A disease network-based deep learning approach for characterizing melanoma

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Abstract
Multiple types of genomic variations are present in cutaneous melanoma and some of the genomic features may have an impact on the prognosis of the disease. The access to genomics data via public repositories such as The Cancer Genome Atlas (TCGA) allows for a better understanding of melanoma at the molecular level, therefore making characterization of substantial heterogeneity in melanoma patients possible. Here, we proposed an approach that integrates genomics data, a disease network, and a deep learning model to classify melanoma patients for prognosis, assess the impact of genomic features on the classification and provide interpretation to the impactful features. We integrated genomics data into a melanoma network and applied an autoencoder model to identify subgroups in TCGA melanoma patients. The model utilizes communities identified in the network to effectively reduce the dimensionality of genomics data into a patient score profile. Based on the score profile, we identified three patient subtypes that show different survival times. Furthermore, we quantified and ranked the impact of genomic features on the patient score profile using a machine-learning technique. Follow-up analysis of the top-ranking features provided us with the biological interpretation of them at both pathway and molecular levels, such as their mutation and interactome profiles in melanoma and their involvement in pathways associated with signaling transduction, immune system and cell cycle. Taken together, we demonstrated the ability of the approach to identify disease subgroups using a deep learning model that captures the most relevant information of genomics data in the melanoma network.

KEYWORDS
autoencoder, disease network, genomics, melanoma, neural network, systems medicine

What’s new?
Genomic heterogeneity in melanoma is vast. Hence, the integration of genomics data with known associations between genomic variations and melanoma prognosis could facilitate the
identification of genomic features most relevant to patient outcome. Here, the authors integrate genomics data with a disease network and deep learning model for the prognostic classification of melanoma patients and assessment of impacts of genomic features on disease classification. The data suggest that deep learning models based on genomics data and disease networks can contribute to personalized prognostic assessment for melanoma patients. The generic nature of the approach suggests that it is applicable to other cancer types.

1 | INTRODUCTION

Cutaneous melanoma is one of the most aggressive forms of skin cancer and is characterized by a lymphogenic and hematogenic metastatic spread which is directly proportional to the vertical depth of invasion of the tumor cells into the skin. Early detection and surgical excision of the primary tumor are essential as the disease becomes life threatening once it metastasizes. The introduction of small-molecule inhibitors targeting the kinases BRAF and MEK as well as immune checkpoint inhibitors have tremendously changed the treatment landscape in the last 10 years, leading to remarkable treatment results in patients with metastatic melanoma. Nevertheless, many patients with advanced melanoma still do not benefit from these new drugs either through primary or acquired treatment resistance. Despite enormous research, the understanding of melanoma progression and certain melanoma subtypes remains very limited. The Cancer Genome Atlas (TCGA) database provides information on copy number, mutation, transcriptomic, methylation and clinical data of melanoma patients. These data allow integrative analysis of the genomic profiles of melanoma and thereby improves our understanding of the progression and development of the disease. Prominent studies include the integration of genomics data to identify novel driver genes of melanoma and informative individual markers and pathways that provide valuable insights into melanoma prognosis. Besides, tumor heterogeneity impedes the efficacy of available therapies for melanoma, imposing additional needs for developing tools that can stratify melanoma patients that show clinical and genomic distinction, therefore facilitating the development of precision medicine.

Deep learning models, which allow efficient extraction of complex data with multiple levels of abstraction, have proven a powerful tool in facilitating the classification of cancer and improving cancer prognosis by integrating genomics data and clinical factors. For instance, Xie et al fed four types of data into a model combining a multimodal neural network with an autoencoder and identified four genomic clusters in 8646 patients with 29 cancer types. Applying the identified genomic clusters to melanoma cohorts treated by anti-CTLA-4 showed that patients with distinct genomic features have different responses to the immunotherapy. Specifically, the patient subtype with high microsatellite instability and somatic copy number alterations but low tumor mutation burden showed the lowest clinical benefit of the immunotherapy and the shortest survival. Although there are variant architectures in deep learning models, most of them consist of multiple fully connected layers for analyzing genomics data, making them difficult to provide biological interpretation. Hence, researchers added annotated information such as pathways into neural networks to increase the interpretability of deep neural networks. Hao et al developed a pathway-based sparse deep neural network that integrates genomics and clinical data to identify prognostic factors for glioblastoma and serous cystadenocarcinoma. The addition of a pathway layer between the input layer (ie, the genomics data) and the hidden layer allowed biological interpretation of the identified genomic features at the pathway level. Similarly, Feng et al built a deep neural network by connecting the transcriptomic and copy number variation profiles of 1967 genes with 46 cancer pathways to predict cancer patients’ survival time. Computation of scores of the pathways quantified their impact on the model outputs and thus explaining the association between the pathways and the patients’ survival time. The interpretable deep learning models not only leverage the full potential of genomics data but also provide biological explanations that are crucial for understanding tumor heterogeneity, therefore allowing for identifying therapeutic targets for specific patient groups.

