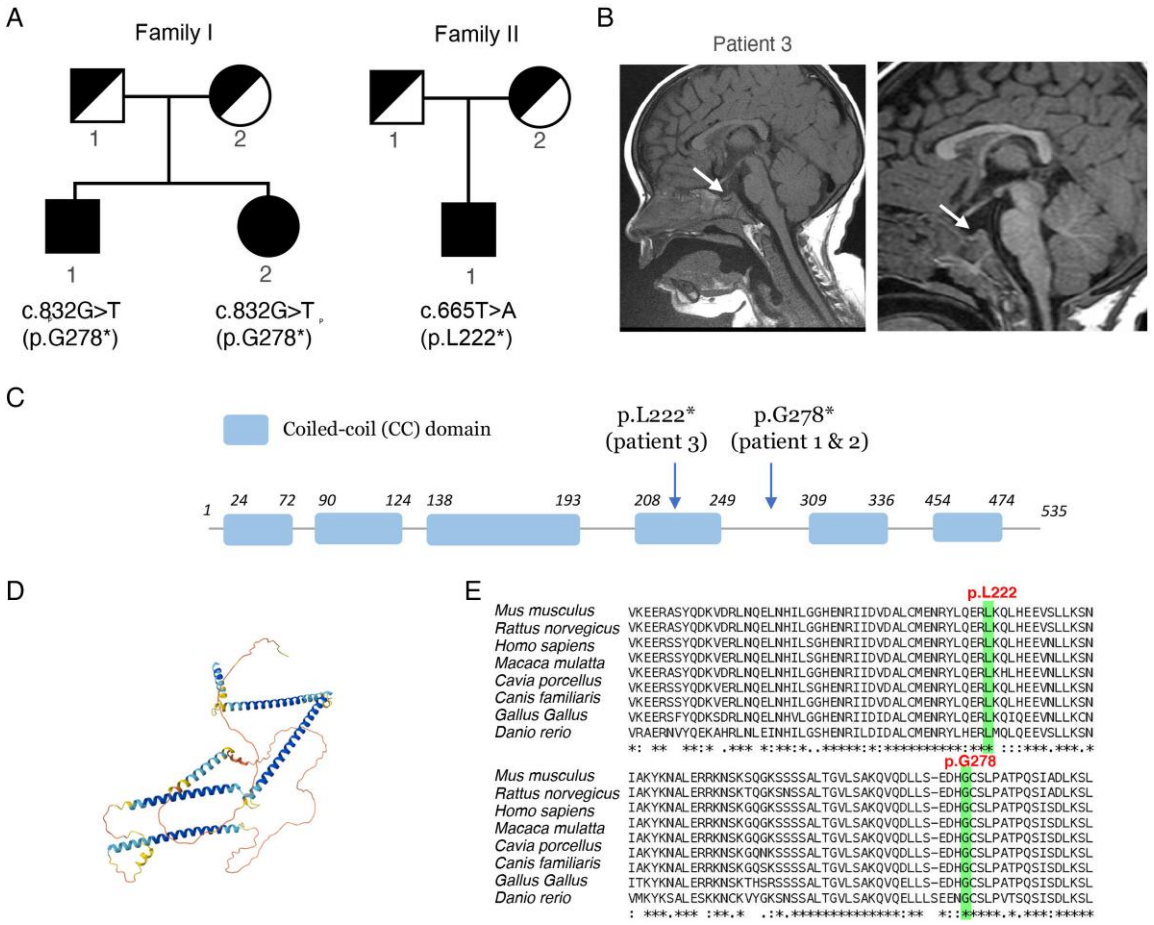

Figure 1 (**A**) *CCDC149* variants in patients with congenital hypopituitarism. Pedigrees illustrating affected patients carrying homozygous frameshifts in *CCDC149*. Variants within each pedigree are shown under each symbol. (**B**) Brain MRI images illustrating a globally normal brain phenotype with a smaller anterior pituitary gland (arrows) in Patient 3. (**C**) Protein structure of CCDC149 illustrating the locations of coiled-coil domains and the locations of two nonsense variants introducing stop codons. (**D**) Protein structure predicted by AlphaFold illustrating coiled-coil domains. (**E**) The two variants identified are within conserved sites in CCDC149 across multiple species suggesting that these sites are crucial for protein function, structure or stability.

L). He was commenced on Depot testosterone (Sustanon) for pubertal induction at the age of 12 years. At 15 years and 7 months his height was 155.2 cm (−2.1 SDS) with a weight of 40.25 kg (−2.3 SDS) (Figure 2). He has not yet reached his final height.

Additionally, three further variants of unknown significance were identified in Patient 3, among the 135 genes sequenced (Figure S1). Although we cannot rule out their contribution to the phenotype, these genes are usually associated with different phenotypic features that are not present in the patient. We therefore predict that the homozygous *CCDC149* variant is the likely pathogenic cause of the CH in this patient.

Both *CCDC149* variants were validated using VariantValidator (https://variantvalidator.org/) according to HGVS nomenclature.

