SÍNDROME DE SHIMMELPENNING BRUNO FERRARI

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SÍNDROME DE SCHIMMELPENNING

- Sexo femenino
- 3 años de edad
- RNT, PAEG

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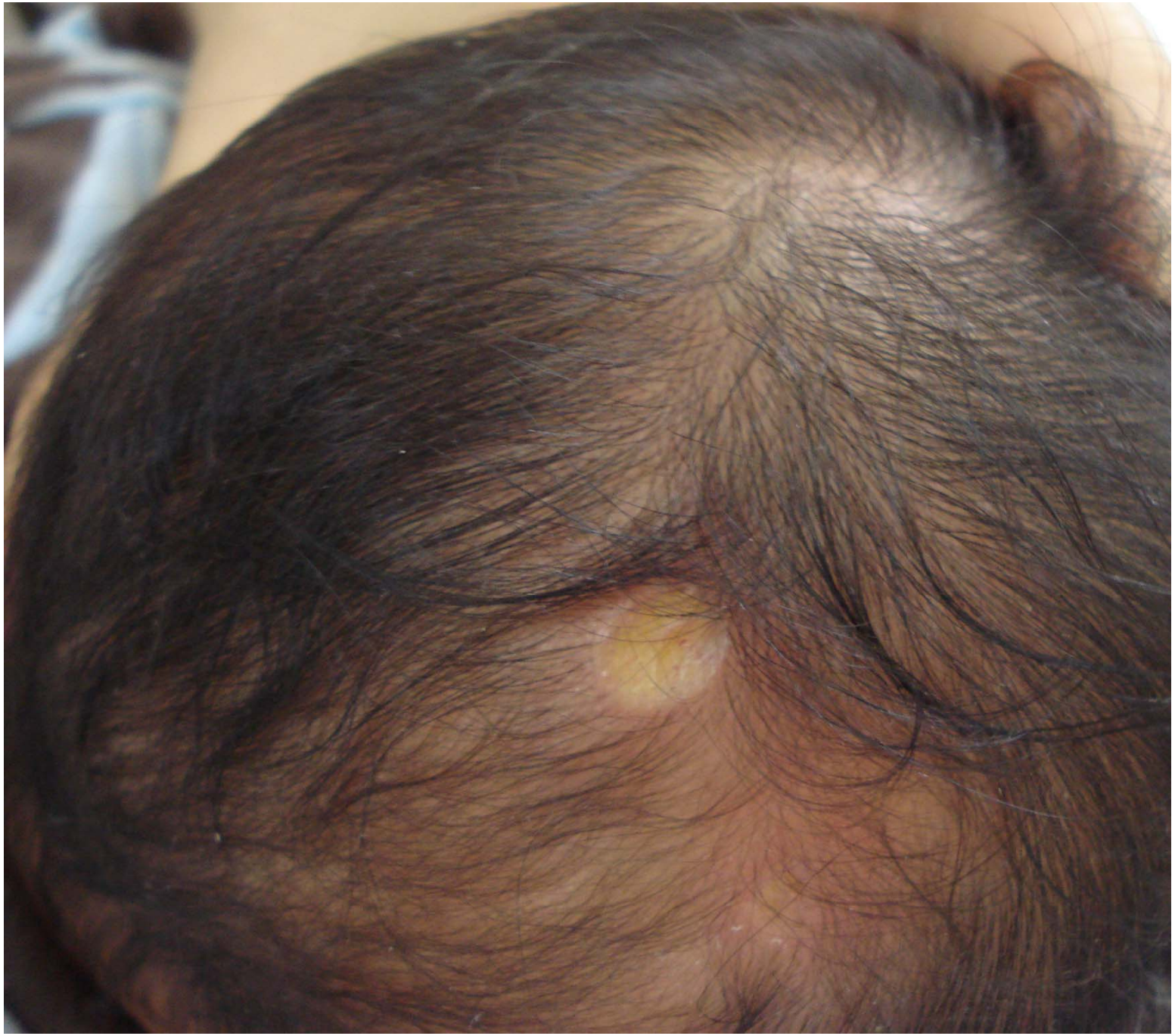