Additionally, carcinogenesis can be viewed as a rewired network due to endogenous perturbations resulting from genomic alterations. Thus, researchers integrate human genomics and network analysis to refine our biological understanding of cancer and identify novel prognostic markers. One advantage of network analysis is that interactome information can be stratified into communities based on network topology, thus permitting a more precise understanding of molecular mechanisms. The success of such approaches has been demonstrated in predicting patient-specific mutation signatures for melanoma, identifying synergistic drug combinations for diverse melanoma genomic subtypes, and detecting cooperative microRNAs (miRNAs) for treating metastatic melanoma resistant to anti-PD-1 therapy. Thus, it is appealing to develop an approach that integrates genomics data and a disease network with a deep learning model to characterize melanoma.

In our study, we integrated genomics data into a melanoma network and applied a deep learning model to identify subgroups in the TCGA melanoma patients (Figure 1). The model utilizes communities identified in the melanoma network to effectively reduce the dimensionality of genomics data into a patient score profile. Using the score profile, we identified three subtypes of melanoma patients. Post hoc analysis of the patients’ survival time and clinical features provided supporting evidence and interpretation of the identified clusters. Furthermore, we applied a machine-learning technique to quantify and rank the impact of genomic features on the score profile. We integrated gene set enrichment analysis with the melanoma network to
perform functional analysis that provides the biological interpretation of the top-ranking genomic features at the pathway and molecular levels. By doing so, we identified a group of genes (e.g., MMP2, PPP3CA and TUBB2B) that are impactful on the patient score profile, characterized their involvement in signaling pathways and depicted their molecular features such as mutation and interactome profiles in melanoma. Taken together, the approach allows for the effective integration of genomics data into a disease network to capture data variation for robust identification of disease subgroups with distinct clinical and molecular features.

2 MATERIALS AND METHODS

2.1 The melanoma network and network community detection

The melanoma map was constructed in our previous study and downloaded from www.vcells.net/melanoma. Briefly, the core map was created and curated through literature reading and annotation (see Supporting Information Materials for details). The principle of network community detection is to find a series of subnetworks with high cohesion and low coupling (see Supporting Information Materials for details). Based on this principle, we used a simulated annealing algorithm to partition the melanoma network. As the algorithm can produce different network partitions, we ran numerous simulations on the melanoma network and ranked them based on network modularity scores. The top 10 partitioned networks have similar modularity scores and a comparable number of communities (Figure S1), suggesting that the identified communities represent the optimal partition of the network. We selected the fully connected partitioned network with 21 communities and the maximum modularity score (0.485) for subsequent analysis. We ran the simulations and performed the analysis using the igraph package in R.

2.2 TCGA data processing

We downloaded the TCGA skin cutaneous melanoma dataset from the Genomic Data Commons Data Portal using the TCGAbiolinks package in R. The dataset includes melanoma patients' clinical features (e.g., gender, age, tumor type, tumor stage and treatment history; Table S1) and genomics data (e.g., transcriptome, DNA methylation, somatic mutation and copy number variation). After processing, we obtained four matrices accounting for the transcriptome, DNA methylation, somatic mutation and copy number variation of patients (see Supporting Information Materials for details). To ensure that the genomic profile of patients is complete, we kept only patient samples with four profiles (463 out of 475). Finally, integrating the genomics data into the network led to 4983 nodes with transcriptome data, 5193 nodes with DNA methylation data, 5015 nodes with somatic mutation data and 4952 nodes with copy number variation data (Table 1).

2.3 Network community scores

We adapted a sparse autoencoder model called PathME to transform genomics data of melanoma patients into a network community-based

![Figure 1](https://wileyonlinelibrary.com) Workflow of the study. We integrated the TCGA data into a melanoma network and performed community identification in the network. The genomic profiles of network community genes were inputs of an autoencoder model that transforms the genomics data into a community score. The scoring profile of patients was used for patient classification followed by subsequent analysis including patients' survival analysis, ranking of genomic features and interpretation of the features [Color figure can be viewed at wileyonlinelibrary.com]
score profile. The model has an unsupervised multimodal neural network architecture that can learn a low-dimensional embedding of genomic features from multiple sources.\textsuperscript{17} The structure of the model is shown in Figure 3, and a detailed description of model configuration and training can be found in Supporting Information Materials. After training the model for the 21 identified network communities sequentially, we concatenated scores of network communities for each patient. This results in a community-based score matrix (21 rows and 463 columns) that represents a reduced representation of the input data and can be used for patient clustering.

2.4 Patient stratification

We performed agglomerative hierarchical clustering using network community scores to identify clusters in patient samples. The algorithm first treated each patient sample as an individual cluster and calculated distances between clusters. The two samples with the shortest distance were merged into one cluster, and this process was repeated until all patient samples were merged into the same cluster. For calculating distances between clusters that have more than one sample, we used the complete-linkage clustering method to calculate their distances. The optimal number of clusters was determined by 26 indices (such as silhouette and C-Index) that are well-established metrics to assess cluster reliability. This analysis was performed using Nbclust package in R.

