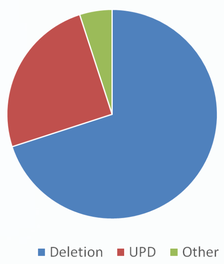
Prader-Willi Syndrome: Toward Automated Identification of Phenotypic Differences

Lior Wolf[1], Carol Clericuzio[2], Suzanne B Cassidy[3], Judith E Allanson[4]

1. FDNA Ltd., Herzlyia, Israel; 2. Department of Pediatrics, University of New Mexico Health Sciences Center, Albuquerque, New Mexico; 3. Division of Medical Genetics, Department of Pediatrics, University of California, San Francisco, San Francisco, California, USA; 4. Children's Hospital of Eastern Ontario, University of Ottawa, Canada

In Prader-Willi syndrome (PWS), the two common etiologies are paternal deletion of chromosome 15q11-13 (~70% of affected persons) and maternal uniparental disomy 15 (UPD) (~25%). 73 persons are included in our retrospective study, 37 under the age of 8 (7 UPD, 30 deletion), and 36 above (15 UPD, 21 deletion). The R Matching package was used to match individuals based on gender and age. The results reveal that, in the younger age group, nasal base and mouth width are significantly reduced in UPD, while in the older individuals, inner canthal distance and ear length are larger in UPD. After normalizing measurements by OFC, these results remain significant. Reduced minimum frontal distance is another differentiator of UPD under the age of 8, while reduced mouth width differentiates above age 8. In addition, facial images of 16 persons (4 UPD, 12 deletion) from the same cohort were evaluated with automatic image analysis tools for UPD/deletion differentiation. This type of analysis provided good discrimination between individuals with UPD and those with deletion.

PREVIOUS WORK – SPECIFIC SYNDROMES



In Prader-Willi syndrome (PWS), the two common etiologies are paternal deletion of chromosome 15q11-13 (~70% of affected persons) and maternal uniparental disomy15 (UPD) (~25%). Cassidy et al. [1] evaluated 37 individuals with deletion PWS and 17 with UPD to determine if there were phenotypic differences and reported that those with UPD have a higher likelihood of an atypical face, often rounder displaying a broader forehead and a flatter/broader nasal bridge. Allanson et al. [2] followed up with an objective study of 109 individuals with PWS. Measurements of eyes, ears, nose, mouth, facial widths, depths, lengths and circumferences were taken. The raw data were compared to norms and converted to Z scores to control for age and sex differences. Results showed agreement with the previous study: persons with UPD have a longer face, more protuberant nose with a narrower base, smaller mouth, and broader or more prominent mandible.

[1] S. B. Cassidy, M. Forsythe, S. Heeger, R. D. Nicholls, N. Schork, P. Benn, and S. Schwartz. Comparison of phenotype between patients with Prader-Willi syndrome due to deletion 15q and uniparental disomy. American Journal of Medical Genetics, 68(4): 443-440, 1997.
[2] J. E. Allanson, C. Clericuzio, and S. B. Cassidy. Prader-Willi syndrome Phenotypic differences observed in an objective study of deletion and disomy. American Journal Of Human Genetics. 65(4): A35, 1999.

OUTLINE OF CURRENT STUDY

	Deletion	UPD	Total per age group
Under the age of 8	30	7	37
8 and above	21	15	36
Total per etiology	51	22	73

We revisited the 1999 study in order to: (1) Validate the analysis using different statistical machinery; (2) Examine the age-related differences between the two etiologies; and (3)Evaluate image-based differentiation.

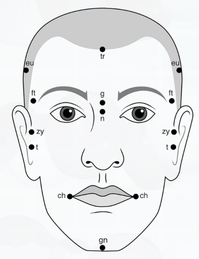
For 1+2, The data of 73 patients from [2] were used. Instead of employing population norms to obtain Z scores, the R Matching package was used to match individuals based on gender and age.

REVISITING THE MEASUREMENT DATA

		Raw measurements		ofc-normalized	
		Under 8	Over 8	Under 8	Over 8
eu.eu	HEAD WIDTH	0.22	0.01	0.14	0.03
t.t	SKULL BASE WIDTH	0.31	0.16	0.06	0.19
ft.ft	MIN FRONTAL DISTANCE	0.16	0.75	0.04	0.97
zy.zy	UPPER FACIAL WIDTH	0.32	0.67	0.19	0.89
go.go	LOWER FACIAL WIDTH	0.36	0.93	0.23	0.55
g.op	HEAD LENGTH	0.97	0.94	0.59	0.63
t.n	UPPER FACIAL DEPTH	0.76	0.18	0.95	0.32
t.sn	MID FACIAL DEPTH	0.89	0.46	0.85	0.70
t.gn	LOWER FACIAL DEPTH	1.00	0.23	0.91	0.30
sn.prn	NASAL PROTRUSION	0.13	0.65	0.11	0.71
n.gn	TOTAL FACIAL HEIGHT	0.18	0.64	0.13	0.72
n.sn	UPPER FACIAL HEIGHT	0.97	0.99	0.80	0.87
al.al	NASAL WIDTH	0.00	0.62	0.00	0.47
ch.ch	MOUTH WIDTH	0.00	0.10	0.00	0.02
en.en	INNER CANTHAL DISTANCE	0.26	0.92	0.16	0.97
ex.ex	OUTER CANTHAL DISTANCE	0.41	0.37	0.15	0.43
pra.pa	EAR WIDTH	0.56	0.19	0.62	0.34
sa.sba	EAR LENGTH	0.97	0.04	0.88	0.05
ofc	HEAD CIRCUMFERENCE	0.71	0.65	-	-
t.gn.t	MANDIBULAR ARC	0.86	0.89	0.62	0.89
t.sn.t	MAXILLARY ARC	0.59	0.84	0.41	0.55