Developmental and adult expression of *CCDC149*

There are limited studies investigating functional roles of *CCDC149* and, to date, there are no published reports on the developmental and spatiotemporal expression of *CCDC149.* Analysis of the Human Protein Atlas (https://www.proteinatlas.org/) revealed that *CCDC149* is expressed in different brain areas, including the hypothalamus, cerebral cortex, cerebellum, basal ganglia, various endocrine glands (pituitary, adrenal) and the gonads (testes and ovary) (Figure S2), suggesting widespread roles in the central and peripheral regulation of hormones and physiological processes.

We next examined the developmental expression of *CCDC149*. Analysis of publicly available single-cell datasets revealed that *CCDC149* is expressed during human hypothalamic (Figure 3A-B) and pituitary (Figure S3A-C) development, and in the adult mouse hypothalamus (Figure 4A-C) and pituitary (Figure S3D-F). We assessed cell-type-specific enrichment of genes associated with primary and motile cilia and their relationship with CCDC149. We found that *CCDC149* and genes associated with primary cilia (eg, *ARL13B*) were expressed in most cell types, whereas genes associated with motile cilia (eg, *DNAH5*), not *CCDC149*, were highly enriched in ependymal cells (Figure 3B-C); specialized ciliated glial cells involved in the production and circulation of CSF.[21] Analysis of single-cell clusters showed that *CCDC149/Ccdc149* is expressed across multiple cell types but enriched in neurons in developing and adult hypothalamus (Figures 3B, D and 4C).

Table 1 Clinical and hormonal phenotype of the patients included in this study with *CCDC149* variants.

	Pedigree I		Pedigree II
Patient	**1**	**2**	**3**
***CCDC149* Variant(ENST00000635206.3)**	c.832G > T p.G278*	c.832G > T p.G278*	c.665T > A, p.L222*
Ethnic origin	Israeli Arab	Israeli Arab	Yemeni
Sex	Female	Male	Male
Age at testing (years)	15.3	19.8	14 months
Height SDS	−5.21	−4.54	−3.76
Weight SDS	−3.23	0.76	−0.08
BMI SDS	0.27	1.78	3.06
GH peak, µg/L	2.0	2.0	1.4
Cortisol peak, nmol/L	515	468	871
ACTH pg/mL	30.8	35.3	16.9
NR	0-46	0-46	0-46
FT4, pmol/L	14.27	14.68	10.6
NR	11.5-22.7	11.5-22.7	10.0-19.8
TSH, mU/L	1.98	3.29	1.3
NR	0.4-4.2	0.4-4.2	0.7-6.0
IGF1, ng/mL	57.1	38.8	18.0
NR	117-323	98.7-289	28.0-156.0
IGFBP3, mg/L	2730	Not measured	Not measured
NR	2900 - 7300	-	-
FSH, IU/L	<0.3	<0.3	0.60
NR	1-5	1.4-18.1	<2.70
LH, IU/L	<0.07	<0.07	<0.1
NR	1-18	1.5-9.3	<3.2
Estradiol pg/mL	<11.8	N/A	N/A
Testosterone nmol/L	N/A	0.12	<0.40
ProlactinmU/L	132	57.2	105
NR	59.5-621	44.7-376.6	86-324
Neurology	Global Neurodevelopmental delay	Global Neurodevelopmental delay	Global Neurodevelopmental delay and autism
Ophthalmology	Intermittent alternating esotropia strabismus, hypermetropia	Left esotropia strabismus, hypermetropia	Healthy, normal examination. Astigmatism, wears glasses
Other	Severe scoliosis	Severe scoliosis	-

CCDC149/Ccdc149 was sparsely expressed across all pituitary cell types with no cell-specific enrichment.

To further validate single-cell expression data and to determine the expression of *CCDC149* across human embryonic development, we performed in situ hybridization which revealed *CCDC149* mRNA transcripts in the developing hypothalamus, Rathke's pouch, and trigeminal ganglia in human embryonic tissue sections from all four Carnegie stages examined; CS16, CS19, CS20, and CS23 respectively (Figure 3E). Neuronal enrichment of Ccdc149 is consistent with previous studies in *C. elegans* that demonstrated expression of *Ccdc149* in most ciliated neurons as well as pharyngeal neurons, touch receptor and motor neurons.[14] Altogether, these observations suggest that CCDC149 could be localized to primary cilia and have a plausible role in neuronal development, differentiation, and signalling.

Ccdc149-knockout mice display suboptimal growth and infertility

To investigate the role of *Ccdc149* in the development and function of the hypothalamo-pituitary axis, a mutant mouse lacking *Ccdc149* using CRISPR gene editing technology was generated at MRC Harwell (Figure 4D-F). Mice homozygous for the *Ccdc149*-knockout allele ($Ccdc149^{-/-}$) were viable and had the expected Mendelian frequency resulting from heterozygous breeding pairs (data not shown). Heterozygous mice appeared phenotypically normal and fertile. However, homozygous mutants exhibited markedly reduced growth compared with wild-type ($Ccdc149^{+/+}$) and heterozygous ($Ccdc149^{+/-}$) littermates (Figure 5A-B). Measurements of body weights at late juvenile stage to adulthood revealed that both male and female mutants had a

