Placenta Gives Clues to Autism Spectrum Disorder

Jen-Mei Chang

Department of Mathematics and Statistics
California State University, Long Beach
jen-mei.chang@csulb.edu

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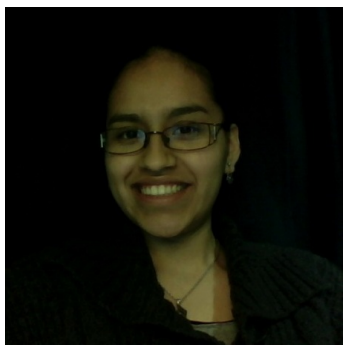
Disclaimer

- **ME:** "I am an **applied** **mathematician** who uses geometric methods to study large data sets, especially data sets that are digital photographs in nature."
- **YOU:** "So, why are you giving a talk that sounds so medical?"
- **ME:** Well, if I had told you that my talk will be on "Vessel enhancement with multi-scale and curvilinear filter matching for placenta images," would you have come?

Carrie Salafia

Nen Huynh



Marilyn Vazquez

My best friend

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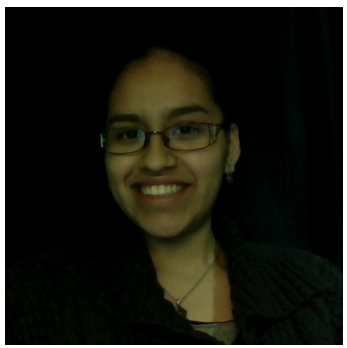

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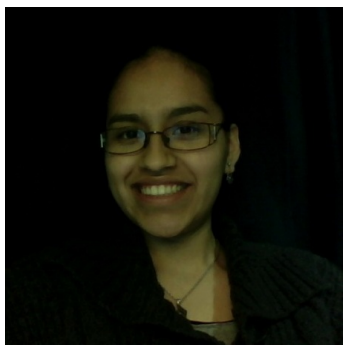

