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Is BCL11B a potential candidate gene for the diffuse cutaneous mastocytosis: A case report

BCL11B geni diffüz kutanöz mastositoz için potansiyel bir aday gen midir: Olgu sunumu

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SUMMARY

Objective: Mastocytosis is a heterogeneous clinical phenotype spectrum characterized by the accumulation of mast cells in various organs. Cutaneous mastocytosis is the skin bounded form of this spectrum. Diffuse Cutaneous Mastocytosis (DCM) is a rare type of cutaneous mastocytosis that accounts for only 1 to 5% of all cases. The aim of this study is to report the molecular characterization of a Turkish patient with DCM with a large duplication on the long arm of chromosome 14, including the *BCL11B (CTIP2*) gene.

Case: A 32-months-old girl was referred to our department because of DCM and stuttering. In our patient who was born at 38 weeks of gestation after an uneventful pregnancy, in the neonatal period; recurrent episodes of diarrhea and atopic dermatitis began and DCM was diagnosed due to diffuse bullous lesions on the skin at the age of 4 months. Although growth and motor development were normal, there was language delay. Routine karyotype analysis of the case was normal (46,XX). In the microarray-CGH analysis, *de novo* 7.7 megabase (Mb) duplication containing 15 morbid OMIM genes including *BCL11B* gene at 14q32.2-q32.33 locus was detected.

Conclusions: *BCL11B*, which is highly expressed during the development of T lymphocytes, is a transcriptional regulatory protein. It has been shown immunohistochemically that *BCL11B* is also expressed in the normal human epidermis. We suggest that the *BCL11B* gene may be a potential candidate gene for diffuse cutaneous mastocytosis. Other cases with such clinical signs should be examined for mutations of the *BCL11B* gene.

Keywords: ArrayCGH; *BCL11B*; chromosome 14q duplication; *CTIP2*; mastocytosis.

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ÖZET

Amaç: Mastositoz, çeşitli organlarda mast hücrelerinin birikmesi ile karakterize heterojen bir klinik fenotip spektrumudur. Kutanöz mastositoz, bu spektrumun deriye sınırlı formudur. Diffüz Kutanöz Mastositoz (DCM), tüm vakaların sadece % 1- 5'ini oluşturan nadir bir kutanöz mastositoz tipidir. Bu çalışmanın amacı, *BCL11B (CTIP2)* geni

dahil olmak üzere kromozom 14'ün uzun kolunda büyük bir duplikasyon saptanan DCM'li bir Türk hastanın moleküler karakterizasyonunu bildirmektir.
Olgu: 32 aylık kız hasta, DCM ve kekemelik bulguları nedeni ile tarafımıza yönlendirildi. Sorunsuz bir gebelik sonrası 38. gebelik haftasında doğan hastamızda, yenidoğan döneminde; tekrarlayan ishal atakları ve atopik dermatit başlamış ve 4 aylıkken derideki yaygın büllöz lezyonlar nedeniyle DCM teşhisi konulmuş. Büyüme ve motor gelişimi normal olmasına rağmen dil gelişiminde gecikme mevcuttu. Olgunun rutin karyotip analizi normaldi (46, XX). Mikroarray-CGH analizinde, 14q32.2-q32.33 lokusunda BCL11B geni dahil 15 morbid OMIM genini içeren de novo 7.7 megabaz (Mb) duplikasyon saptandı.
Sonuç: T lenfositlerin gelişimi sırasında yüksek oranda eksprese edilen *BCL11B*, transkripsiyonel bir düzenleyici proteindir. *BCL11B*'nin normal insan epidermisinde de eksprese edildiği immünohistokimyasal olarak gösterilmiştir. *BCL11B* geninin diffüz kutanöz mastositoz için potansiyel bir aday gen olabileceğini önermekteyiz. Bu tür klinik belirtileri olan diğer vakalar *BCL11B* geninin mutasyonları açısından incelenmelidir.
Anahtar sözcükler: ArrayCGH, *BCL11B*, kromozom 14q duplikasyonu; *CTIP2*; mastositozis.

