Artificial intelligence and dysmorphology at the service of PMM2-CDG

Dr. Antonio Martinez-Monseny
Clinical Genetics
Genetics and Molecular Medicine Department
Instituto Pediátrico Enfermedades Raras – IPER
Sant Joan de Déu Hospital
How can dysmorphology and AI improve PMM2-CDG diagnosis?
Clinical, laboratory and molecular long-term follow-up data in PMM2-CDG (phosphomannomutase disorder of glycosylation)

Manuel Schiff,1,2 Céline Roda,3 Marie- Louise Sarron,3 Nathalie Bednarek,8 Maud Bidet,9 Catherine Delphine Borgel,5 Anais Brassier,3 Alexis Roger Buissinière,19 Brigitte Chabrol,20 Valérie Cormier-Daire,22,23,24 Claire De Baere,27 Anne De Saint-Martin,27 Nathalie Doriso Bernard Echenne,35 Patrick Edery,31 Françoise Francannet,34 François Labarthe, Marie Hully,3 Sylvie Lamothe,38 Domin Gilles Morin,40 Tiffany Pasceau,6,7 Olivier Agathe Roubertie, Christel Thauvin-Robinet, Sandrine Vuillaumier-Barrot,18 Nathalie S
Phosphomannomutase-2 deficiency (PMM2-CDG) is associated with recognizable dysmorphic features.

There are no early severity predictors and no phenotype–genotype correlation.

We performed detailed dysmorphology evaluation:

1. To describe facial gestalt
2. To train digital recognition facial analysis tools and
3. To identify early severity predictors
DFs classification  32 DF selected

Major DFs
Presented by PMM2-CDG patients showing a prevalence >50% over the control group prevalence

| A | MAJOR DYSMORPHIC FEATURES | B |
|---|-----------------------------|---|---|
| | STRABISMUS (HP:0000486) | | LONG FINGERS (HP:0100807) |
| | Patients | 83.87% | | Patients | 70.97% |
| | Controls | 3.85% | | Controls | 11.54% |
| p <0.001 | p =0.006|
| | UPSLANTED PALPEBRAL FISSURES (HP:0000582) | | INVERTED NIPPLES (HP:0003186) |
| | Patients | 90.32% | | Patients | 58.06% |
| | Controls | 11.54% | | Controls | 0% |
| p <0.001 | p <0.001|
| | LIPODYSTROPHY (HP:0009125) | | LONG PHILTRUM (HP:0000343) |
| | Patients | 67.74% | | Patients | 61.29% |
| | Controls | 3.85% | | Controls | 7.69% |
| p <0.001 | p =0.002|
| | WIDE MOUTH (HP:0000154) | | JOINT LAXITY (HP:0001388) |
| | Patients | 74.19% | | Patients | 70.97% |
| | Controls | 7.69% | | Controls | 19.25% |
| p <0.001 | p =0.003|

Predictive diagnostic value

AUC= 0.983 (p<0.001)
S 96.77%, and E 92.31%
What is Face2Gene?
AI mathematical algorithms for facial recognition analysis

Face2Gene (FDNA)

Deep learning

Universally used and free access
How does Face2Gene work?

Face2Gene is a suite of phenotyping applications that provide comprehensive and precise genetic information.
Initially, the Face2Gene CLINIC application did not assign PMM2-CDG to any of the patients facial photos.

Its mathematical algorithm was not yet trained to discriminate PMM2-CDG
3

What are the main results from training Face2Gene for PMM2-CDG?
To train Face2Gene for facial recognition analysis of PMM2-CDG patients

The work was divided into three phases (RESEARCH app): (I) training of the algorithm within the tool, (II) assessment of distinctness of facial phenotypes and (III) study of facial phenotypes per age group.
In order to assess how specific the facial phenotype of PMM2-CDG patients was, two cohorts of controls were selected for comparison: Angelman syndrome and unaffected controls.

(Angelman syndrome was chosen because it was the most frequently suggested syndrome by the tool.)

