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Novel CYLD1 truncating mutation in Brooke-Spiegler syndrome: A case report

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Abstract

Brooke–Spiegler Syndrome (BSS) is a rare, inherited, autosomal dominant disorder characterized by development of multiple adnexal cutaneous neoplasms. Pathogenic variants in the *CYLD* gene represent the major genetic risk factor for BSS. In this study we reported the genetic analysis in a 45 years old woman with clinical diagnosed BSS and a positive family history for suspected BSS.

Genetic analysis, of *CYLD* gene, revealed the c.2578G>T (p.Glu860Ter) truncating variant. This is a novel variant not reported in the population databases (ExAC and Gnomad) and in the literature. However, it could be classified as a pathogenic variant, based on America College of Medical Genetics guidelines and on *in silico* analyses.

In conclusion we suggested the classification of c.2578G>T *CYLD* variant as pathogenic, increasing the catalog of known *CYLD* pathogenic variants in patients with BSS. Overall, the identification of new *CYLD* pathogenic variants could improve knowledge on BSS and its prognosis, with implications in the clinical management of the patients and their relatives.

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Introduction

Brooke–Spiegler syndrome (BSS) is a rare, inherited, dominant disorder characterized by development of multiple adnexal cutaneous neoplasms (cilindromas, trichoepithelioma and spiradenoma), typically occurred in the head and neck region, particularly on the scalp, and increasing in size and number during the lifetime. Although congenital, BSS typically manifests in the second or third decade with major frequency in female individuals [1,2].

Tumors included in the spectrum of this syndrome are usually benign, but may occasionally evolved in malignant disease [3].

Germ line pathogenic variants of *CYLD* gene represent the major genetic risk factor for BSS, since they are reported in 80-85% of patients with classical BSS phenotype [2,4,5]. *CYLD* is a tumor suppressor gene that encodes for a cytoplasmic deubiquitinating enzyme that regulates the activities of many cellular and signaling pathways, and its pathogenic variants, causing functional inactivation of CYLD protein, may results in aberrant activation of these signaling pathways, which contribute to the development of skin adnexal tumors [6].

The majority of *CYLD* pathogenic variants reported are truncating variants that affect the catalytic box which extends to the carboxy-terminus of the protein, between exons 9 and 20 [2,4-7] and produce an inactive enzyme. Very few missense variants have been reported. No convincing genotype-phenotype correlations have been identified. There is a suggestion that individuals with pathogenic missense variants may have a milder phenotype, compared with who carried truncating variants. However, as missense variants constitute a minority of pathogenic variants in affected individuals, further studies are needed to investigate this hypothesis [8].

Overall, the specific biological aspects, such as the molecular mechanisms of phenotypic variation and the impact of different type of mutations, of cutaneous syndrome related to *CYLD* mutation are still poorly understood. Here we report genetic analysis in a case with clinical diagnosis of BSS.

Case report

We reported a case of 45 years old woman with multiple nodular lesions on the scalp, trunk and upper limbs and showing white small milia on the face, and numerous and asymptomatic papules besides milia in the glabellar and perinasal regions (Figure 1).

Histopathological examination of the two scalp nodules and of the lesion of the trunk, revealed typical characteristics of cutaneous cylindroma, with clusters of basophilic cells, well-distributed, organized, in the context of the proliferation, and arranged in an interlocking "jigsaw" pattern (Figure 2).

Histopathological examination at low magnification of one perinasal popular lesion showed histological features corresponding to trichoepitelioma, with a well-organized dermal proliferation, constituted by clusters of basophilic, monomorphic, totipotent cells, arising from the hair follicle. We diagnosed BSS on the basis of clinical and histological data.

A positive family history for suspected BSS by paternal lineage (grandmother, aunt and cousin), was also referred to the genetic counselling (Figure 3).

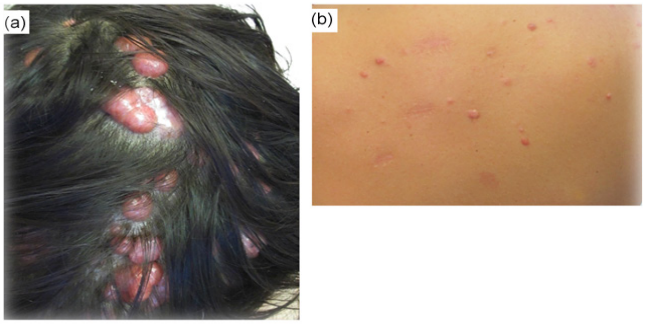

Figure 1: (a) Encapsulated proliferation composed of numerous islands of epithelial cells, varying in size and shape, separated by their hyaline sheath and a narrow of band of collagen. **(b)** The islands of epithelial cells seem to fit together like as pieces of a jigsaw puzzle. Droplets of hyalin are present in many islands.

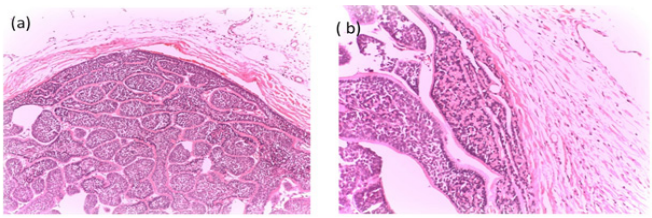

Figure 2: (a) Encapsulated proliferation composed of numerous islands of epithelial cells, varying in size and shape, separated by their hyaline sheath and a narrow of band of collagen. **(b)** The islands of epithelial cells seem to fit together like as pieces of a jigsaw puzzle. Droplets of hyalin are present in many islands.

