Can fetal teratogens mimic genetic disorders?

ESHG Dysmorphology and Syndromology Course
2026

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Teratogenic Agents

- Infections – toxoplasmosis, CMV, varicella zoster etc
- Environmental chemicals
- Maternal smoking, ingestion of alcohol, metabolic factors
- Drugs - prescribed and ‘recreational’

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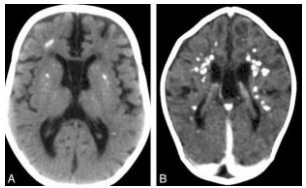
How teratogens exert their effects

1) Infection of fetus in utero causes
   - Miscarriage
   - Low birth weight
   - Calcification brain and other organs
   - Microcephaly/hydrocephalus
   - Seizures
   - Cataracts, chorioretinitis
   - Hearing loss

Can infections mimic genetic disorders?
- AR/AD microcephaly
- Seizure syndromes
- Cataracts
- AR deafness
- Syndromes with brain calcification eg Aicardi-Goutieres S



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How teratogens exert their effects

2) Generalised slowing of growth - ↓cell division
   - Low birth weight, small placenta
   - Microcephaly
   - Non-specific facial features
   - Malformations due to ‘failure to finish off’ a normal developmental process
     - ASD, VSD, hypospadias, NTD, CL/P, coloboma

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Generalised slowing of growth - decreased cell division Examples

- Fetal alcohol
- Smoking
- Maternal PKU
- ?fetal phenytoin











Can these 'fetal insults' mimic genetic syndromes?

Similar syndromes to infections

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How teratogens exert their effects

3) Disruption of a specific function/developmental pathway

- Thalidomide
- Lithium
- Androgens
- Warfarin
- Carbimazole
- Retinoic acid
- Valproic acid
- Fentanyl

Almost all of these have a ‘matching’ genetic syndrome

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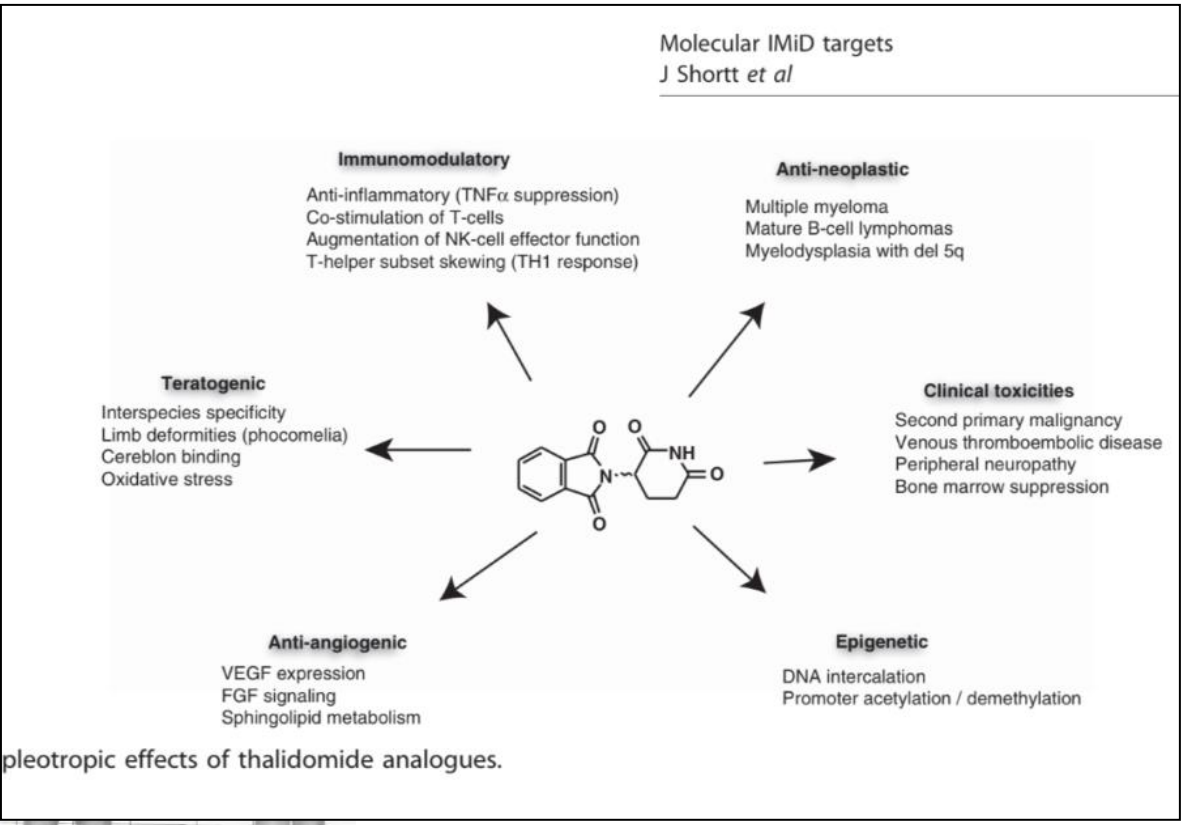
Thalidomide embryopathy

