GENETIC ARRAY ANALYSIS OF FOLLICULAR DENDRITIC CELL SARCOMA

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Abstract

Follicular dendritic cell sarcoma (FDCS) is a rare neoplasm of hematopoietic derivation. Until now, little has been known about the genetic changes of FDCS. Few cases have been evaluated by conventional cytogenetics or other genetic techniques. We evaluated 14 cases of FDCS using a molecular inversion probe (MIP)-based assay, which is optimized to evaluate genomic alterations in archived formalin fixed, paraffin-embedded (FFPE) tissues.

A total of 14 deidentified patient samples were recruited from several institutions. Genomic DNA was isolated from FFPE tissues and analyzed by MIP array to assess for copy number (CN) alterations and loss-of-heterozygosity (LOH) in the samples. Genomic alterations were observed in 11 of 14 FDCS cases analyzed. Most cases showed complex genomic profiles with a high number of CN/LOH calls observed. Comparison of abnormalities across samples showed a predominance of losses and LOH, with several recurrent regions observed in 45% (5 cases) or more. Some recurrent regions/genes have known associations with other hematopoietic disorders and sarcomas, including *RB1*, *TP53*, *CDKN2A* and *BIRC3*.

We report detailed genetic analysis in the largest series of FDCS to date. Importantly, we identified many areas of recurrent abnormalities in our series of cases. In addition to providing novel genomic profiling, which will aid in genetic diagnosis, this effort may lead to identification of genes contributing to development and/or differentiation of FDCS and potentially actionable target genes, which may suggest new therapies for these rare disorders in the future.

Background

Follicular dendritic cell sarcoma (FDCS) is a rare neoplasm of follicular dendritic cells (Fig. 1). Normal follicular dendritic cells are possibly a specialized form of myofibroblasts and are likely derived from non-bone marrow origins, in contrast to most other accessory/dendritic cells. Normal follicular dendritic cells represent the fixed antigen-presenting dendritic cells of follicles. FDCS occurs in all ages and without a sex predilection. Patients typically present with a slow growing mass, without any systemic symptoms. At present, treatment consists of surgical excision, with or without adjuvant therapy or local radiotherapy. Local recurrences occur in about 50% of patients, with distant metastases eventually occurring in about 25% of patients. Little has been known about the genetic changes of FDCS. We analyzed 14 patient samples by MIP array to characterize the genomic profile of FDCS.

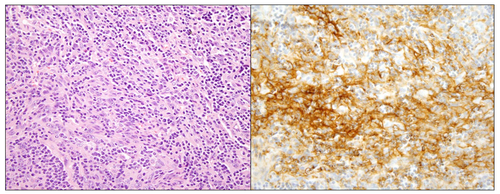

Figure 1. Representative histologic images of FDCS (H&E) and staining for CD21 (right).

Samples

The diagnosis of FDCS was made based on standard WHO classification criteria. A total of 14 de-identified patient samples were recruited from several institutions. Tumor content was estimated by pathologist review of H&E stained slides (range 40-90%; mean 70%). Genomic DNA was extracted from formalin-fixed, paraffin-embedded tissue using the QIAamp DNA FFPE Tissue Kit (QIAGEN, Valencia, CA) and quantitated by Qubit PicoGreen (Life Technologies).

Genomic Analysis

Genomic DNA (~80 ng) was analyzed using the Affymetrix OncoScan™ kit (Affymetrix, Santa Clara, CA). Data analysis was performed using Nexus Express software for OncoScan (Biodiscovery, El Segundo, CA). Files were processed using Nexus TuScan or SNP-FASST2 algorithms. Call filters of ≥20 probes per segment and for LOH, >3 Mb size, were used. All calls were manually reviewed and modified, added, or omitted based on call confidence, significance and genomic context. Recurrent regions were defined as present in ≥45% (5/11) cases; regions were delineated manually by smallest region of overlap. Cancer genes list is from the Catalogue of Somatic Mutations in Cancer (COSMIC) database (Forbes et al., 2014).

