Prognostic Value of Dynactin mRNA Expression in Cutaneous Melanoma

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Background: Dynactin (DCTN) is a multi-subunit protein encoded by DCTN genes for 6 subunits. In different diseases the DCTN genes may have different roles; therefore, we investigated the prognostic potential of DCTN mRNA expression in cutaneous melanoma (CM).

Material/Methods: Data for DCTN mRNA expression in CM patients were obtained from the OncoLnc database, which contains updated gene expression data for 459 CM patients based on the Cancer Genome Atlas. Kaplan-Meier analysis and a Cox regression model were used to determine overall survival (OS) with calculation of hazard ratios (HRs) and 95% confidence intervals (CIs).

Results: The multivariate survival analysis showed that individually low expression of DCTN1, DCTN2, and DCTN5 and high expression of DCTN6 were associated with favorable OS (adjusted \( P=0.008 \), HR=0.676, 95% CI=0.506–0.903; adjusted \( P=0.004 \), HR=0.648, 95% CI=0.485–0.867; adjusted \( P=0.011 \), HR=0.686, 95% CI=0.514–0.916; and adjusted \( P=0.018 \), HR=0.706, 95% CI=0.530–0.942, respectively). In a joint-effects analysis, combinations of low expression of DCTN1, DCTN2, and DCTN5 and high expression of DCTN6 were found to be more highly correlated with favorable OS (all \( P<0.05 \)).

Conclusions: Our findings suggest that downregulated DCTN1, DCTN2, and DCTN5 and upregulated DCTN6 mRNA expression in CM are associated with favorable prognosis and may represent potential prognostic biomarkers. Moreover, use of the 4 genes in combination can improve the sensitivity for predicting OS in CM patients.

MeSH Keywords: Dynactin • Melanoma • Prognosis

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Background

Cutaneous melanoma (CM) is one of the most aggressive tumors of the skin and mucosa [1], accounting for 6380 out of 9250 skin cancer-related deaths in the United States in 2017 [2]. With improved awareness and treatment options, the 5-year relative survival rate has reached 92% and the 10-year relative survival rate has reached 89% [3]. Still, early detection is important, as the prognosis is much better if the cancer is detected early. The primary treatment for CM is surgery, and adjuvant immunotherapy, immunotherapy, and targeted therapy drugs also are used to treat various stages of melanoma [3].

Dynactin (DCTN) is a multi-subunit protein that drives retrograde transport in cells [4–7]. The 6 subunits of DCTN are referred to as dynactin 1–6 (DCTN1–6). All subunits of DCTN are critical to the structure and function of DCTN [4,8–10]. DCTN1 was shown to act as a fusion partner in some but not all Spitz tumors [11] as well as in a non-small cell lung cancer (NSCLC) [12]. DCTN1 and DCTN3 are upregulated in sporadic ALS [13]. DCTN2 is upregulated in the osteosarcoma SISA-1 cell line, but a link between its altered expression and the prognosis of CM has not been reported [14]. Another study showed that the intronic regions of DCTN6 pre-mRNA interact with the SPRIGHTLY long non-coding (lnc)RNA of melanoma [15]. Based on this evidence for pathogenic roles of mutations in DCTN subunits, we questioned whether mutations in DCTN genes are associated with CM.

According to these previous studies, DCTN1 and DCTN2 are expressed in human epidermal melanocytes [16]. However, the relationships between DCTN family members and CM patients have not been investigated. Therefore, in the present study, we investigated the prognostic value of the mRNA expression levels of individual DCTN subunits and conducted a joint-effects analysis using data from 459 CM patients available in the OncoLnc database based on the Cancer Genome Atlas.

