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Validation of a New Multiple Osteochondromas Classification Through Switching Neural Networks

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Multiple osteochondromas (MO), previously known as hereditary multiple exostoses (HME), is an autosomal dominant disease characterized by the formation of several benign cartilage-capped bone growth defined osteochondromas or exostoses. Various clinical classifications have been proposed but a consensus has not been reached. The aim of this study was to validate (using a machine learning approach) an "easy to use" tool to characterize MO patients in three classes according to the number of bone segments affected, the presence of skeletal deformities and/or functional limitations. The proposed classification has been validated (with a highly satisfactory mean accuracy) by analyzing 150 different variables on 289 MO patients through a Switching Neural Network approach (a novel classification technique capable of deriving models described by intelligible rules in if-then form). This approach allowed us to identify ankle valgism, Madelung deformity and limitation of the hip extra-rotation as "tags" of the three clinical classes. In conclusion, the proposed classification provides an efficient system to characterize this rare disease and is able to define homogeneous cohorts of patients to investigate MO pathogenesis.

Key words: multiple osteochondromas; patients classification; *EXT1/EXT2*; switching neural network; genotype–phenotype correlation

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INTRODUCTION

Multiple osteochondromas (MO, OMIM# 133700 and 133701) is an autosomal dominant rare disease with an estimated over-all prevalence of 1/50,000, (male-to-female ratio 1.5:1) [Bovée, 2008; Orphanet, 2008]. This syndrome is characterized by the presence of exostoses (EXs), cartilage-capped benign growths that arise on the metaphyseal regions of long bones. Deriving from growth plate, EXs develop through childhood until skeletal maturity and typically acquire a sessile (broad based) or pedunculated (cauliflower shaped) aspect [Khurana et al., 2002]. MO patients can present with a multiplicity of symptoms, ranging from almost imperceptible clinical signs to severe complications, with a significant intra- and inter-familial variability [Schmale et al., 1994]. During adulthood, in less than 5% of patients, an EX could progress to secondary peripheral chondrosarcoma (SPCh) [Evans et al., 1977; Schmale et al., 1994; Bjornsson et al., 1998; Bovée, 2008; Orphanet, 2008].

The majority (90%) of patients have a germ-line mutation either in Exostosin-1 (*EXT1*; 8q24.11–8q24.13) or in Exostosin-2 (*EXT2*; 11p11–p12), usually leading to the loss of EXT protein functions [Pedrini et al., 2005]. In genotype–phenotype studies, subdivision of patients in homogeneous groups is a critical aspect; in fact, classification categories need to be easily applicable in the daily clinical practice and should discern intermediate disease presentation. Regarding MO, attempts for classification of patients have been performed: Francannet et al. analyzed 42 French families (217 affected subjects) by two different approaches that included both a functional rating and a five-factor system to define the phenotype

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severity, a modified version of Musculoskeletal Tumor Society. This classification defined two groups (S, severe; M, mild) and four subclasses (I–IV) for the S group, depending on the number of EXs [Francannet et al., 2001]. Porter et al. [2004] proposed a six-factor evaluation including functional (forearm rotation, elbow and knee rotations) and deformities-dependent (ulnar length, forearm, and knee deformities) variables. Moreover, other aspects like number of EXs, height (compared with age and gender), previous surgical operations, and functional effects of EXs were also included [Porter et al., 2004]. Jäger et al. [2007] evaluated 52 affected subjects considering patient's age, age of disease onset, detailed surgery reports, number of EXs, range of motion of multiple joints. Patients were then classified as either mildly or severely affected according to number of EXs [Jäger et al., 2007]. Another taxonomical system, proposed by Alvarez et al. [2006], evaluated 76 MO parameters divided in three categories (lesion quality, limb alignment, and limb segment length) in 32 patients.

The classifications systems are not easy to apply and are difficult to discern disease presentations. In collaboration with the Orthopaedic Oncologic Clinic of our institution, we propose a new clinical classification validated on a cohort of 289 patients. A total of 150 different variables (clinical data, X-rays, molecular screening, etc.) have been evaluated and correlated in each individual by an innovative machine-learning model (named Switching Neural Network-SNN-) that generates statistical models described by intelligible rules.