2.5 Shapley additive explanations

Shapley additive explanations (SHAP) is a game theoretic approach that provides interpretation to the output of machine learning models.\textsuperscript{18} SHAP makes use of the Shapley values to quantify the impact of features on the autoencoder model. The Shapley value is the average contribution of a feature \( i \) to the model output \( f(x) \) in all possible models trained on subsets of features. The Shapley value \( \psi_i(f, x) \) is a single numerical value representing the impact of feature \( i \) on the output of the model \( f \) when given the input \( x \). In our case, the input is the community-based feature values (ie, gene expression profile and DNA methylation profile of network nodes) and the output is the reconstructed data of the input data. Given a specific output \( f(x) \), the Shapley values using a weighted sum that represents the impact of each feature being added to the model-averaged over all possible feature value combinations (Equation 1):

\[
\psi_i(f, x) = \sum_{S \subseteq \mathbb{X}/\{i\}} \frac{|S|!(|M| - |S| - 1)!}{M!} [f_S(x) - f_{S \cup \{i\}}(x)],
\]

where \( f_S(x) = E[f(x)|x_S] \), \( x_S \) is a subset of the input vector with only the features in the set \( S \) present. \( M \) is the number of input features. SHAP approximates the Shapley values by a sampling procedure to avoid calculating the sum of all possibilities. To evaluate the importance of genomic features, we used the mean of summed absolute SHAP values per feature of all patient samples, and features with larger values are more important. As the autoencoder model was trained individually for each network community, we only compared features of gene expression and methylation data of the same community.

2.6 Survival analysis and statistical tests on clinical features

We applied chi-squared analysis to test interdependences between the patient clusters and their clinical information such as gender, age, tumor types, tumor stages and whether receiving any treatment (ie, radiation and pharmaceutical therapy). The number of clustered patients in different categories of clinical features was used for this test. We applied Kruskal-Wallis tests to detect interdependences between the patient clusters and their genomic profiles such as somatic mutation frequency and copy number variation frequency. The somatic mutation frequency of a patient is a sum of counts of any type of mutations identified in all genes in the melanoma network. Copy number variation frequency of a patient is the number of loss and gain in copies of all genes in the melanoma network. The Kruskal-Wallis test was used for comparing all three clusters and any two of

\[\text{TABLE 1} \quad \text{Overview of the genomics data}\]

| Category                  | Value and range | Raw Identifier | No. of features | Processed Identifier | No. of features | Matrix No. of features |
|---------------------------|-----------------|----------------|----------------|----------------------|----------------|-----------------------|
| Transcriptome (gene expression) | FPKM \( R \geq 0 \) | Ensemble ID | 56 457 | Gene symbol | 55 500 | 4983 |
| DNA methylation          | Beta value \( R \in [0, 1] \) | Probe ID | 485 577 | Gene symbol | 33 487 | 5193 |
| Somatic mutation         | Frequency \( Z \geq 0 \) | Gene symbol | 19 303 | Gene symbol | 19 303 | 5015 |
| Copy number variation    | Gene-level value \( [1, 0, -1] \) | Ensemble ID | 19 729 | Gene symbol | 19 059 | 4952 |

Note: The table shows the way of processing the data. The raw data were first mapped from identifiers to genes and then integrated into the melanoma network, resulting in four matrices for further analysis.
the three clusters. P-value ≤ 0.05 was considered significant. The statistical analysis was performed in R.

Patients’ survival time after the diagnosis of melanoma was used for performing survival analysis. We performed log-rank tests to compare the survival curves among the clustered patients. In 453 of 463 patients, survival information was available in TCGA data and used to draw the Kaplan-Meier plot using the TCGAbiolinks package.

The mutation annotation format file of melanoma from TCGA was obtained using TCGAbiolinks. We draw somatic mutation profiles of genes of interest using maftools in R.

2.7 | Gene set enrichment analysis

To identify pathways for which genes in each network community are enriched, we performed gene set enrichment analysis using the Reactome database. The pathways in the database were classified into 26 root categories, such as signaling transduction, immune system and cell cycle. P-values of Fisher’s exact test were corrected using the Benjamini-Hochberg method. Pathways with a false discovery rate (FDR) ≤ 0.05 were regarded as significant. This analysis was performed using ReactomePA package in R. In addition, we selected pathways containing at least 10 genes for drawing heat maps that show top-ranking features and the corresponding genomic information and drug-target interaction in different pathway categories. The heat maps were drawn using Complexheatmap in R.

2.8 | Data visualization

The melanoma network annotated with the identified communities and the networks for the top-ranking features were visualized using Cytoscape 3.82. The individual network communities annotated with genomic profiles were drawn using igraph and ggplot2 in R.

3 | RESULTS

3.1 | Community identification in the melanoma network

We used a manually curated map that accounts for state-of-the-art knowledge on the molecular biology of melanoma and contains 16 signal transduction pathways, such as growth factor receptor signaling, melanocortin signaling, death-ligand signaling, TNFα signaling and P53 signaling. We expanded the map by considering miRNA-gene interactions, gene regulation by transcription factors, protein phosphorylation catalyzed by kinases and drug-gene interactions (see Section 2). The resulted melanoma network contains 5860 molecules (5384 protein-coding genes, 385 protein complexes, 32 miRNAs and 59 drugs) and 14 494 interactions (Figure 2A). The topology of the network is scale free, as its degree distribution approximates a power law (Figure 2B).