Table 1. Grouping according to 2 selected genes.

| Group | Composition | Group | Composition |
|-------|-------------|-------|-------------|
| I     | Low DCTN1 + low DCTN2 | X     | Low DCTN2 + low DCTN5 |
| II    | Low DCTN1 + high DCTN2 | XI    | Low DCTN2 + high DCTN5 |
| III   | High DCTN1 + low DCTN2 | XII   | High DCTN2 + high DCTN5 |
| IV    | Low DCTN1 + low DCTN5  | XIII  | DCTN2 + high DCTN6    |
| V     | Low DCTN1 + high DCTN5 | XIV   | Low DCTN2 + low DCTN2 |
|       | High DCTN1 + low DCTN5  |       | High DCTN2 + high DCTN6 |
| VI    | High DCTN1 + high DCTN5 | XV    | High DCTN2 + low DCTN6 |
| VII   | Low DCTN1 + high DCTN6  | XVI   | Low DCTN5 + high DCTN6 |
| VIII  | Low DCTN1 + low DCTN6  | XVII  | Low DCTN5 + low DCTN6 |
|       | High DCTN1 + high DCTN6  |       | High DCTN5 + high DCTN6 |
| IX    | High DCTN1 + low DCTN6  | XVIII  | High DCTN5 + low DCTN6 |

DCTN – dynactin.
Table 2. Grouping according to 3 selected genes.

| Group | Composition | Group | Composition | Group | Composition |
|-------|-------------|-------|-------------|-------|-------------|
| i     | Low DCTN1 + low DCTN2 + low DCTN5 | iv    | Low DCTN1 + low DCTN2 + high DCTN6 | vii   | Low DCTN2 + low DCTN5 + high DCTN6 |
| ii    | High DCTN1 + low DCTN2 + low DCTN5 | v     | High DCTN1 + low DCTN2 + high DCTN6 | viii  | High DCTN2 + low DCTN5 + high DCTN6 |
|       | Low DCTN1 + high DCTN2 + low DCTN5 |       | Low DCTN1 + high DCTN2 + high DCTN6 |       | Low DCTN2 + high DCTN5 + high DCTN6 |
|       | Low DCTN1 + low DCTN2 + high DCTN5 |       | Low DCTN1 + low DCTN2 + low DCTN6  |       | Low DCTN2 + low DCTN5 + low DCTN6  |
| iii   | High DCTN1 + high DCTN2 + high DCTN5 | vi    | High DCTN1 + high DCTN2 + low DCTN6 | ix    | High DCTN2 + high DCTN5 + low DCTN6 |

DCTN = dynactin.

analysis. GO functional analysis included molecular function (MF), cellular component (CC), and biological process (BP). A gene function prediction website (GeneMANIA: http://genemania.org/, accessed November 15, 2017) [21] was used to analyze interactions among DCTN family members.

Survival analysis

For each DCTN mRNA, patients were divided into high- and low-expression groups according to a 50th percentile cutoff. The prognosis of CM was evaluated based on overall survival (OS). The Kaplan-Meier estimator with a log-rank test was used to identify correlations between the 6 DCTN mRNAs and patient survival. Adjustment was made for race, age, sex, and TNM stage in the Cox proportional hazards regression model.

Joint-effects analysis

A joint-effects analysis was performed for the combination of genes identified as significant by the survival analysis. Groups were formulated by summarizing the selected expression of genes associated with better OS in one group, worse OS in another group, and others in the last group, as outlined in Tables 1–3.

Statistical analyses

Kaplan-Meier survival analysis and the log-rank test were used to calculate OS and P values for all associations. The Cox proportional hazards regression model was used for uni- and

Table 3. Grouping according to 4 selected genes.

| Group | Composition |
|-------|-------------|
| 1     | High DCTN1 + high DCTN2 + high DCTN5 + low DCTN6 |
|       | High DCTN1 + high DCTN2 + high DCTN5 + high DCTN6 |
|       | High DCTN1 + low DCTN2 + high DCTN5 + high DCTN6 |
|       | Low DCTN1 + high DCTN2 + low DCTN5 + high DCTN6 |
|       | Low DCTN1 + low DCTN2 + high DCTN5 + high DCTN6 |
| 2     | High DCTN1 + low DCTN2 + low DCTN5 + high DCTN6 |
|       | High DCTN1 + low DCTN2 + high DCTN5 + low DCTN6 |
|       | Low DCTN1 + high DCTN2 + low DCTN5 + low DCTN6 |
|       | Low DCTN1 + high DCTN2 + low DCTN5 + high DCTN6 |
| 3     | Low DCTN1 + low DCTN2 + low DCTN5 + high DCTN6 |

DCTN = dynactin.
Table 4. Demographic and clinical data for 459 CM patients.