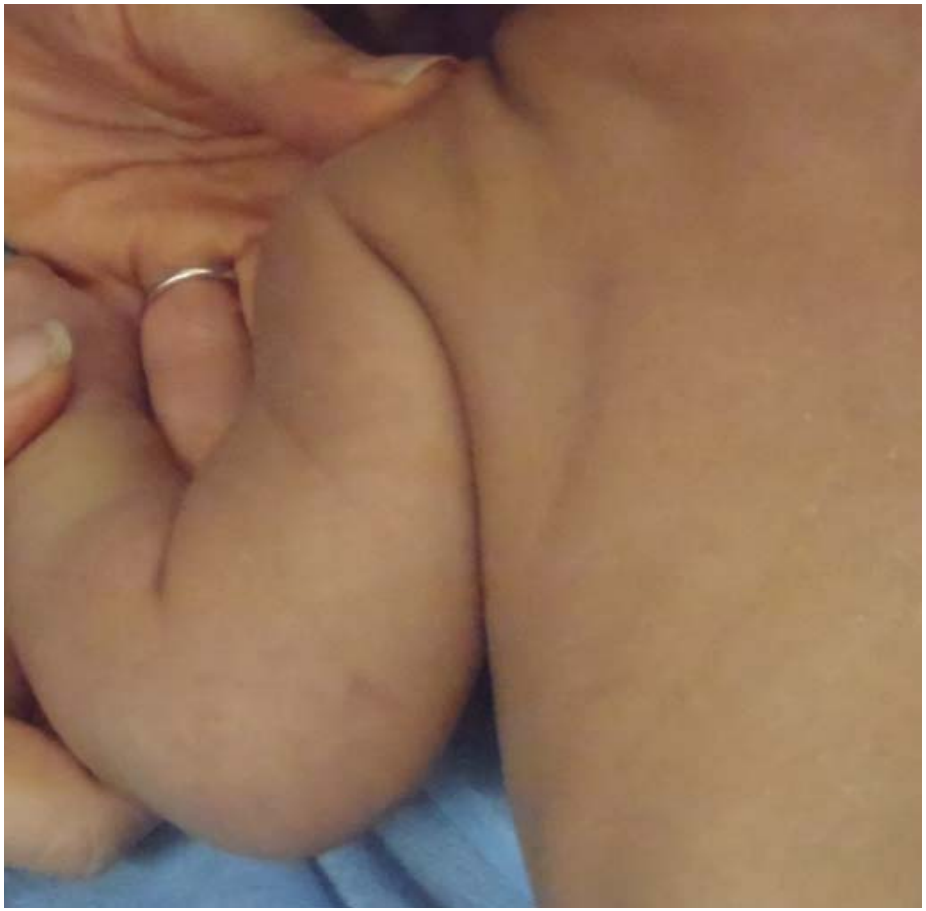

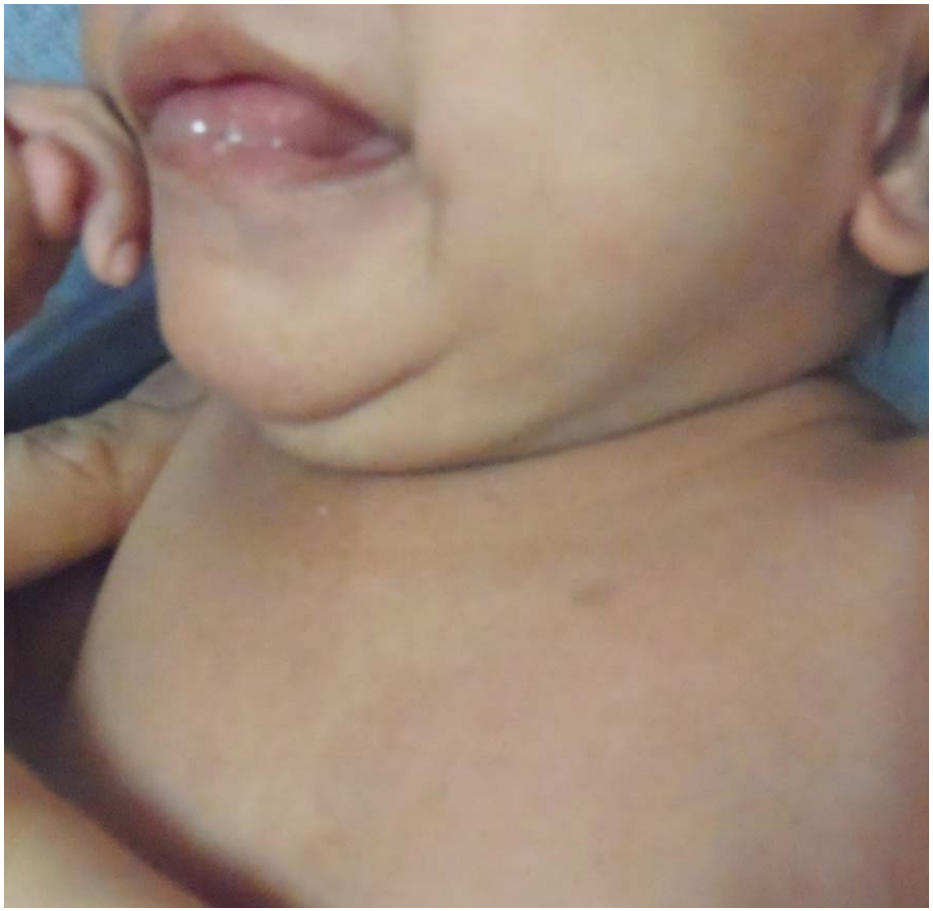

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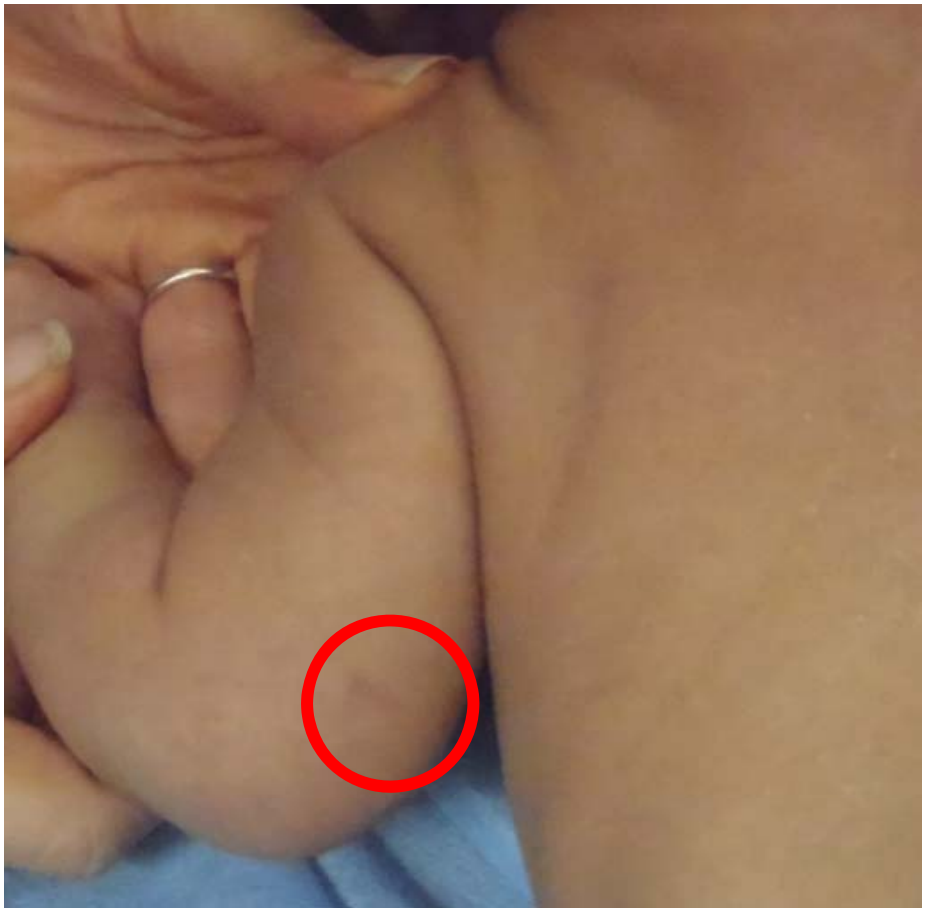

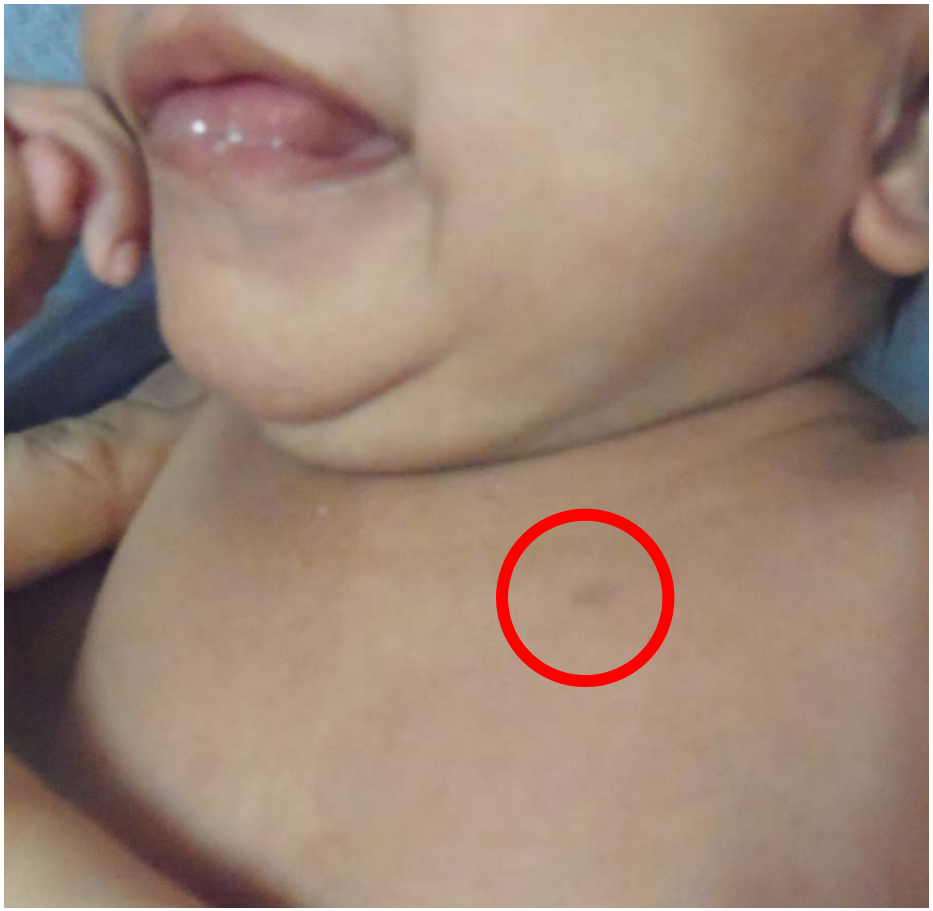

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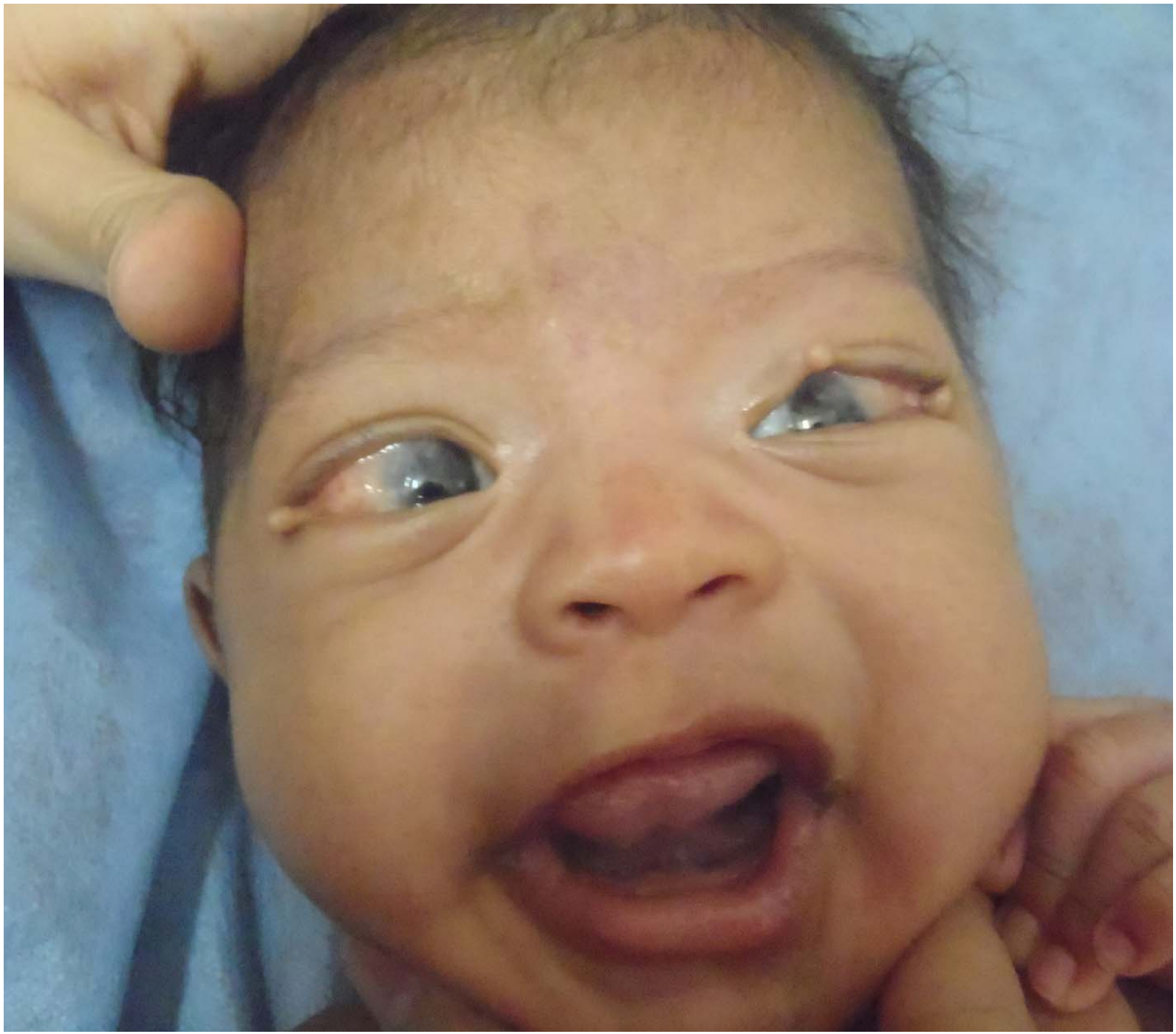
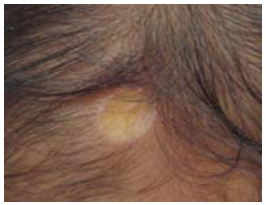


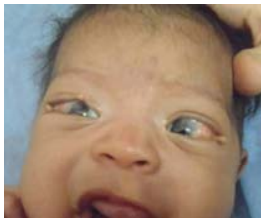
DIAGNÓSTICO PRESUNTIVO

Síndrome oculoectodérmico:

-Aplasia Cutis Congénita



-Coristomas epibulbares



-Otras alteraciones

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ESTUDIOS COMPLEMENTARIOS

- Ecografía cerebral
- Prueba de pesquisa neonatal
- Otoemisiones acústicas
- Rx de cráno, columna total, tórax y miembros
- Cariotipo: 46, XX, 9 ph (variante cromosómica normal)