We integrated the network with genomics data of 463 melanoma patients, including transcriptome, DNA methylation, somatic mutations and copy number variation (see Section 2). Such a network provided us with a comprehensive view of genomic profiles and molecular interactome underlying the pathogenesis and development of melanoma (Figure 2C). By using a simulated annealing method, we identified 21 network communities with a modularity score of 0.485 (see Section 2; Figure 2). The size of the identified communities ranges from 6 to 579 nodes with the number of edge size ranging from 6 to 1914. Among the communities, 18 are scale free and the rest have a star topology (Figure S3). The identified network communities annotated with melanoma patients’ genomic profiles allowed us to cluster patients and analyze their clinical characteristics.

3.2 | Patient stratification based on community-based scores

An autoencoder is a type of artificial neural network that can be used for dimensionality reduction and feature learning in an unsupervised manner. Such a neural network is composed of two parts: an encoder that maps input data to a hidden layer and a decoder that maps the hidden layer to an output layer. An autoencoder can reconstruct data by minimizing the error between the input layer and the reconstructed layer. Specifically, if the size of the hidden layer is less than the size of the input layer, the hidden layer can capture the significant features of the input data.

To detect potential clusters in melanoma patients, we fed the identified network communities with gene expression and DNA methylation data into an autoencoder model (see Section 2; Figure 3). For the reason that the mutation and copy number variation data are sparse and not continuous, we did not consider them as inputs of the autoencoder model but used them for analyzing the genomic differences in clustered patients. The model reduced the dimension of the genomics data by transforming them into a network-community score profile, which is a matrix with 21 communities and 463 patients. Next, we applied hierarchical clustering on the community score profile to classify the patient samples and obtained three patient clusters (see Section 2). Such classification was systematically estimated and supported by 14 indices out of 26 (Figure 4A). In addition, the identified clusters showed a clear pattern in their community scores that were not seen using genomics data (Figures 4B and S4). Compared to the individual genomics data, the community score profile showed better classification of patient samples while applying a nonlinear dimensionality reduction method to embed the high-dimensional data in a 2-dimensional space (Figure 4C). Taken together, the results suggested that the community score has the advantage in identifying subgroups in patients compared to using the genomics data alone. The identified patient clusters may have different clinical features that require further analysis.
3.3 Association between the patient clusters and their clinical features and genomic profiles

We performed statistical tests to investigate whether the identified patient clusters have differences in clinical features and genomic profiles such as somatic mutation and copy number variation (see Section 2). The identified patient clusters showed significant differences in survival time—Cluster 3 has a much shorter median survival time and lower surviving probability than the other two clusters (Figure 4D). Besides, the clusters showed a significant difference in tumor types—Cluster 3 has a lower percentage of patients with metastasis than the other clusters (Table 2). No significant differences among the clusters were identified in other clinical features such as patients’ gender, age, tumor stage and treatment differences (Table 2). Furthermore, Clusters 1 and 2 showed significant differences in frequency of somatic mutation, and no significant difference was identified in copy number variation between the patient clusters (Table 2; Figure S5). Taken together, the data showed that the identified patient clusters have differing survival times and different profiles in terms of tumor types and somatic mutation. Thus, it is interesting to explain such differences at the molecular level.

3.4 Interpretation of genomic features learned for patient stratification

We combined the SHAP method and gene set enrichment analysis to interpret the genomic features learned by the autoencoder model for patient stratification. The former quantified the importance of genomic features (see Section 2), and the latter helps to explain the function of the network community genes at both pathway and molecular levels. For most network communities, the gene expression data show a much stronger contribution to the community score used for patient clustering than the methylation data, as the corresponding SHAP values are much higher (Figure 5). The only exception is community 12, and its features in the methylation data have much higher SHAP values than the features in the gene expression data. Besides, the contribution of the molecular features on the community scores is similar for individual patient clusters (Figure S6).