In order to measure the statistical significance, p value random permutation tests and train models were calculated 1000 times.
Phase II: Composite photos-computed from age-matched images of PMM2-CDG patients vs unaffected controls

The ability of the tool to recognize physical characteristics at different ages was also tested. All of the photos from children evaluated in this study were divided into three age groups: 0–5, 6–11 and 12–18 years.
Through the RESEARCH application, differences between the groups, healthy controls and Prader-Willi syndrome controls from the same age group were examined.

(Prader-Willi syndrome was chosen as it was the most frequently suggested syndrome by the tool for younger children)
AI with dysmorphology in PMM2-CDG prognosis
Severity correlation

Dysmorphology categorisation
inverted nipples (IN) & lipodystrophy (LD)

Phenotypic groups:
Mild: IN- & LD- (15 pt)
Mod: IN+/LD- OR LD+/IN- (9 pt)
Sev: IN+ AND LD+ (7 pt)

Correlation with clinical severity
From gestalt to gene: early predictive dysmorphic features of PMM2-CDG

Antonio Martinez-Monseny, Daniel Cuadras, Mercè Bolasell, Jordi Muchart, César Arjona, Mar Borregan, Adi Algrabli, Raquel Montero, Rafael Artuch, Ramón Velázquez-Fraga, Alfons Macaya, Celia Pérez-Cerdá, Belén Pérez-Dueñas, Belén Pérez, Mercedes Serrano, the CDG Spanish Consortium
Take home messages

PMM2-CDG patients have a characteristic and differentiated facial *gestalt*

DF have diagnostic and prognostic value

Widely used AI tools such as Face2Gene can be trained to help the clinician at any age

In the clinical context, when suspicion of PMM2-CDG is present, we suggest:
- determining whether the child possesses three or more Major DFs
- uploading a frontal face picture to Face2gene CLINIC app
5 Challenges and solutions of dysmorphology and AI in CDG
Decreasing the diagnostic odyssey

Training Face2Gene to discriminate other syndromic CDG

Training digital tools based on HPO diagnosis (Face2Gene, phenomizer, mendelian...)

Achieving a most early diagnosis

Training digital tools to facilitate a newborn diagnosis of PMM-2CDG and other CDG
It is time to make the **clinics** great again!

...but this time, with the help of AI
| 1. VICTOR DE DIEGO ALMARZA  
| 2. BELÉN PÉREZ-DUEÑAS  
| 3. INMA GARCIA JIMENEZ  
| 4. PILAR POO ARGUELLES  
| 5. BERNABE ROBLES DEL OLMO  
| 6. PILAR QUIJADA FRAILE  
| 7. M TERESA GARCÍA SILVA  
| 8. RAMÓN VELÁZQUEZ FRAGUA  
| 9. LORENA MONGE GALINDO  
| 10. LUIS GONZALEZ GUTIÉRREZ SOLANA  
| 11. SERGIO AGUILERA ALBESA  
| 12. EDUARDO LOPEZ LASO  
| 13. FRANCISCO CARRATÁLÁ  
| 14. ANA FELIPE  
| 15. ALFONS MACAYA  
| 16. RAMÓN CANCHO CANDELA  
| 17. CONCHI MIRANDA  
| 18. LLANOS CARRASCO  
| 19. SUSANA ROLDÁN  
| 20. MARI LUZ COUCE  
| 21. EDUARDO AISA  
| 22. PAULA T  
| 23. ALBERT  
| 24. ALBA  
| 25. LIDIA  
| 26. HÉCTOR  
| 27. MARTA  
| 28. JOSE MARIA  
| 29. SERGIO  
| 30. JUANJO  
| 31. GABRIEL  
| 32. CARLOS  
| 33. OSCAR  
| 34. AITOR  
| 35. ELENA  
| 36. ALMA  
| 37. JORGE  
| 38. POL  
| 39. MARTA  
| 40. MIGUEL  
| 41. PAULA S  
| 42. CRISTINA  
| 43. INES  
| 44. JOSE CARLOS  
| 45. IVÁN  
| 46. SANTIAGO  
| 47. IAGO  
| 48. MARTINA  
| 49. MAMEN  
| 50. ANTONIO  
| 51. LUCHO  
| 52. LUCIA  
| 53. MARTIM  
| 54. NIKOLAY  
| 55. DANIEL  
| 56. LARISA  

"Una manera de hacer Europa"