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EVALUACIÓN CARDIOLÓGICA

- Coartación de aorta leve
- Estenosis pulmonar leve
- Foramen oval permeable
- HTA

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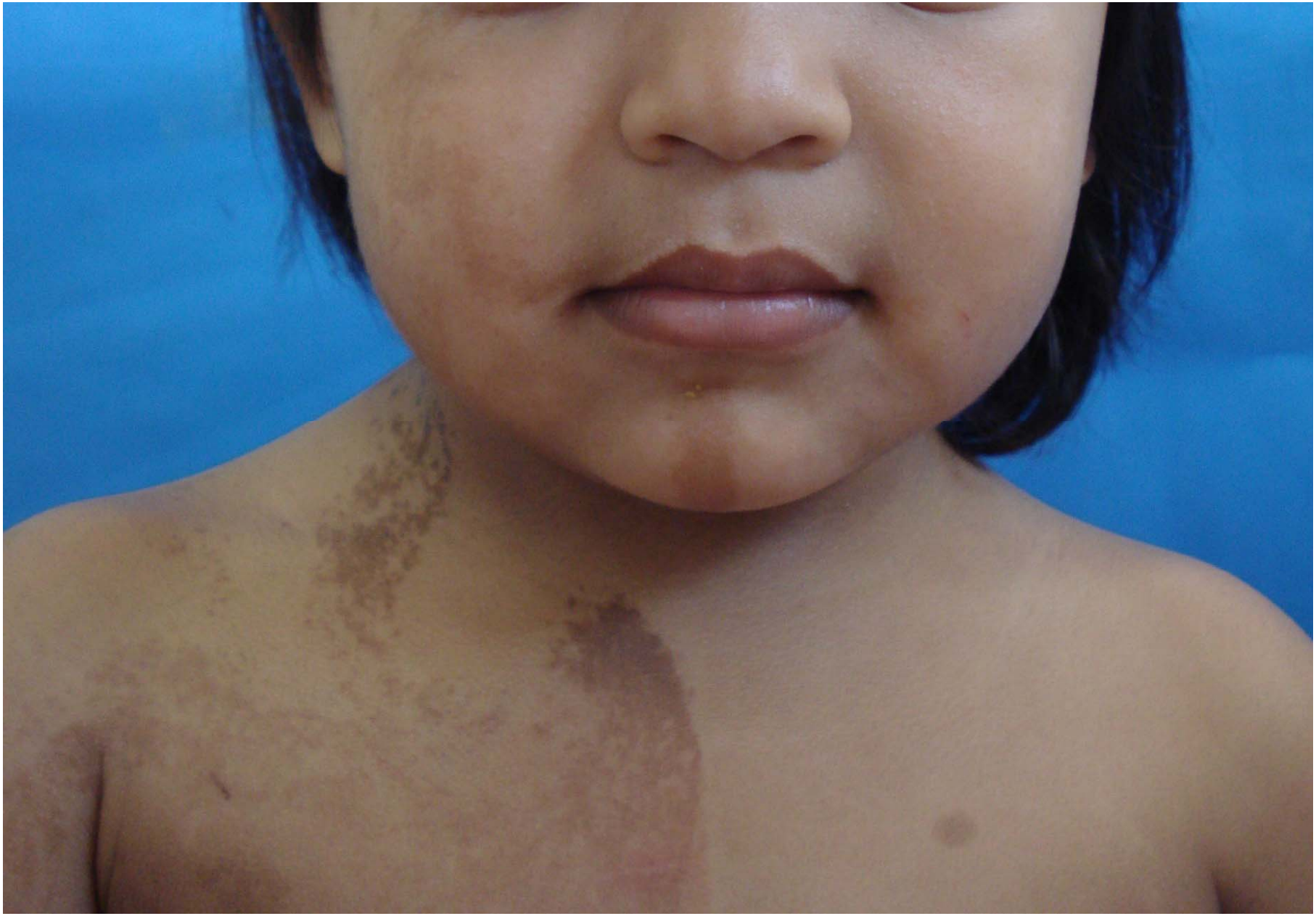