INTRODUCTION

Mastocytosis is usually a sporadic and heterogeneous group of rare clonal disorders resulting from the expansion and accumulation of neoplastic mast cells and their progenitors in the skin and various internal organs, such as the bone marrow, spleen, lymph nodes and the gastrointestinal tract [1]. It can be limited to the skin known as cutaneous mastocytosis (CM), which is not associated with hematologic disorders and occurs typically as urticaria pigmentosa [2] and has three major subtypes: maculopapular type/urticarial pigmentosa, diffuse cutaneous mastocytosis (DCM) and solitary mastocytoma [3]. Age of onset has a bimodal distribution, with pediatric-onset occurring from birth to 2 years of age and adult-onset occurring in those over age 15 [4]. Mastocytosis can also involve extra-cutaneous tissues such as the liver, spleen, bone marrow and lymph nodes as in systemic mastocytosis (SM) [4].

Diffuse cutaneous mastocytosis is a rare variant of CM, accounting for only 1-5% of all cases and occurs mainly at birth or in early infancy [5]. A review of 173 cases of pediatric mastocytosis by Hannaford *et al* [6] reported only three cases of DCM. Furthermore, in a study that contains 101 cases of pediatric mastocytosis, only 6 cases were described as DCM, all with bullous lesions [7]. In a few cases, particularly in the neonatal diffuse cutaneous form, mastocytosis can be fatal as a result of hypovolemic shock, although infrequent, systemic forms can occur in children. In these cases, the disease may remain active through adolescence as systemic adult mastocytosis [8]. The heterogeneity of clinical presentation in mastocytosis is a result of mast cell (MC) burden and MC activity, the type of skin lesions, the patient's age at the onset and the associated hematological disorders [9].

The symptoms of mast cell activation include sudden onset of flush, urticaria, angioedema, pruritus, abdominal pain, headache, diarrhea, hypotension, syncope and musculoskeletal pain which are the results of mast cell mediator release and infiltration into target organs [10]. Blistering generalized erythroderma, nodules and plaques are also observed in some cases of DCM [11]. Only a small proportion of children who do not recover spontaneously before puberty will experience transformation into SM. The amount and variation of the skin lesions, the patient's age at the onset, and associated hematological disorders make the treatment of the disease challenging [12]. Although considerable research effort has been directed in the past, this complex disease has challenged a clear understanding of pathogenesis. In addition, clinical or biological factors that predict the evolution and severity of the disease in affected children have not been identified yet [8].

In mastocytosis, the presence of *KIT* gene mutations in the extracellular, transmembrane, juxta-membrane or activating loop domains, interrupts the normal signaling cascade characterized by constitutive receptor activation independent from stem cell factor [4, 13]. In 90% of cases, mastocytosis is associated with somatic D816V activating mutations of the mast cell growth factor receptor *KIT* gene in bone marrow MC progenitors [14]. In the case of cutaneous mastocytosis, sporadic D816V activating *KIT* mutation is found in 20%-40%, while other activating *KIT* mutations are present in 60% [15]. Moreover, the molecular abnormality of DCM has been associated only with *KIT* D816F, *KIT* E839K, *KIT* D816Y [16].

Here we aimed to present the molecular characterization of a girl presenting diffuse cutaneous mastocytosis, in which a partial duplication of chromosome 14q was found.

CASE REPORT

A 32 months-old girl was referred to our medical genetic outpatient clinic with a diffuse cutaneous mastocytosis and language delay. The proband

was the first and the only child of the family and was born from non-consanguineous healthy parents. Prenatal ultrasonographic evaluations revealed an echogenic focus of the brain lateral ventricles but no congenital defect associations were reported at birth. Birth weight and length were 3250 gr and 47cm recpectively. She was born by Cesarean section at 38 weeks of gestation after an uneventful pregnancy.

In the neonatal period, the early neurological assessment revealed normal growth and neuromotor development. Additionally, recurrent diarrhea attacks have appeared and the diagnosis of atopic dermatitis was thought because of the clinical appearance. Then it was thought to be a cow's milk allergy, but symptoms did not improve despite cow's milk-free diet. The features of diffuse cutaneous mastocytosis, the diffuse bullous lesions with contact in the skin, have been evident in the proband since the 4th month. In the pathological examination of her skin biopsy, it was reported as urticaria pigmentosa and the targeted analysis for D816V mutation of the *KIT* gene from peripheral blood sample was normal but the clinicians considered her diagnosis as diffuse cutaneous mastocytosis because of her diffuse bullous lesions. She has also chronic anemia despite iron therapy. Her language development was subnormal and stuttering began at 30 months-old, especially when she was excited. There was no history of recurrent bacterial, viral or fungal infections in our patient. In the family history; the uncle of her father and her maternal grandmother exhibited language delay in childhood.

