GENOTYPE-PHENOTYPE CORRELATION IN PATIENTS WITH FIBRILLIN-1 GENE MUTATIONS

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Abstract

Fibrillin-1 (FBN1) gene mutations are clinically associated with the Marfan syndrome (MFS), an autosomal dominant connective tissue disorder with prominent clinical manifestations in the cardiovascular, musculoskeletal and ocular system. Data of molecular genetic analysis and a catalogue of clinical symptoms were mined in order to discover novel correlations between MFS’s genotype and phenotype using hierarchical cluster analysis and logistic regression analysis. A score measure describing the similarity between a patient’s clinical symptoms and a characteristic phenotype was introduced.

Four different phenotype classes were clustered in patients with classic or suspected MFS. A probabilistic model built on clinical symptoms was established to predict the presence of a FBN1 missense mutation. Highest correlation between a missense mutation, which manifested as ectopia lentis, skeletal major and skin minor criteria, and two out of four clustered phenotypes was found. The probability for the presence of a missense mutation in both phenotype classes is approximately 70%.

Genotype-phenotype correlation between FBN1 gene mutations and clinical manifestations may contribute to anticipate the clinical consequences of specific mutations more comprehensively and may be helpful to identify and treat at-risk patients at an early stage of disease.

Key Words

Fibrillin-1 (FBN1) gene mutations; Marfan syndrome; phenotype-genotype correlation; data mining.

1. Introduction

Mutations in the gene encoding fibrillin-1 (FBN1, OMIM #134797) are clinically associated with the Marfan syndrome (MFS, OMIM #154700). MFS is an autosomal dominant inherited connective tissue disorder with variable clinical manifestations in the cardiovascular, musculoskeletal and ocular system showing a prevalence of approximately 1/5000. At present more than 600 mutations in the gene encoding fibrillin-1 are known and have been observed in at least 80% of cases [1].

The diagnosis of MFS is based on a catalogue of clinical diagnostic criteria which are described in the so-called ‘Gent nosology’ [2]. Milder and more severe clinical symptoms organized as minor and major criteria, which affect at least two organ systems (major criteria) and the involvement of a third system (minor criteria), are required for classic MFS. Weakness of the aortic wall accounts for 80% of known causes of death of patients with MFS [3]. Before life threatening complications like dissection or rupture occur, alterations of aortic elastic properties due to defective FBN1 can be detected by the examination and monitoring of aortic elasticity [4]. In addition, molecular genetic analysis may be helpful to identify at-risk individuals at an early stage of disease. Most of the reported mutations are so-called missense mutations mainly affecting the epidermal growth factor (EGF)-like protein domain structure and the calcium-binding (cb) site [5].

The aim of our study was to investigate the correlation between FBN1 missense mutations and the clinical phenotype of classic or suspected MFS patients by using hierarchical cluster analysis and logistic regression analysis. A score value was introduced to quantify phenotypic similarity or dissimilarity of patients’ clinical symptoms and characteristic phenotypes.

2. Methods

Molecular genetic analysis

FBN1, which is translated into fibrillin-1, lies on the long arm of chromosome 15 (15q15-q21.1). This very large gene (> 230 kb) is highly fragmented into 65 exons, transcribed in a 10 kb mRNA that encodes a 2,871 amino acid protein. Fibrillin-1 is a large glycoprotein (320 kDa) ubiquitously distributed in connective tissues [6].

In molecular genetic analysis, genomic DNA samples were amplified exon by exon by means of a polymerase chain reaction (PCR) using intron-specific
primers. Amplicons were analyzed by denaturing high-performance liquid chromatography (DHPLC) followed by direct sequencing of amplicons with abnormal elution profiles. The mutations found were verified by repeated sequencing on newly amplified PCR products. In the case of splice site mutations and when no mutation was detected by DHPLC, \( FBN1 \) transcripts were analyzed by reverse transcription (RT)-PCR of RNA templates isolated from fibroblasts. RT-PCR amplifications and sequencing of putatively mutated transcripts were performed by standard procedures [7].