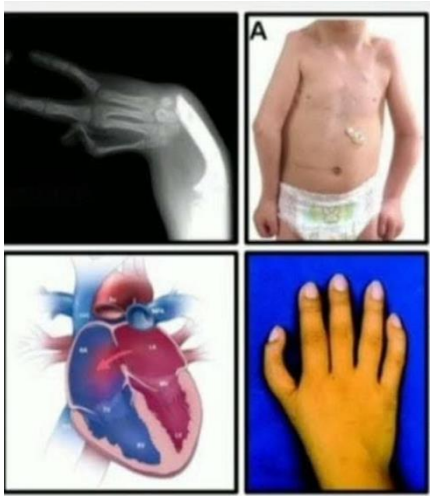


pleotropic effects of thalidomide analogues.

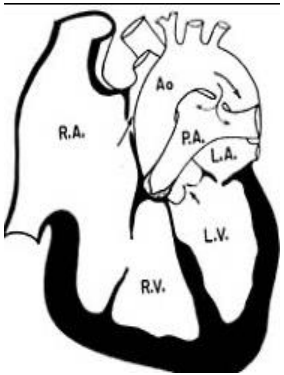


Genetic syndromes

Eg Holt-oram syndrome
TBX5



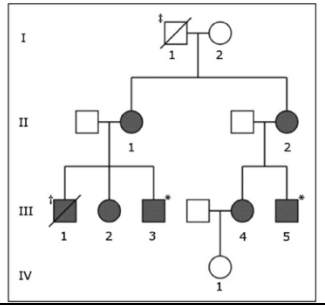
Lithium prescribed in pregnancy



Ebstein anomaly

Jacobson SJ, Prospective multicentre study of pregnancy outcome after lithium exposure during first trimester. Lancet 1992;1:530-533.

Familial Ebstein Syndrome



Familial Ebstein Anomaly
Whole Exome Sequencing Identifies Novel Phenotype Associated With *FLNA*

Catherine L. Mercer, MD*; Gaia Andreoletti, PhD*; Aisling Carroll, MD; Anthony P. Salmon, MD; I. Karen Temple, MD; Sarah Ennis, PhD

Mutation Within *FLNA*

The p.G1554R mutation segregating in our family with EA sits within the 14th repeated rod-domain (Figure 2). The mutation replaces a nonpolar amino acid with a polar amino acid and is likely to impact tertiary structure as indicated by PolyPhen2 and GERP scores.