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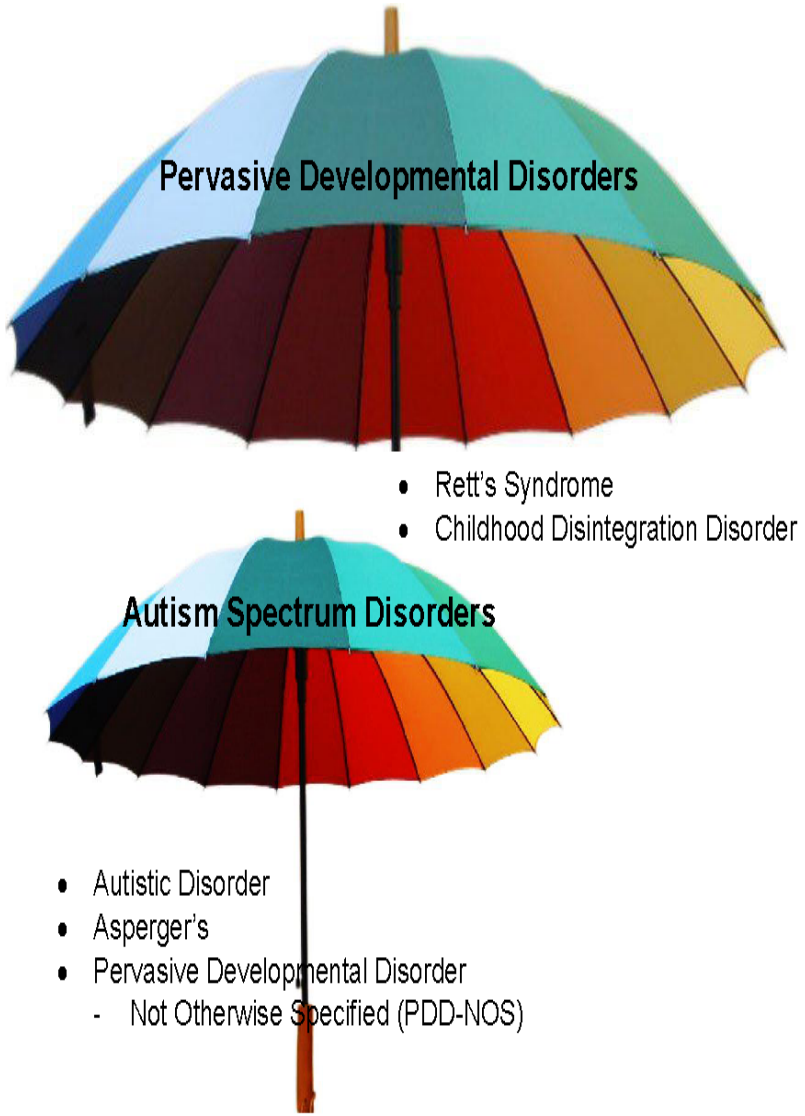
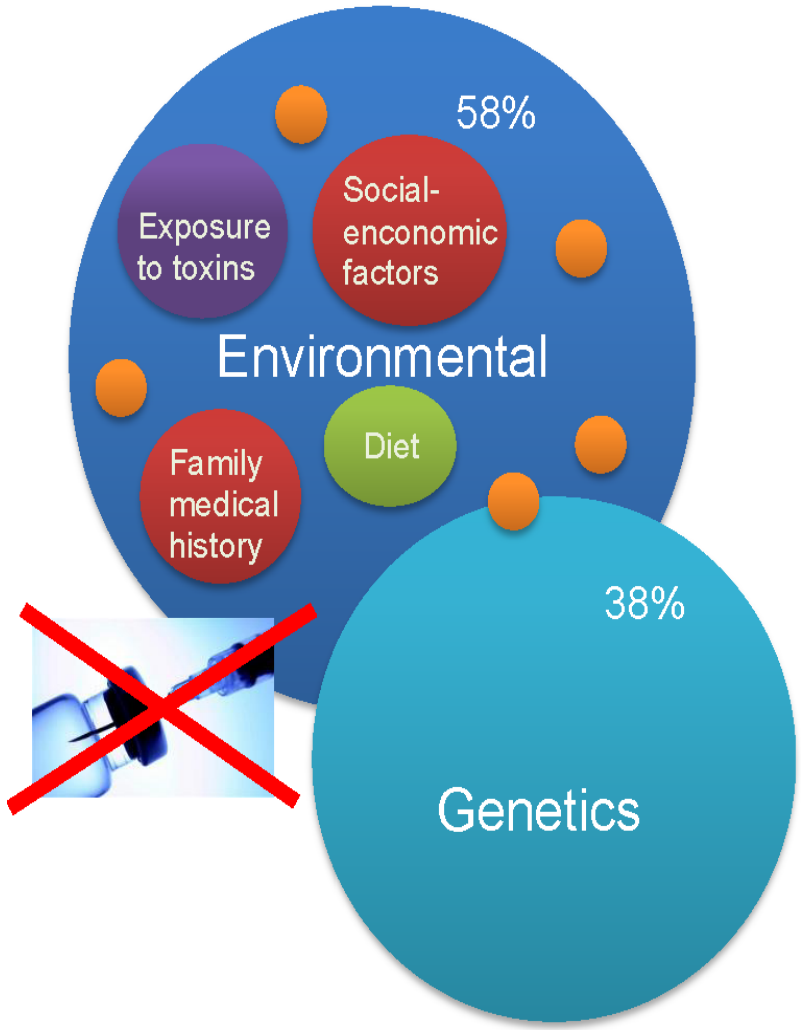
What is ASD?

- First identified in 1943 by Leo Kanner.
- Autism is a neurodevelopmental disorder with 3 defining areas of deficit:
  1. Social reciprocity
  2. Communication
  3. Restricted, repetitive patterns of behaviors, interests, or activities.
- Symptoms are developed by 36 months of age.
- The term “spectrum” refers to a wide range of symptoms, skills, and levels of impairment or disability.



Causes

- The causes of autism are diverse: genetic and non-inherited factors or exposures.
  - **Genetic:** In identical twins, if one has ASD, the other twin also has ASD in nearly 9 out of 10 cases.
  - **Environmental:** Family medical history, demographic factors, exposure to toxins, complications during birth or pregnancy, diet, etc.
- Although no definitive answers yet, health experts are confident that there is little connection between vaccines and autism.



Statistics

- Percentage of U.S. population diagnosed with ASD[1]:

$$\begin{cases} \frac{1}{5000} & \text{in 1975} \\ \frac{1}{88} & \text{in 2011} \\ \frac{1}{68} & \text{in 2012} \\ \frac{1}{50} & \text{in 2013} \end{cases}$$

It is the fastest growing developmental disability in the U.S.