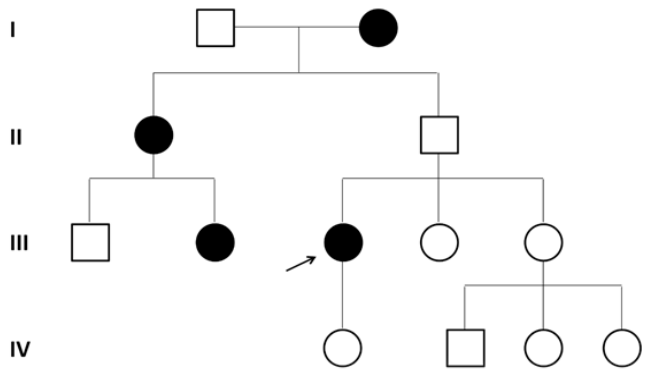

Figure 3: Genealogic pedigree. Proband is indicate by the arrow. Affected female (black circle) are spread over several generations. Note the incomplete penetrance in male subjects (II-2).

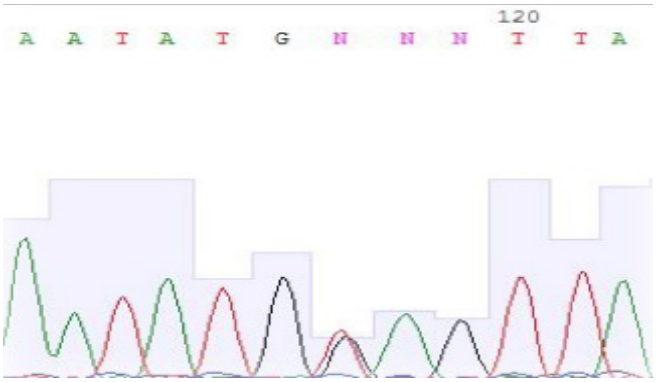

Figure 4: Electropherogram for the heterozygous G to T trans version at codon 860 of the CYLD gene (black narrow), leading to a nonsense mutation.

To confirm the clinical evidence of BSS, Sanger sequencing of *CYLD* gene (NM_015247.3) on germ line DNA has been performed. A detailed list of methods and primers list are available upon request.

Molecular analysis identified a novel truncating variant, c.2578G>T (Figure 4), not reported in the population databases (ExAC and Gnomad) and in the literature. It is located in exon 17, in the ubiquitin-specific protease domain (Figure x) and introduces a premature stop codon (p.Glu860Ter). *In silico* analyses using SIFT, PolyPhen-2, Align-GVGD, Mutpred Mutation Taster and Proven software indicate this variant as possible pathogenic/damaging/deleterious, and predict it may result in a truncated CYLD protein. Overall, it may be classified as pathogenic variant, according to ACMG-AMP guidelines [9], as meets the criteria that combined lead to pathogenic classification, in particular 1 very strong (PVS1) + 1 moderate (PM2) + 1 supporting (PP3) criteria [9].

Unfortunately, it was not possible to perform genetic analyses of the proband's family members showing BSS clinical pattern.

Discussion

BSS is a disease in which affected individuals are genetically predisposed to develop numerous cutaneous adnexal tumors predominantly in head and neck region [2,4]. BSS is inherited as an irregular autosomal dominant trait and pathogenic variants in *CYLD* gene are detected in almost all patients affected by BSS [2,4,5].

To date, a total of 107 different *CYLD* germ line pathogenic variants were reported in literature in patients developing a *CYLD* cutaneous syndrome [10]. The majority of these variant are deleterious, with a major frequency of frame shift and non-sense variants. Here we reported a case of 45 years old woman with clinically diagnosed BSS and positive family history for suspected BSS, for which *CYLD* molecular screening showed a novel germ line substitution, c.2578G>T (p.Glu860Ter), located in the ubiquitin-specific protease domain (exon 17) and determining a truncated untreated protein. Non-sense variants in exon 17 of *CYLD* gene has been reported in in other studies and it had been associated with cutaneous syndrome including BSS [10].

Based on *in silico* analysis and the ACMG guidelines, c.2578G>T variant could be classified as pathogenic. In particular, it meets the criteria of strong pathogenicity evidence (PVS1), as nonsense variants in *CYLD*, associated with cutaneous syndrome including BSS, moreover it has not been found in popular database such as Gnomad, meeting one criteria of moderate pathogenicity (PM2) and one criteria of supporting pathogenity (PP3) due the fact that *in silico* analysis indicate this variant as pathogenic [9].

The identification of new *CYLD* pathogenic variants could improve knowledge on BSS and its prognosis; in particular, with regard to the disease's severity. The correlation between type of pathogenic variant and clinical phenotype is not yet significant, but the variability of phenotypic expression of BSS cannot be separated from different germ line *CYLD* pathogenic variants [10].

The main limitation of this study was the impossibility of performing genetic analyses of the proband's relatives showing clinical history of suspected BSS.

Conclusion

Overall, by combining the clinical evidences with the genomic information provided by molecular analysis, we suggested the classification of the novel c.2578G>T *CYLD* variant as pathogenic, increasing the spectrum of *CYLD* pathogenic variants associated to BSS. Our report reinforces the need for health professionals to be prepared to host, care, and provide genetic counseling for those patients. Moreover, the broadening of knowledge on the spectrum of *CYLD* pathogenic variants and the molecular mechanisms underlying this type of tumorigenesis could contribute to the achievement of new methods of prevention and therapy for subjects suffering from a *CYLD* related cutaneous syndrome, with implications in the clinical management of the patients and their relatives.

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