Mercer et al Circ;Cardiovasc Genet 10;(6) 2017

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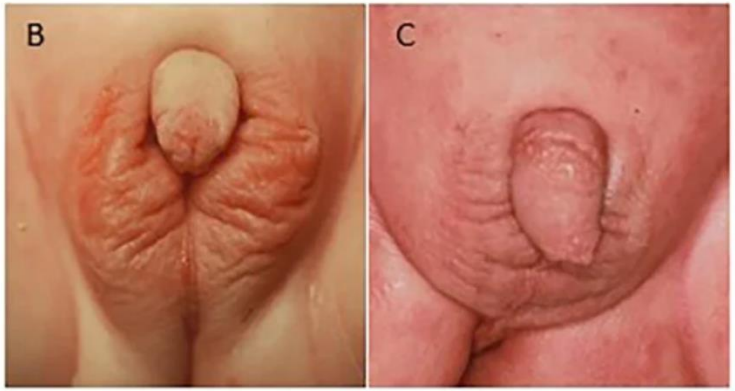
Androgens taken in pregnancy



Masculinisation of female fetuses

Congenital Adrenal Hyperplasia



CYP21 causing 21-hydroxylase deficiency

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Warfarin



Arylsulphatase E action inhibited by warfarin

1 in 6 infants affected, 1 in 6 stillbirth

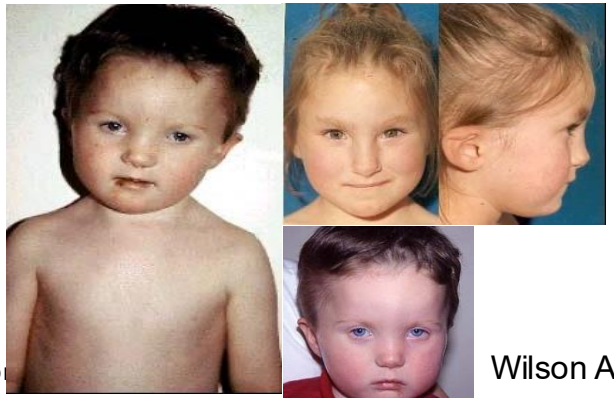
Genetic syndrome

X-L chondrodysplasia punctata, Xp22.3

mutations in *ARSL* gene encoding arylsulphatase E

Hall JG et al Maternal and fetal sequelae of anticoagulation during pregnancy. Am J Med 1980;68:122-140.

Carbimazole



Scalp defects
Characteristic face
Choanal atresia
A/hypothelia

Crosses placenta, inhibits thyroid hormone synthesis, blocks organification of iodine

Scalp-ear-nipple syndrome
KCTD1
AD scalp defect-choanal atresia

Marneros AJHG 92, 621–626, 2013

Wilson AJMG 75:220;1998

Følso

Retinoic acid

Craniofacial

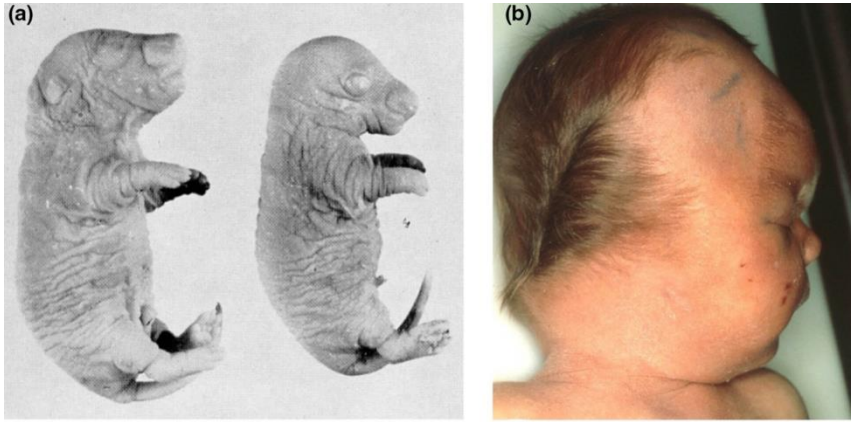
- Small/missing ears
- Micrognathia –often asymmetrical
- Cleft palate