p-values (lower is more significant) depicting the deletion/upd discriminativity of each measurement (raw or normalized by ofc) in each age group

Method:
A series of anthropometric measurements was obtained on each subject using published methods. These dimensions were chosen to represent craniofacial widths, depths, lengths and circumferences plus details of ears, eyes, nose and mouth structure. Measurements were taken by one of the authors (JEA).

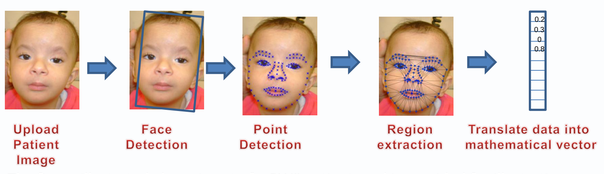


Samples were matched within each age group separately, by age and gender, and the p-value was obtained based on matched t-test.

Results:
The results reveal that, in the younger age group, nasal base and mouth width are significantly reduced in UPD, while in the older group, inner canthal distance and ear length are larger in UPD. After normalizing measurements by OFC, these results remain significant. Reduced minimum frontal distance is another differentiator of UPD under the age of 8, while reduced mouth width differentiates above age 8. The successful utilization of normalized measurements supports the future use of ratios of distances extracted from images.

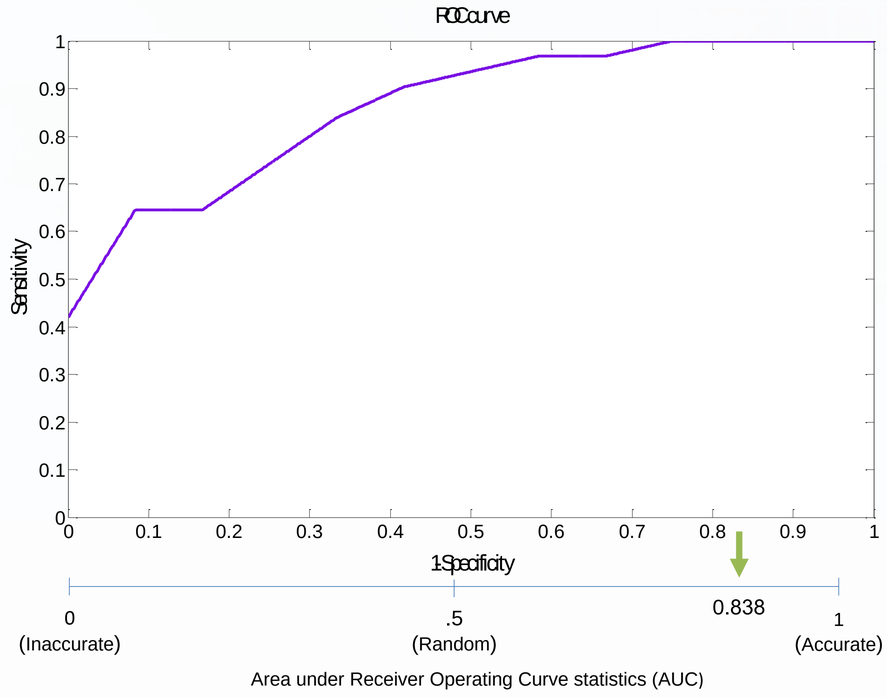
IMAGE-BASED ANALYSIS

Method:
Facial images of 16 persons (4 UPD, 12 deletion) from the same cohort were available. These were evaluated with automatic image analysis tools for UPD/deletion differentiation. Each face was encoded as a vector using FDNA's computer vision algorithms. Then, Leave One Out (LOO) experiments were conducted to evaluate the classification accuracy.



The figure illustrated above is not of a PWS patient, and is provided for illustration purposes only.

Results:
Even though the number of persons was very limited, it is evident that this type of analysis provided good discrimination between UPD and deletion individuals.



CONCLUSIONS AND FUTURE WORK

Since UPD is the less prevalent etiology and has a subtly different phenotype, there is a risk of under-diagnosis. In a future study we plan to test this hypothesis using blinded dysmorphologist assessment and automatic facial analysis tools. We would assess whether this risk could be reduced by training automatic systems to identify the individual etiologies.