Putative phenotype modifying genetic factors associated with phenotypic diversity in Brooke-Spiegler syndrome

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INTRODUCTION

Brooke-Spiegler syndrome (BSS; OMIM 605041) is a rare monogenic skin disease characterized by the development of skin appendage tumors caused by mutations in the *cylindromatosis* (*CYLD*) gene. Despite the described phenotypes and reports of the underlying *CYLD* mutations, it has been difficult to establish genotype-phenotype correlations in BSS. We recently investigated two BSS pedigrees (Hungarian with Bukovinian origin and Anglo-Saxon), carrying the same disease-causing mutation (c.2806C>T, p.Arg936Ter) of the *CYLD* gene, in which the affected family members exhibit striking differences in their phenotypes.¹
The aim of our study was to identify putative phenotype-modifying genetic factors to further the understanding of genotype- phenotype correlations in BSS.

The Hungarian BSS pedigree

The English BSS pedigree

METHODS

High-throughput deep sequencing was performed on Illumina platform. The Agilent SureSelect Human All Exon V6 Kit was used for library construction. The sequencing data quality-control requirements were as follows: sequencing error rate <1%, average Q20 ratio >90%, average Q30 ratio >80%, average error rate <0.1%, sequencing read alignment rate ≥95%, read depth ≥10X. High-quality sequences were aligned with the human reference genome (GRCh37/hg19).

RESULTS

Comparing the WES data from the Hungarian and Anglo-Saxon BSS patients, three putative phenotype-modifying genetic variants were identified, which are present only in the Hungarian individuals: the rs1053023 SNP of the **signal transducer and activator of transcription 3 (STAT3)** gene, the rs1131877 SNP of the **tumor necrosis factor receptor-associated factor 3 (TRAF3)** gene and the rs202122812 SNP of the **neighbor of BRCA1 gene 1 (NBR1)** gene.

SNP ID (gene)	Location (variant type)	SIFT Polyphen2 MutationTaster	Clinical associations
rs1053023 (STAT3)	3'UTR region (3'UTR variant)	– – Polymorphism	Multiple sclerosis ² B-NHL ³ BSS
rs1131877 (TRAF3)	Exon (missense)	Tolerated Benign Polymorphism	Postradiotherapy toxicity ⁴ BSS
rs202122812 (NBR1)	Exon (missense)	Deleterious Probably damaging Disease causing	BSS

Pathogenicity predictions and clinical associations of the identified phenotype-modifying factors

Proposed mechanisms of the identified phenotype-modifying genetic factors

CONCLUSIONS

Our study contributes to the accumulating evidence for the clinical importance of phenotype-modifying genetic factors, which are potentially important for the elucidation of genotype–phenotype correlations and disease prognosis. In addition to these phenotypic modifying genetic variants, environmental or lifestyle factors might also contribute to the phenotypic diversity of BSS.

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