**Figure 2** The melanoma network. (A) We identified 21 communities in the network based on its topological properties. The number of nodes in the identified communities ranges from several (e.g., community 12) to hundreds (e.g., community 7). (B) The node degree of the network genes follows a power-law distribution. A few nodes have many interactions with other nodes and most nodes have only a few or single interactions. (C) The integration of the genomic profiles into the network communities (e.g., community 21) allowed further analysis. The circus plot for each community gene has four layers and each represents a genomic profile. For visualization, the data were normalized into the interval $[0, 1]$. Specifically, we performed min-max normalization (i.e., $1 - 2 \times (\text{value} - \min)/(\max - \min)$) on the expression (the first layer) and methylation (the second layer) data; the third layer shows whether a gene has a mutation in a corresponding patient (1: mutation, 0: no mutation); the most inner layer shows the copy number variation using gene-level copy number values (-1: loss, 0: unchanged, 1: gain) [Color figure can be viewed at wileyonlinelibrary.com]
Furthermore, we performed gene set enrichment analysis to provide biological interpretation to the top-ranking features identified by the SHAP method (see Section 2). The identified enriched pathways for the network genes were found in 19 Reactome root categories, and the top three categories with the most enriched pathways are signaling transduction, immune system and cell cycle (Figure 6). Besides, most of the enriched pathways contained genes from the network communities 3, 7, 10, 14, 17 and 20. For instance, genes from the biggest network community 7 are involved in 352 Reactome pathways, of which 86 belong to the category signal transduction, 63 to immune system and 35 to cell cycle. This suggested the important role of the community genes in regulating signaling pathways, immune response and cell cycle underlying melanoma. For better understanding the identified top features that impact patient stratification, we analyzed their molecular function and their association with melanoma using the information from the melanoma network. In the following, we mainly presented and discussed the results of the network communities 7, 10 and 14 because they are top-ranking communities with their genes enriched in pathways related to signaling transduction, immune system and cell cycle that are important for carcinogenesis.22

The top 20 features (from both gene expression and methylation data) of network community 7 contain known melanoma genes, such
as MLANA encoding melanoma antigen Melan-A and PMEL encoding melanocyte transmembrane glycoprotein (Figure S7A). TYRP1 is the top molecular feature in gene expression data contributing to the community score learned for community 7, and the gene is a prognostic marker and a potential therapeutic target for metastatic melanoma.\textsuperscript{23} For methylation data, SPRY1 has the largest impact on the community score for its largest SHAP value. The four mammalian SPRY proteins SPRY1-4 are involved in inhibiting FGF and RAS/RAF/ERK signaling, which play a central role in melanoma formation, progression and drug resistance.\textsuperscript{24} Loss of SPRY1 can reduce the growth of BRAF V600-mutant cutaneous melanoma and improve response to targeted therapy.\textsuperscript{25} Another SPRY family member named SPRY4 was ranked first in the gene expression data in network community 11 (Figure S10).

At the pathway level, seven of the top-ranking features (four from the gene expression data and three from the methylation data) are involved in signaling transduction by receptor tyrosine kinases (such as PDGF, EGFR and VEGF) and their downstream pathways (such as MAPK family signaling and RAF/MAP kinase cascades) (Figure 7A). Activation of these pathways ultimately results in changes in gene

\textbf{FIGURE 4} Classification of melanoma patients. (A) The bar plot shows the number of indices that vote for the optimal number of clusters in the patients. Among 26 indices, 14 vote for three clusters in the patient samples. (B) The heat map shows the hierarchical classification of the patients using the community-based score matrix. The grids of the heat map show the community scores after z-score normalization. Patients and communities are hierarchically clustered by Euclidean distance and complete linkage. The community score of patients can be found in Table S4. (C) The clustered patients are visualized in the T-SNE (t-stochastic neighborhood embedding) plots using the community score, gene expression profile or methylation profile of the patients. The color of nodes represents patient clusters, and the shape of nodes denotes tumor types: metastatic tumor (TM) and primary tumor (TP). We used all genes in the melanoma network to draw the plot. (D) The Kaplan-Meier plot of the clustered patients. The dashed line shows the median survival times of the clustered patients. The table shows the corresponding statistics used to draw the plot. The $P$-value was obtained using the log-rank test [Color figure can be viewed at wileyonlinelibrary.com]
expression and cellular metabolism. Ten of the top-ranking features (three from the gene expression data and seven from the methylation data) are involved in immune system pathways, including interleukin signaling (such as IL-1, IL-4, IL-10 and IL-13), interferon signaling, and T cell receptor signaling that are important for regulating tumor killing by immune cells. Among the top features, MMP2 ranked the 17th feature in the gene expression data and 19th in the methylation data. It is involved in IL-4 and IL-13 signaling pathways and its upregulation can increase tumor growth and metastasis of melanoma. Copy number variations of MMP2 identified in the Cluster 3 are fewer in terms of proportion of patients than the other two clusters, and no somatic mutations in MMP2 were found in the Cluster 3 patients (Figure S8A). For network community 14, the top 20 ranking features from both datasets contain well-studied cancer genes (Figure S7B). For example, PIK3R3 encoding a subunit of PI3K complex that regulates key signaling pathways associated with cellular growth, proliferation, survival and migration in cancer, and HRAS belonging to the Ras family that are often mutated in human cancers.