Results

- 11/14 FDCS cases showed genetic abnormalities (Fig. 2)
  - Complex genomic profiles, with a high number of calls per case were common (n=8/11 cases with ≥20 calls, range 20-69)
  - Losses and LOH calls were predominant
- 16 genomic regions were recurrently affected by losses/LOH, observed in 45% (n=5) cases or greater (Fig. 2, asterisks; Table 1)
  - Alterations of 3p, 13q and 14q were observed in 91% (10/11)
  - No recurrent gains were observed
- Some recurrent regions/genes have known associations to other hematopoietic disorders and/or sarcomas: *RB1*, *TP53*, *CDKN2A* and *BIRC3*

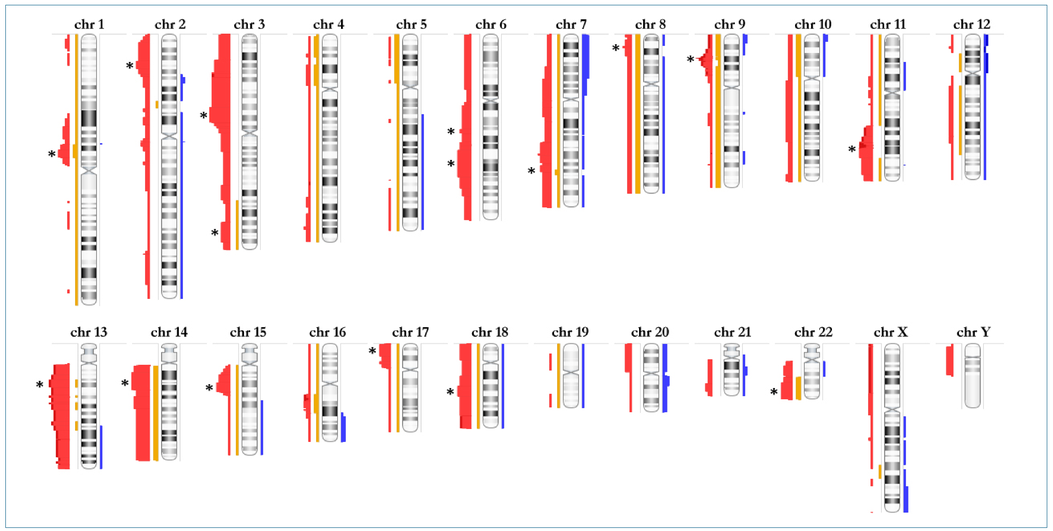

Figure 2: Summary of CN and LOH calls across abnormal FDCS cases (n=11/14). Calls are aggregated and displayed next to corresponding genomic position by chromosome. Single copy losses are shown in red, two or greater copy losses are shown in dark red, LOH in orange, single copy gains in blue and two or greater copies gained in dark blue. Asterisks indicate regions with losses and/or LOH observed across >45% cases (see Table 1). Image was modified from the summary view in NexusExpress software in Adobe Photoshop.

Conclusions

We report detailed genetic analysis in the largest series of FDCS to date. Importantly, we identified many areas of recurrent abnormalities in our series of cases. In addition to providing novel genomic profiling, which will aid in genetic diagnosis, this effort may lead to identification of genes contributing to development and/or differentiation of FDCS and potentially actionable target genes, which may suggest new therapies for these rare disorders in the future.

TABLE 1. SUMMARY OF RECURRENT LOSSES/LOH REGIONS IN FOLLICULAR DENDRITIC CELL SARCOMA

Genomic region	1p proximal	2p distal	3p proximal	3q distal	6q prox	6q mid	7q mid	8p distal	9p (CDKN2A) region	11q (BIRC3) region	13q prox	14q prox	15q mid	17p	18q mid	22q distal
Cyto band	1p21.1-1p13.2	2p23.3-2p23.1	3p14.1-3p12.2	3q26.31-3q28	6q14.3-6q15	6q21-6q23.2	7q31.1-7q31.33	8p23.1-8p22	9p21.3	11q22.2	13q13.1-13q14.3	14q12-14q21.1	15q14-15q15.3	17p13.3-17p11.2	18q12.3-18q21.2	22q12.3-22q13.3
Approx. Size	7.1 Mb	7.4 Mb	14.0 Mb	18.9 Mb	4.1 Mb	25.3 Mb	17.3 Mb	2.1 Mb	52.9 kb	130 kb	22.1 Mb	16.3 Mb	8.9 Mb	18.5 Mb	10.0 Mb	15.8 Mb
% Abnl cases (n=11)	55	55	91	45	45	55	72	45	64	55	91	91	64	55	64	55
Cancer genes list	RBM15	NCOA1, DNMT3A, ALK	MITF, FOXP1	PIK3CA, SOX2, ETV5, EIF4A2, BCL6, LPP	none	PRDM1, ROS, GOPC, STL	MET	none	CDKN2A	BIRC3	BRCA2, LHFP, LCP1, RB1	NKX2-1	BUB1B	YWHAE, USP6, TP53, PER1, GAS7, MAP2K4	none	MYH9, PDGFB, MKL1, EP300