Because of DCM and language delay in the current proband, the routine GTG banded karyotype analyses and Array-CGH (Agilent® Sureprint 180K and Agilent Cytogenomics Software) techniques were used for the chromosomal assessment. Informed written consent was obtained from the parents of the proband. All experiments have been performed in accordance with the ethical standards laid down in the 1964 Declaration of Helsinki.

RESULTS

GTG-banded metaphases showed a normal karyotype 46,XX after conventional lymphocyte cell culture (Figure 1). The array CGH profiling of the proband showed a *de novo* 7.7 Mb duplication in the 14q32.2-q32.33 locus (Figure 2) that contains 15 morbid OMIM genes (*EML1, YY1, WARS, DYNC1H1, BRF1, INF2, ADSSL1, AKT1, TRAF3, AMN, XRCC3, APOPT1, TECPR2, ZBTB42, BCL11B*). Among them, the *BCL11B* gene was suspected to be responsible for her DCM clinic. Parental karyotypes and array CGH analyses were normal, compared to the current case presenting a partial duplication of chromosome 14q (Figure 3).

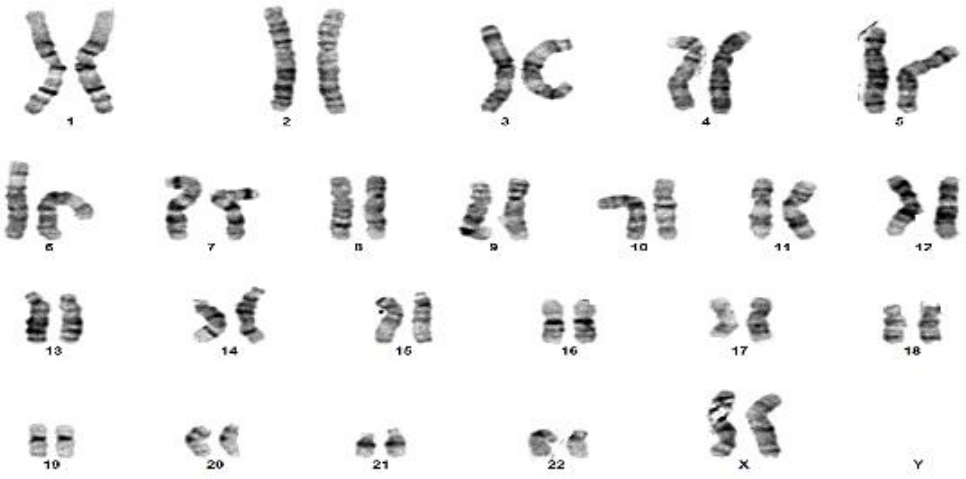

Figure 1: The karyotype profile of the current proband case was diagnosed as normal 46,XX structure.

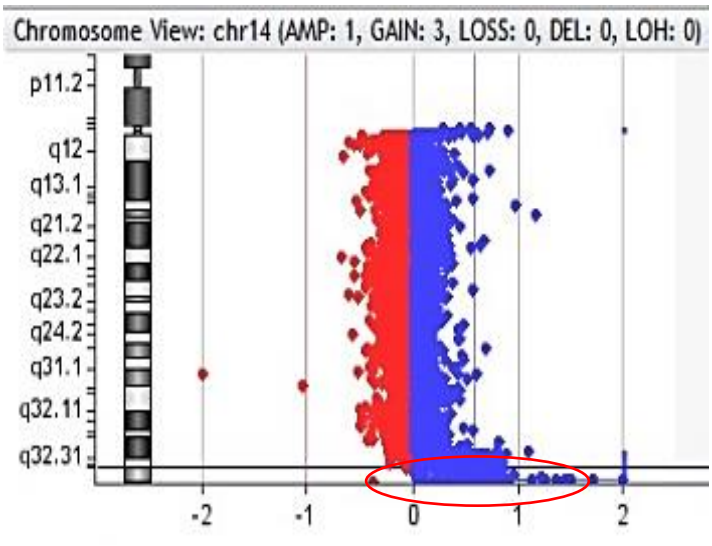

Figure 2: Shows microarray-CGH profile for chromosome 14 in the current proband case. A *de novo* 7.7 Mb duplication in 14q32.2-q32.33 were detected in the current mastocytosis case (red circle).