| Variables   | Patients (n=459) | No. of events (%) | MST (days) | HR (95% CI) | Log-rank P |
|-------------|------------------|-------------------|------------|-------------|------------|
| Race        |                  |                   |            |             |            |
| White       | 436              | 208 (47.7%)       | 2470       | Ref.        | 0.004      |
| Others      | 13               | 8 (61.5%)         | 636        | 0.347 (0.170–0.707) |          |
| Missing     | 10               |                   |            |             |            |
| Sex         |                  |                   |            |             | 0.259      |
| Male        | 284              | 146 (51.4%)       | 2454       | Ref.        |           |
| Female      | 175              | 72 (41.1%)        | 2030       | 0849 (0.638–1.128) |          |
| Age (years) |                  |                   |            |             | 0.001      |
| ≥60         | 240              | 116 (48.3%)       | 3564       | Ref.        |           |
| <60         | 219              | 102 (46.6%)       | 1860       | 1.619 (1.227–2.136) |          |
| TNM stage   |                  |                   |            |             | <0.001     |
| 0+I+II+I/II nos | 232 | 108 (46.6%)       | 3259       | Ref.        |           |
| III+IV     | 191              | 91 (47.6%)        | 1960       | 1.673 (1.253–2.235) |          |
| Missing     | 36               |                   |            |             |            |
| BMI (kg/m²) |                  |                   |            |             | 0.437      |
| >25         | 80               | 25 (31.3%)        | 2101       | Ref.        |           |
| ≤25         | 160              | 61 (38.1%)        | 3136       | 0.830 (0.519–1.327) |          |
| Missing     | 219              |                   |            |             |            |

MST – median survival time; HR – hazard ratio; CI – confidence interval.

Figure 1. MERAV boxplots for DCTN gene expression in normal skin tissue and primary CM tissue: (A) DCTN1 expression; (B) DCTN2 expression; (C) DCTN3 expression; (D) DCTN4 expression; (E) DCTN5 expression; and (F) DCTN6 expression.
multivariate survival analyses. Hazard ratios (HRs) and 95% confidence intervals (CIs) were calculated with the Cox proportional hazards regression model with adjustment for influential clinical characteristics such as race, sex, age, TNM stage, and BMI. \(P < 0.05\) was considered statistically significant. Statistical analyses were carried out using SPSS v.22.0 software (IBM, Chicago, IL, USA). Vertical scatter plots and survival curves were generated in GraphPad Prism v.7.0 (La Jolla, CA, USA).

### Ethics statement

All data used in this study were obtained from a public database; therefore, approval of the study by an ethics committee was not required.

### Results

#### Patient characteristics influencing survival and differential DCTN expression in CM

The detailed demographic and clinical data for the 459 included patients are provided in Table 4. Race, age, and TNM stage were significantly associated with median survival time (MST; \(P=0.004, P=0.001, \) and \(P<0.001\), respectively; Table 4). Boxplots illustrating differences in the expression of the 6 DCTN genes in normal skin tissue versus primary CM tissue were generated using MERAV (Figure 1). The median expression levels of DCTN2 and DCTN3 were higher in normal skin tissue than in primary CM tissue, whereas the median expression levels of DCTN5 and DCTN6 were higher in primary CM tissue than in normal skin tissue. The median expression levels of DCTN1 and DCTN4 did not differ significantly between normal skin tissue and primary tumor.
Correlations among expression levels of DCTN genes and functions of DCTN genes

Correlations among the expression levels of individual DCTN genes were identified by Pearson correlation coefficient analysis. For DCTN1, DCTN2, DCTN3, and DCTN4, the expression level of each gene was correlated with that of each of the other genes (all \( P < 0.05 \)), but not with the expression levels of DCTN5 and DCTN6. DCTN5 expression was only correlated with DCTN1 expression (\( P < 0.05 \)). DCTN6 expression was correlated with DCTN1, DCTN3, and DCTN4 expression (all \( P < 0.001 \); Figure 2A).

Interactions among the expression levels of DCTN1, DCTN2, DCTN3, DCTN4, DCTN5, and DCTN6 are shown in Figure 2B.

Scatter plots for the expression of the 6 genes according to the 50th percentile cutoff are shown in Figure 2C.