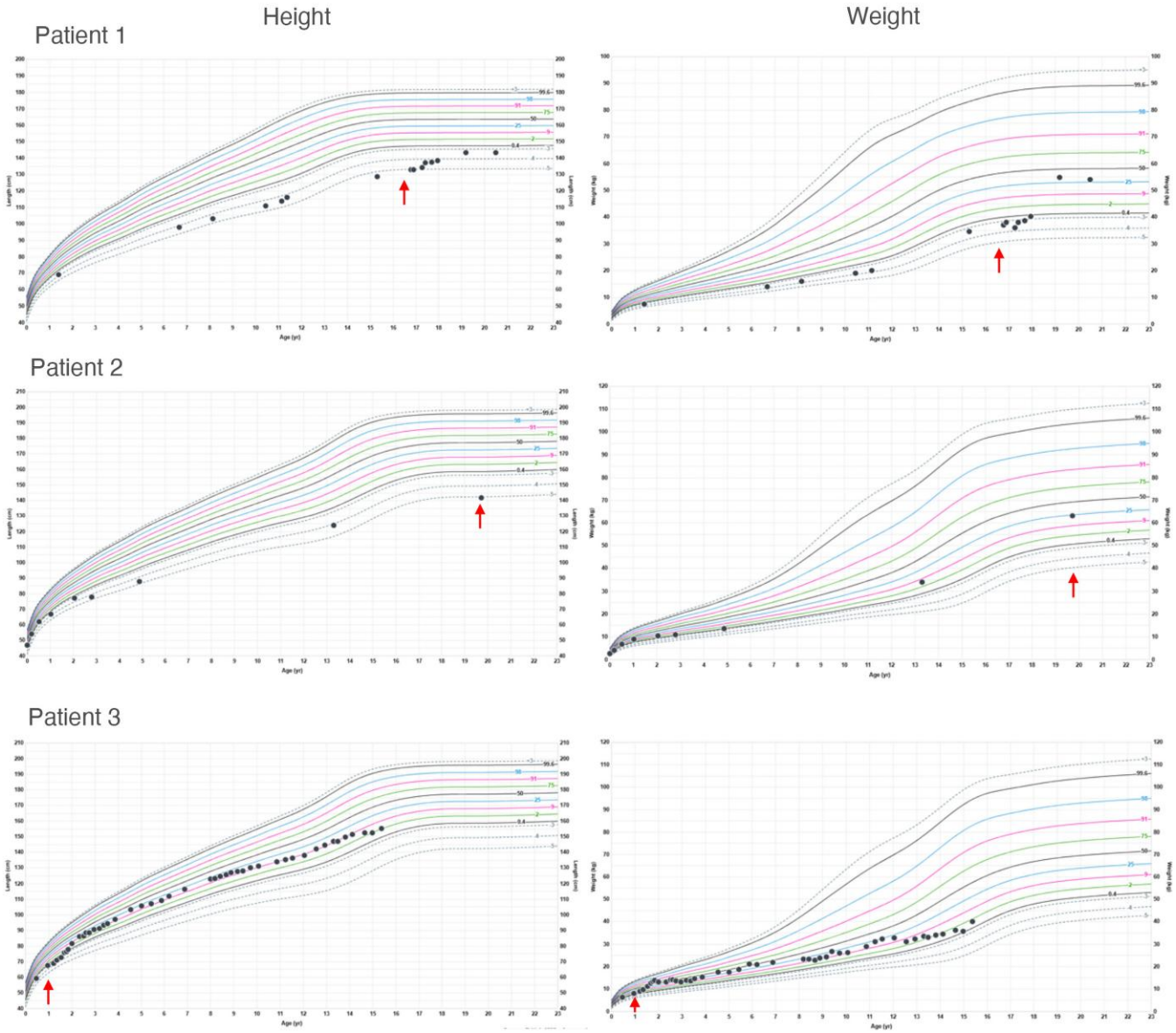

Figure 2 Growth phenotype of patients. Charts illustrating height and weight of the three patients. Arrows indicate the age at which GH treatment was initiated.

significantly reduced body weight as early as postnatal day 21 compared with wild-type and heterozygous littermates, which persisted into adulthood until 10 weeks of age. At 4 weeks of age, male mutants weighed 38.75% less than wild-type controls, whereas female mutants weighed 26.75% less than wild-type controls. Between 11 and 18 weeks, body weight measurements revealed lighter mutants than wild-type littermates; however, this did not reach statistical significance due to a smaller sample size (Figure S4A).

Despite their reduced size, knockout animals appeared grossly normal without any obvious phenotypes in their ocular and skeletal development, or behaviour and external morphology. However, we cannot rule out the possibility of any developmental or structural defects at a tissue or cellular level.