**Marfan phenotype according to the Gent criteria**

The diagnosis of the MFS phenotype is dependant on a catalogue of international diagnostic criteria as introduced in [2]. Clinical symptoms are organized in major and/or minor criteria of the following organ systems:

**Skeletal system**

Major criteria: pectus carinatum or pectus excavatum requiring surgery; reduced upper to lower or increased arm-span to height ratio; positive wrist and thumb signs; scoliosis (>20\(^\circ\)); reduced elbow extension (<170\(^\circ\)); pes planus; protrusio acetabuli.

Minor criteria: pectus excavatum of moderate severity; joint hypermobility; highly arched palate with dental crowding; characteristic facial appearance.

**Ocular system**

Major criterion: ectopia lentis.

**Cardiovascular system (CVS)**

Major criteria: dilatation of the ascending aorta with or without aortic regurgitation and involving at least the sinuses of Valsava; dissection of the ascending aorta.

Minor criteria: mitral valve prolapse with or without mitral valve regurgitation; dilatation or dissection of the descending thoracic or abdominal aorta below the age of 50 years.

**Skin and integument**

Minor criteria: striae atrophicae (stretch marks) not associated with marked weight changes, pregnancy or repetitive stress; recurrent inguinal or incisional herniae.

Data of the pulmonary system (minor criteria), the ocular system (minor criteria), the dura (major criterion) and two minor criteria of the CVS system was partly not available so this additional clinical information was not considered for data analysis.

**Patient data**

Currently our database consists of 100 patients’ entries (age 18.7 ± 11.9 years) with 88 different mutations including anonymous data from three MFS clinical centers worldwide [4, 5, 8].

More specifically, mutation data is represented by the nucleotide change (e.g. 3973G>C for substitution, missense mutation), the position of the affected exon/intron on the gene (e.g. exon no. 32) and the type and consequence of mutation. Our investigated data contains the following mutations: Sub/Mis = substitution/missense mutation (n=55), Sub/Stop = substitution/nonsense mutation (n=9), Sub/Splice = substitution/splice site mutation (n=13), Del/Fs = deletion/frameshift (n=18), Dup/Fs = duplication/frameshift (n=1), Ins/Fs = insertion/frameshift (n=1), Del/inF = deletion/in frame (n=2) and Del/Splice = deletion/splice site mutation (n=1).

Phenotype data is available as the accumulated number of symptoms of each organ system separated into major and/or minor criteria. The following example demonstrates one tuple of our anonymous dataset which is organized as follows: \{Nucleotide change:= 6794G>A, type of mutation:= Sub/Mis, number of exon:= 55; skeletal (major):= 4, skeletal (minor):= 3, ocular (major):= 1; CVS (major):= 1, CVS (minor):= 1, skin (minor):= 1\}.

**Biomedical data analysis**

Data mining techniques like hierarchical cluster analysis and probabilistic models were applied to mine novel correlations between mutation data and the disease’s clinical phenotype.

**Hierarchical cluster analysis**

Hierarchical cluster analysis was performed to subdivide MFS phenotypes into meaningful subgroups where each of them was showing a characteristic phenotypic pattern. Some clustering algorithms, such as k-means, require users to specify the number of clusters as an input, but users rarely know the right number beforehand [9, 10]. Hierarchical clustering algorithms, which do not need a predetermined number of clusters as input, enable the users to determine the natural grouping with interactive visual feedback (dendrogram and color mosaic). To determine a proper number of clusters the minimum similarity threshold (between 0 and 1) needs to be changed.

