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Genital Lentigines in a 6-Year-Old Boy with a Family History of Cowden's Disease: Clinical and Genetic Evidence of the Linkage Between Bannayan–Riley–Ruvacalba Syndrome and Cowden's Disease

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Abstract

Background: In 1997, it was reported that a PTEN gene deletion, a common genetic mutation in Cowden's disease (CD), was identified in a patient with Bannayan–Riley–Ruvacalba (BRR), suggesting that the two diseases were allelic. However, the clinical overlap between the two diseases has largely remained unclear.

Objective: To confirm the genetic and clinical association in a family segregating both CD and BRR.

Methods: Clinical evaluation and genetic analysis using a denaturing gradient gel electrophoresis (DGGE), temporal temperature gradient electrophoresis (TTGE), and DNA sequencing techniques.

Results: Our patient presents with typical BRR clinical manifestations, including multiple lentigines on his penis, while his mother presents with typical manifestations of CD, including multiple malignancies. Genetic analyses of leukocytes from the patient and his mother showed mutations in exon 8 that was identified as the presumably truncating mutation R335X.

Conclusion: This report provides clinical evidence that both BRR and CD are closely related and confirms the PTEN gene mutation in BRR and CD patients segregating in the same family, thus confirming the genetic linkage between the two genodermatoses.

Sommaire

Antécédents: En 1997, Arch et ses collaborateurs ont été les premiers à rapporter la délétion du gène PTEN mutation génétique fréquemment observée dans la maladie de Cowden, chez un patient atteint de la maladie de Bannayan-Riley-Ruvacalba, indiquant que les deux maladies sont alléliques. Toutefois, le chevauchement clinique entre les deux maladies est demeuré en grande partie inexpliqué.

Objectifs: Confirmer le lien sur les plans génétique et clinique entre la maladie de Cowden et la maladie de Bannayan-Riley-Ruvacalba dans une famille où les deux maladies coexistent.

Méthodes: Évaluation clinique et analyse génétique par électrophorèse sur gel-SDS, temporal temperature gradient electrophoresis (TTGE) et techniques de séquençage de l'ADN.

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Résultats: Notre patient présente des signes cliniques caractéristiques de la maladie de Bannayan-Riley-Ruvacalba, y compris la présence de lentigines multiples sur le pénis, alors que sa mère présente des signes caractéristiques de la maladie de Cowden, y compris de multiples lésions malignes. Les analyses génétiques des leucocytes du patient et de ceux de sa mère ont montré une mutation dans le gène Exon 8 qui a été identifiée comme la mutation par troncation R335X probable.

Conclusion: Ce rapport fournit des données cliniques à l'effet que la maladie de Bannayan–Riley–Ruvacalba et la maladie de Cowden sont étroitement liées et confirme la mutation du gène PTEN chez les membres d'une même famille où les deux génodermatoses coexistent, confirmant ainsi leur liaison génétique.

Bannayan–Riley–Ruvacalba (BRR) or Banayan–Zonana (BZ) syndrome is an exceedingly rare autosomal dominant genodermatosis characterized by macrocephaly, genital lentigines, motor and speech delay, mental retardation, colonic hamartomatous polyps, myopathies, lipomas, and hemangiomas.[1] Other occasional findings include pseudopapillomas, diabetes mellitus, Hashimoto's thyroiditis, acanthosis nigricans, lymphangiomas, angiokeratomas, verrucous vulgaris-type facial lesions, café-au-lait spots, tongue polyps, supernumerary nipples, enlarged testes, and an enlarged penis. Arch et al.[2] first described a PTEN gene deletion, a mutation reported to cause Cowden's disease (CD), in an 18-month-old patient previously diagnosed with BRR syndrome. However, whether this PTEN gene mutation is associated with clinical manifestations remains unclear. We report a family segregating both BRR and CD that showed the same PTEN gene mutation in exon 8.

Case Report

A six-year-old Caucasian boy with mild mental retardation and developmental delay was brought to the dermatology clinic for evaluation of multiple brown lesions on his penis. The patient was born with macrocephaly and multiple small papules on the occipital scalp. At the age of 9 months, light brown spots developed on his penis. Dermatological examination of this boy revealed multiple well-marginated brown macules located on his penis glans and shaft (Fig. 1). Additionally, several discrete verrucous papules were observed on his face and nose. Over time, these genital lentigines progressively darkened, multiplied, and enlarged. The patient's 29-year-old mother was diagnosed with CD at age 10 and developed a wide spectrum of clinical manifestations, including facial trichilemmomas, thyroid carcinoma, bilateral breast fibroadenomas, benign fibrocystic disease, and osteomas.[1]

In view of the possible overlap between the two genodermatoses, the boy and his mother were referred to the Department of Human Genetics at Mount Sinai Medical Center and leukocytes from both patients were collected. The specimens were shipped to a research laboratory at Harvard University School of Medicine. Using denaturing gel electrophoresis (DGGE) and temporal temperature gradient electrophoresis (TTGE), the results showed that both patients had a variant in PTEN exon 8. The further sequencing of exon 8 identified the presumably truncating mutation in both patients.

