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A Case of Congenital Hypopituitarism Associated With a 1p31 Microdeletion: A Possible Role for *LEPR* and *JAK1*

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Context: Genetic defects affecting the expression and function of factors involved in pituitary development have been found to be associated with congenital hypopituitarism (CH). However, for most cases of CH, the etiology remains unknown.

Case Description: We present an unusual case of an infant with CH, associated with septo-optic dysplasia with an absent anterior pituitary and an ectopic posterior pituitary gland, resulting from a *de novo* 8.04-Mb interstitial deletion of chromosome 1p31.1-1p31.3. The deleted region includes several genes that might be involved in pituitary development, including *LEPR* and *JAK1*.

Conclusions: Haploinsufficiency of *LEPR* and/or *JAK1* might be associated with CH. This finding suggests a role for *LEPR*-mediated glycoprotein 130 signaling in human pituitary development.

Freeform/Key Words: chromosome 1p31, congenital hypopituitarism, microdeletion, *LEPR* gene, *JAK1* gene, leptin

Genetic defects affecting the expression and function of factors involved in pituitary development have been found to be associated with congenital hypopituitarism (CH) [1]. However, for most cases of CH, the etiology remains unknown. The identification of other causative genes for CH could provide insight into the interplay of signaling molecules, transcription factors, and other molecular networks involved in pituitary development. We present a case of CH associated with a chromosome 1p31.3 microdeletion involving *LEPR* and *JAK1* that suggests an unusual mechanism for this condition in humans.

1. Methods

Genomic DNA was isolated from whole blood using the Puregene kit (Gentra Systems, Minneapolis, MN). Array comparative genomic hybridization using an oligonucleotide plus single nucleotide polymorphism-based microarray containing 180,000 features (SurePrint G3 GGXChip plus SNP, version 1.0 4x180k; Agilent Technologies, Santa Clara, CA) was performed according to manufacturer's protocol by Detroit Medical Center University Laboratories (Detroit, MI). The array design and genomic coordinates were based on the National Center for Biotechnology Information Build 37 (hg19) for the Agilent array. Variants were categorized using the American College of Medical Genetics standards and guidelines for interpretation and reporting [2].

Abbreviations: CH, congenital hypopituitarism; gp130, glycoprotein 130.

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The exonic regions of all known genes in the 1p31.3-p31.1 region and 14 additional genes involved in pituitary development (*GLI2, HESX1, LHX3, LHX4, OTX2, PITX1, PITX2, POU1F1, PROP1, SHH, SIX3, SOX2, SOX3,* and *TGIF1*) were sequenced using XomeDxSlice testing by GeneDx (Gaithersburg, MD) using the Illumina HiSEquation 2000 sequencing system (Illumina, San Diego, CA).

2. Case Report

The patient was the full-term male of a nonconsanguineous relationship, born to 28-year-old mother with a history of gestational diabetes treated with glyburide. His birth weight was 3.42 kg (50th percentile), his birth length was 48 cm (12th percentile), and his head circumference was 36.1 cm (70th percentile). He was initially vigorous but developed respiratory distress and hypoglycemia soon after birth and required admission to the neonatal intensive care unit.

At the time of birth, he was noted to have multiple dysmorphic features, including trigonocephaly with a prominent brow and metopic ridge; hypotelorism with almond-shaped eyes and infraorbital creases; a flat nasal bridge with anteverted nostrils; small, low-set, posteriorly rotated ears with overfolded helices; a long philtrum, micrognathia, a high arched palate; widely spaced, hypoplastic nipples; a small scrotum and phallus; unilateral cryptorchidism; clenched hands with deep palmar creases and long-appearing fingers; fifth digit clinodactyly of both feet; and a sacral dimple. He also had hyperreflexia in the lower extremities.

Extensive neonatal imaging studies were performed. A head ultrasound scan on his first day of life revealed midline abnormalities, including the absence of the septum pellucidum and mild lobularity of the medial cortical surfaces, along with ventricular enlargement and several periventricular cystic areas. These findings were subsequently corroborated by magnetic resonance imaging of the brain, which also noted a diminutive sella, ectopic posterior pituitary, and nonvisualization of the anterior pituitary gland (Fig. 1). The corpus callosum appeared hypoplastic. Computed tomography of the head showed evidence of metopic synostosis, and a spinal magnetic resonance imaging study revealed sacralization of L5. At 1 week of age, an electroencephalogram showed a discontinuous electroencephalographic pattern,