MATERIALS AND METHODS

Patient Dataset

The dataset was composed of 289 individuals affected by MO who were enrolled at the Genetic Day Clinic of the Rizzoli Orthopaedic Institute. Each was evaluated following a previously defined diagnostic *iter* that included accurate physical examination, X-Rays evaluation, molecular screenings, and, when possible, follow-up [Pedrini et al., 2011]. All data were collected on a web-based platform GePh-CARD (Genotype–phenotype-correlation, analysis and research database) according to rules for confidentiality.

All 150 variables were subdivided in five different categories: (a) affected sites (localization, side, etc.); (b) severity of clinical manifestations (number and type of deformities, functional limitations, pain, etc.); (c) genetic data (gene, type of mutation, etc.); (d) family data (hereditary transmission, sporadic or familiar case); and (e) other variables like age, gender, weight, and height. The list of tested variables and generated intelligible rules are available at the website http://www.ge.ieiit.cnr.it/~muselli/ajmg-2012.html.

Classification

The classification scheme (shown in Table I) identifies three classes of MO patients characterized by presence/absence of deformities and/or functional limitations. In addition, each clinical class was sub-divided into two groups according to the number of affected sites (A and B). Each SNN classifier was trained and adopted to determine the subset of attributes that characterized the three classes, together with a measure of relevance for each variable. Moreover, the accuracy scored by rule sets generated through SNN allowed the evaluation of its ability in delineating homogeneous cohort of MO affected individuals.

Switching Neural Network

Switching neural networks (SNN) is a novel approach for forecasting and extracting information from any set of labeled data regarding an a priori unknown phenomenon. Consider a collection of n examples, usually called the *training set*, pertaining to a specific classification problem; each record consists of a vector of d variables (inputs) and an output that represents the associated class. For instance, in the case of MO classification analysis, each example (patient) includes inputs derived from clinical evaluation as well as *EXT1* and *EXT2* gene screening; the output provides the class (I, II, III) assigned to it. Starting from the training set, a classification method (i.e., logistic regression, decision tree, or linear discriminant analysis) has the aim of deriving a functional dependence, that is, a model that better describes the relationship between the input vector and the output class. After the construction of the model, its quality must be evaluated by estimating the probability of correctly classifying any input vector different by those included in the training set. This measure is usually obtained by analyzing the accuracy of the model on an independent set of examples through a cross-validation approach, as shown in the Results Section.

In most cases, the model is given by algebraic or transcendent equations, whose meaning is difficult to be analyzed or understood. To avoid this limitation, classification techniques, called rule generation methods, have been developed to provide intelligible functional dependences described by simple "*if-then* rules". The well-known approach of this kind is a "decision tree," generally characterized by poor validation accuracy if compared to other classification methods, such as sigmoidal neural networks or support vector machines.

Switching neural network (SNN) is an innovative rule-generation method capable of achieving excellent levels of validation accuracy besides providing intelligible models [Muselli, 2006;

TABLE I. Proposed Classification: Simple and Exhaustive Classification for Patients Affected by Multiple Osteochondromas

Class	Subclass
No deformities—no functional limitations	
I	
IA	≤5 sites with EX
IB	>5 sites with EX
Deformities—no functional limitations	
II	
IIA	≤5 sites with deformities
IIB	>5 sites with deformities
Deformities—functional limitations	
III	
IIIA	1 site with functional limitation
IIIB	>1 site with functional limitations

Ferrari and Muselli, 2009; Muselli and Ferrari, 2011]. The construction of an SNN is based on two advanced techniques for Boolean function reconstruction, hamming clustering (HC) and shadow clustering (SC), which have been successfully employed in the analysis of biomedical data [Paoli et al., 2000; Mangerini et al., 2011].

RESULTS AND DISCUSSION

Each enrolled patient has been evaluated and included in one of the three classes; 96 fit in class I (33%), 137 in class II (48%), and 56 in class III (19%). The age ranged from 6 to 73 years; the majority (77%) were older than 16 years while 11% were less than 10 years old.

According to SNN methodology, some preliminary tests were performed to identify superfluous or redundant information, to select the set of variables involved in the definition of classes and to confirm the reliability, which excluded unrelated information (i.e., place of birth, phone number, ...).