The biological functions of the DCTN genes were evaluated according to the BP, MF, and CC categories for GO functional analysis (Figure 2D), and the results of KEGG pathway analysis are shown in Figure 2D.

Survival influence of differential DCTN gene expression

The results of univariate survival analysis were showed as Figure 3A–3F. The results showed that low expression levels of DCTN2 and DCTN5 separately were significantly associated...
Table 5. Prognostic survival analysis according to high or low expression of DCTN family genes.

| Gene | Patients (n=459) | No. of events (%) | MST (days) | Crude HR (95% CI) | Crude P | Adjusted HR* (95% CI) | Adjusted P* |
|------|-----------------|-------------------|------------|-------------------|---------|----------------------|------------|
| DCTN1 | High 229 | 112 (48.9%) | 1910 | Ref. | 0.803 | Ref. | 0.614–1.048 | 0.008 |
| Low | 229 | 105 (45.9%) | 3259 | | | | (0.506–0.903) |
| Missing | 1 | | | | | | |
| DCTN2 | High 229 | 111 (48.5%) | 1860 | Ref. | 0.590 | Ref. | (0.449–0.774) | 0.004 |
| Low | 229 | 107 (46.7%) | 3379 | | | | (0.485–0.867) |
| Missing | 1 | | | | | | |
| DCTN3 | High 229 | 94 (41.0%) | 2273 | Ref. | 0.974 | Ref. | (0.744–1.275) | 0.437 |
| Low | 229 | 124 (54.1%) | 2454 | | | | (0.671–1.188) |
| Missing | 1 | | | | | | |
| DCTN4 | High 229 | 114 (49.8%) | 2470 | Ref. | 1.017 | Ref. | (0.779–1.329) | 0.140 |
| Low | 229 | 104 (45.4%) | 2071 | | | | (0.606–1.073) |
| Missing | 1 | | | | | | |
| DCTN5 | High 229 | 123 (53.7%) | 1910 | Ref. | 0.673 | Ref. | (0.514–0.882) | 0.004 |
| Low | 229 | 94 (41%) | 3195 | | | | (0.514–0.916) |
| Missing | 1 | | | | | | |
| DCTN6 | Low 229 | 125 (54.6%) | 2071 | Ref. | 0.659 | Ref. | (0.503–0.864) | 0.002 |
| High | 229 | 92 (40.2%) | 3195 | | | | (0.530–0.942) |
| Missing | 1 | | | | | | |

* Adjustment for race, sex, age, and TNM stage. DCTN – dynactin; MST – median survival time; HR – hazard ratio; CI – confidence interval.

with favorable OS in CM patients (P<0.01 and P=0.004, respectively; Figure 3B, 3E). High expression of DCTN6 also was significantly associated with favorable OS (P=0.002; Figure 3F). The multivariate Cox proportional hazards regression analysis identified associations of sex, race, age, and TNM stage with the prognosis of CM patients. The multivariate survival analysis showed that, individually, low expression levels of DCTN1, DCTN2, and DCTN5 and high expression level of DCTN6 were associated with favorable OS (adjusted P=0.008 HR=0.676 95% CI=0.506–0.903; adjusted P=0.004, HR=0.648, 95% CI=0.485–0.867; adjusted P=0.011, HR=0.686, 95% CI=0.514–0.916; and adjusted P=0.018, HR=0.706, 95% CI=0.530–0.942, respectively; Table 5).

Survival influence of combinations of DCTN gene expression

Based on the DCTN genes identified as influential by the multivariate survival analysis, a joint-effects model was used to determine the combined effects of DCTN genes on the OS of CM patients. The different groups for this analysis were generated according to the expression of DCTN1, DCTN2, DCTN5, and DCTN6 (Tables 1–3). The Kaplan-Meier estimator with a log-rank test was used to evaluate the prognostic value of the gene expression combinations represented by each group (Figures 4, 5). In the analysis of low DCTN1, DCTN2, and DCTN5 expression with high DCTN6 expression, the combinations in groups I, IV, XII, X, XVI, i, iv, vii, and 1 were found to be more highly correlated with favorable OS (all P<0.05; Table 6). On the contrary, in the analysis of high expression of DCTN1, DCTN2, and DCTN5 and low DCTN6 expression, the combinations in groups III, VI, IX, XV, XVIII, iii, ix, and 3 were found to be more highly correlated with poor OS (all P<0.05; Table 6).