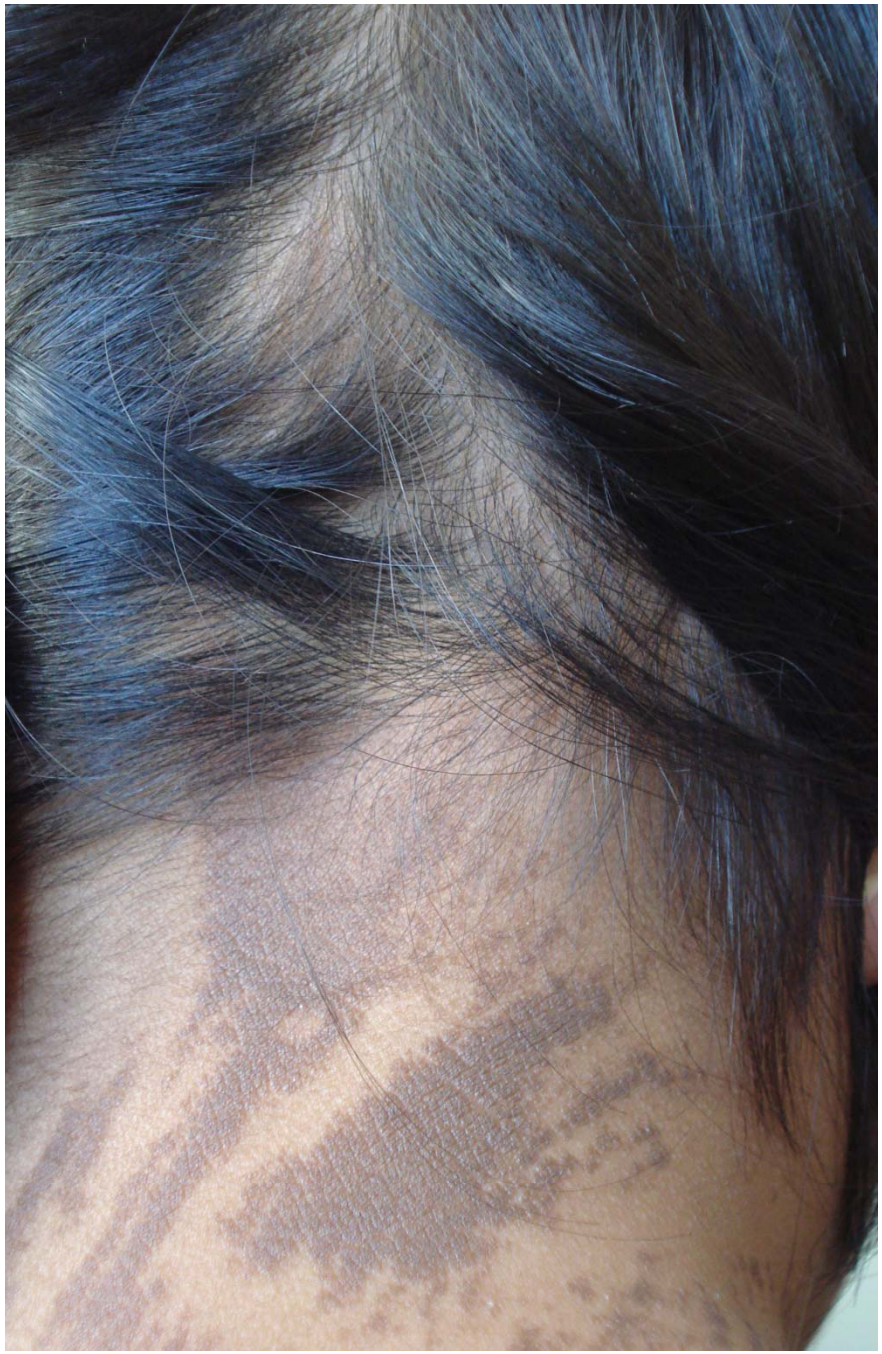
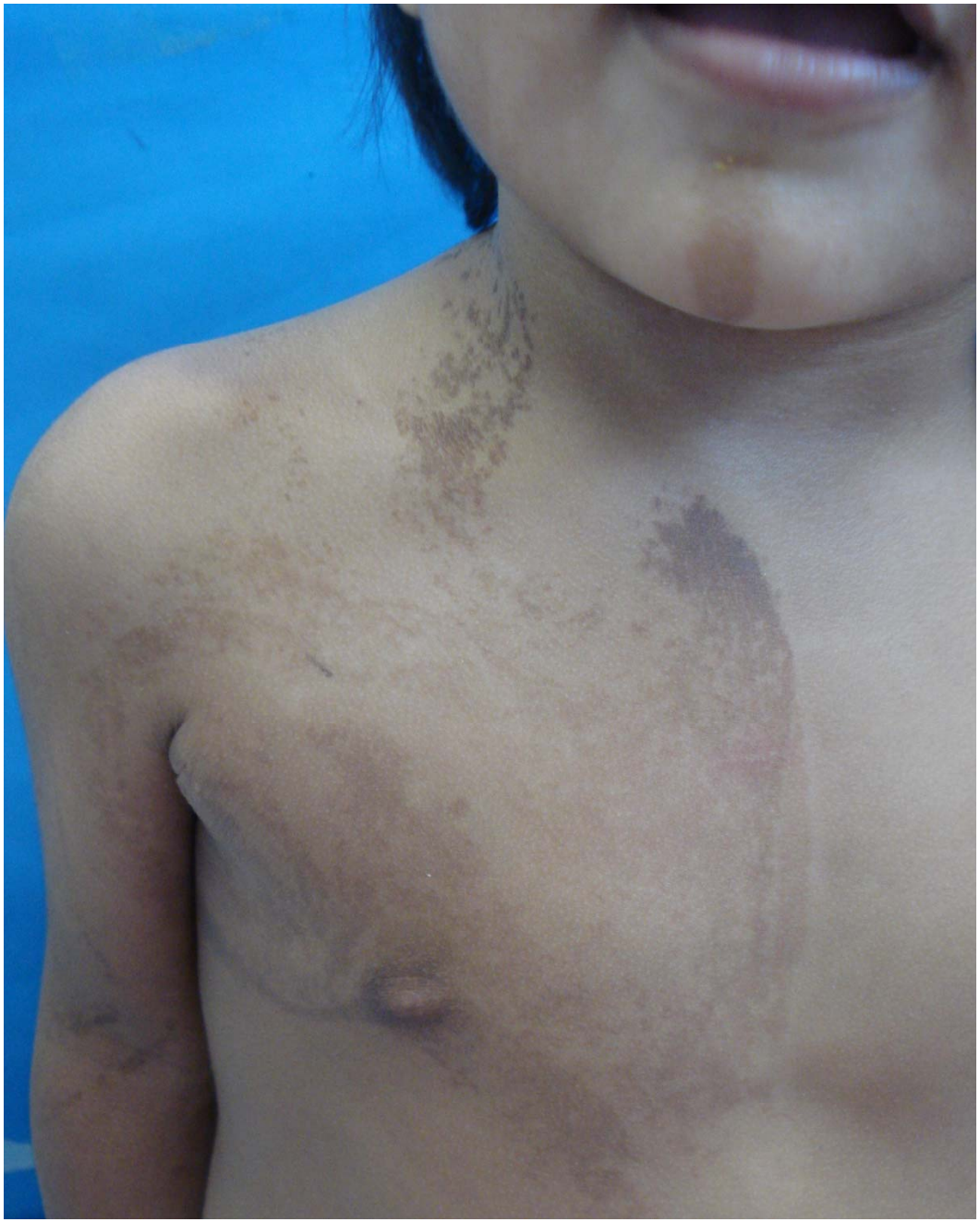
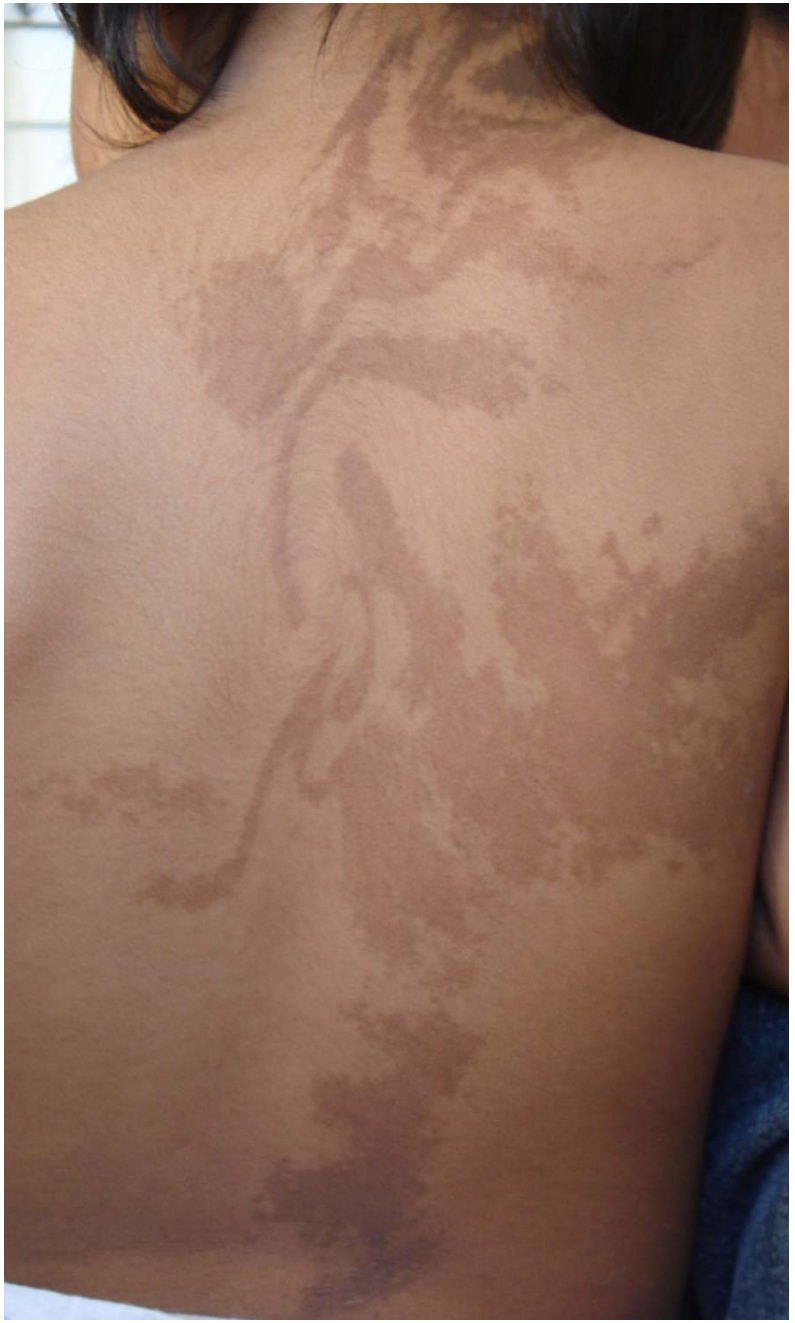
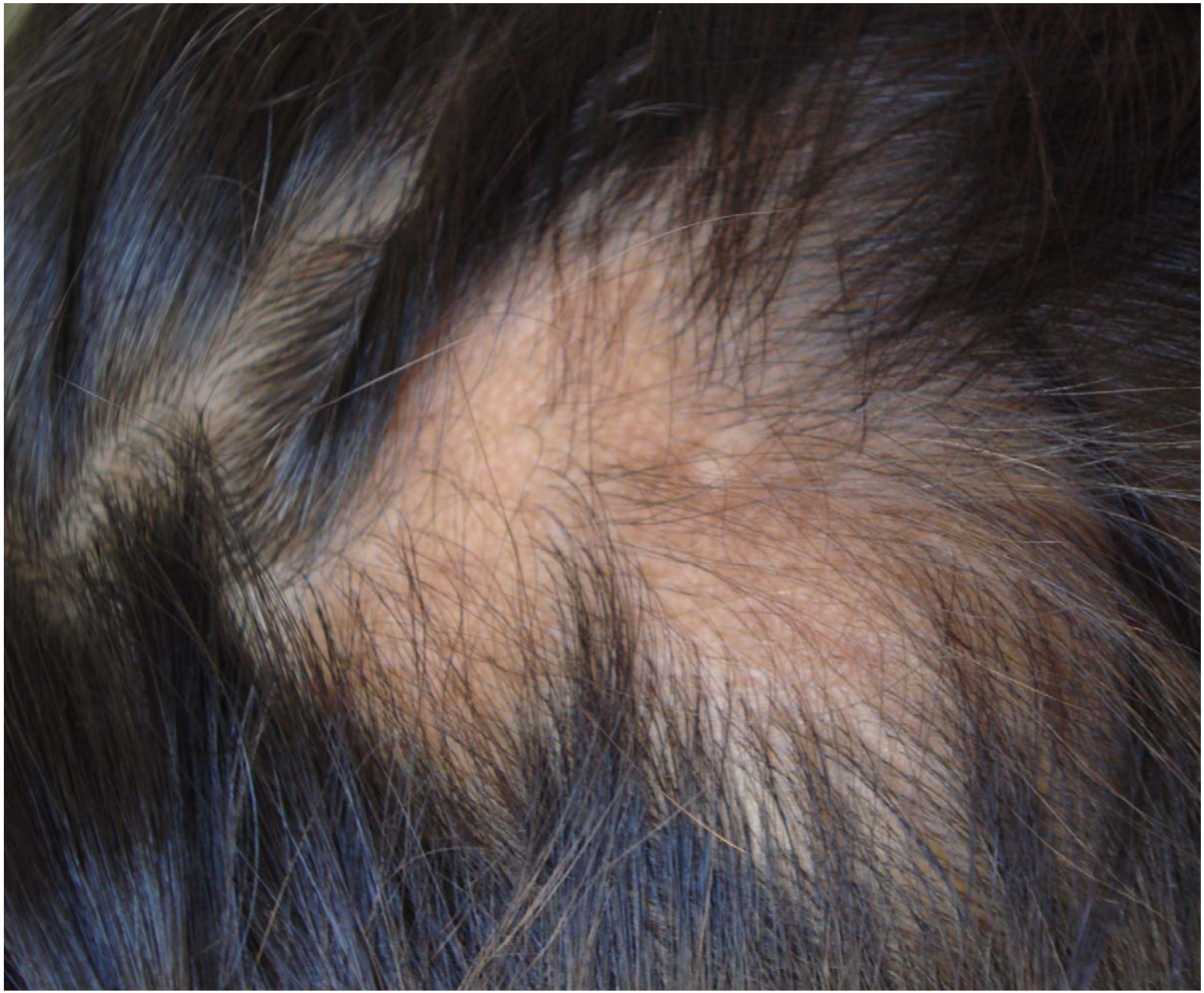
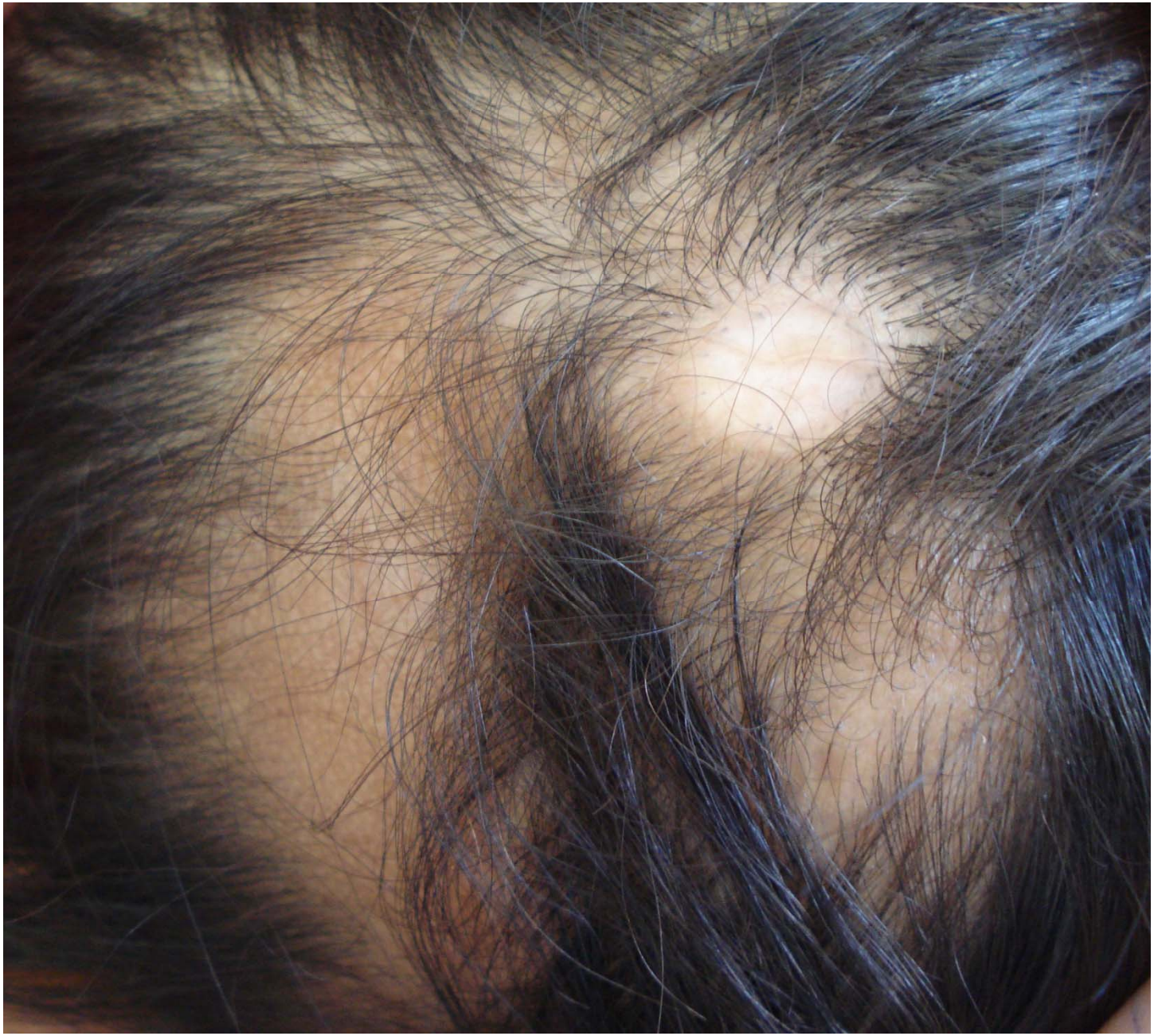