Unlike previous correlation studies [Francannet et al., 2001; Porter et al., 2004; Alvarez et al., 2006, 2007; Jäger et al., 2007] that evaluated a maximum of 76 variables, we started from 150 different features. After the first analysis, some of them (i.e., weight) were deemed not influential and/or equally/comparably occurring in the control population. Other variables were deemed too detailed, which leads to data fragmentation. To avoid this effect, original features were grouped in "categories" (for instance: "Short Finger" takes into account all subtypes of hand-shortening involving carpal and metacarpal bones and phalanges). As a result, 30 (25 were Boolean) out of the initial 150 variables emerged (Table II) as discriminating variables and they were utilized for the subsequent analyses of the 289 MO patients (Fig. 1).

Data were then analyzed according to a 10-fold cross-validation approach: a subset of patients, including about 10% of the cases (*test set*), was not considered in the model construction (*training* phase) and subsequently used to verify the correctness of the resulting set of rules in if-then form obtained by analyzing the remaining examples (90%). For instance, one of the most important rules generated by SNN that relate patient variables to the class of disease gravity can be written as:

if *Hip Limitation* = TRUE and *Leg Dysmetria* = FALSE and *Short Finger* = FALSE **then** *Class* = III

The generated rules were then applied to the test set (*test* phase) and their accuracy, that is, the percentage of correctly classified cases, was measured. The higher the accuracy scored by the rules on the test set the better is their ability of classifying previously

TABLE II. Variables for Testing Suggested Classification: List of 30 Variables Considered for Testing Suggested Multiple Osteochondromas Classification, After Three Preliminary Screenings

General	Orthopedic	Genetic
ID lab	Site EXs number	Genetic alteration Type
Age	Short finger	*EXT1* mutation
Gender	Upper limb dismetry	*EXT2* mutation
Familiarity	Lower limb dismetry	Exon mutation
Height	Pain	Intron mutation
Height percentile	Limitation arm	
	Limitation knee	
	Limitation hip	
	Limitation pronosupination forearm	
	Distal radius dislocation	
	Madelung	
	Scoliosis	
	Forearm valgus	
	Ankle valgus	
	Finger valgus	
	Leg valgus	
	Ankle varus	
	Leg varus	
	Wrist varus	

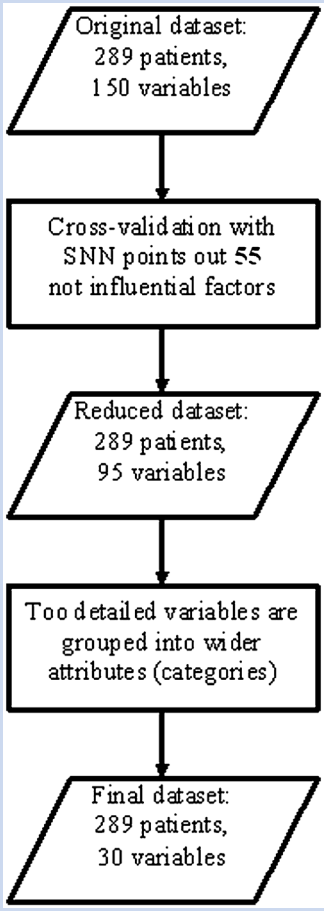

FIG. 1. Flowchart for variables selection. Graphical flowchart of analytical steps for identification of final 30 variables from the starting dataset of 150.

unseen patients. Thus, if a random assignment is performed, then about 33% of the cases would be correctly classified. A considerably higher accuracy implies that the method detected a significant correlation between the patient information and the relative clinical class.

To ensure the statistical representativeness of the results, the training-test procedure was repeated 10 times by varying the test set across all the possible subsets of the collection of patients. The average number of rules generated by the training phases was 45.8, whereas the mean accuracy on the 10 test sets was 85%. We suppose that the 15% error was caused by a multiplicity of factors, the main of which could be related to the overbalanced number of class II patients.

The number of generated rules and the resulting mean accuracy were distributed across the three classes as follows:

Class I → average number of rules: 13,4; mean accuracy: 94%
Class II → average number of rules: 20.9; mean accuracy: 80%
Class III → average number of rules: 11.5; mean accuracy: 79%

The mean accuracies across the three classes are more than satisfactory, thus demonstrating the consistency of the proposed classification.