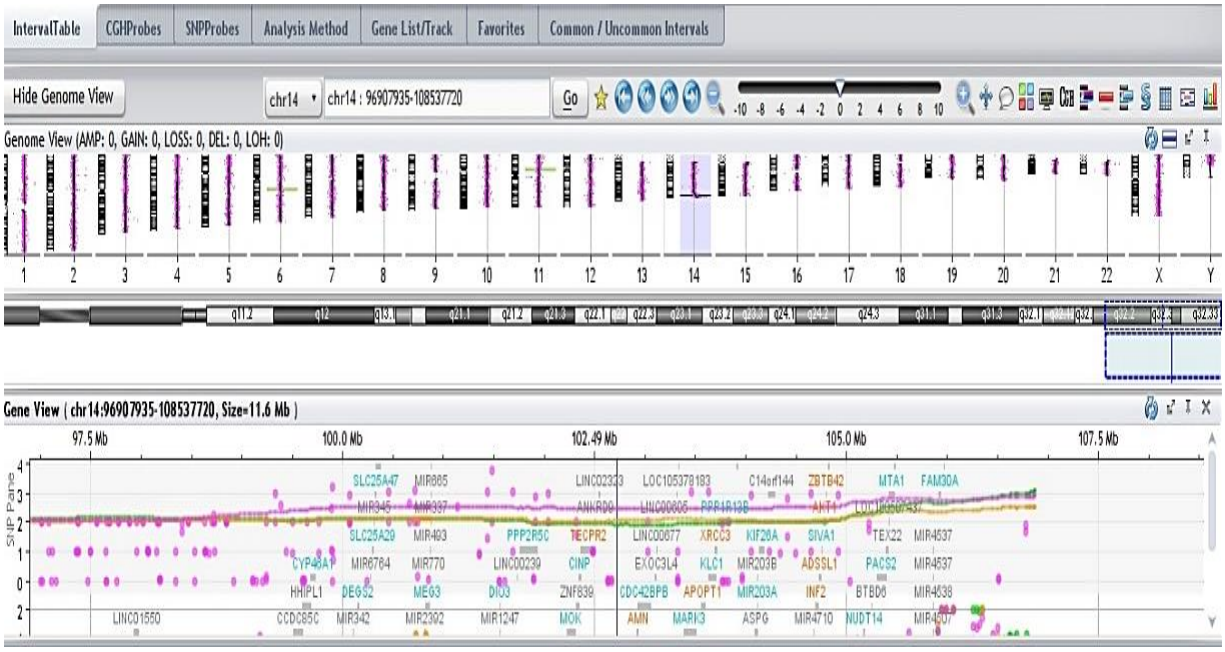

Figure 3: Shows the Array CGH triage view for chromosome 14q32.2-q32.33 of the proband (pink), her mother (orange) and father (green).

DISCUSSION

Mastocytosis is a group of rare clonal disorders resulting from the expansion of neoplastic mast cells and their progenitors in the skin and various internal organs. Mastocytosis can be systemic or local to the skin [17]. A number of *KIT* mutations have been detected in patients with CM and SM [18]. Some of these mutations, such as K509I, are more common in pediatric cases, sometimes being detected in germline DNA [8]. Bodemer *et al* [8] identified several genetic alterations in *KIT* in a population, some of which have not been identified previously in childhood or adult mastocytosis. These alterations were located mainly in exons 8 and 9 (44% of patients), which encode the fifth Ig (D5) domain and the extracellular region near the transmembrane domain, regions that have previously been shown to be affected in core-binding factor-acute myeloid leukemia and in gastrointestinal stromal tumor; respectively [19, 20].

Previous studies suggest that it is a result of the absence of genetic alterations within *KIT* in some mastocytosis patients [21, 22]. This implies that these patients have alterations in proteins other than *KIT* that regulate mast cell proliferation and function. In general, these results confirm that familial childhood-onset mastocytosis can occur both in the presence and in the absence of *KIT* mutations [8]. They performed a multicenter study to examine the association of c-*KIT* mutations with childhood-onset mastocytosis and found the D816V mutation (exon 17), which is frequently associated with adult mastocytosis in 18 of 50 (36%) children in this study. Three additional patients (6%) had other mutations in codon 816, including two with a D816Y mutation and one with a previously unreported D816I mutation. As with the D816V mutation, they found that both the D816Y and D816I mutations cause a ligand-independent activation of *KIT*.