- Possible factors contributing to the increase:
  - Change in diagnosis criteria (accounts for $\approx 20\%$ of the overall $\uparrow$)
  - Trend towards younger age at diagnosis ($\approx 4\%$)
  - Broadening to include milder cases ($\approx 9.3\%$)
  - order ages of mothers ($\approx 0.67\%$)

The remaining 66% deserves serious investigation.

[1] CDC

Facts about ASD

Gender

$$\frac{\text{Boys}}{\text{girls}} = \frac{5}{1}$$

Risk

Couples with a child with autism are 9 times more likely to have another child with autism.

Diagnosis

- A standard two-stage screening process is currently in practice (for children at 18 and 24 months of age.).
- A diagnosis is usually made when a child is 3 to 4 years of age or older.
- EEG brain scans may detect signs of ASD in 2-year-olds [1].

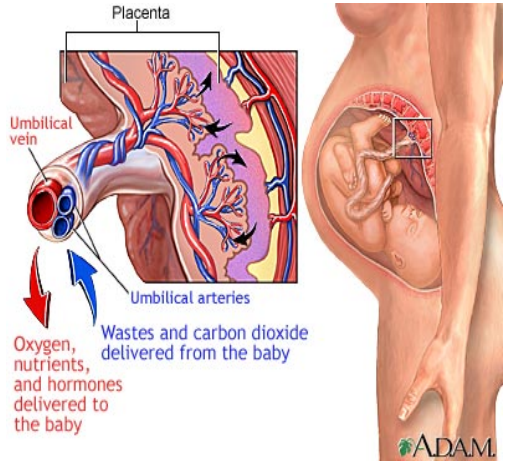
Treatment

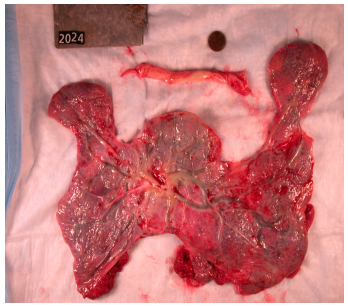
- There is no proven cure yet for ASD.
- The brain is most responsive to treatment in the first year of life.
- Early intervention (e.g., with intensive Early Start Denver Model (ESDM) that uses techniques of **Applied Behavioral Analysis**) is associated with normalized brain activities in young children with ASD (i.e., improved cognitive and language skills) [2].
- But, since a diagnose of ASD is usually not made until the child is 3 or 4 years old, **the best opportunities for intervention have already been lost then**.

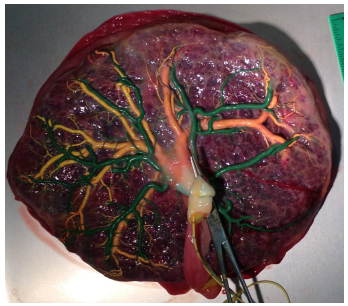
We are in great need to discover a reliable biomarker in assessing prenatal/neonatal ASD risk. So, why not consider the gestational origin of life — placenta?

What is placenta?

- Nutrients, wastes, and gases are exchanged between the mother's and the baby's blood in the placenta.
- An analysis of the placenta may help to predict risks for certain diseases that develop in the womb such as diabetes, autism, and heart disease.
- For centuries the placenta has received ceremonial handling by many cultures around the world. (e.g., in China, placenta is considered as a rich source of nutrients and can be added to the diet to increase a person's energy and vitality.)





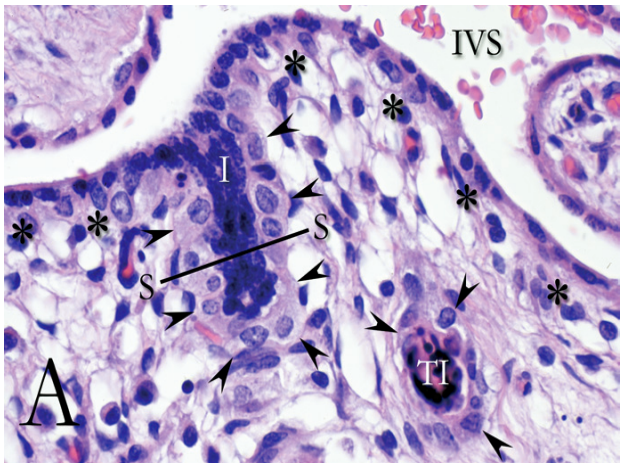


Why studies placenta?