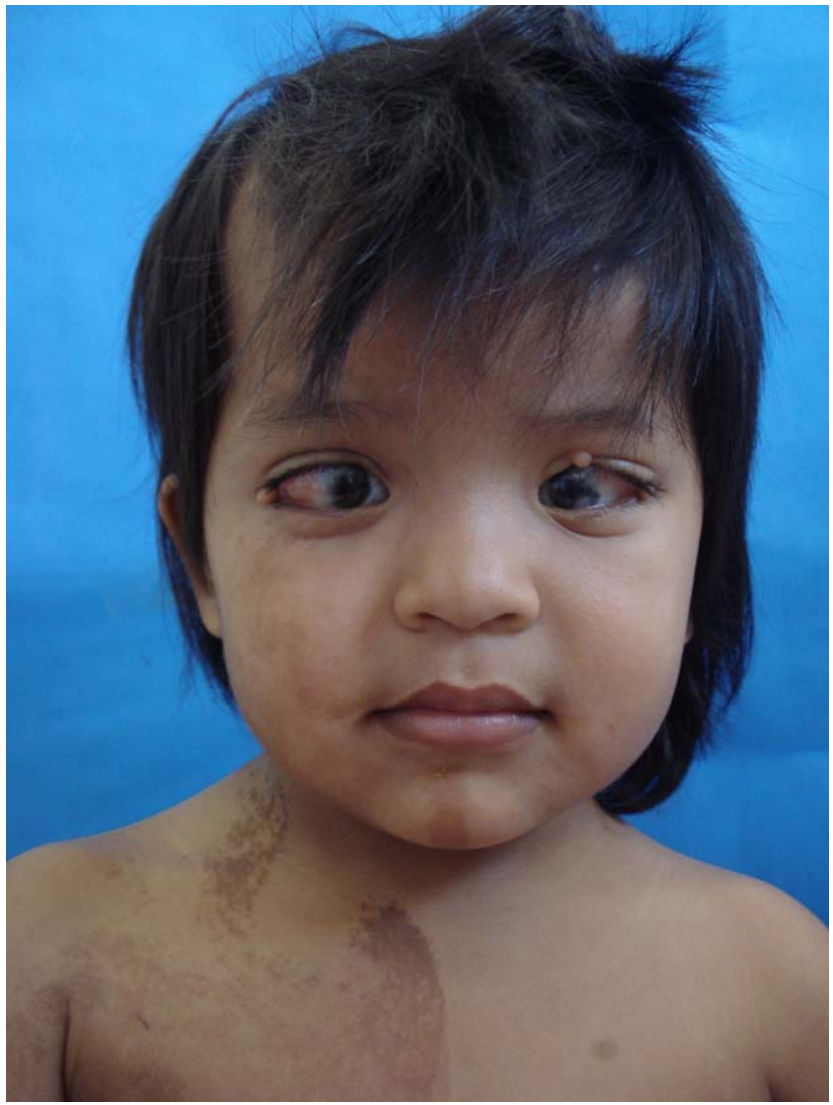






ALTERACIONES ESQUELÉTICAS

- Defectos craneofaciales
- Frente prominente
- Base ancha nasal
- Cifoescoliosis



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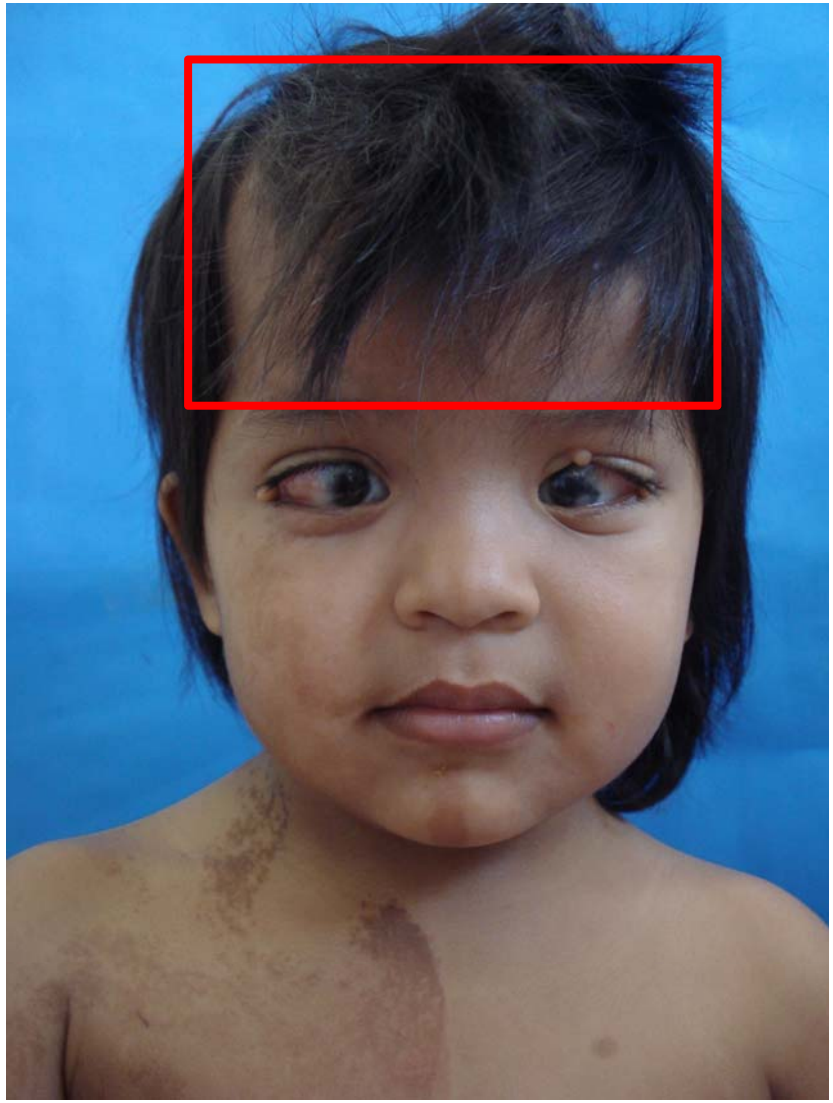