When hierarchical clustering algorithm merges two clusters to generate a new bigger cluster, it should calculate the distances between the new cluster and remaining clusters. We used the “average linkage approach” (Unweighted Pair Group Method with Arithmetic Mean). Let \( C_i \) be a new cluster, a merge of \( C_j \) and \( C_k \). Let \( C_i \) be a remaining cluster:

\[
DIST(C_i, C_j) = \frac{|C_i|}{|C_i| + |C_j|} DIST(C_i, C_j) + \frac{|C_j|}{|C_i| + |C_j|} DIST(C_j, C_i)
\]

A column-by-column normalization by rescaling from 0.0 to 1.0 was performed. The Euclidean distance was chosen as the distance/similarity measure. Cluster analysis was applied to accumulated symptoms of (1) skeletal major, (2) skeletal minor, (3) CVS major, (4) CVS minor criteria, (5) ocular major criterion and (6) skin minor criteria.
**Phenotype score**

Based on the clustered phenotype classes we introduced a quantitative measure which describes the similarity between a patient’s phenotype and a characteristic phenotype class by a score value. To characterize the symptomatic similarity within a phenotype class the following definitions are required:

1. \( \mu_{\text{system}} \): mean value of diagnosed symptoms in an organ system (major and minor criteria separated),
2. \( \sigma_{\text{system}} \): standard deviation of symptoms in an organ system (major and minor criteria separated),
3. \( k_{\text{system}} = \frac{l}{\sigma_{\text{system}}} \): Factor quantifying phenotypic purity of an organ system within a clustered phenotype class. \( k \) is thus defined for the interval \((0, 1]\).

The phenotype score \( s_i \), calculating the similarity between a query tuple (patient’s accumulated symptoms for each organ system) and a phenotype class \( i \) is given as:

\[
s_i = c \cdot \sum_{\text{system} \in S} \left| t_{\text{system}} - \mu_{\text{system}} \right| k_{\text{system}}
\]

where \( i \in \{1 \ldots m\}, \ m = \text{number of phenotype classes.} \)

\( t \) is the accumulated number of diagnosed symptoms in an organ system (major and minor criteria separated) of the query tuple, \( S \) is the organ system collection, \( \text{system} \) is a single organ system and \( c \) is a scaling factor (we set \( c = 10 \)). Factor \( k_{\text{system}} \) weights each attribute according to its phenotypic purity within a phenotype class.

A query tuple is thus classified to that phenotype class whose score value \( s_i \) (distance) is minimal:

\[ \min[s_i] \Rightarrow \text{classified phenotype class, for } i \in \{1 \ldots m\} \]

**Probabilistic model**

For genotype-phenotype correlation we propose logistic regression analysis (LRA) as a predictor for the presence of a specific \( FBN1 \) gene mutation dependant on the selected clinical symptoms. The conditional probability \( p \) for class membership to one of two classes (e.g. Sub/Mis vs. no Sub/Mis mutations or exon vs. intron mutations) is denoted by the equation \( p = \frac{1}{1 + \exp(-z)} \) for \( P(Y=1) \) or \( p = 1 - \frac{1}{1 + \exp(-z)} \) for \( P(Y=0) \) respectively. The equation \( z = b_1x_1 + b_2x_2 + \ldots + b_nx_n + c \) indicates the logit of the model. Parameter selection – we used the “forward selection” approach – was performed to search through the space of parameter subsets to identify the optimal ones with respect to a performance measure [11]. For the model-building process we used stratified 10-fold-cross validation on our (training) datasets which is preferred when datasets are small [12].

**3. Results**

Accumulated clinical symptoms of four affected organ systems (skeletal major and minor, CVS major and minor, ocular major and skin minor system) were clustered using hierarchical cluster analysis (Fig. 1). Four phenotype classes (I, II, III, and IV) were identified at a minimum similarity threshold of 0.5. Statistical analysis (\( \mu, \sigma \)) of each detected phenotype class is shown in table 1.
Phenotypic purity within a clustered phenotype is given by the introduced k factor (maximum purity: k = 1, maximum impurity: k → 0). Maximum dissimilarity between the four clustered phenotype classes however is primarily caused by the alternating presence of the ocular major criterion (ectopia lentis) and the CVS major criterion (aortic root dilatation) in the different clusters. Moreover, both dichotomous attributes showed maximum purity (k = 1) within each phenotype class.