Cardiovascular

- Conotruncal/aortic arch

Other

- CNS
- Thymus and parathyroid



Control vitamin A excess isotretinoin

Oral retinoids. Risk 5-20%

Isotretinoin – *Accutane* for acne

Topical. Risk low

Common use – acne and 'beauty treatment' lower risk

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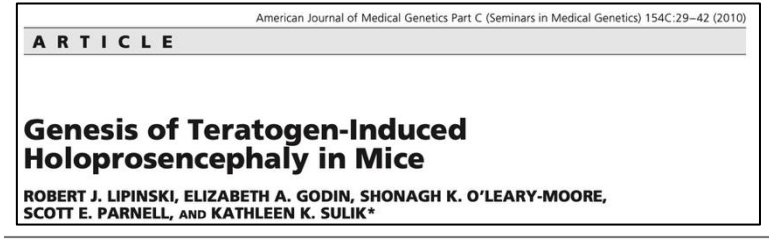
Retinoic acid signalling

Central role in vertebrate development

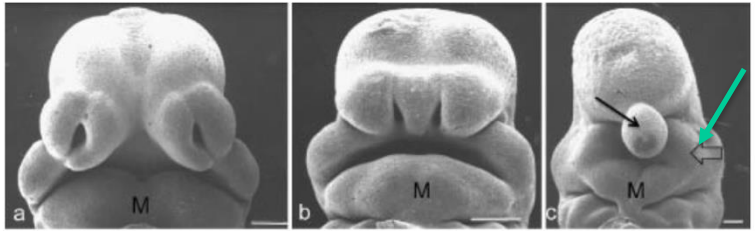
RA causes HPE spectrum and first arch abnormalities in mice


American Journal of Medical Genetics Part C (Seminars in Medical Genetics) 154C:29–42 (2010)

ARTICLE

Genesis of Teratogen-Induced Holoprosencephaly in Mice

ROBERT J. LIPINSKI, ELIZABETH A. GODIN, SHONAGH K. O'LEARY-MOORE, SCOTT E. PARNELL, AND KATHLEEN K. SULIK*



Genetic phenocopies

Exogenous teratogens (retinoic acid, cholesterol biosynthesis inhibitors) act on identical developmental windows as mutations in *SHH*, *PTCH1*, and *GLI2/GLI3*.



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Fetal valproate syndrome



NTD in ~ 5% babies exposed to sodium valproate









grooves under eyes

thin upper lip

pencilled eyebrows

metopic ridge

flat nasal bridge

radial aplasia

iris coloboma

cardiac anomaly

mental retardation

Clayton-Smith J, Donnai D. Fetal valproate syndrome. J Med Genet 1995;32:724-727.

Fetal Valproate syndrome

frontiers in Neuroscience

BRIEF RESEARCH REPORT
published: 25 November 2020
doi: 10.3389/fnins.2020.591196

Anticonvulsants and Chromatin-Genes Expression: A Systems Biology Investigation

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[1] Postgraduation Program in Genetics and Molecular Biology, Universidade Federal do Rio Grande do Sul (UFRGS), Porto Alegre, Brazil, [2] Laboratory of Immunobiology and Immunogenetics, Universidade Federal do Rio Grande do Sul (UFRGS), Porto Alegre, Brazil, [3] National Institute of Population Medical Genetics (INAGEMP), Porto Alegre, Brazil, [4] Genomic Medicine Laboratory, Hospital de Clínicas de Porto Alegre (HCPA), Porto Alegre, Brazil, [5] National System of Information on

Discovery of DNA methylation signature in the peripheral blood of individuals with history of antenatal exposure to valproic acid

Sadegheh Haghshenas[1], Audrey Putoux[2,3], Jack Reilly[4], Michael A. Levy[1], Raissa Relator[1], Sourav Ghosh[4], Jennifer Kerkhof[1], Haley McConkey[1,4], Patrick Edery[2,3], Gaetan Lesca[2,5], Alicia Besson[5], Christine Coubes[6], Marjolaine Willems[6], Nathalie Ruiz-Pallares[7], Mouna Barat-Houari[7], Eduardo F. Tizzano[8,9,10], Irene Valenzuela[8,9,10], Quentin Sabbagh[6], Jill Clayton-Smith[11,12], Adam Jackson[11,12], James O'Sullivan[12], Rebecca Bromley[13,14], Siddharth Banka[11,12], David Genevieve[6,15,10,*], Bekim Sadikovic[1,4,*]

Results: Genomic DNA methylation analysis was applied, and a distinct DNA methylation profile was identified in the majority of affected individuals. This profile was used to develop a diagnostic episignature classifier. The valproate exposure episignature exhibited high sensitivity and specificity relative to a large reference data set of unaffected controls and individuals with a wide spectrum of syndromic disorders with episignatures. Gene set enrichment analysis demonstrated an enrichment for terms associated with cell adhesion, including significant overrepresentation of the cadherin superfamily.