| Clinical features | Cluster 1 | Cluster 2 | Cluster 3 | Chi-squared test |
|------------------|-----------|-----------|-----------|-----------------|
| Age < 20         | 2         | 3         | 0         | 0.58            |
| [20,60]          | 126       | 89        | 26        |                 |
| > 60             | 99        | 81        | 29        |                 |
| Gender           | Female    | 75        | 74        | 26              | 0.069           |
| Male             | 154       | 104       | 30        |                 |
| Tumor type       | Metastasis| 202       | 126       | 32              | 6.11e–08        |
| Primary          | 27        | 52        | 24        |                 |
| Tumor stage      | 0         | 4         | 1         | 2               | 0.16            |
| i                | 45        | 26        | 4         |                 |
| ii               | 61        | 55        | 23        |                 |
| iii              | 79        | 65        | 23        |                 |
| iv               | 12        | 10        | 1         |                 |
| Radiation        | Yes       | 67        | 39        | 7               | 0.020           |
| No               | 162       | 139       | 49        |                 |
| Therapy          | Yes       | 71        | 56        | 17              | 0.99            |
| No               | 158       | 122       | 39        |                 |
| Genomic data     |           |           |           |                 |
|                  | KWT (overall) | KWT (Cluster 1 vs 2) | KWT (Cluster 2 vs 3) | KWT (Cluster 1 vs 3) |
| Somatic mutation | 0.003     | 0.0008    | 0.63      | 0.11            |
| Copy number variation | 0.37 | 0.45 | 0.36 | 0.19 |

Note: For the clinical features, the table shows the number of patients in each cluster and the corresponding P-value of the chi-squared test. The clinical information includes patients’ age, gender, tumor type, tumor stage and treatment differences (see Table S1 for details). For the genomics data, the table shows the corresponding P-value of the Kruskal-Wallis test (KWT) for the overall comparison between three clusters and individual comparisons among them.
FIGURE 5  The SHAP values of genomic features in the network communities. The plot shows the mean of the absolute SHAP values of gene expression and DNA methylation in the network communities (A). The higher the value is the more impact the corresponding genomic feature has on the community score. The SHAP value is comparable only within communities as the autoencoder model is trained sequentially for each community. As an example, the top 20 genomic features ranked by the SHAP values for network community 7 is shown (B). The genes highlighted with asterisks are annotated as known melanoma genes in the core melanoma network. The top-ranking features in other communities can be found in Figure S10 [Color figure can be viewed at wileyonlinelibrary.com]
Gene set enrichment analysis of the network communities. The figure shows the involvement of the 21 network communities in immune function by inhibiting T-cell activation.39 The network showed in vivo.38 Calcineurin can be inhibited by pimecrolimus that suppresses and persistent activation of calcineurin/NFAT signaling is prooncogenic calcium-dependent serine-threonine phosphatase (a.k.a. calcineurin), in Cluster 3 patients (Figure S8B). The gene encodes a subunit of expression data. Its copy number variation is higher in the Cluster. Among the top features, PPP3CA ranked the 11th feature in the gene the gene expression data and two from the methylation data) were found to be associated with immune system pathways, such as with C-type lectin receptor (CLR) and Fc epsilon receptor (FCERI) signaling (Figure 7B). CLR is a pattern recognition receptor on dendritic cells that secret cytokines to induce T cell differentiation by recognizing pathogen-associated molecular patterns.36 FCERI signaling in mast cells includes a network of signaling molecules and adaptor proteins that play important roles in inflammatory and immediate allergic reactions. Nine of the top-ranking features (four from the gene expression data and five from the methylation data) are involved in signaling transduction pathways, like AKT signaling and signaling by receptor tyrosine kinases such as VEGF, NTRKs and ERBB2 (Figure 7A). The AKT signaling plays important roles in cell survival and metabolism.37 Among the top features, PPP3CA ranked the 11th feature in the gene expression data. Its copy number variation is higher in the Cluster 3 patients than the other two clusters, and the gene shows no mutation in Cluster 3 patients (Figure S8B). The gene encodes a subunit of calcium-dependent serine-threonine phosphatase (a.k.a. calcineurin), and persistent activation of calcineurin/NFAT signaling is prooncogenic in vivo.38 Calcineurin can be inhibited by pimecrolimus that suppresses immune function by inhibiting T-cell activation.39 The network showed that PPP3CA can interact with melanoma genes including BAD, YWHAH, NFATC3, ORAI and ITPR2 (Figure 7D). BAD plays an important role in coordinating the apoptotic machinery, and calcium can induce apoptosis through calcineurin-mediated (encoded by PPP3CA) dephosphorylation of BAD.40 The dephosphorylation of BAD is in conjunction with the protein 14-3-3 encoded by YWHAH.

For network community 10, we found only one melanoma gene TBX3 from the top 20 features of both profiles (Figure S7C). The gene encodes a transcription factor that can enhance melanoma invasiveness through repressing E-cadherin expression.41 RCN3 and miR-25 are the top molecular features in gene expression and methylation data, respectively. RCN3 is a calcium-binding protein and has not been reported to be associated with cancer. Upregulation of miR-25 that targets DKK3 can promote proliferation and invasion of melanoma cells.42 The community genes are mainly enriched in mitotic cell cycle processes, including four top-ranking features (RAD21 and NUF2 in the gene expression data and TUBB2B and EMD in the methylation data) involved in the mitosis phase, mitotic G2-G2/M phase and S phase (Figure 7C). Besides, TUBB2B is involved in the Hedgehog signaling pathway whose activity plays a crucial role in melanoma tumorigenesis.43 TUBB2B has a higher copy number variation frequency in the Cluster 3 patients than the other two clusters, and it shows mutations in only two melanoma patients that belong to Clusters 1 and 3, respectively (Figure S8C). It has been shown that the mRNA and protein expression levels of TUBB2B are upregulated in metastatic melanoma cells, suggesting its important role in regulating melanoma.44 Besides, the network showed that TUBB2B is targeted by miR-93a-3p and such post-transcriptional regulation is identified using a high throughput technique called CLASH that can recover RNA duplexes bound by Argonaute protein (Figure S9B).
FIGURE 7  Biological interpretation of the top-ranking genomic features in the network communities. The heat map shows the involvement of top-ranking features in three categories: signal transduction (A), immune system (B) and cell cycle (C). The rows represent terms of the pathway categories.