Discussion

The 6 DCTN genes are known to encode the 6 subunits of DCTN, which are all essential for the DCTN activity of driving retrograde transport in cells [4–7]. Specific functions of individual DCTN subunits have also been reported. In human epidermal melanocytes, DCTN1 expression was detected in the dendrite tips, and DCTN2 expression was also localized in the perinuclear area and dendrite tips [16]. Notably, overexpression of...
**DCTN3** is lethal to cells, and overexpression of **DCTN2** leads to the disruption of the Golgi apparatus [6,22]. Mutations of **DCTN1** have been identified in many serious motor neuron diseases, including ALS, ALS-frontotemporal dementia ALS/FTD, and PS [23–28], and a mutation in **DCTN4** was linked to Pa airway infection, chronic Pa infection, and mucoid Pa in cystic fibrosis patients [29,30]. Finally, the interaction between **DCTN4** and the P-type ATPase (ATP7B) is a key component of Wilson disease [31].

Most studies to date have investigated associations between **DCTN** genes and nervous system diseases, infection diseases, both through functional studies and mutational studies. Only a few reports have been published on connections between **DCTN**

**Figure 4.** Joint-effects analysis of the influence of combined **DCTN** gene expression on OS with stratification according to 2 selected **DCTN** genes among **DCTN1**, **DCTN2**, **DCTN5**, and **DCTN6**. (A) **DCTN1** and **DCTN2**, (B) **DCTN1** and **DCTN5**, (C) **DCTN1** and **DCTN6**, (D) **DCTN2** and **DCTN5**, (E) **DCTN2** and **DCTN6**, and (F) **DCTN5** and **DCTN6**. I, low **DCTN1**+low **DCTN2**; III, high **DCTN1**+high **DCTN2**; IV, low **DCTN1**+low **DCTN5**; VI, high **DCTN1**+high **DCTN5**; VII, low **DCTN1**+high **DCTN6**; IX, high **DCTN1**+low **DCTN6**; X, low **DCTN2**+low **DCTN5**; XII, high **DCTN2**+high **DCTN5**; XIII, low **DCTN2**+high **DCTN6**; XV, high **DCTN2**+low **DCTN6**; XVI, low **DCTN5**+high **DCTN6**; XVIII, high **DCTN5**+low **DCTN6**; II, V, VIII, XI, XIV, and XVII correspond to other combinations of genes as detailed in Table 1.
genes and cancer, although the DCTN family may play a crucial role in some cancers via their effect on the function and structure of DCTN. For example, it was reported that DCTN1 and DCTN2 could coprecipitate with human EB1, which may be correlated with human adenomatous polyposis coli in vivo [32]. Most relevant to our study, the intronic regions of DCTN6 pre-mRNA were shown to interact with the SPRIGHTLY lncRNA of melanoma [15]. Still, there were no reports about the connection between DCTN mRNA expression and the prognosis of CM. Here, we used data for DCTN mRNA expression and clinical information in CM patients from the OncoLnc database according to the Cancer Genome Atlas to investigate the correlation of DCTN family mRNA expression and prognosis in CM patients and assess whether expression of any DCTN genes, individually or in combination, could be used as biomarkers for predicting prognosis in CM.

In our study, we found high expression levels of DCTN2 and DCTN5 in normal tissue, while the Kaplan-Meier curves from univariate survival analysis showed that low expression of DCTN2 and DCTN5 in tumor tissue was correlated with favorable OS in all CM patients, suggesting that DCTN2 and DCTN5 act as oncogenes in CM. In contrast, DCTN6 was highly expressed in primary skin tumor tissue, and high expression of DCTN6 was found to be correlated with favorable OS. This may be because DCTN6 can act as a tumor suppressor. DCTN2 was downregulated in CM but upregulated in the SISA-1 osteosarcoma cell line [14], indicating that DCTN2 may have different roles in different cancers.