### Table 1: Phenotypic purity within a class

<table>
<thead>
<tr>
<th>Phenotype</th>
<th>Skeleton Major (0-7)</th>
<th>Skeleton Minor (0-4)</th>
<th>Ocular Major (0-1)</th>
<th>CVS Major (0-2)</th>
<th>CVS Minor (0-2)</th>
<th>Skin Minor (0-2)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Phenotype I</td>
<td>µ 2.74</td>
<td>σ 1.29</td>
<td>k 0.28</td>
<td>µ 2.04</td>
<td>σ 1.09</td>
<td>k 0.33</td>
</tr>
<tr>
<td>Phenotype II</td>
<td>µ 2.42</td>
<td>σ 1.39</td>
<td>k 0.25</td>
<td>µ 2.06</td>
<td>σ 1.36</td>
<td>k 0.26</td>
</tr>
<tr>
<td>Phenotype III</td>
<td>µ 1.69</td>
<td>σ 1.35</td>
<td>k 0.26</td>
<td>µ 1.56</td>
<td>σ 1.21</td>
<td>k 0.30</td>
</tr>
<tr>
<td>Phenotype IV</td>
<td>µ 1.71</td>
<td>σ 1.11</td>
<td>k 0.33</td>
<td>µ 2.29</td>
<td>σ 1.11</td>
<td>k 0.33</td>
</tr>
</tbody>
</table>

Mean value (µ), standard deviation (σ) and factor k of diagnosed symptoms are denoted for each organ system (major and minor criteria separated). Maximum purity is given by σ = 0 and k = 1. Four clusters (I, II, III, IV) were identified at a minimum similarity threshold of 0.5 (dendrogram, Fig. 1). Ocular major criterion (ectopia lentis) and CVS major criterion (aortic root dilatation) showed maximum purity within each clustered phenotype class (k=1).

In detail, types I and III are characterized by the presence of an ectopia lentis, type I and II by an aortic root dilatation, while type IV manifests neither an ectopia lentis nor an aortic root dilatation. However, the coincidence of both major symptoms ectopia lentis and aortic root dilatation in type I corresponds well with a more severe clinical picture, the absence of both symptoms with a milder clinical picture of the MFS phenotype. In contrast, skeletal major and minor criteria, CVS minor and skin minor criteria yielded a lower purity in all four clustered phenotypes classes expressed by a k factor < 1. Individuals with the mildest clinical manifestations of skeletal and CVS symptoms are represented in phenotype class III while phenotype class I indicates the most severe manifestations in the same organ systems. Type IV, however, represents the mildest MFS phenotype without ocular manifestation, with marginal CVS and skin, and moderate skeletal symptoms.

LRA was performed to discriminate FBN1 missense mutations from all other types of mutations by selecting the most relevant organ systems from the entire attribute space. The model was trained and cross-validated on 55 cases with a Sub/Mis mutation (class 0) and 45 cases representing the pool of no Sub/Mis mutations (class 1). The model revealed a sensitivity of 57.8%, a specificity of 78.2% and an accuracy of 69% (see figure 2). The probability for the presence of a Sub/Mis mutation - independent on the position in the gene - is thus given by the following equation:

\[
P(\text{Sub/Mis} = 1) = 1 - 1/[1+\exp(0.113 + 1.708\cdot\text{ocular (major)} - 0.275\cdot\text{skeletal (major)} - 0.471\cdot\text{skin (minor)})]
\]

Ocular major, skeletal major and skin minor criteria are the selected attributes when using forward selection, which can be interpreted as the predominant clinical phenotype of MFS patients with a FBN1 missense mutation.

