Machine learning to detect the Klinefelter syndrome endocrine profile

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BACKGROUND

Klinefelter syndrome (KS) is the most common sex-chromosome disorder and genetic cause of infertility and hypo-gonadism in males[1]. However, KS remains an underdiagnosed condition with the majority of expected cases escaping clinical diagnosis and follow-up[2]. Generally, the mid-puberty endocrine profile associated with KS is characterized by abnormal levels of gonadotropins due to diminished testosterone feedback. Supervised machine learning (ML) is an artificial intelligence approach to produce an inferred function from labelled data in order to classify new cases[3].

OBJECTIVES

To devise and test the reliability and predictive value of a supervised machine learning model to identify cases of KS amongst healthy controls based on inter-individual endocrine profiles. We also wanted to characterize prepubertal KS endocrine profile perturbations using principal component analysis (PCA).

METHODS

Retrospective hospital records of 15 genomically confirmed and untreated cases of prepubertal KS (47,XXY) age 6 - 13 years (total 35 visits). Serum hormone profile data was obtained with respect to testosterone, dehydroepiandrosterone sulfate (DHEAS) and 17-hydroxyprogesterone (17-OHP) and androstenedione [LC-MS/MS], sex hormone-binding globulin (SHBG) and anti-Müllerian hormone (AMH) [Beckman-Coulter Access] and gonadotropins follicle-stimulating hormone (FSH) and luteinizing hormone (LH) [Perkin Elmer Delfia] as described previously[4]. A random forest machine learning algorithm was trained and applied to classify cases of KS relative to the endocrine profiles of n=107 healthy, prepubertal (testicular vol. < 4 ml) and age-matched boys, using the 'randomForest' and 'caret' packages in *R*. PCA was conducted in *R* as shown previously[5].

RESULTS

Benchmarking the KS endocrine profile

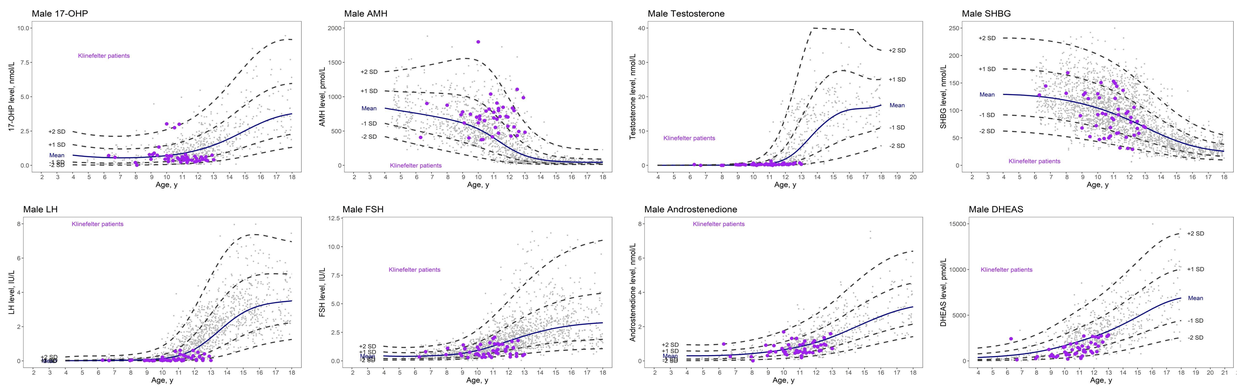

Figure 1. Klinefelter syndrome endocrine profile in relation to normal reference ranges for indicated hormones
Hormone level equvalent z-scores for KS patients (purple dots) overlaid on reference curves made with the 'gamlss' *R* package.

REFERENCES

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RESULTS CONT'D

Machine learning classification method and performance

A

		Reference	
		0	**1**
Prediction	**0**	*26*	*1*
	1	*0*	*7*

B

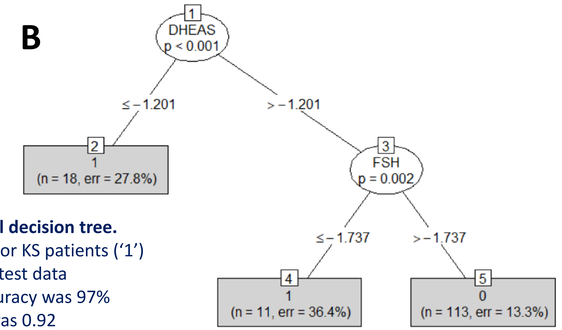

Figure 2. Classification performance, agreement and clinical decision tree.
A) Representative confusion matrix for healthy controls ('0') or KS patients ('1') obtained from applying the trained ML algorithm to unseen test data (75%-25% dataset split). With repeated simulations, the accuracy was 97% (95%CI, 96% to 98%) and the Cohen's Kappa of agreement was 0.92 (95%CI, 0.89 to 0.94). **B)** Clinical decision tree component of the random forest algorithm to classify healthy controls ('0') or KS patients ('1').

Elucidating the Klinefelter syndrome endocrine profile by principal component analysis (PCA)

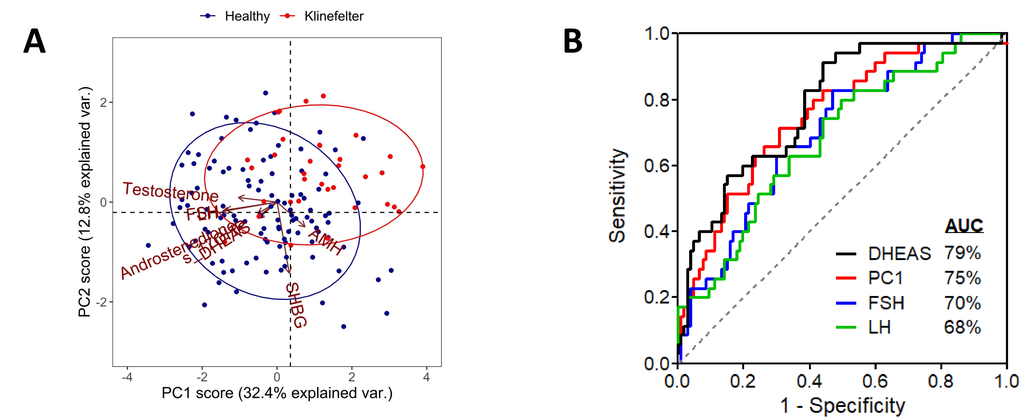

Figure 3. PCA and receiver operating characteristics (ROC) analyses to detect Klinefelter syndrome
A) PCA biplot indicating how the endocrine profile components contribute to the dataset variance and biochemical differences between healthy subjects (blue dots) and KS patients (red dots), clustered by 1.5 SD confidence ellipses.
B) Ability of PCA-derived principal component 1 (PC1) scores and hormone z-scores to correctly classify healthy subjects and KS patients was evaluated by ROC analyses. Z-score levels of DHEAS was the best biomarker to detect KS (p<0.001).

CONCLUSIONS

- Machine learning applied to biochemical data was able to make valid predictions to accurately classify cases of KS in this retrospective pilot study, but the model must be verified prior to clinical use.
- The random forest classification model outperformed all individual markers of KS and may yet be improved by addition of anthropometric and other biochemical markers.
- PCA provided a systemic exploration of biochemical differences between healthy boys and KS patients.