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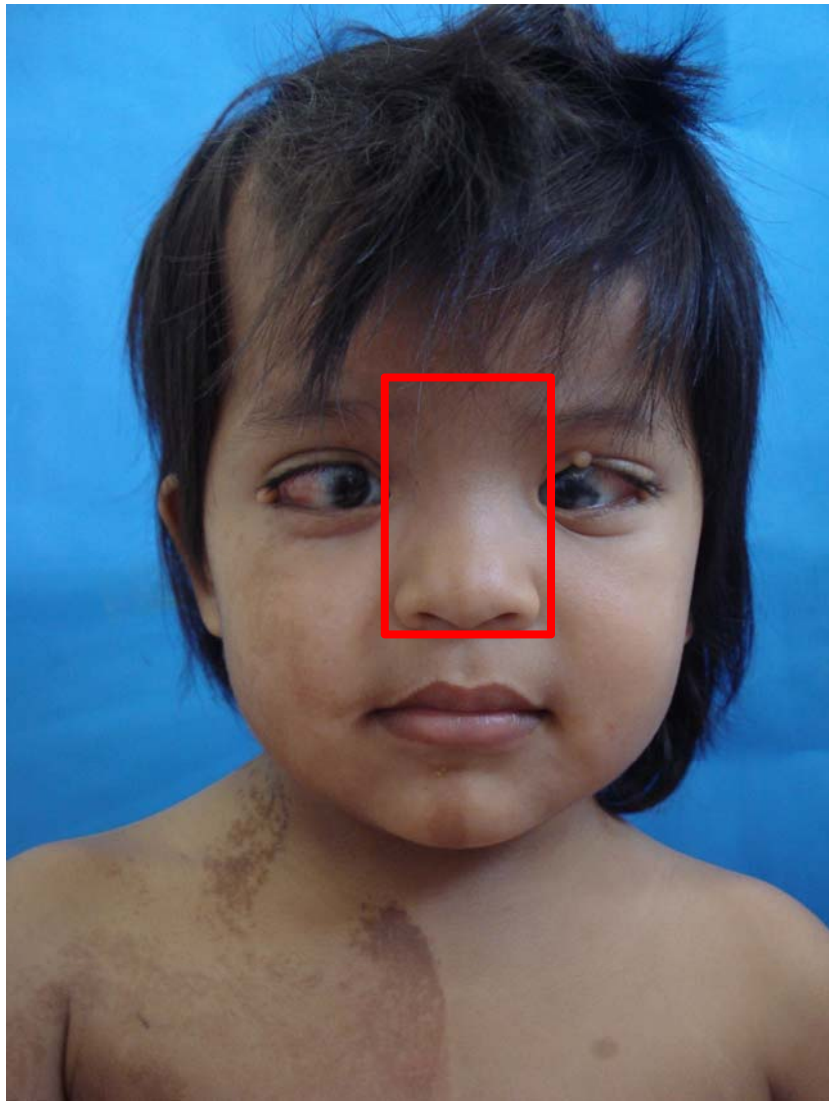

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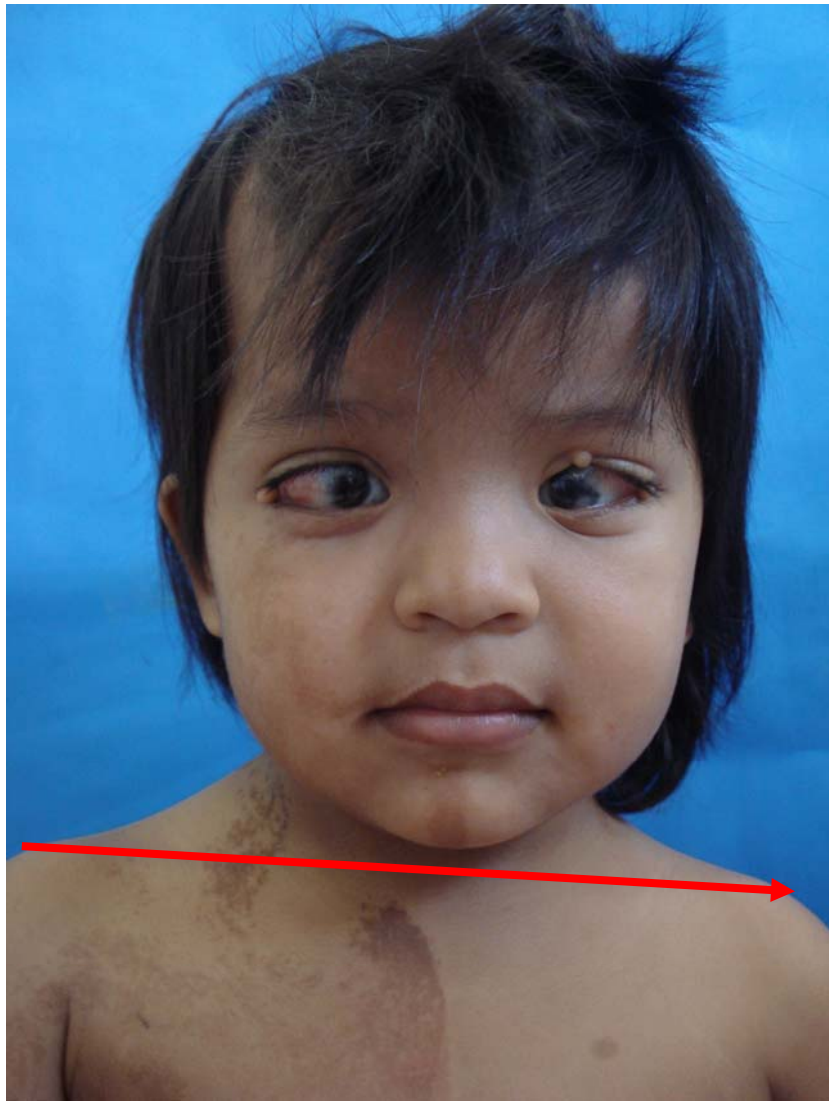
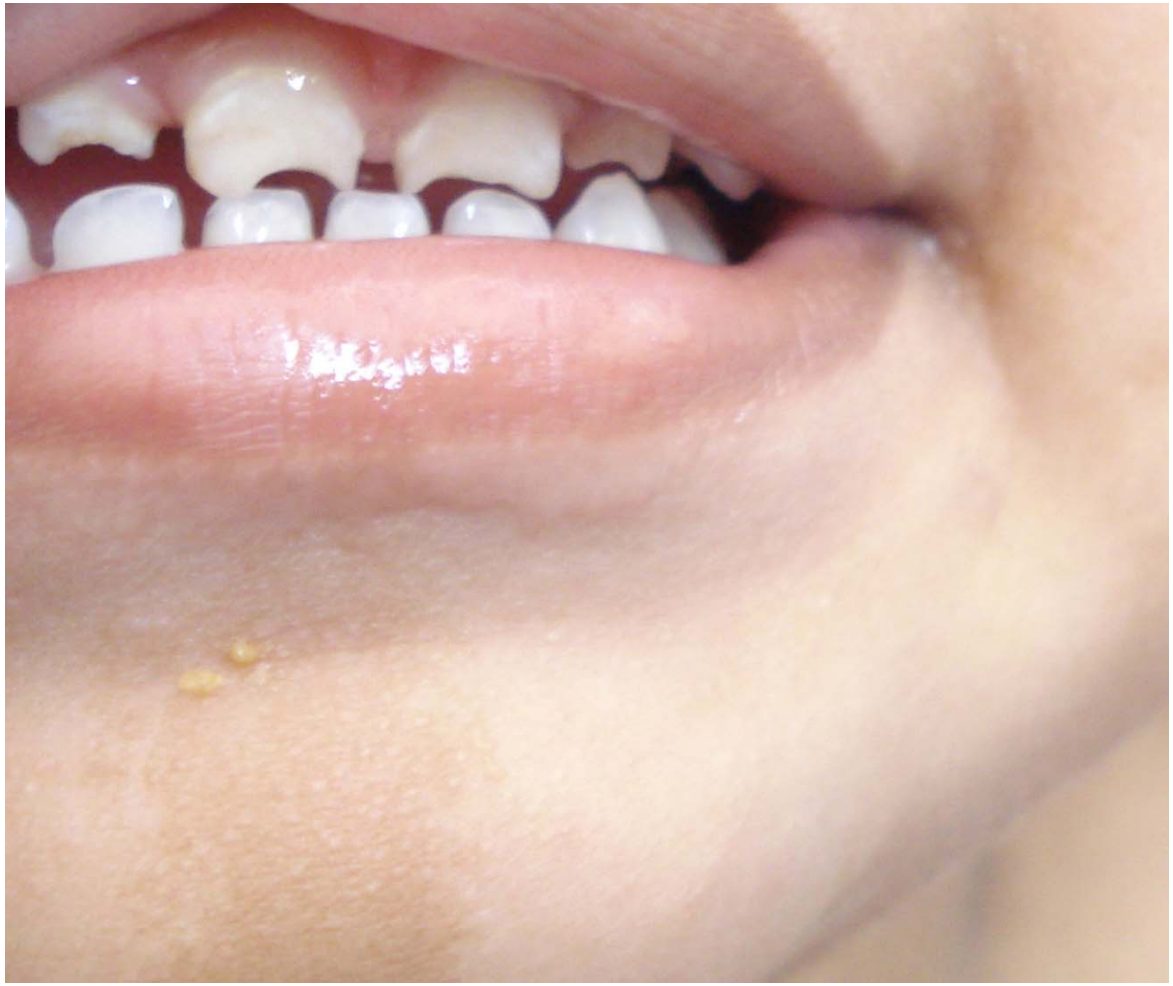