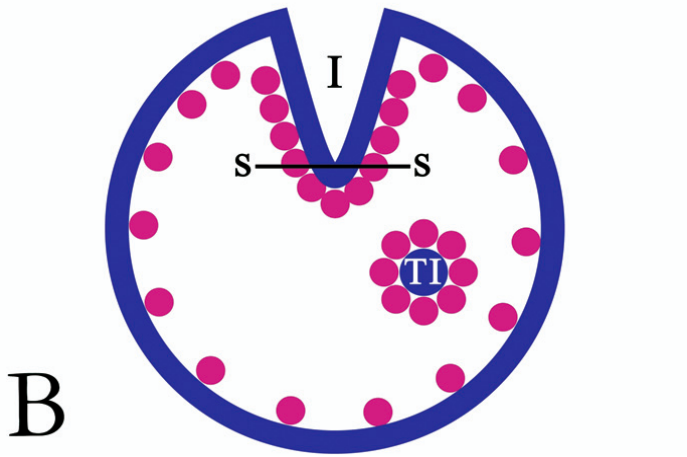
- In western medicine the human placenta is usually regarded as nothing more than human waste.
- In fact, only 10-15% of the placentas are analyzed, usually after pregnancy complications or a newborn's death.
- Altered patterns of angiogenesis $\Leftrightarrow$ variation in mature vascular network structures $\Leftrightarrow$ functional alterations of many viscera (e.g., lung, kidney, and pancreas).
- The gene families that control branching morphogenesis are shared between those permanent viscera and the temporary fetal organ – placenta.
- Placenta, hence, provides unique insights into the effects of genes and/or environment (or both) on key mechanisms required for conceptus development, including fetal origins of disease from hypertension to diabetes and autism.

Placenta & ASD: Trophoblast inclusions [3]

- Placentas from at-risk pregnancies (in which the families already had 1 or more children with ASD) were 8 times more likely to have two or more TIs than placentas from uncomplicated pregnancies.
- The more trophoblast inclusions you have, the more severe the abnormality.



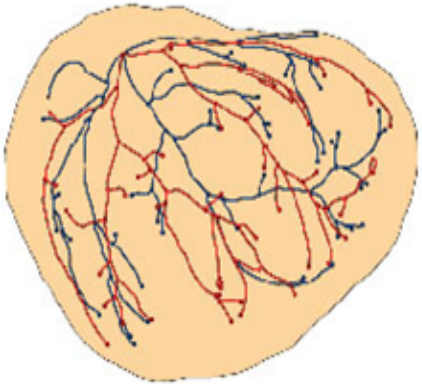
histology



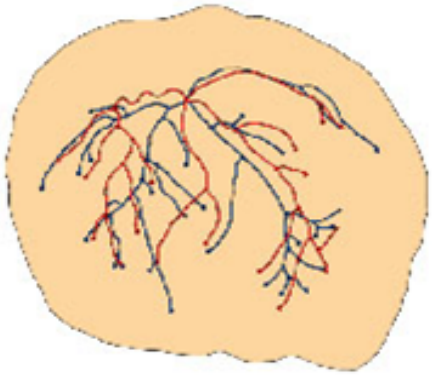
villus cross-section

Figure: [4] **(A)** histologic section of a placental villus which exhibits a trophoblast inclusion (TI). **(B)** Diagram of a villus cross-section showing the outer syncytiotrophoblast layer (blue line) and inner cytotrophoblast layer (pink circles) with a trophoblast inclusion (TI).

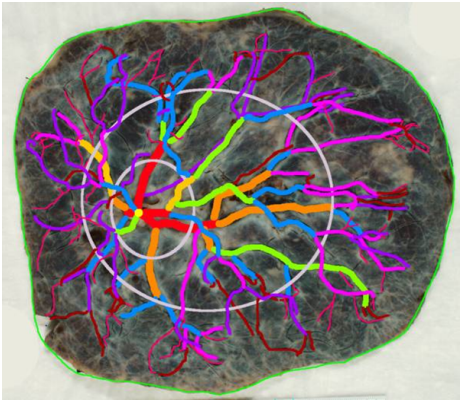
Placenta & ASD: Angiogenesis [5]