We next characterized the fertility and neuroendocrine reproductive features of *Ccdc149*$^{-/-}$mutants and their littermates. Adult mice were bred for at least 6 months and monitored for the number of litters born, litter size, and frequencies. We found that the fertility is severely impaired in *Ccdc149*$^{-/-}$ mutants (Figure 5C-E). On average, the breeding cages from control littermates (WT × WT and Het × Het) yielded a normally expected 0.71 and 0.79 litters per month, respectively (Figure S4B), whereas in contrast, the mutants yielded a significantly reduced 0.07 litter per month (Figure 5C). Interestingly, when we crossed mutants with wild-type or heterozygous mice, we found that female mutants were severely affected by the lack of Ccdc149. On average, the breeding between a male mutant and a heterozygous female yielded a normally expected 0.72 litter per month; the female mutant crossed with a wild-type or a heterozygous male mouse yielded a significantly reduced 0.17 litter per month.

To further characterize the reproductive and neuroendocrine features of the mutants, we quantified the number of pups born and survived the first week of postnatal life. We found

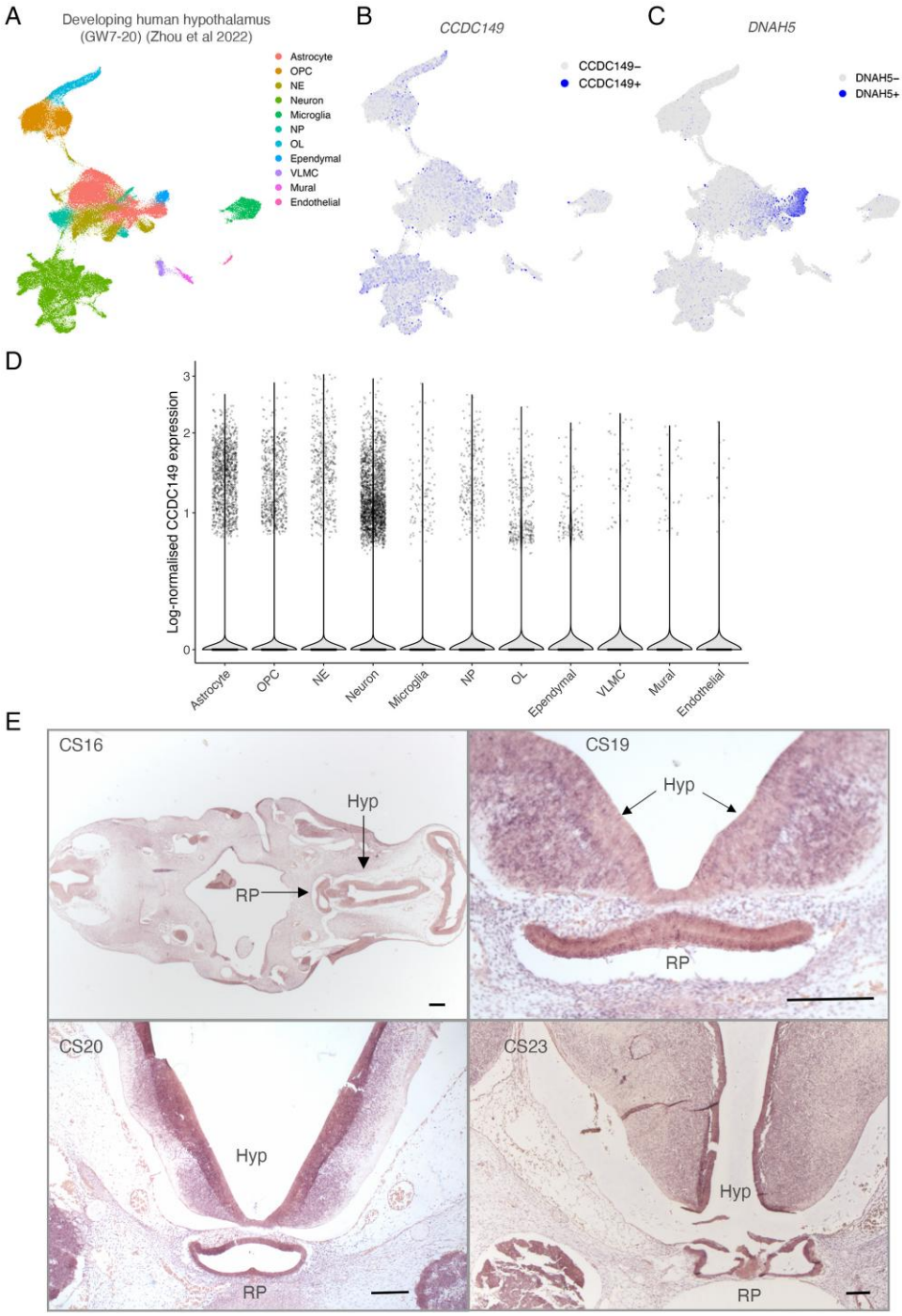

Figure 3 Expression of *CCDC149* during human brain development. (**A**) UMAP plot illustrating molecularly defined single-cell clusters in developing human hypothalamus.[16] (**B-C**) UMAP illustrating cells expressing *CCDC149* and DNAH5 in different subclusters. (**D**) Violin plot illustrating cell-type-specific expression of CCDC149 in different cell types of developing human hypothalamus. (**E**) Photomicrographs illustrating *CCDC149* mRNA transcripts are present in the hypothalamo-pituitary region of the brain at Carnegie stages (CS) 16, 19, 20, and 23 in development, and are visible in the trigeminal ganglia in sections from CS20 and 23. Scale bars = 200 µm. RP, Rathke's pouch; Hyp, hypothalamus; TG, trigeminal ganglia.

that the female mutants demonstrated severe inadequacies in their maternal care. On average, the wild-type and heterozygous females gave birth to litter sizes of 7.7 and 7.1 pups when crossed with a wild-type or a heterozygous male, respectively. In contrast, the litter size from female mutants was significantly reduced to an average of 3 and 0.8 pups when crossed with a control (wild-type or heterozygous) or mutant male, respectively (Figure 5D). As expected, most pups from the control females (wild-type and heterozygous) survived, however surprisingly none of the pups born to female mutants survived their first few days of postnatal life (Figure 5E).