In addition, analyses of the whole dataset allow more precise detection of both crucial and irrelevant variables. For example, limitation of hip extra-rotation, Madelung deformity and ankle valgism were identified by SNN as "tags" to define a clinical class. Madelung deformity is the most common malformation in individuals affected by MO and clearly defines class II (in absence of other functional limitations), while a reduction of the hip extra-rotation is frequently present in class III patients. Ankle valgism, even if equally frequent in all the classes, could define class I patients when additional malformations or functional impairments are absent. The number of EXs, considered essential in previous studies [Francannet et al., 2001; Porter et al., 2004; Alvarez et al., 2006; Jäger et al., 2007], has an equivalent influence as other variables, while the number of affected sites (evaluated in our clinical classification) clearly emerges as an essential element in patient clinical class definition. Gender and familiarity came out as important variables (females present a milder form of disease compared to males) as described in two different genotype –phenotype correlation studies [Porter et al., 2004; Pedrini et al., 2011].

Another important clinical feature of MO is the progression to secondary peripheral chndrosarcoma; however, in the current study, cases of SPCh in the dataset (5%) were inadequate for the SNN analysis.

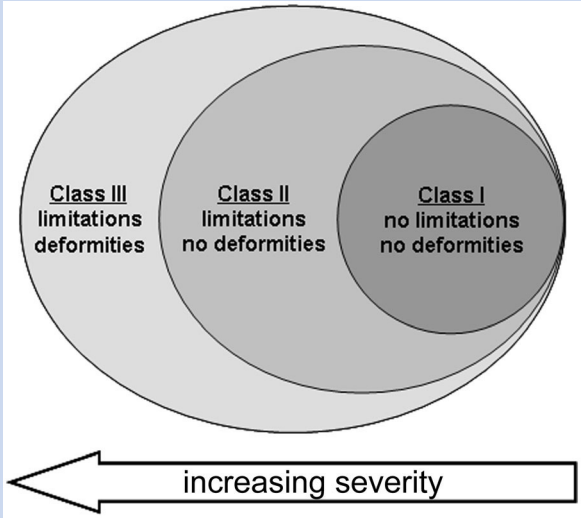

FIG. 2. Disease worsening. A graphical visualization of three classes interdependent discriminators according to increasing severity.

CONCLUSIONS

We developed a clinical classification system through the application of Switching Neural Network analyses on 289 MO patients. Our results sustain the validity of the proposed classification model. Moreover, SNN analyses identified specific factors as "tags" for clinical classes, simplifying patient phenotype evaluations. The proposed classification scheme shows that class III discriminators are a super-set containing a subset of class II discriminators that incorporate the class I discriminators (Fig. 2); for this reason, this taxonomy schema is able to follow-up disease worsening and/or progression, meaning that an MO patient that undergoes to an increasing severity of pathological condition, can be easily be moved from a mild class to a more severe class according to the presence/absence of skeletal deformities and/or functional limitations. Unfortunately SNN does not help in individuation of tags for progression to SPCh, but we are currently increasing the number of SPCh from collaborating groups to identify variables involved in malignant transformation and to define how potential variables can be included in the proposed classification.

Finally, the proposed classification could easily be adopted for cooperative studies between different Institutions, as shown in the recent publication by Pedrini et al. [2011]. In fact Pedrini applied the described classification scheme (Table I) to 529 MO patients with heterogeneous genetic background (400 from Italy and 129 from Belgium, Netherlands and other countries). Utilizing the proposed taxonomy, this genotype–phenotype study representing the biggest dataset of MO patients reported, identified protective factors and risk factors for manifestation of this condition. The advantage of this "easy to use" taxonomy is the ability to identify homogeneous groups of patients for investigation of MO pathophysiology. For instance, we are currently evaluating intra-familiar and inter-familiar variability by SNP/CNV genotyping in a series of 150 MO patients characterized according to the proposed classification.

By combining collections of a substantial number of similarly characterized patients using the technique outlined in this report, one can achieve statistically relevant results in studies of rare disease pathophysiology.

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