ALTERACIONES ODONTOLÓGICAS



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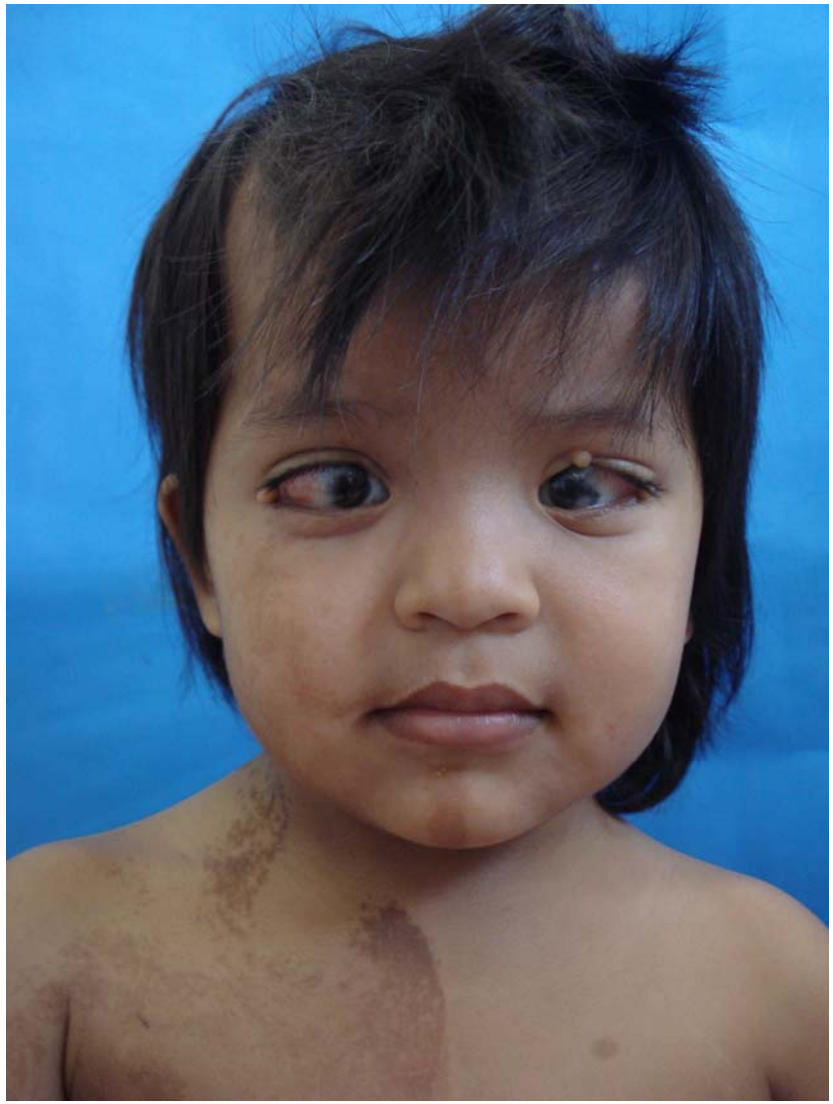
ALTERACIONES OCULARES

- Lipodermoide

epibulbar

- Coloboma



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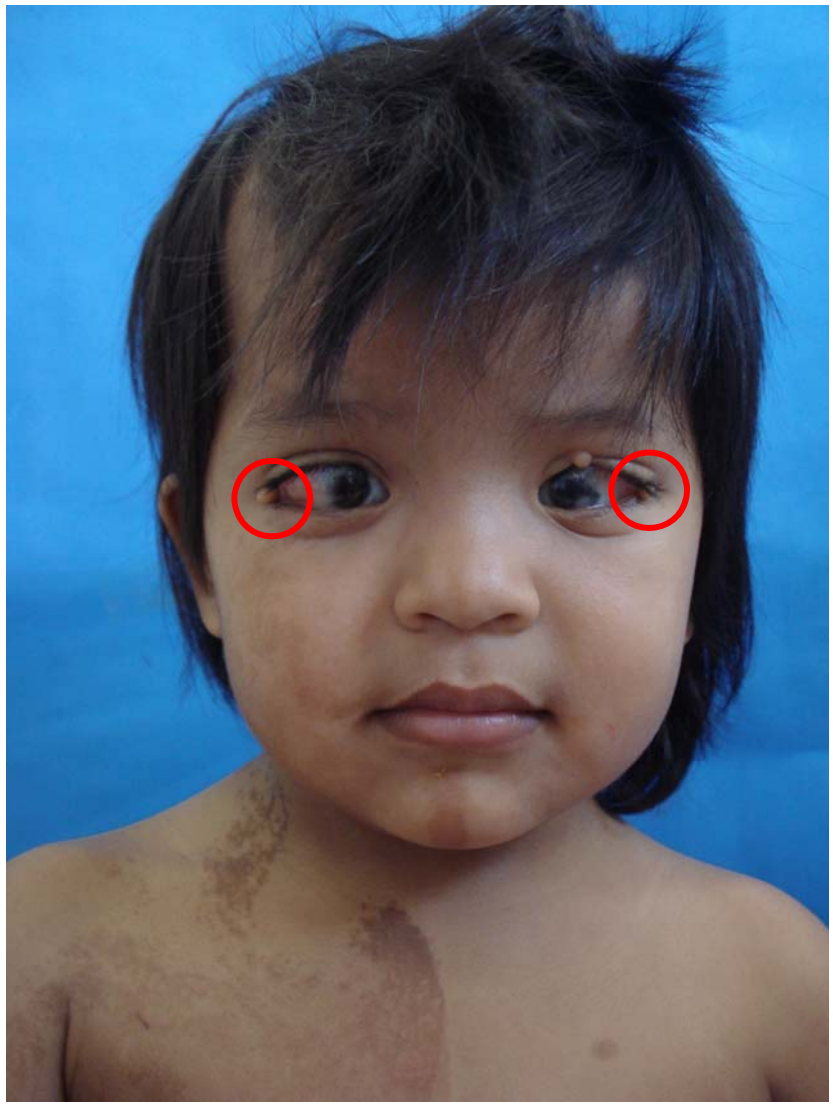

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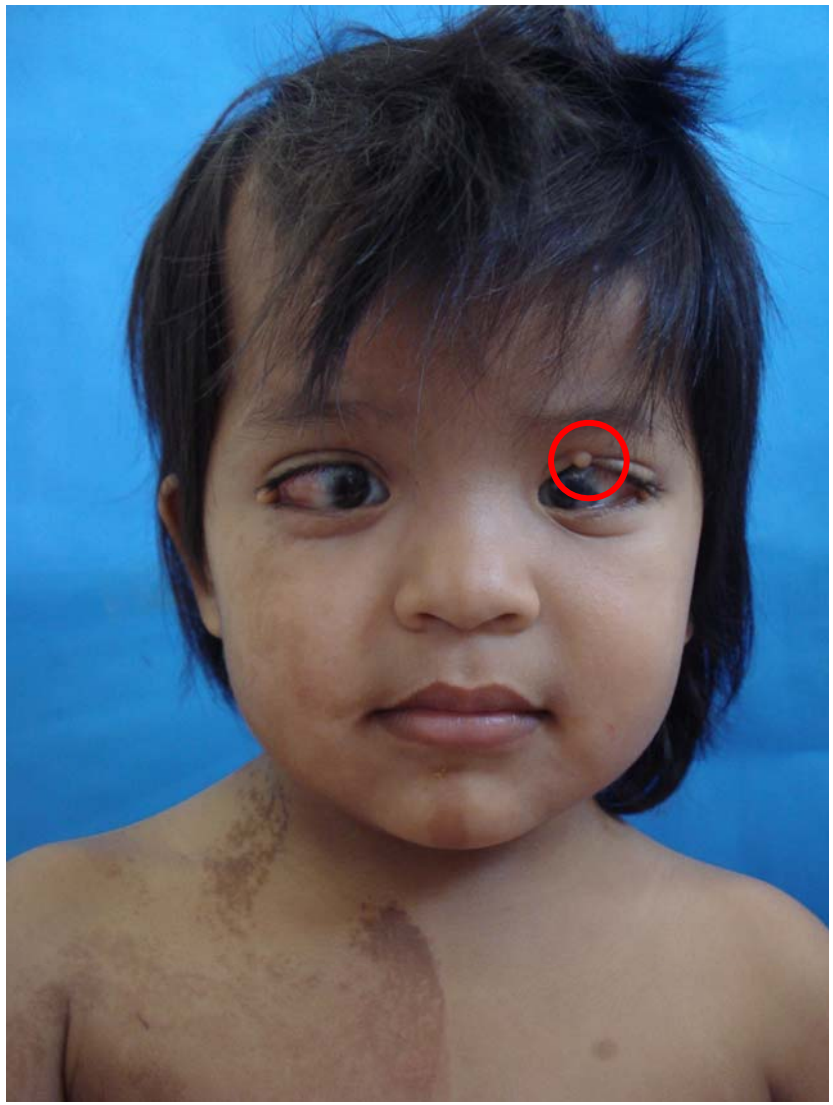

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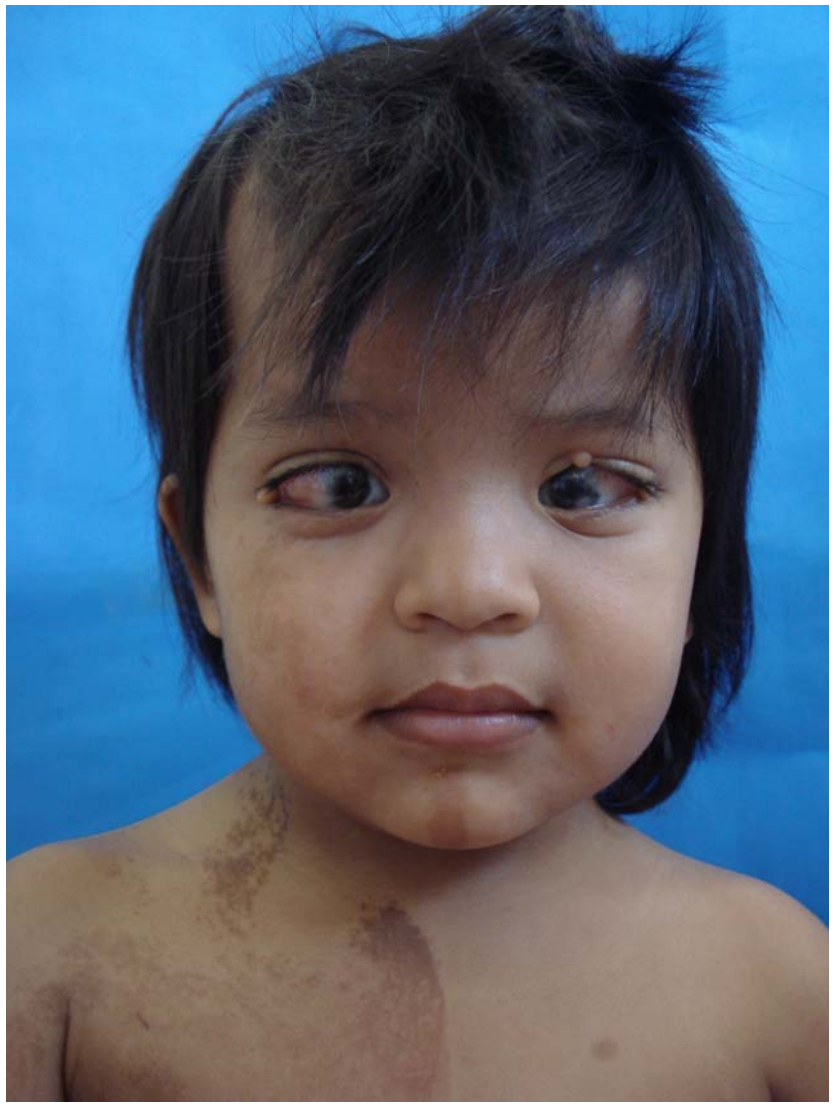