These observations suggest that the neuroendocrine axes, including reproductive hormones and those implicated in parturition, lactation, and nursing, may be severely impaired in

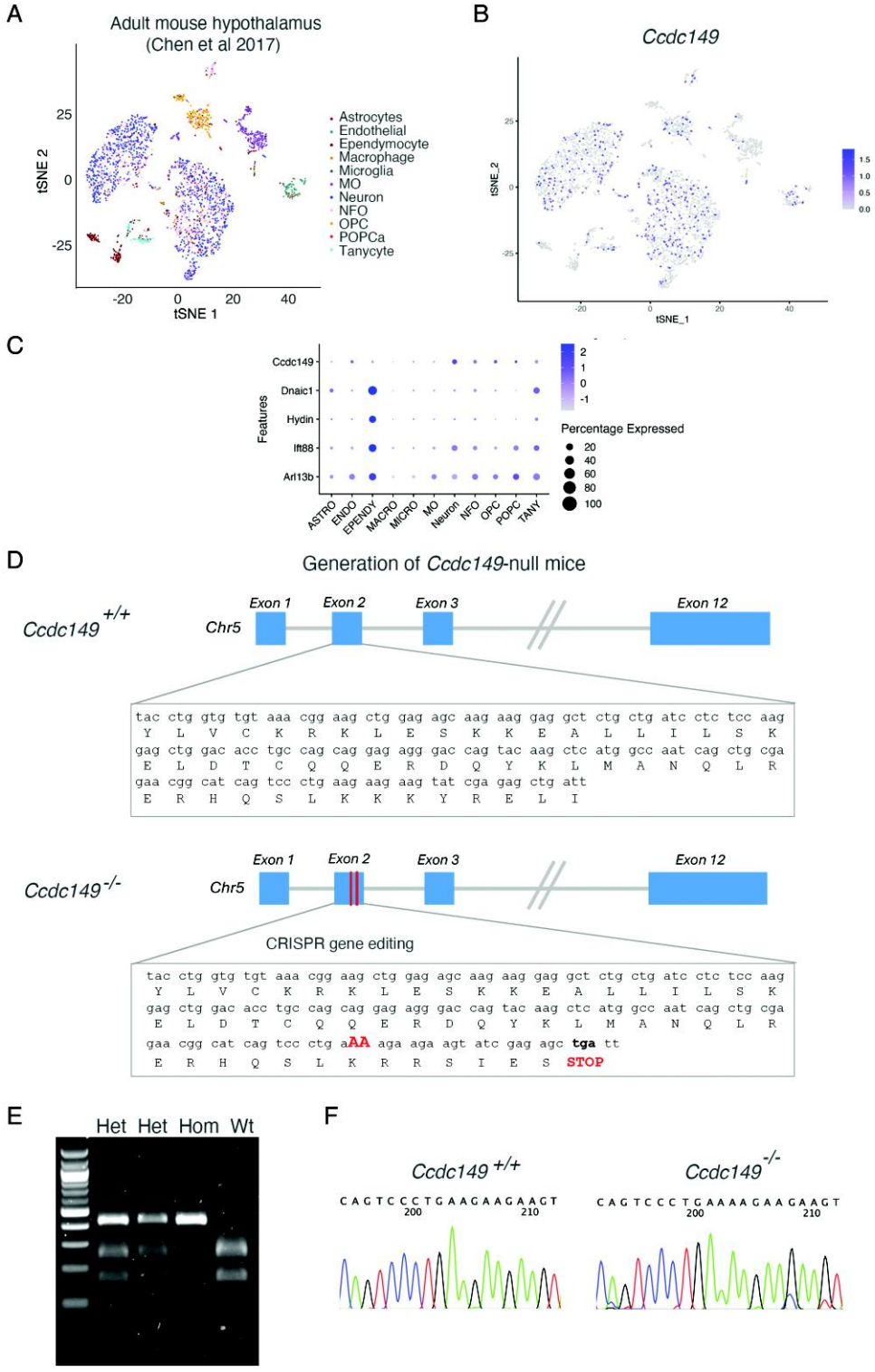

Figure 4 Generation of *Ccdc149*-knockout mouse using CRISPR-mediated gene editing. (**A-C**) Ccdc149 expression in adult mouse hypothalamus. (**A**) UMAP plot illustrating molecularly defined single-cell clusters in adult mouse hypothalamus.[18] (**B-C**) UMAP and dotplot illustrating enrichment of Ccdc149 in neuronal subclusters, respectively. Consistent with expression of *CCDC149* expression in human hypothalamus, genes encoding primary ciliary proteins (Arl13b, Ift88) are expressed in most cell types whereas genes encoding motile ciliary proteins (Hydin, Dnaic1), but not *Ccdc149*, are enriched in ependymal cells and tanycytes. (**D**) Schematic representation of the mouse *Ccdc149* gene containing 12 protein coding exons on chromosome 5. CRISPR-mediating gene editing strategy inserting two AA in exon 2 that introduces a premature stop codon (bottom panel). (**E**) A representative DNA gel illustrating