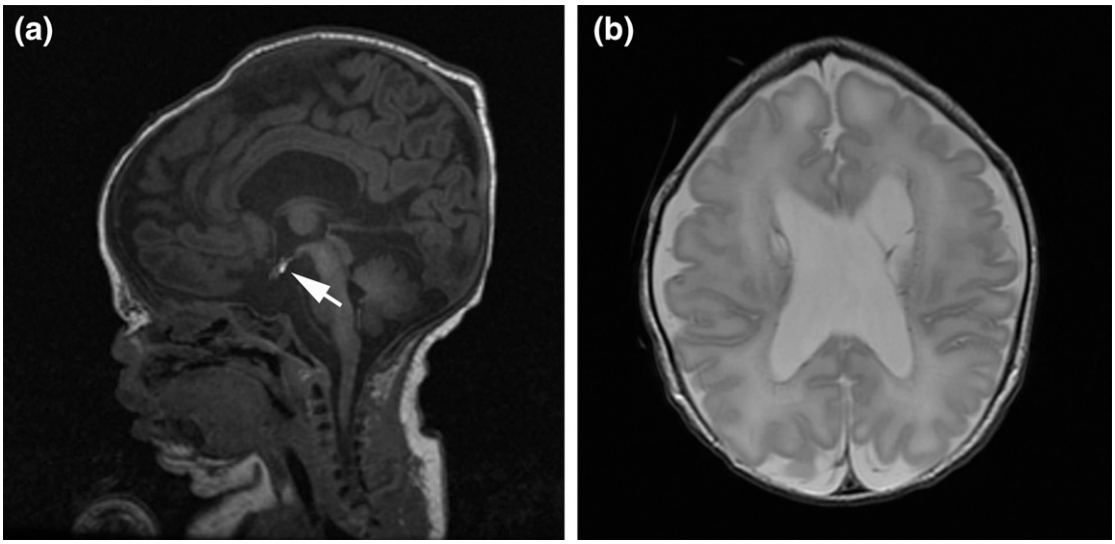

Figure 1. Brain magnetic resonance images showing brain and craniofacial anomalies. (a) Sagittal T_1-weighted image showing ectopic location of the posterior pituitary bright spot (arrow), consistent with an ectopic posterior pituitary with a flattened and empty sella turcica. Micrognathia is also apparent. (b) Axial T_2-weighted image showing absent septum pellucidum with mildly enlarged lateral ventricles.

suggesting diffuse neuronal dysfunction; however, no seizure activity was present. The findings of an ophthalmologic evaluation were normal. The results of his newborn hearing screening test were abnormal, and auditory brainstem response testing performed at 8 months of age found moderate to severe bilateral sensorineural hearing loss. The findings of a newborn echocardiogram were normal, except for a patent foramen ovale, and a skeletal survey showed no abnormal findings and a normal bone mineral density.

Neonatal measurement of the anterior pituitary hormones revealed a low free thyroxine level (0.7 ng/dL) with inappropriately low thyrotropin (13.4 μIU/mL), low adrenocorticotropic hormone (<5 pg/mL), low cortisol (0.8 μg/dL), and low growth hormone levels during two episodes of hypoglycemia (<0.05 ng/mL). His testosterone level was low (<20 ng/dL), the luteinizing hormone level was 0.3 mIU/mL, and the follicle-stimulating hormone level was 2.0 mIU/mL. These findings were consistent with hypopituitarism. Levothyroxine, hydrocortisone, and growth hormone replacement were initiated. His clinical course was notable for substantial global developmental delays. At 1 year of age, he was hypotonic. He was not sitting or crawling, nor did he have any words or meaningful articulations.

The array comparative genomic hybridization revealed a 46XY male chromosomal complement with a *de novo* 8.04-Mb interstitial deletion of chromosome 1p31.1-1p31.3 involving 30 Online Mendelian Inheritance in Man genes, including *LEPR*, *JAK1*, and *NFIA* (Supplemental Table 1). Sequencing all 30 genes in the 1p31.3p31.1 region did not identify any mutations or variants in the alternate allele. In addition, we did not identify a pathogenic sequence variation in any of the 14 genes outside this locus known to be involved in pituitary development (*GLI2, HESX1, LHX3, LHX4, OTX2, PITX1, PITX2, POU1F1, PROP1, SHH, SIX3, SOX2, SOX3,* and *TGIF1*).

3. Discussion

We present the case of an infant with a *de novo* 8.04-Mb interstitial deletion of chromosome 1p31.1-1p31.3 associated with CH, multiple congenital anomalies, and global developmental delays. Multiple signaling molecules and transcription factors are known to orchestrate the various stages of pituitary development [1]. Mutations in these genes (*HESX1, POU1F1, PROP1, LHX3, LHX4, PITX1, PITX2, OTX2, SOX2,* and *SOX3*) result in pituitary dysfunction, including CH [1, 3]. Our patient did not harbor a pathogenic sequence variation in any of these genes, suggesting that cause of his hypopituitarism was the result of an unusual genetic change. Therefore, we postulate that haploinsufficiency of one or more genes in the deleted segment might have been responsible for his CH. Among these genes, several could be involved in pituitary development, including *LEPR*, *NFIA*, and *JAK1*.

Few patients with interstitial deletions of the chromosome 1p31.3 region have been described [4–11] (Table 1). Deletions in this region, in particular, those involving *NFIA* but not *LEPR* and *JAK1* (Table 1), are typically associated with structural brain abnormalities, including hypoplasia of the corpus callosum and ventriculomegaly, and craniofacial anomalies, metopic synostosis, urinary tract abnormalities, hypotonia, and developmental delays [7]. However, CH has not been described in these cases, suggesting that haploinsufficiency of *NFIA* is not solely involved in pituitary development.