Multivariate survival analysis confirmed the results of the univariate survival analysis, except for DCTN1. Multivariate survival analysis showed that a low expression of DCTN1 was correlated with favorable prognosis, whereas in univariate survival analysis, neither low nor high expression of DCTN1 was found to be correlated with OS. This may be due to adjustment in the Cox proportional hazards regression model, which indicated that DCTN1 expression affects CM prognosis. Expression of both DCTN1 and DCTN2 was previously found in

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**Figure 5.** Joint-effects analysis of the influence of combined DCTN gene expression on OS with stratification according to 3 or 4 selected DCTN genes among DCTN1, DCTN2, DCTN5, and DCTN6. (A) DCTN1, DCTN2, and DCTN5; (B) DCTN1, DCTN2, and DCTN6; (C) DCTN2, DCTN5, and DCTN6; (D) DCTN1, DCTN2, DCTN5, and DCTN6. i, low DCTN1+low DCTN2+low DCTN5; ii, high DCTN1+high DCTN2+high DCTN5; iii, high DCTN1+low DCTN2+high DCTN6; iv, low DCTN1+low DCTN2+high DCTN6; vi, high DCTN1+high DCTN2+low DCTN6; vii, low DCTN2+low DCTN5+high DCTN6; ix, high DCTN2+high DCTN5+low DCTN6; 1, high DCTN1+high DCTN2+high DCTN5+low DCTN6; 2, low DCTN1+low DCTN2+low DCTN5+high DCTN6; ii, v, viii, and 2 correspond to other combinations of genes as detailed in Tables 2 and 3.
Table 6. Joint-effects analysis of the prognostic value of combinations of DCTN1, DCTN2, DCTN5, and DCTN6 expression in CM.

| Group | Patients (n=459) | MST (days) | Crude P | Crude HR (95% CI) | Adjusted P* | Adjusted HR* (95% CI) |
|-------|-----------------|------------|---------|------------------|-------------|----------------------|
| I     | 141             | 3424       | 0.001   | Ref.             | 0.001       | Ref.                 |
| II    | 176             | 2711       | 0.415   | 1.146 (0.826–1.589) | 0.509       | 1.118 (0.803–1.558)  |
| III   | 142             | 3733       | <0.001  | 1.855 (1.323–2.601) | <0.001      | 1.859 (1.315–2.629)  |
| IV    | 130             | 3587       | 0.007   | Ref.             | 0.003       | Ref.                 |
| V     | 199             | 2030       | 0.201   | 1.248 (0.888–1.754) | 0.277       | 1.803 (1.255–2.590)  |
| VI    | 130             | 1544       | 0.002   | 1.749 (1.220–2.509) | 0.001       | 1.210 (0.858–1.705)  |
| VII   | 124             | 3564       | 0.001   | Ref.             | 0.001       | Ref.                 |
| VIII  | 210             | 2993       | 0.289   | 1.206 (0.853–1.704) | 0.341       | 1.186 (0.835–1.686)  |
| IX    | 125             | 1506       | 0.001   | 1.895 (1.304–2.752) | <0.001      | 2.012 (1.375–2.944)  |
| X     | 114             | 4648       | 0.001   | Ref.             | <0.001      | Ref.                 |
| XI    | 231             | 2071       | 0.001   | 1.785 (1.256–2.536) | 0.004       | 1.680 (1.180–2.391)  |
| XII   | 114             | 1544       | 0.001   | 2.567 (1.729–3.812) | 0.001       | 2.307 (1.542–3.452)  |
| XIII  | 115             | 4222       | 0.001   | Ref.             | <0.001      | Ref.                 |
| XIV   | 228             | 2927       | 0.002   | 1.765 (1.238–2.516) | 0.005       | 1.673 (1.170–2.392)  |
| XV    | 116             | 1691       | 0.001   | 2.643 (1.776–3.933) | 0.001       | 2.443 (1.628–3.665)  |
| XVI   | 119             | 4000       | 0.001   | Ref.             | 0.001       | Ref.                 |
| XVII  | 220             | 2711       | 0.016   | 1.559 (1.088–2.234) | 0.018       | 1.546 (1.078–2.217)  |
| XVIII | 120             | 1766       | 0.001   | 2.185 (1.495–3.193) | 0.001       | 2.089 (1.421–3.071)  |
| i     | 78              | 4648       | 0.001   | Ref.             | <0.001      | Ref.                 |
| ii    | 302             | 2184       | 0.020   | 1.598 (1.076–2.374) | 0.036       | 1.531 (1.028–2.281)  |
| iii   | 79              | 1413       | 0.001   | 2.999 (1.873–4.802) | <0.001      | 3.013 (1.870–4.857)  |
| iv    | 68              | 4000       | 0.001   | Ref.             | <0.001      | Ref.                 |
| v     | 307             | 2927       | 0.056   | 1.503 (0.990–2.281) | 0.104       | 1.422 (0.931–2.171)  |
| vi    | 84              | 1486       | 0.001   | 2.780 (1.659–4.422) | 0.001       | 2.679 (1.630–4.404)  |
| vii   | 56              | 6598       | 0.001   | Ref.             | <0.001      | Ref.                 |
| viii  | 339             | 2421       | 0.001   | 2.530 (1.513–4.231) | 0.001       | 2.354 (1.403–3.949)  |
| ix    | 64              | 1544       | 0.001   | 4.088 (2.226–7.375) | 0.001       | 3.572 (1.955–6.524)  |
| 1     | 34              | 6598       | 0.001   | Ref.             | <0.001      | Ref.                 |
| 2     | 373             | 2470       | 0.008   | 2.493 (1.275–4.875) | 0.009       | 2.451 (1.248–4.816)  |
| 3     | 52              | 1429       | 0.001   | 5.271 (2.500–11.113) | <0.001      | 5.216 (2.455–11.080) |