genotyping of wild-types (Wt), heterozygous (Het), and homozygous (Hom) littermates. (**F**) Sanger sequencing confirming gene editing and the insertion of two bp in Exon 2.

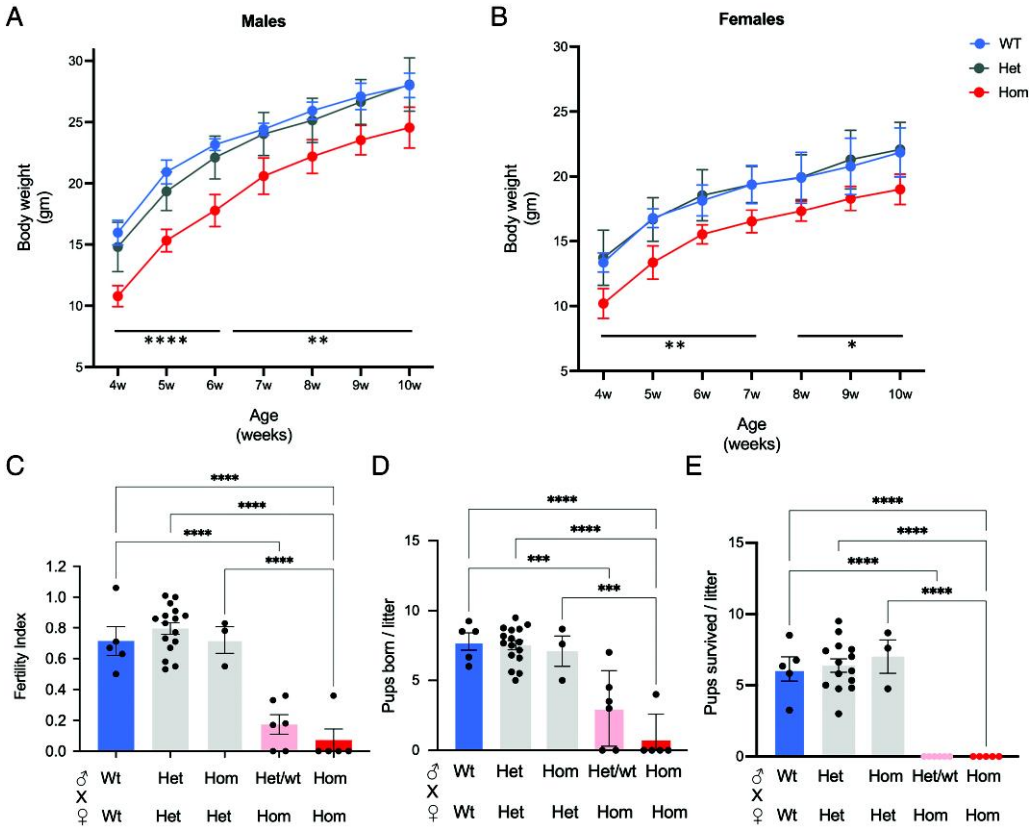

Figure 5 *Ccdc149*-knockout mice exhibit retarded growth and infertility. (**A-B**) Body weight analysis. Line graphs illustrating changes in body weight of male (**A**) (Wt, $n = 3$; Het, $n = 10$; Hom, $n = 6$) and female (**B**) (Wt, $n = 4$; Het, $n = 4$; Hom, $n = 6$) mice from juvenile age (4 weeks) to adults (10 weeks). (**C-E**) Reproductive phenotype. Bar graphs illustrating (**C**) the number of litters born per month (fertility index), (D) the number of pups born per litter, and (**E**) the number of pups per litter that survived (male × female: Wt × Wt, $n = 5$; Het × Het, $n = 16$; Hom × Het, $n = 3$; Het/Wt × Hom, $n = 6$; Hom × Hom, $n = 5$). Data presented as mean ± SEM; ns, not significant; $*P < .05$, $**P < .005$, $***P < .0005$, $****P < .0001$ (Two-way ANOVA followed by Bonferroni's multiple comparisons test was used in A-B and one-way ANOVA followed by Tukey's multiple comparisons test in C-D).