![ROC Curve of Type of Mutation](image)

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Correlating the presence of Sub/Mis mutations with the clustered phenotype classes I-IV, highest correlation was found with phenotype classes I and III (table 2). Both phenotypes yielded a mean probability of ~ 0.7 for the presence of a Sub/Mis mutation which corresponds well with the observed frequency of Sub/Mis cases (71.7% for type I and 62.5% for type III) within these classes. Only phenotype class IV showed a discrepancy between the frequency of missense mutations and the P(Sub/Mis) value primarily caused by the small number of clustered cases (n=7). On the other hand phenotype class II, which constituted more severe manifestations of all investigated systems, but without the presence of an ectopia lentis, contains a fraction of 45% of Del/Fs mutations and represents 78% of all investigated Del/Fs mutations.

### Table 2: Correlation between Sub/Mis mutations and phenotype classes I-IV

<table>
<thead>
<tr>
<th>Phenotype</th>
<th>N</th>
<th>Sub/Mis (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>46</td>
<td>71.7</td>
</tr>
<tr>
<td>II</td>
<td>31</td>
<td>22.6</td>
</tr>
<tr>
<td>III</td>
<td>16</td>
<td>62.5</td>
</tr>
<tr>
<td>IV</td>
<td>7</td>
<td>71.4</td>
</tr>
</tbody>
</table>

N is the number of cases representing phenotype classes I - IV, P(Sub/Mis=1) is the mean probability for the presence of a Sub/Mis mutation in phenotype classes I – IV. The observed frequency of Sub/Mis mutations within each phenotype class is shown in the last line.

No correlations between the position and the nature of a FBN1 mutation, and the severity of the phenotype was
found when comparing e.g. intron with exon mutations, or mutations on exons 1-23 with those on exons 33-68.

Table 3 demonstrates an example of an MFS affected family (father with his three children and two nieces) with a detected Del/Fs mutation (508delT; frameshift + PTC). The minimum score value, which was calculated for all phenotype classes I-IV, related all family members to phenotype class II. The probability for a Sub/Mis mutation within the family was lower than 34%, which corresponds well to the probability that a Sub/Mis mutation is present in phenotype class II (cf. table 2).

**Table 3: MFS phenotype within members of a family**

<table>
<thead>
<tr>
<th>Age</th>
<th>Detected mutation</th>
<th>Type of mutation</th>
<th>P(Y=1)</th>
<th>Phenotype class</th>
<th>Scores for phenotype class</th>
<th>FS</th>
<th>PTC</th>
</tr>
</thead>
<tbody>
<tr>
<td>8</td>
<td>508delT; FS+PTC</td>
<td>Del/Fs</td>
<td>100</td>
<td>II</td>
<td>21 11 31 23</td>
<td>24</td>
<td></td>
</tr>
<tr>
<td>9</td>
<td>508delT; FS+PTC</td>
<td>Del/Fs</td>
<td>100</td>
<td>II</td>
<td>23 11 34 27</td>
<td>24</td>
<td></td>
</tr>
<tr>
<td>10</td>
<td>508delT; FS+PTC</td>
<td>Del/Fs</td>
<td>100</td>
<td>II</td>
<td>18  7  31 26</td>
<td>24</td>
<td></td>
</tr>
<tr>
<td>16</td>
<td>508delT; FS+PTC</td>
<td>Del/Fs</td>
<td>100</td>
<td>II</td>
<td>17  7  28 22</td>
<td>24</td>
<td></td>
</tr>
<tr>
<td>18</td>
<td>508delT; FS+PTC</td>
<td>Del/Fs</td>
<td>100</td>
<td>II</td>
<td>25 12 35 29</td>
<td>24</td>
<td></td>
</tr>
<tr>
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<td>100</td>
<td>II</td>
<td>22  9  26 22</td>
<td>24</td>
<td></td>
</tr>
</tbody>
</table>

FS = frameshift, PTC = premature stop codon. Minimum score values were calculated for phenotype class II.