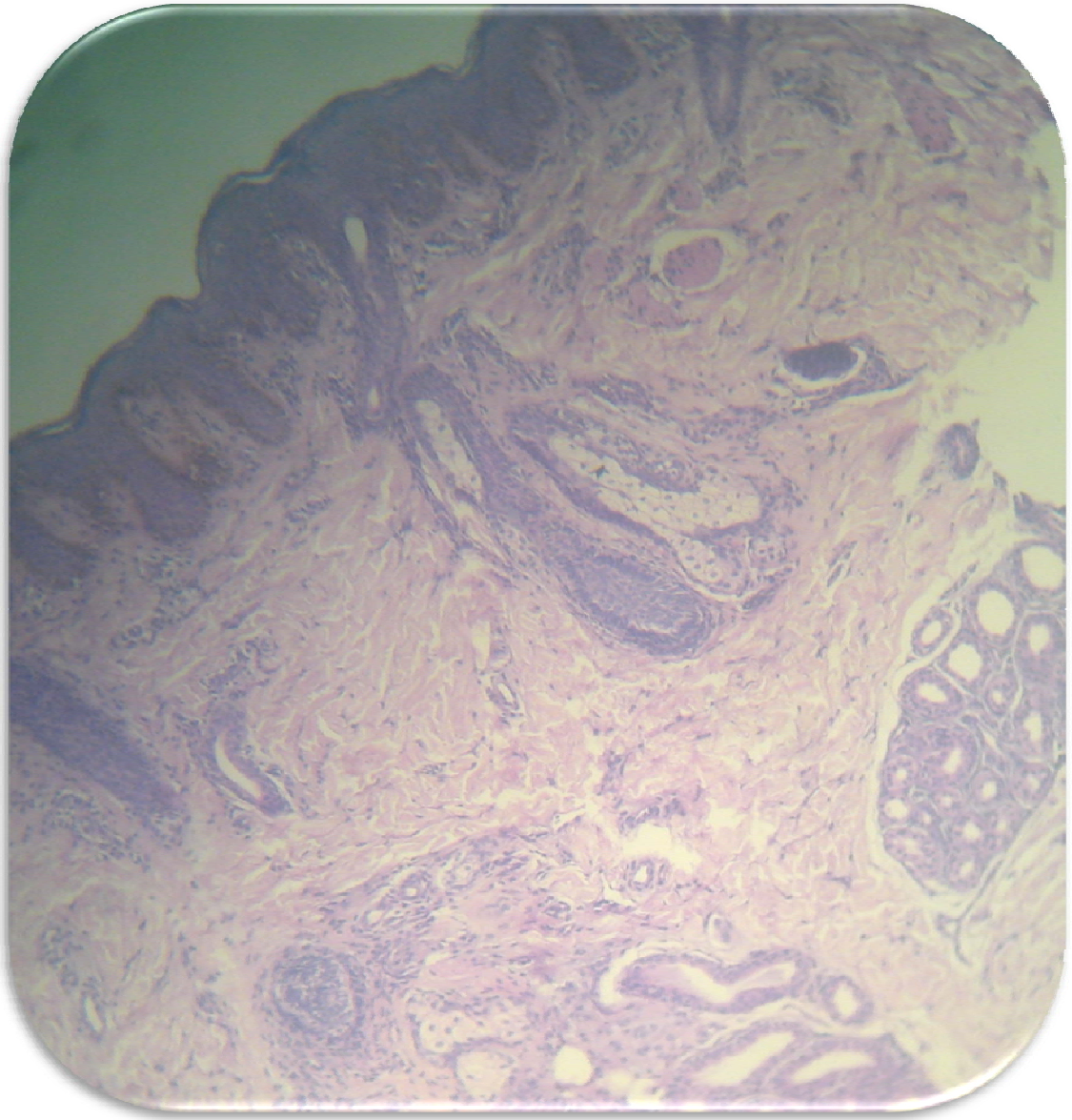

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NEVO SEBÁCEO DE JADASSOHN

ESTUDIOS COMPLEMENTARIOS

- RMN de cerebro: Atrofia de cavidades ventriculares derechas (dimensiones mayores a las normales)
- RMN de órbitas: sin particularidades
- Angio RMN de cerebro: Hipoplasia de segmento A1 derecho

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SÍNDROME DE SCHIMMELPENNING

TRATAMIENTO

- Control evolutivo
- HTA: Enalapril
- Lesiones oftalmológicas: excéresis quirúrgica
- Seguimiento multidisciplinario

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SINDROME DE SCHIMMELPENNING

- Nevo sebáceo
- Alteraciones neurológicas
- Alteraciones esqueléticas
- Alteraciones oftalmológicas

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nature genetics

Postzygotic *HRAS* and *KRAS* mutations cause nevus sebaceous and Schimmelpenning syndrome

Leopold Groesser[1], Eva Herschberger[1], Arno Ruetten[2], Claudia Ruivenkamp[3], Enrico Lopriore[4], Markus Zutt[5], Thomas Langmann[6,7], Sebastian Singer[1], Laura Klingseisen[8], Wulf Schneider-Brachert[8], Agusti Toll[9], Francisco X Real[10,11], Michael Landthaler[1] & Christian Hafner[1]

Nevus sebaceous is a common congenital cutaneous malformation. Affected individuals may develop benign and malignant secondary tumors in the nevi during life. Schimmelpenning syndrome is characterized by the association of nevus sebaceous with extracutaneous abnormalities. We report that of 65 sebaceous nevi studied, 62 (95%) had mutations in the *HRAS* gene and 3 (5%) had mutations in the *KRAS* gene. The *HRAS* c.37G>C mutation, which results in a p.Gly13Arg substitution, was present in 91% of lesions. Nonlesional tissues from 18 individuals had a wild-type sequence, confirming genetic mosaicism. The *HRAS* c.37G>C mutation was also found in 8 of 8 associated secondary tumors. Mosaicism for *HRAS* c.37G>C and *KRAS* c.35G>A mutations was found in two individuals with Schimmelpenning syndrome. Functional analysis of *HRAS* c.37G>C mutant cells showed constitutive activation of the MAPK and PI3K-Akt signaling pathways. Our results indicate that nevus sebaceous and Schimmelpenning syndrome are caused by postzygotic *HRAS* and *KRAS* mutations. These mutations may predispose individuals to the development of secondary tumors in nevus sebaceous.

Schimmelpenning syndrome (MIM 163200) is defined by the association of nevus sebaceous with cerebral, ocular or skeletal defects[7] (**Fig. 2**). In a study of 196 individuals with nevus sebaceous, 7% were found to have neurological abnormalities such as mental retardation, seizures and hemimegalencephaly[8]. Ocular abnormalities in the context of Schimmelpenning syndrome may include lipodermoids and coloboma. Skeletal defects comprise incomplete formation of bony structures, hypoplastic bones, short stature and vitamin D–resistant hypophosphatemic rickets[1,9]. It has been proposed that both nevus sebaceous and Schimmelpenning syndrome result from genetic mosaicism, limited to the skin in nevus sebaceous and extending to other organs in Schimmelpenning syndrome[9,10]. However, the underlying genetic causes of nevus sebaceous and Schimmelpenning syndrome have remained unknown.

We analyzed tissue from 65 individuals with nevus sebaceous and two individuals with Schimmelpenning syndrome for the presence of *RAS* hotspot mutations. Sanger sequencing of *HRAS* exon 1 and a *RAS* SNaPshot multiplex assay identified *HRAS* and/or *KRAS* mutations in 63 sebaceous nevi (97%; **Fig. 1c**, **Table 1** and **Supplementary Table 1**). *HRAS* mutations were present in 62 of the lesions (95%). *HRAS* c.37G>C represented a hotspot mutation found in 59 sebaceous nevi (91%). We also identified the following

SINDROME DE SCHIMMELPENNING

- Alteraciones esqueléticas:
- Defectos craneofaciales
- Frente prominente
- Cifoescoliosis
- Dislocación de cadera
- Deformidad de extremidades
- Raquitismo hipofosfatémico

- Alteraciones oculares:
- Lipodermoide epibulbar
- Coloboma
- Opacidad corneal
- Defectos de nervio óptico

SINDROME DE SCHIMMELPENNING

- Deficiencia mental
- Deficiencia cognitiva
- Convulsiones
- Hemimegalencefalia
- Agiria cortical, microgiria o paquigiria

- Agenesia de cuerpo calloso
- Displasia de vasos cerebrales
- Malformación de Dandy-Walker

SÍNDROME DE SCHIMMELPENNING

- Genodermatosis poco frecuente
- Rasopatía en mosaico
- Alteraciones neurológicas ipsilaterales a lesiones cutáneas
- Tratamiento variable

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MUCHAS GRACIAS