Several other genes within the deleted 1p31.1-1p31.3 region are interesting candidates for the phenotype, including *LEPR* and *JAK1*. Individuals with homozygous and compound heterozygous mutations in *LEPR* resulting in leptin receptor deficiency show evidence of pituitary dysfunction with low growth hormone and thyrotropin levels and impaired pubertal development resulting from central hypogonadism [4, 5]. Patients with large interstitial deletions of this region have brain malformations; however, hypopituitarism has not been clearly described [4, 7]. One patient with a homozygous 80-kb deletion of chromosomal 1p31.3 involving the proximal promoter and exons 1 and 2 of *LEPR* (Table 1) presented with early-onset obesity, mental retardation, and epilepsy, but not CH [5]. Only one other patient with a 3.2-Mb deletion of the chromosome 1p31.3 region that included deletion of *LEPR* and *JAK1* has been

Table 1. Summary of Cases With Interstitial Deletions of the Chromosome 1p31.3 Region

Variable	Barton *et al.* [10], 1995	Campbell *et al.* [4], 2002; Lu *et al.* [7], 2007		Koehler *et al.* [5], 2010	Petti *et al.* [6], 2011	Chen *et al.* [8], 2011	Vauthier *et al.* [9], 2012	Rao *et al.* [11], 2013	Present Study
Time of diagnosis	Postnatal	Postnatal	Postnatal	Postnatal	Postnatal	Prenatal	Postnatal	Postnatal	Postnatal
Method of diagnosis	Karyotyping, FISH	Karyotyping, FISH	Karyotyping, FISH	aCGH	Karyotyping, aCGH	aCGH, FISH	aCGH, MPLC	Karyotyping, FISH, aCGH	aCGH
Deletion size	NR	12 Mb	12 Mb	4.93 Mb	3.2 Mb	22.2 Mb	80 Kb	0.12 Mb	8 Mb
Genes involved	NR	48	48	17	17	91	2	1	30
LEPR	NR	+	+	–	+	NR	+ (exon 1,2)	–	+
NFIA1	NR	+	+	+	–	+	–	+ (exon 4–9)	+
JAK1	NR	+	+	–	+	NR	–	–	+
Age, gender	18 mo, F	3 y, F	11 mo, M	0.5 y, F	15 y, M	30 wk GA, F	7 y, M	8 y, F	2 y, M
Phenotype									
Abnormal corpus callosum	?	+	+	+	?	+	?	+	+
Hydrocephalus or ventriculomegaly	?	+	+	+	?	+	?	+	+
Pituitary abnormality	?	–	–	–	?	–	?	–	+
Dysmorphic features	+	+	+	+	+	+	+	+	+
Macrocephaly	–	+	+	+	–	+	–	+	–
Metopic synostosis	–	–	–	–	–	–	–	+	+
Developmental delay	+	+	+	?	+	NA	+	+	+
Urinary tract abnormality	?	+	+	–	?	?	?	+	–
Tethered spinal cord	?	+	+	–	?	–	?	–	+
Seizures	–	+	+	–	–	NA	+	–	+
Obesity	?	–	–	–	+	NA	+	+	–

Abbreviations: +, present; –, absent; ?, no investigations performed to rule it out; aCGH, array comparative genomic hybridization; F, female; FISH, fluorescence *in situ* hybridization; GA, gestational age; M, male; MPLC, multiplex polymerase chain reaction/liquid chromatography; NA, not applicable; NR, not reported.

reported [6]. The patient had facial dysmorphism, obesity, behavioral problems, and mild intellectual impairment [6]. However, the findings from neuroimaging and endocrinological studies were not reported. The case we have presented is unique in its comprehensive characterization of CH.

The *LEPR* gene encodes the leptin receptor. Its longest isoform, LEPRb, is a single-transmembrane-domain receptor that belongs to the glycoprotein 130 (gp130) family of cytokine receptors that use the JAK-STAT signal transduction pathway. LEPRb is uniquely expressed in the hypothalamus and pituitary in both rodents and humans [12, 13]. Based on studies in model organisms, it has been suggested that gp130 cytokine signaling mediated by the JAK/STAT signal transduction pathway might have a critical role in hypothalamic and pituitary development [13–16]. In this context, *JAK1*, a widely expressed membrane-associated phosphoprotein, plays a critical role in neuronal development and survival, mediated by gp130 cytokine signaling [17]. While $Jak1^{-/-}$ neurons cultured in the absence of growth factor are not viable, their viability is maintained in the presence of gp130 receptor family ligands, suggesting an obligate and synergistic relationship between gp130 receptor family members and *Jak1* is needed for neuronal development [17]. Extrapolating from these data, we speculate that the combined effect of both *LEPR* and *JAK1* haploinsufficiency could have affected normal pituitary development, resulting in our patient's phenotype. Future studies are needed to confirm the role gp130 cytokine signaling might have in human pituitary development.

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