4. Discussion

Genotype-phenotype correlation in heritable multisystemic diseases like the MFS syndrome is a big challenge for clinical bioinformatics because it influences diagnostic and clinical decisions. In particular, the age-related nature of some clinical manifestations, the variable phenotypic expression within and between families with MFS, and the diversity of detected mutations emphasize the complex nature of the disease [13, 14]. For instance, the so-called neonatal region in the FBN1 gene comprises one of the few generally accepted genotype-phenotype correlations showing a clustering of mutations in exons 24-32 [15]. Further efforts in data analysis are warranted to understand the complex structure of cause (mutation) and effect (clinical manifestation) more comprehensively.

Missense mutations, which are caused by the substitution of solely one base pair of the gene sequence (point mutation), are the most common type of reported mutations – 55% in our data [13]. In this study we focused on missense mutations for genotype-phenotype correlation and established a probabilistic model to predict Sub/Mis mutations on the level of accumulated symptoms in four organ systems with a classification accuracy of 69%. However, the age-related and pleiotropic nature of some symptoms may hinder a further increase of the model’s moderate accuracy. A more detailed analysis of clinical data at the level of the single symptoms – not as in our study groups of symptoms occurring in a certain organ system – may be helpful to further enhance classification accuracy.

Hierarchical cluster analysis was used to subdivide different clinical manifestations into clinical meaningful phenotype classes. At a minimum similarity threshold of 0.5 four classes were identified, while at a lower similarity threshold (< 0.5) the merged phenotype classes of type I and II with a common presence of the CVS major criterion seem to be more related than type III and IV with absence of the CVS major criterion. At a minimum similarity threshold of > 0.5, phenotype class I is subdivided into two meaningful sub-classes showing significant differences in skin minor criteria. Based on the identified phenotype groups we determined the frequency of Sub/Mis mutations within each type. The highest frequency of Sub/Mis mutations was observed within classes I and III, a fact which corresponds well with the probabilistic model P(Sub/Mis = 1) showing probability values in the same range of ~ 0.7. It is also interesting to note that phenotype class II characterized by the absence of ectopia lentis, but the presence of more severe manifestations in the CVS, skeletal and skin system showed the highest frequency of Del/Fs mutations (78% of all investigated Del/Fs mutations). Further investigations and correlations were not feasible due to the small number of patient data in our current MFS database.

We presented data of a family affected by classic MFS with the detected mutation 508delT; frameshift + PTC. All six family members could be classified as phenotype class II showing a very similar intra-familial phenotypic expression. However, our findings may not be generalized because variable phenotypic expressions due to the age-related or pleiotropic nature of some symptoms within affected families can be observed. In order to describe the phenotypic similarity within families and individuals with the same detected mutation, and between one of the clustered phenotype classes we introduced a novel phenotype score. This score value enables us to quantify a patient’s phenotypic similarity to a characteristic phenotype pattern by minimizing the distance to that phenotype class. We could demonstrate that our approach is practical for phenotype classification on the level of accumulated criteria. However, an extension of this approach on the level of each single symptom (~ 30 single symptoms according to the Gent nosology) may have potential for more detailed phenotype classification. Nevertheless more data are essential to generate representative score values, in particular for phenotype class IV.

5. Conclusion

Our results revealed a correlation between FBN1 missense mutations and the manifestation of ectopia lentis, accompanied by skeletal and skin criteria predominantly present in phenotype classes I and III. 78% of all deletion/frameshift mutations were related to the clustered phenotype II with absent ectopia lentis, but presence of more severe manifestations in the CVS, skeletal and skin system. Our analysis of mutation data and the clinical phenotype of patients with MFS may contribute to anticipate the clinical consequences of specific FBN1 mutations more comprehensively and may be helpful to identify at-risk patients early.
6. Acknowledgements

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References