female mutants. To gain further insights into the hypothalamic-pituitary dysfunction in *Ccdc149*-knockout mice, we assessed the gonads (Figure S5). Testes weighed slightly less in the mutants and seminal vesicles appeared much thinner than their wild-type and heterozygous littermates (Figure S5G). Visualization of histological sections of testes revealed normal testes with cells at different stages of spermatogenesis (Figure S5I), although subtle but critical defects (eg, sperm motility) cannot be ruled out. In sharp contrast, uterine weights of female mutants were significantly lower than the wild-type littermates (Figure S5B-C). Ovarian histology revealed fewer post-ovulation corpora lutea compared with wild-type littermates (Figure S5H). To further evaluate the hypothalamic-pituitary axes in the mutants, females were subjected to the Whitten effect[22] (male-pheromone induced estrous) which is mediated by GnRH neurons.[23] All wild-type females (5/5) tested reached an estrous cycle at the end of a 72 hours (H) exposure, and uteri weighed significantly greater than the uteri of wild-type females in diestrous (Figure S5C and F). However, all the mutant females (5/5) examined at the end of the 72H exposure were found in diestrous with significantly smaller uteri compared with wild-types exposed to male bedding. Together, these observations suggest neuroendocrine defects in GnRH-LH secretion in *Ccdc149* mutants.

Discussion

In this study, we identified recessive truncated variants in *CCDC149* in 1/140 patients with CH, sequenced on a targeted CH-gene panel from the UK cohort, and in two siblings from a pedigree from Israel that had WES performed. There has been limited investigation into CCDC149 in mouse and human. Our in-situ hybridization studies showed that *CCDC149* is expressed in the hypothalamo-pituitary region during the early stages of human development (Figure 3E). To corroborate these data with other studies, we analysed single-cell datasets, revealing expression and neuronal enrichment of *CCDC149* in developing human hypothalamus and adult mouse hypothalamic datasets, suggesting its potential role in neurodevelopment, maturation, and regulation of neuroendocrine systems. These findings are consistent with other studies that have shown that the *CCDC149* *C. elegans* orthologue is expressed in most ciliated neurons including pharyngeal, touch-receptor, and motor neurons, and is specifically located in ciliary basal bodies and along the dendrite of the ciliated neuron in *C.elegans*.[14] We then functionally validated the role of CCDC149, through the generation and phenotypic characterization of a novel *Ccdc149*-null mutant. Mutants revealed reduced body weight growth and severe infertility compared with wild-type littermates. This high degree of phenotypic

concordance between CH patients (without a prior genetic diagnosis) and *Ccdc149*-null mutants indicates that *CCDC149* truncations are likely to be the genetic cause of CH in these patients, thereby establishing a novel molecular basis of CH and neurodevelopmental conditions.

Patient 3 had a small anterior pituitary and autism, and all three patients manifested global developmental delay, suggesting the presence of neurodevelopmental defects, consistent with a primarily hypothalamic phenotype. It is however possible that these patients may have defects in brain connectivity and functional organization. These neurodevelopmental deficits could be due to the lack of CCDC149 during embryonic development or during early years of life (fetal and postnatal), due to pituitary and peripheral hormonal deficiencies (eg, IGF1 and sex steroids), which are known to play a strong organizational role in brain development, maturation, and function.[24,25] Together, these observations suggest that CCDC149 plays a crucial role in brain development.

All three patients displayed severe short stature and absent puberty. Concomitantly, all three patients had severe deficiencies in GH, LH, and FSH secretion. Consistently, the *Ccdc149*-null mutants also displayed severe defects in growth and fertility. Our murine phenotypic data are consistent with a recent study reporting a similar growth phenotype in another *Ccdc149*-null model,[26] with defects in testicular descent associated with a reduced sperm count. Importantly, all three patients in our study had normal concentrations of other pituitary hormones measured, including ACTH and prolactin, suggesting that CCDC149 truncations selectively affect specific pituitary subpopulations (somatotrophs, gonadotrophs) but not other anterior pituitary cell types (corticotropes, lactotrophs). Although TSH secretion was normal in Patients 1 and 2, Patient 3 was commenced on Levothyroxine on the basis of a low-normal FT4. These observations with our murine model suggest that CCDC149 has selective and specific roles in the development and function of hypothalamo-pituitary growth and reproductive axes.

CCDC149 is located on chromosome 4p15.2, with most annotated transcripts consisting of 13 exons. It belongs to the "Coiled-Coil Domain-containing" family of proteins, that are frequently involved in protein-protein interactions or structural roles.[27] In our study, variants were located in exons 9 and 7, respectively. Importantly, we found that these two sites are highly conserved across species (mice, humans, zebrafish), highlighting their critical function (eg, protein structure, stability, active- or binding- site). While our studies are the first to report pathogenic CCDC149 truncations in CH and developmental delay, Du et al recently reported a homozygous truncating variant in *CCDC149* in a single patient with bilateral cryptorchidism.[26] The authors suggested that CCDC149 has a role in testicular development, however, it is plausible that the cryptorchidism was secondary to reduced GnRH and gonadotrophin secretion from the hypothalamus and pituitary gland, a possibility not explored in their study. The reduction in murine size demonstrated in two independent studies using two different *Ccdc149* KO murine models, in addition to the GHD in all three of our patients, suggests that *Ccdc149/CCDC149* plays a critical role in regulating the hypothalamo-pituitary somatotroph axis in mice and humans.