Conclusion: This study provides evidence of a robust peripheral blood-based diagnostic epigenetic biomarker for a prenatal teratogenic disorder.

Gouisanker et al Nat. reviews genetics. 2024:25. p. 340-361. Chromatin remodelers.



Fetal Valproate



CHARGE



Kabuki syndrome

Opioids in pregnancy

Prescription Opioids in Pregnancy and Birth Outcomes: A Review of the Literature

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J Pediatr Genet 2015;4:56–70.

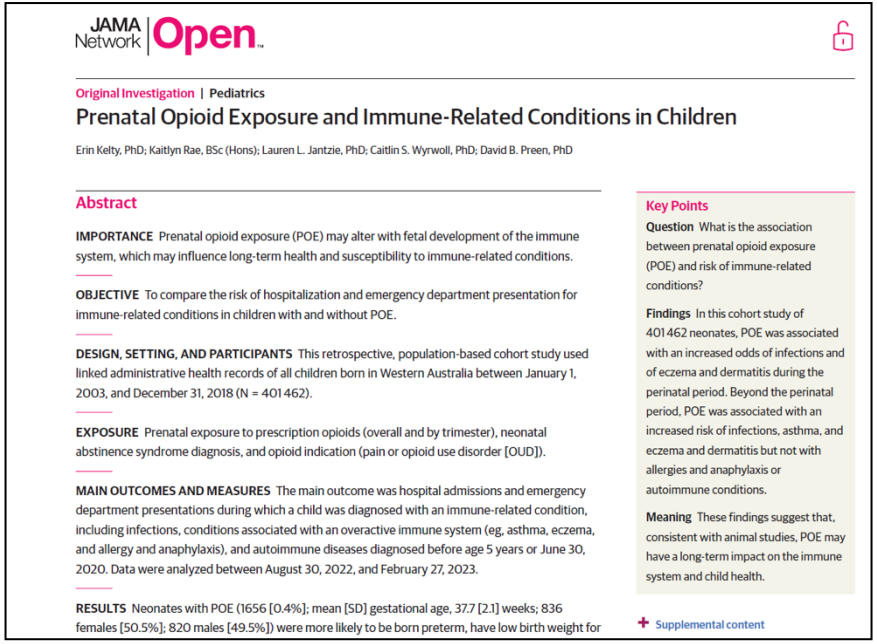
Abstract

Prescription opioids are used prenatally for the management of pain, as well as for opiate dependency. Opioids are known to cross the placenta and despite the evidence of possible adverse effects on fetal development, studies have consistently shown prescription opioids are among the most commonly prescribed medications and the prevalence of use is increasing among pregnant women. This article summarizes the available literature documenting potential harms associated with prescription opioid use during pregnancy, including poor fetal growth, preterm birth, birth defects, and

Keywords
- opioids
- pregnancy
- fetal growth
- birth weight
- birth defects

J Pediatr Genet 2015

Literature review



JAMA Network Open

Original Investigation | Pediatrics

Prenatal Opioid Exposure and Immune-Related Conditions in Children

Erin Kelty, PhD; Kaitlyn Rae, BSc (Hons); Lauren L. Jantzie, PhD; Caitlin S. Wyrwoll, PhD; David B. Preen, PhD

Abstract

IMPORTANCE Prenatal opioid exposure (POE) may alter with fetal development of the immune system, which may influence long-term health and susceptibility to immune-related conditions.

OBJECTIVE To compare the risk of hospitalization and emergency department presentation for immune-related conditions in children with and without POE.

DESIGN, SETTING, AND PARTICIPANTS This retrospective, population-based cohort study used linked administrative health records of all children born in Western Australia between January 1, 2003, and December 31, 2018 (N = 401 462).