mean of low-risk



mean of high-risk



manually traced

Placental angiogenesis and ASD	Low-ASD risk		High-ASD risk		Significance
	Arterial	Venous	Arterial	Venous	
# branch generations	8.86±1.69	9.24±2.11	7.65±1.72	8.07±1.76	high-risk group has fewer branch generations
# branch pts in network	29.94±11.13	32.86±11.92	21.67±8.96	26.91±9.45	high-risk group has fewer branch points
mean dist of vessel endpts to disk edge	2.24±.50	2.34±0.51	2.78±.63	2.51±0.55	placenta from high-risk group fails to extend as close to the chorionic perimeter as low-risk group does.

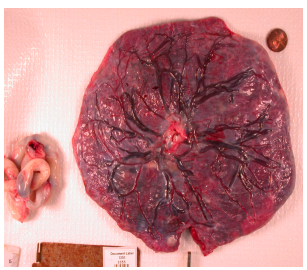
Significant implications

- These methods open options for prenatal/neonatal ASD risk assessment.
- **Early detection and intervention for newborns with elevated risks for ASD can be realized.**
- Challenges for prime time: data set sizes and time it takes to make a diagnosis.

Data set	# of cases used	Data description/purpose
MARBLE (Markers of Austism Risk in Babies - Learning Early Signs)	117	cohort of families who have one or more previous biological children with ASD
EARLI (Early Autism Risk Longitudinal Investigation)	46 traced placentas (from 150 available ones)	self-enrolled group of mothers of children with autism at the start of another pregnancy. The newborn child's development is examined through three years of age.
NCS (National Children's Study)	78 traced placentas (from 250 available ones)	NCS examines the effects of the environment (e.g., air, water, diet, sound, family dynamics, community and cultural influences, and genetics on the growth, development, and health of children across the U.S.), following them from before birth until 21 years of age.

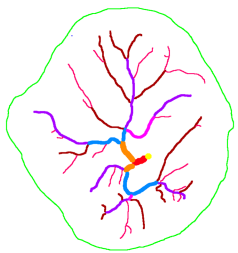
Research challenge

Currently, extracting blood vessel network of the human placenta is done through a laborious process that is very time consuming, hence making large-scale studies and real-time diagnosis intractable.

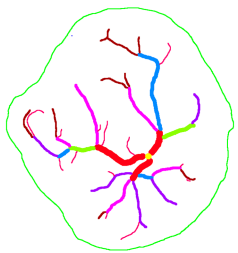


raw image

$\longrightarrow$ human

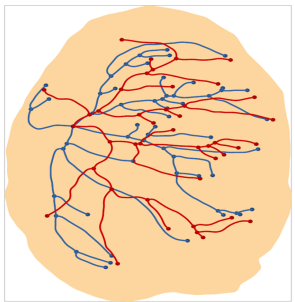


traced



traced

$\longrightarrow$ machine



desired

Research goal

- My research project aims to develop an **automated** program that **detects** and **enhances vessels** in digital **placenta images**.

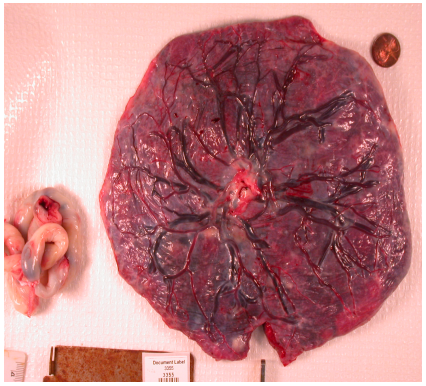
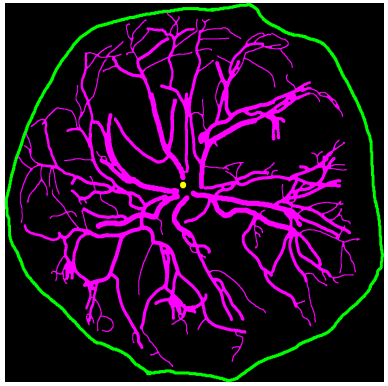