The human genome contains ~180 CCDC-family genes, encoding proteins with varied functions, eg, *CCDC141* variants are associated with self-limited delayed puberty.[28] Several CCDC genes are known to play a crucial role in the structure and function of primary and/or motile cilia[27,29]; *CCDC28B* is involved in ciliogenesis and is frequently associated with ciliopathies (eg, Joubert syndrome), in which pituitary defects are a common feature.[30,31] Others, such as *CCDC39* and *CCDC40*, are associated with motile cilia and commonly associated with primary ciliary dyskinesia.[32]

Our clinical and mouse data suggest that *CCDC149* may be associated with primary ciliary function due to the following reasons: (i) the three patients and *Ccdc149-null* mutants in our study lack classical symptoms of a motile ciliopathy (eg, chronic respiratory infections, hydrocephalus, laterality defects); (ii) our in situ hybridization on human embryonic tissue shows *CCDC149* expression in the hypothalamo-pituitary region of the brain and related tissues, but not in the ependymal cells that have motile cilia. Consistently, our single-cell data analysis shows enrichment of *CCDC149* expression in neuronal subsets, but not in ependymal cells, with enriched expression of genes associated with both motile and primary cilia (*DNAI1*, *ARL13B*, respectively); and (iii) the expression described in the *CCDC149* orthologue in *C.elegans* is expressed in most ciliated neurons.[14] We cannot rule out the possibility that CCDC149 may have a role associated with primary cilia in certain cell types (eg, neurons) and with motile cilia in others (eg, astrocytes), or furthermore, in transmembrane signal transduction independent of cilia.

There are limited data on the spatiotemporal expression profiles of *CCDC149*, with the exception of single-cell transcriptomic data in The Human Protein Atlas showing enhanced expression in inhibitory neurons in the brain (https://www.proteinatlas.org/).[33] Our clinical data show that all three patients manifested neurodevelopmental deficits, suggesting CCDC149 could play a broader role in brain development beyond CH. In line with this, studies have reported that differentially methylated *CCDC149* single-nucleotide polymorphisms negatively correlated in male patients with schizophrenia,[34] and *CCDC149* and *anaplastic lymphoma kinase* (*ALK*) fusion (*CCDC149-ALK*) results in enhanced ALK activity in association with thyroid cancer.[35-37] In addition, genome-wide association studies (GWAS) suggest an association between *CCDC149* and memory performance,[38] longitudinal changes in brain structure,[39] and lean body mass.[40]

The variants identified in *CCDC149*, in pedigrees with similar phenotypes, are likely deleterious. The scoliosis and ocular features in patients 1-2 may have also resulted from the recessive frameshift in *CCDC149* and thus be a variation of the phenotype associated with this genetic defect. This will become clearer as more CH patients are identified with recessive *CCDC149* variants. However, we cannot rule out the possibility that undetected intronic, structural or epigenetic variants that are not detected through WES may contribute to these clinical features. As we did not perform WES/WGS in patient 3, we cannot rule out the possibility that other genetic variants in unidentified CH-related genes or any other variants in the genome may be contributing towards the phenotype.

The phenotypes of our patients and murine mutants generated in this study suggest that CCDC149 impairment disrupts hypothalamic signalling to the pituitary gland, thereby affecting reproductive (LH and FSH secretion from gonadotroph cells) and growth (GH secretion from somatotroph cells) axes, resulting in infertility and GHD. Future studies investigating the development and function of neuroendocrine cells and related circuits in the

hypothalamo-pituitary axis using *Ccdc149*-null mutants *in vivo*, patient-derived fibroblasts and/or induced-pluripotent cells *in vitro*, will provide further insights into the functional roles of CCDC149 in ciliary function and associated signalling pathways; SHH and WNT, critical for correct hypothalamo-pituitary development.[41,42] Taken together, our studies reveal *CCDC149* as a novel genetic cause of CH that plays a crucial role in the development and function of the hypothalamo-pituitary axis. This gene should be considered in CH-related panels, especially when screening patients with GHD with HH.

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Supplementary material

Supplementary material is available at *European Journal of Endocrinology* online.

Conflicts of interests

The authors declare that there is no conflict of interest that could be perceived as prejudicing the impartiality of the research reported.

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Data availability

All Individual participant data that underlie the results reported in this article, after de-identification (text, tables, and figures), and the study protocol and any statistical analysis plan, will be available immediately following publication, for anyone who wishes to access the data. The variants reported in this study will be uploaded to the Clinvar database to be included in the online open access resource.

Ethics declaration

Ethical committee approval was obtained from UCL Great Ormond Street Institute of Child Health/Great Ormond Street Hospital for Children Joint Research Ethics Committee, and informed written consent was obtained from patients and/or parents for all clinical and genetic studies carried out on their blood/DNA and any subsequent publication of clinical and genetic information. Ethical approval for the study involving Patients 1 and 2 in Israel was obtained from the Helsinki Committee of Ziv Medical Center in Safed (Approval Number: ZIV-0089-0017). Written informed consent was obtained from all participants and/or their legal guardians for the conduct of clinical and genetic testing on blood and/or DNA samples, as well as for the publication of associated clinical and genetic information.

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