FIGURE 1 Well marginated brown macules located on penis glans and shaft. (Color figure available online).

Discussion

Cohen[3] coined the term Bannayan–Riley–Ruvacalba (BRR) syndrome in 1990 when he reported that the three conditions described by Bannayan, et al. and by Ruvacalba et al. actually represented one etiological entity[2]. The syndrome is inherited autosomal dominantly and has a male predominance. Approximately 80% of cases occur in males. Since Bannayan[4] first described this disorder in 1971, only a limited number of cases have been reported.

TABLE I

Clinical features of BRR syndrome and CD

	BRR	*CD*	*Overlapping features*
Inheritance	Autosomal dominant	Autosomal dominant	Autosomal dominant
Mucocutaneous	Facial papules Lipomas[a] Genital lentigines Hemangiomas Acanthosis nigricans[a]	Facial papules (trichilemmomas and verrucae) Oral papillomas Acral keratosis Hemangiomas	Facial papules Hemangiomas
Thyroid	Carcinoma	Goiter/adenoma Hyper/hypothyroidism Carcinoma	
Gastrointestinal	Polyps Carcinoma	Polyps	Polyps
Mammary		Fibrocystic disease Adenocarcinoma	
CNS	Mental retardation Seizures	Mental retardation Lhermite–Duclos disease	Mental retardation
Skeletal anomalies	Macrocephaly Pectus excavatum Down-slanting palpebral fissures Joint hyperextensibility	Macrocephaly Pectus excavatum	Macrocephaly Pectus excavatum

[a] These cutaneous features are occasionally found in CD.

Our 6-year-old patient presented with characteristic clinical manifestations of BRR, including macrocephaly, genital lentigines, motor and speech delay, mental retardation, and verrucous vulgaris-type facial lesions. The patient has no family history of BRR; however, his mother was diagnosed with CD at age 10. We first reported this family segregating both BRR and CD at the 1998 summer meeting of the American Academy of Dermatology and speculated that there might be a correlation or overlap between BRR syndrome and CD. Although both disorders are autosomal dominantly inherited, they have distinct phenotypic features with partial clinical overlap (Table I). The former is a childhood disease whereas the latter primarily occurs in adults.[5] Most recently, two similar cases reported the coexistence of features common in both genodermatoses within the same family.[6]

Evidence has recently surfaced that these two diseases may genetically have the same allele. Arch et al.[2] first reported an interstitial gene deletion of 10q23.2–q24.1 in an 18-month-old boy previously diagnosed with BRR[2]. This mutation region includes the PTEN gene, a mutation that has been reported to cause CD. However, the parents of the patient did not have clinical features of CD or BRR syndrome. Therefore, the correlation remained skeptical.

A number of studies have confirmed a genetic link between CD and BRR syndrome, suggesting that a PTEN gene halo insufficiency plays a crucial role in CD and BRR syndrome.[7,8] Although genetic analyses[2,7,8] and clinical observation[3,6] suggest an association between CD and BRR syndrome, this is the first report that provides both clinical and genetic evidence of segregation of these two diseases. However, why the deletion or mutation of the same allele exhibits different clinical features in adults and children and what is the mechanism by which the gene product modifies the clinical manifestations is not currently understood and clearly requires further investigation.

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References

1. Yen BC, Kahn H, Schiller AL, et al. Multiple hamartoma syndrome with osteosarcoma. Arch Pathol Lab Med 1993; 117:1252–1254.
2. Arch EM, Goodman BK, Van Wesep RA, et al. Deletion of PTEN in a patient with Bannayan–Riley–Ruvacalba syndrome suggests allelism with Cowden's disease. Am J Med Genet 1997; 71:489–493.
3. Cohen Jr MM. Bannayan–Riley–Ruvacalba syndrome: remaining three formerly recognized syndromes as one etiological entity. Am J Med Genet 1990; 35:291.
4. Bannayan GA. Lipomatosis, angiomatosis, and macrocephaly: a previously undescribed congenital syndrome. Arch Pathol 1971; 92: 1–5.
5. Fargnoli MC, Orlow SJ, Semel-Conception J, et al. Clinicopathologic findings in the Bannayan–Riley–Ruvacalba syndrome. Arch Dermatol 1996; 132:1214–1218.
6. Perrriard J, Saurat JH, Harms M. An overlap of Cowden's disease and Bannayan–Riley–Ruvacalba syndrome in the same family. J Am Acad Dermatol 2000; 42:348–350.
7. Di-Cristofano A, Pesce B, Cordon-Cardo C, et al. PTEN is essential for embryonic development and tumour suppression. Nat Genet 1998; 19:348–355.
8. Marsh DJ, Coulon V, Lunetta KL, et al. Mutation spectrum and genotype–phenotype analyses in Cowden disease and Bannayan–Zonana syndrome, two hamartoma syndromes with germline PTEN mutation. Hum Mol Genet 1998; 7:507–515.