* Adjustment for race, sex, age, and TNM stage. Bold type highlights statistically significant values (P≤0.05). DCTN – dynactin; MST – median survival time; HR – hazard ratio; CI – confidence interval.
References:

1. Situm M, Bujan M, Kolic M, Vucic M: Melanoma – clinical, dermatosocopical, and histopathological morphological characteristics. Acta Dermatovenereol Croat. 2014; 22(1): 1–12
2. Siegel RL, Miller KD, Jemal A: Cancer Statistics, 2017. Cancer J Clin, 2017; 67(1): 7–30
3. Miller KD, Siegel RL, Lin CC et al: Cancer treatment and survivorship statistics, 2016. Cancer J Clin, 2016; 66(4): 271–89
4. Schroer TA: Dynactin. Annu Rev Cell Dev Biol, 2004; 20: 759–79
5. Echeverri CJ, Paschal BM, Vaughan KT, Vallee RB: Molecular characteriza-
tion of the 50-kD subunit of dynactin reveals function for the complex in chromosome alignment and spindle organization during mitosis. J Cell Biol, 1996; 132(4): 617–33
6. Karki S, LaMonte B, Holzbaur EL: Characterization of the p22 subunit of dy-
nactin reveals the localization of cytoplasmic dynein and dynactin to the midbody of dividing cells. J Cell Biol, 1998; 142(4): 1023–34
7. King SM: The dynemin microtubule motor. Biochim Biophys Acta, 2000;
1496(1): 60–75
8. Eckley DM, Gill SR, Melkonian KA et al: Analysis of dynactin subcomplexes reveals a novel actin-related protein associated with the arp1 minifila-
ment pointed end. J Cell Biol, 1999; 147(2): 207–20
9. Karki S, Tokito MK, Holzbaur EL: A dynactin subunit with a highly conserved cysteine-rich motif interacts directly with Arp1. J Biol Chem, 2000; 275(7): 4834–39
10. Garces IA, Clark IB, Meyer DJ, Vallee RB: Interaction of the p62 subunit of dynactin with Arp1 and the cortical actin cytoskeleton. Curr Biol, 1999;
9(24): 1497–500
11. Li X, Wang W, Wang J et al: Proteomic analyses reveal distinct chromatin-
associated and soluble transcription factor complexes. Mol Syst Biol, 2013; 11(5): 775
12. Iyevleva AG, Raskin GA, Tiurin VI et al: Novel ALK fusion partners in lung cancer. Cancer Lett, 2015; 362(1): 116–21
13. Kuzma-Kozakiewicz M, Kazmierczak B, Chudy A et al: Alteration of mo-
tor protein expression involved in bidirectional transport in peripheral blood mononuclear cells of patients with amyotrophic lateral sclerosis. Neurodegener Dis, 2016; 16(3–4): 235–44
14. Bransfield KL, Ashkan JM, Leek JP et al: Phenotypic changes associated with DYNACTIN-2 (DCTN2) over expression characterise S5A-1 osteosar-
coma cells. Mol Carcinog, 2006; 45(3): 157–63
15. Lee B, Sahoo A, Marchica J et al: The long non coding RNA SPRYRHLA1 acts as an intranuclear organizing hub for pre-mRNA molecules. Sci Adv, 2017;
3(5): e1602505
16. Vancoillie G, Lambert J, Haeghen YV et al: Colocalization of dynactin sub-