EXPOSURE Prenatal exposure to prescription opioids (overall and by trimester), neonatal abstinence syndrome diagnosis, and opioid indication (pain or opioid use disorder [OUD]).

MAIN OUTCOMES AND MEASURES The main outcome was hospital admissions and emergency department presentations during which a child was diagnosed with an immune-related condition, including infections, conditions associated with an overactive immune system (eg, asthma, eczema, and allergy and anaphylaxis), and autoimmune diseases diagnosed before age 5 years or June 30, 2020. Data were analyzed between August 30, 2022, and February 27, 2023.

RESULTS Neonates with POE (1656 [0.4%]; mean [SD] gestational age, 37.7 [2.1] weeks; 836 females [50.5%]; 820 males [49.5%]) were more likely to be born preterm, have low birth weight for

Key Points

Question What is the association between prenatal opioid exposure (POE) and risk of immune-related conditions?

Findings In this cohort study of 401 462 neonates, POE was associated with an increased odds of infections and of eczema and dermatitis during the perinatal period. Beyond the perinatal period, POE was associated with an increased risk of infections, asthma, and eczema and dermatitis but not with allergies and anaphylaxis or autoimmune conditions.

Meaning These findings suggest that, consistent with animal studies, POE may have a long-term impact on the immune system and child health.

+ Supplemental content

JAMA Network Open 2024

Notes review

Fetal Fentanyl syndrome



- Microcephaly
- Anteverted nares hemangioma
- Cleft palate
- Transverse creases
- 2/3 syndactyly toes
- Genital abn

Transient abnormal cholesterol metabolism

GIM Open 2023 vol. I 100834. Wadman et al.

Smith-Lemli-Opitz syndrome





Autosomal recessive
DHCR7 variants

Severe neonatal form
Mostly lethal

Milder type compatible with survival - MR, microcepaly, characteristic face etc



Fetal Fentanyl syndrome

FFS
elevated 7- and 8-DHC at age 8 days, normal 7-DHC and less elevated 8-DHC at age 19 days, and normal 7- and 8-DHC at age 5 months.

VS

SLO
Autosomal recessive
Biallellic *DHCR7* variants
Persistent changes

Fentanyl is a Sigma-1 protein ligand, similar to cholesterol and many cholesterol precursors. The polycyclic binding pocket of Sigma-1 protein binds most of the inhibitors of the enzymes in the distal half of the cholesterol synthetic pathway (C27 sterols).

Because fentanyl is a Sigma-1 ligand, it is reasonable to consider that fentanyl inhibits cholesterol synthesis. Early prenatal exposure to fentanyl may affect cholesterol synthesis by inhibition of DHCR7 in the developing fetus

Korade et al Mol. Psych online june 2024

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Conclusions: In this perinatal OUD cohort, prenatal fentanyl exposure was more commonly documented among infants with at least one compared with none of these infant features. However, features were rare and contextual factors differed among dyads by prenatal fentanyl exposure status. Further analyses examining these infant features, while considering multiple exposures, are needed before substantiating a fetal fentanyl syndrome.

Corpus callosum abnormalities	< 5
Microcephaly	
Diagnostic and procedural codes	169/5053 (3.3)
Head circumference ≤ 3rd percentile¶	358/4275 (8.4)
Genital anomalies	
Males#	142/2267 (6.3)
Females#	10/2130 (0.5)

Take home messages

- There will be new teratogen syndromes
- Large scale studies/lit and notes review don’t always help
- Prospective studies needed

- As ever, examination of individual patients by someone experienced in syndromes does help
- Consider pathways suggested by drug metabolism
- Look for genetic phenocopies

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Teracopy – an agentic AI project

Buske.github.io/teracopy



"With over **7000 different rare diseases** the diagnostic odyssey can be really long and arduous. The reasons for this are complicated, but one of them is just lack of familiarity with so many different diseases. This is what we address here at PhenoTips, bringing that sort of workflow and informatics into the clinical setting so that we can **diagnose these diseases sooner**."

– Dr. Orion Buske, Chief Executive Officer, PhenoTips

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