The top annotation highlights from which genomics data a gene comes, and the percentage in the three patient clusters that show copy number variation (CNV) and simple nucleotide mutation (SNV). The bottom annotation shows known drug-gene interactions. The bar plot on the left shows the number of genes of a pathway. (D) The interacting genes of MMP2 and PPP3CA. The interaction information was extracted from the comprehensive interaction profiles of the top-ranking features in pathway categories (Figure S9). The color of nodes indicates whether a gene is a top-ranking feature in gene expression, methylation or both datasets. If not, it is in gray. The color of node names indicates whether a gene is annotated as a melanoma gene from the core melanoma network. The interactions are derived either from the literature or the databases used for expanding the network. The color of edges shows interaction types including stimulation, inhibition and protein-protein interaction [Color figure can be viewed at wileyonlinelibrary.com]
In addition, several other genes that have been shown to influence melanoma progression and drug resistance ranked among the top 20 features in the other network communities (Figure S10). The endopeptidase MMP16 (a.k.a. MT3-MMP) ranked 10th in the gene expression data and 13th in the methylation data of network community 4. MMP16 is anchored to the cell membrane via a transmembrane domain and is involved in the degradation of several extracellular matrix components such as collagen type III, fibrin, laminin and fibronectin. The gene activates MMP2 by cleaving its inactive proMMP2.45 MMP16 is highly expressed in melanoma metastases but not in primary tumors46 and has been identified as an effector that promotes melanoma cell invasion depending on the matrix composition.46 Additionally, MMP16 overexpression has been linked to increased lymphatic invasion and a worse clinical prognosis of melanoma patients,46 and it seems to cooperate with melanoma chondroitin sulfate proteoglycan (MCSP) to promote melanoma invasion.47 In network community 6, FGFR1 coding for fibroblast growth factor receptor 1 ranked seventh in gene expression data. FGF signaling triggers the activation of a variety of signaling pathways including MAPK, PKC, PI3K/AKT and STAT signaling,48 and may be inhibited by members of the SPRY family.48 FGFR1 is highly expressed in melanoma and mediates adaptive resistance to BRAF and MEK inhibitors in BRAF-mutant melanoma.49 Notably, FGFR1 can be targeted by a variety of FGFR inhibitors (e.g., inifritinib) that have been developed recently. S100B ranked first in the methylation data of network community 13. This calcium-binding protein has been previously described as an independent prognostic biomarker in melanoma because its elevated baseline serum levels are associated with poor overall survival.50 EIF1AX, which ranked sixth in gene expression data of network community 15, is frequently mutated in uveal melanoma,51 a rare melanoma subtype that was not included in the analyzed dataset. Mutations in EIF1AX lead to an aberrant translational regulation and have been associated with a low risk for developing metastasis in uveal melanoma.52 ERBB3 ranked ninth in gene expression data of network community 16 and encodes Erb-B2 receptor tyrosine kinase 3, a frequently overexpressed member of the epidermal growth factor receptor (EGFR) family of receptor tyrosine kinases in melanoma.53 ERBB3 is associated with adaptive drug resistance in melanoma as its activation mediates resistance to BRAF and MEK inhibitors by activating PI3K/AKT signaling.54 Interestingly, its expression can be directly regulated by the transcription factor SOX10, which is also among the top-ranking features of network community 7.55 ERBB3 inhibition using neutralizing antibodies enhances the efficacy of MEK inhibitors in BRAF and NRAS wild-type melanoma.56 Additionally, ERBB3 can be targeted by the small molecule inhibitor sapitinib (AZD8931) that also inhibits ERBB1 and ERBB2.57 The neural crest stem cell marker NGFR ranked first in gene expression data of network community 21. The gene is upregulated in dedifferentiating melanoma cells that acquire a neural crest stem cell-like phenotype as a response to BRAF and MEK inhibition.58

Taken together, combining the SHAP method, the melanoma network and the gene set enrichment analysis provides us with a powerful tool to interpret the impactful features that are learned by the autoencoder model to stratify melanoma patients. This not only elaborates the molecular function of the relevant genes but also unravels their association with signaling pathways that underlie the pathogenesis and development of melanoma. Furthermore, analyzing the genomic features of the patient clusters helps to explain differing survival times and potential differences in treatment response.