units P150Glued and P50 with melanosomes in normal human melanocytes. Pigment Cell Res, 2000; 13(6): 449–57
17. Shaul YD, Yuan B, Thiru P et al: MERA: A tool for comparing gene expres-
sion across human tissues and cell types. Nucleic Acids Res, 2016; 44(D1):
D560–66
18. Anaya J: OncoLnc: Linking TCGA survival data to mRNAs, miRNAs, and In-
cRNAs. PeerJ Computer Science, 2016; 2: e67
19. Huang da W, Sherman BT, Lempicki RA: Bioinformatics enrichment tools: Paths toward the comprehensive functional analysis of large gene lists. Nucleic Acids Res, 2009; 37(1): 1–13
20. Huang DW, Sherman BT, Lempicki RA: Systematic and integrative analysis of large gene lists using DAVID bioinformatics resources. Nat Protoc, 2008;
4(1): 44–57
21. Warde-Farley D, Donaldson SL, Comes O et al: The GeneMANIA prediction server: Biological network integration for gene prioritization and predicting gene function. Nucleic Acids Res, 2010; 38(Web Server issue): W214–20
22. Burkhardt JK, Echeverri CJ, Nilsson T, Vallee RB: Overexpression of the dy-
namin (p50) subunit of the dynactin complex disrupts dynein-dependent maintenance of membrane organelle distribution. J Cell Biol, 1997; 139(2):
469–84
23. Munch C, Seddlemeier R, Meyer T et al: Point mutations of the p50 subunit of dynactin (DCTN1) gene in ALS. Neurology, 2004; 63(4): 724–26
24. Munch C, Rosenbom A, Sperfeld AD et al: Heterozygous R1101K mutation of the DCTN1 gene in a family with ALS and FTD. Ann Neurol, 2005; 58(5):
777–80
25. Farrer MI, Huilhan MM, Kachergus JM et al: DCTN1 mutations in Perry syn-
drome. Nat Genet, 2009; 41(2): 163–65
26. Steele JC, Guella I, Szu-Tu C et al: Defining neurodegeneration on Guam by targeted genomic sequencing. Ann Neurol, 2015; 77(3): 458–68
27. Araki E, Tsuboi Y, Daechsel J et al: A novel DCTN1 mutation with late-onset parkinsonism and frontotemporal atrophy. Mov Disord, 2014; 29(9): 1201–4
28. Ohshima S, Tsuboi Y, Yamamoto A et al: Autonomic failures in Perry syndrome with DCTN1 mutation. Parkinsonism Relat Disord, 2010; 16(9): 612–14
29. Emond MJ, Louie T, Emerson J et al: Exome sequencing of extreme phenotypes identifies DCTN4 as a modifier of chronic Pseudomonas aeruginosa infection in cystic fibrosis. Nat Genet, 2012; 44(8): 886–89
30. Viel M, Hubert D, Burget PR et al: DCTN4 as a modifier of chronic Pseudomonas aeruginosa infection in cystic fibrosis. Clin Respir J, 2016; 10(6): 777–83
31. Lim CM, Cater MA, Mercer JF, La Fontaine S: Copper-dependent interaction of dynactin subunit p62 with the N terminus of ATP7B but not ATP7A. J Biol Chem, 2006; 281(20): 14006–14
32. Berrueta L, Tirnauer JS, Schuyler SC et al: The APC-associated protein EB1 associates with components of the dynactin complex and cytoplasmic dynein intermediate chain. Curr Biol, 1999; 9(8): 425–28