image captured

automatically



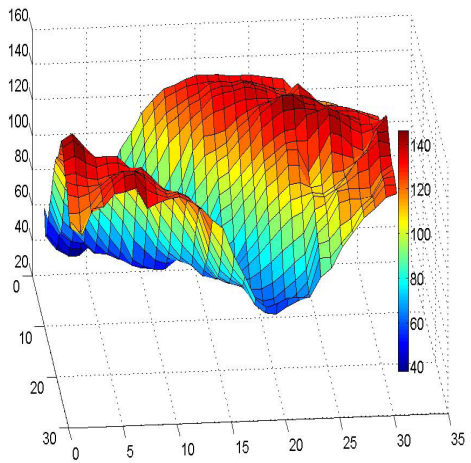
desired output

- **Compute** vessel features that are proxies for predicting health risks. Such possible features include (but not limited to) surface area, surface area ratio, number of endpoints, distribution of distance from endpoints to perimeter, arc length, mean vessel width, variability in vessel width, number of branch points, etc.

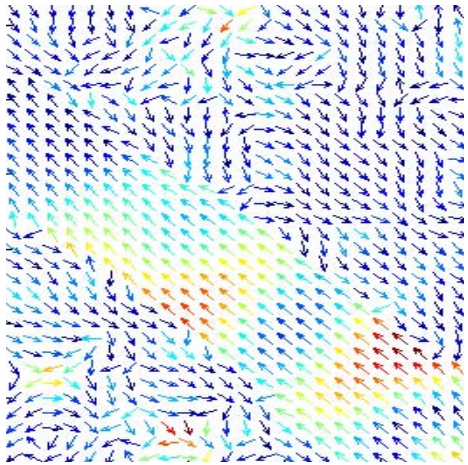
Work-in-progress [6]

- A **multiscale** filtering process that is based on images' 2nd-order feature is used to highlight **locally curvilinear** structures and minimize surrounding non-vessel noise.

a vessel



intensity surface

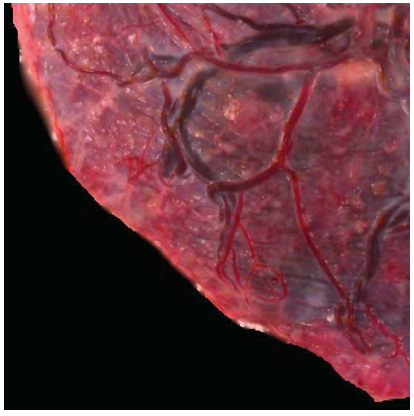


$\mathbf{v}_1$ of $\mathbf{H}$

- The proposed method performs superior than all existing competitor's work.

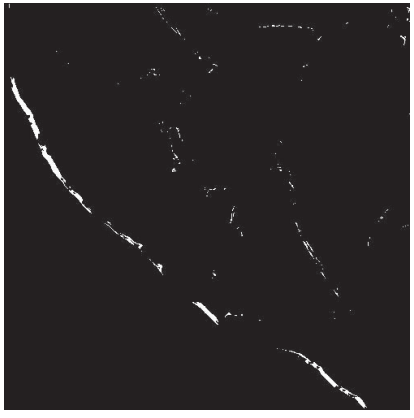
A sample visual result [6]

64-bit laptop w/Windows
Intel(R) Core(TM) i7-3770
@ 3.4GHz CPU, 8GB RAM
implemented in MATLAB
$\sigma \in \{4,6\}, \beta = 0.5, c = 15$
$\omega = 5, \ell = 14, \alpha = 0.04$
NN = 36.68s, MVE = 0.92s
C.L. Enhancement = 4.44s



(a) original

(b) hand traced



(c) neural network

(d) multiscale

(e) proposed

Figure: placenta ID 3355 from the UNC data set.

Summary

1. Understanding the causes for ASD is of national urgency.
2. Early intervention is the best treatment plan.
3. Placenta, as a diary of gestational life, should be carefully studied.
4. Interdisciplinary collaboration can greatly contribute to the overall understanding of the problem.

THANK YOU

References

[1] F. Duffy, H. Als, "A stable pattern of EEG spectral coherence distinguishes children with autism from neuro-typical controls - a large case control study," *BMC Medicine*, 10(64), 2012.

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[3] C. Walker, K. Anderson, K. Milano, S. Ye, D. Tancredi, I. Pessah, I. Hertz-Picciotto, H. Kilman, "Trophoblast inclusions are significantly increased in the placentas of children in families at risk for autism," *Biological Psychiatry*, 74(3), 204–211, 2013.

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