中文題目: 發生於一對姊妹的複合型腦下腺功能低下症之基因研究

英文題目: Genetic study for combined pituitary hormone deficiency in two siblings

作　　者: 溫緯倫[1], 洪薇鈞[2], 蔡宜純[3], 賴嘉緯[1], 黃尚志[3], 蕭璧容[4], 洪薇雯[4]

服務單位: 高醫大附設醫院內科部[1],高醫大醫學系微生物暨免疫學科[2], 高醫大附設醫院內科部腎臟科[3],高醫大附設醫院內科部內分泌新陳代謝科[4]

Background: In adults, hypopituitarism can occur in women after giving birth as in the case of postpartum hypopituitarism (PPHP). PPHP is associated with intrapartum or postpartum hemorrhage due to coagulation abnormality. Besides, combined pituitary hormone deficiency (CPHD) due to genetic factors can also lead to hypopituitarism, although the onset of CPHD in adulthood is rare. Here we reported hypopituitarism in two siblings and studied for the possible genetic etiology.

Case report and method: Of the two siblings, the younger sister, at the age of 31, was the first to visit our hospital due to failure of lactation after delivering her first baby by Caesarean section. Her pituitary function tests showed ACTH=4.36pg/ml, cortisol<1.0μg/dl, TSH<0.03μIU/mL, FT4=0.29ng/dl and prolactin<2.2ng/ml. Two years later, the elder sister, at the age of 37 after her second pregnancy, presented to our hospital with the same symptoms. Pituitary function tests of the elder sister also showed ACTH=6.96pg/ml, cortisol<1.0μg/dl, TSH<0.03μIU/mL, FT4<0.29ng/dl and prolactin<2.2ng/ml. Both of the sisters had smooth parturition processes without intrapartum or postpartum hemorrhage. The pituitary MRI of the two siblings did not show any hemorrhagic sign or empty sella. As both sisters developed hypopituitarism postpartum, genetic studies were conducted. After DNA was extracted from blood samples of the sisters, PCR and subsequent sequencing were performed for *PROP1*, *POU1F1* and *HESX1* genes reported to be involved in the pathogenesis of CPHD.

Results: Both of the siblings had three homozygous mutations in the *PROP1* gene: c.-347G>T (upstream gene variant), c.59G>A (missense mutation) and c.109+3G>A (splice region variant). The last mutation, known to cause CPHD, alters the conserved region of intron 1, and is predicted to cause abnormal splicing of the transcription. In the remaining two genes *POU1F1* and *HESX1*, no mutations were detected.

Discussion: We reported the two siblings diagnosed with postpartum hypopituitarism not related to any coagulation abnormality, but might be associated with genetic factors causing combined pituitary hormone deficiency. Further studies should be carried out in their family members without hypopituitarism to elucidate the mutation of *PROP1* as the causative gene leading to hypopituitarism in the two siblings.