Recently, it was found that the mastocytosis phenotype may be linked to abnormalities in GPCR downstream targeting due to G protein beta subunit activation. Szczałuba *et al* [2] described a case of the condition with manifestations of cutaneous mastocytosis associated with a novel *de novo* mutation *GNB1* NM_001282539.1: c.230G>T; p.(Gly77Val). They also present the detailed clinical and etiopathogenetic discussion on previously diagnosed patients as well as suggestions for the link of the mutation with skin disease.

Yoda *et al* [23] showed that downstream signaling of the mutated beta subunit of G protein complex results in leads activation of cell growth. These receptors are also present in mast cells residing in the skin which might explain chronic urticarial phenotypes [24]. Some findings suggest that in many cases, primary mast cell activation syndrome (MCAS) may be due to excessive allelic gene duplication, particularly of the α-tryptase gene, *TPSAB1*. Five percent of individuals are thought to have allelic *TPSAB1* gene duplications inherited in an autosomal dominant pattern. Adults and children with *TPSAB1* gene duplications have serum MC tryptase ≥8.0 ng/mL and clinical features of MCAS [25].

COUP-TF-interacting protein 2 (*CTIP2*), also known as *BCL11B*, is a C_2H_2 zinc finger protein that has been shown to regulate transcription through interaction with COUP-TF nuclear receptor proteins as well as through direct, sequence-specific DNA binding [26]. It is a transcriptional regulatory protein that is highly expressed in and plays a critical role(s) during the development of T lymphocytes, the central nervous system and it is also highly expressed in mouse skin during embryogenesis and in adulthood as revealed by immunohistochemical analyses [27]. The mutations of the *BCL11B* gene are reported to cause Immunodeficiency-49 (IMD49) and also associated with the intellectual developmental disorder with speech delay, dysmorphic facies and T cell abnormalities (IDDSFTA; 618092), both of these disorders are inherited with autosomal dominant manner. It was shown that *CTIP2* is also expressed in layer V of the cerebral cortex and plays a critical role in the establishment of connections of corticospinal motor neurons to the spinal cord [28]. In their study Ganguli-Indra *et al* [29] have demonstrated by immunohistochemistry that *BCL11B* is expressed in normal human epidermis. Enhanced expression of *CTIP2* was observed in hyperproliferative skin of atopic dermatitis and allergic contact dermatitis patients. It is likely that an optimum level of *CTIP2* expression is required for the maintenance of skin homeostasis. An increase in *CTIP2* expression might lead to an increase in epidermal proliferation and subsequently altered differentiation in atopic dermatitis (AD) and/or allergic contact dermatitis skin. Duplication in the 14q32.2-32.33 region was reported to be associated with primordial short stature, mild developmental delay and distinct facial dysmorphism which were absent in our patient. But absence of *BCL11B* gene located in this region was reported to be associated with AD-like skin inflammation and extensive infiltration of immune cells including mast cells in adult mice skin, as well as systemic immune responses that share similarity with human AD patients, consistent with DCM clinic of our patient [30].

CONCLUSION

Mastocytosis is an important disease that affects the social life of the patient. The increase in mast cell mediators can be triggered by sudden heat change, scrubbing/friction, excessive sweating, heavy physical exercise, intense UV light exposure, stress, fear and some medications. It's a worrying health risk for patients and their families. These patients need to carry epinephrine with them all day. In the presented case report it was suggested that the *BCL11B* gene is a candidate gene for diffuse cutaneous mastocytosis. This finding may shed light on research into pharmacological agents that reduce *BCL11B* gene expression for the treatment of DCM. Further analysis is required for any other possible genetic changes that may be related to the

patient's clinic and this association needs to be supported by research results involving multiple cases.

Declarations

****Ethics approval and consent to participate**

All experiments have been performed in accordance with the ethical standards laid down in the 1964 Declaration of Helsinki.

****Consent for publication**

Informed written consent was obtained from the parent of the proband for the genetic analyses and the publication, separately.

****Availability of data and material**

All data generated or analyzed during this study are included in this published article

****Competing interests**

The authors declare that they have no competing interests.

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****Authors' contributions**

F.S., B.A. and M.O.; acquisition of data, analyzed the clinical data and designed the clinical experiments, F.S., O.Y., M.O., and R.B.; designed the experiments, performed PCR, analyzed the sequencing data, B.A. and R.B.; wrote the manuscript. O.O.; interpretation of data, supervised the study and review the manuscript. All authors read and approved the final manuscript.

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