4 | DISCUSSION AND CONCLUSIONS

The rapid production and easy access of genomics data have created an unprecedented opportunity to study cancer biology. However, multidimensional data pose a huge challenge for data analysis. In our study, we developed an integrative approach that combines genomics data, a disease network, and a deep learning model to identify and analyze subtypes of melanoma patients. The genomics data of melanoma have high dimensionality, is noisy, and contains sparse signals.59 Thus, it is appealing to develop and apply advanced methods that help us to extract useful information from the data for patient classification. The approach proposed integrates genomics data and a melanoma network with an autoencoder model to classify TCGA melanoma patients, and three subgroups with distinct prognostic implications and molecular characteristics were identified. In addition, the complex architectures of deep learning models make them difficult to interpret.21 We combined the feature-ranking method, the melanoma network and gene set enrichment analysis to interpret the genomic features learned by the autoencoder model for patient stratification. Such a method not only allowed us to provide the biological explanation of the genomic features at the pathway level but also to characterize their molecular features such as mutation and interactome profiles.

We used a melanoma network that is manually constructed and curated using the literature and further expanded using relevant databases. Such a knowledge-based network allowed us to put the newly discovered relevant interactions into the context of the existing knowledge and facilitate the mining and interpretation of the genomics data. However, it may be compromised by not considering other intracellular interactions that are known to be important but not yet found to be relevant for melanoma. An all-encompassing network can be reconstructed using databases such as BioGRID50 and Omnipath51 but may introduce redundant information and thus increasing the computational cost and potential risk of overfitting while training the deep learning model. Furthermore, there is no guarantee that an identified community structure of a network is unique because the procedure is complicated by a multiplicity of community detection algorithms and multiple and conflicting definitions of communities.62 We identified several different partitions with comparable modularity values, and systematic analysis of their properties ensured that the selected community structure of the melanoma network is optimal and representative.

The autoencoder model transforms the genomics data of the identified network communities to a score separately, and one could take advantage of the fact that the melanoma network is a whole and
design a model in which all the network community scores are simultaneously learned. However, although such a model may be biologically more reasonable, it may face a trade-off that requires more computation time and increases the number of parameters such as weights and biases, therefore raising the risk of overfitting due to the high dimensionality of genomics data. Furthermore, applying deep learning approaches to high-dimensional genomics data faces the interpretation challenge. Model interpretation is often more important than predicting with high accuracy, for example, identifying prognosis factors for predicting the survival time of patients. However, hidden nodes, computed by fully connected layers, are not able to represent explicit biological components. We demonstrated the interpretable ability of the approach, combining SHAP analysis, annotated pathway knowledge and the melanoma network, to provide contributing features for patient classification with the biological explanation.

In the future, we can modify the model by linking to survival prediction or considering multiple tasks. The upgraded model may serve as a novel, powerful tool for dermato-oncologists to identify patients with a high risk for progressive disease and poor survival who will benefit from modified, cluster-adapted follow-up schemes or more aggressive treatment strategies. Vice versa, patients with a low risk according to their gene expression and DNA methylation profiles may also take advantage of the model by saving them from unnecessary treatment-related toxicities. They may receive “wait-and-see” care only instead of adjuvant treatments that are often accompanied by severe adverse events and decrease the patients’ quality of life. Therefore, such kinds of deep learning model may support physicians in selecting the best individual therapy and follow-up scheme for each patient based on genomics data.

To date, the usability of the model is limited as generating gene expression and DNA methylation data from single patients remain costly and currently not feasible in a daily clinical setting. Additionally, processing, analysis and interpretation of sequencing data are still challenging. However, the model has the potential to facilitate analysis and interpretation by reducing a large amount of genomics data to network community scores for stratifying patients. Furthermore, the model may serve as a powerful tool for complementing already existing predictive biomarker panels that investigate the expression of a few genes, for example, the MelaGenix score. Besides, a future step might be the validation of the model using an independent patient cohort and expanding such a model on treatment response to immunotherapy.

Taken together, the approach provides an effective integration of genomics data and a disease network into a deep learning model. Although we demonstrated the capability of the approach with only melanoma data, it is a generic approach and therefore applicable to other cancer types and possibly other types of diseases, too. Besides, our study also shows the necessity of developing and implementing multiple analysis approaches given the complexity of multidimensional data.

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CONFLICT OF INTEREST
The authors declare no potential conflict of interest.

AUTHOR CONTRIBUTIONS
Conceptualization: XL; Data curation: XL, JFZ; Formal analysis: XL; Funding acquisition: XL, AM, CB, JV; Investigation: XL, JFZ; Methodology: XL; Project administration: XL, JV, LZ; Resources: XL, CB, JV, LZ; Software: XL, JFZ; Supervision: XL, JV, LZ; Validation: XL, JFZ; Visualization: XL, JFZ; Writing-original draft: XL, JFZ; Writing-review & editing: XL, JFZ, AW, MH, AM, CB, JV, LZ.

DATA AVAILABILITY STATEMENT
The data and code for this work are deposited at https://doi.org/10.5281/zenodo.5556063. Further details and other data that support the findings of our study are available from the corresponding author upon request.

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