



## Prenatal identification of autism propensity

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### ABSTRACT

The innovative method described involves antepartum testing to determine if the fetus has the potential of later developing autism. A technique is detailed which allows examining the maternal blood for SNPs (single-nucleotide polymorphisms) known to be associated with IGF1/IRS1 cellular pathway malfunction potentially leading to brain dysconnectivity in neonates. Results can then be corroborated with umbilical cord sampling at birth by the Autism Index test.

[The discussion presented here is the follow-up to the recent prior report: Steinman, G. IGF – Autism prevention/amelioration, Medical Hypotheses 2019;122:45–47].

### Introduction

Autism (ASD) is to be differentiated from less common syndromic neuro-pathologies which bear some of the characteristics of ASD, but are distinguishable from it. For example, repetitive movements are found in both autism and Rett Syndrome (RS); however, RS is almost unique to girls but ASD is much more common in boys (4:1). RS has a distinguishing major genetic mutation (MECP2) whereas autism does not [1]. However, autism can coexist with other genetic disorders such as Down Syndrome in about 10% of the cases.

There is increasing evidence that the etiology of autism is related to disorders of the IGF/IGFR/IRS1/PI3K/AKT/mTOR cellular signaling pathway [2–7]. This conduit effects the translation of IGF in particular. For example, in the autistic brain, phosphorylated AKT is decreased (2). Deficiency of insulin-like growth factor-1 (IGF) can reduce anabolic functions promoted by this sequence. Rather than being due to a major genetic defect, the dysconnectivity characteristic of autism appears to be the result of diminished effect of IGF-1 on neonatal neurogenesis, secondary to impediments in the PI3K/AKT pathway or to insufficient IGF-1 initially.

Further supporting the IGF hypothesis is the observation that the rate of cancer in autistic patients is about one-third that of neurologically normal individuals [8]. This may be due to the lower level of IGF in children and adults with ASD. One of the characteristics of IGF is its mitogenic properties. Similarly, the tumor suppressor PTEN also acts to reduce the activity of PI3K, thereby diminishing the active translation of IGF. This could also lessen neuronal myelination in children destined to display autistic behavior later. On the other hand, chemical inhibition of PTEN can enhance myelination [2].

Genetic polymorphic regulation of the cellular insulin-receptor

substrate (IRS1) factor can retard the translation of the IGF signal [3]. IGF stimulation of oligodendrocytes is essential for axonal myelination and synapsis development in the prenatal and neonatal stages, especially in the brain [9]. Thus, it is important to elevate the activity of biologically operational IGF early in a newborn's development. This functionality is to avoid unalterable dysconnectivity (“miswiring”) in the crucial stages of brain neural circuit genesis, especially with the posterior-to-anterior connections [10].

### Evaluation/resolution

A number of ways to enhance the inadequate amount of IGF in an affected neonate have been discussed previously [9,11]. Critical to this approach is being able to assess the *in vivo* level of this growth factor as early as possible, preferably before birth. In this way, preventive therapy can begin in the early neonatal period, before the neurological characteristics of autism become established in babies with the limited potential to produce/supply adequate IGF.

One way to execute this determination, as noted previously, would be amniocentesis to retrieve fetal cells [9]. However, methodology has been developed which allows testing of the gravida's blood, which contains factors that originate from the growing fetus, to evaluate particular entities active in her unborn baby. One example of this is placental growth hormone [12]. Unlike the baby after delivery, the level of IGF in the fetus which is synthesized mainly in the placenta is determined by placental, rather than pituitary, growth hormone. The two growth hormones (fetal placental and maternal pituitary) mixed in the gravida's circulation are sufficiently different to be detectable and quantifiable independently. At 28 weeks of gestation, the level of human placental growth hormone in the mother's circulation is

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significantly higher if she is carrying a female fetus than a male. This is consistent with the lower relative incidence (1:4) of autism in female children than male.

Fetal SNPs can be discerned and quantified in the maternal circulation during gestation [3,13–17]. Hence, SNP rs1801123 in the maternal circulation, in the case of a fetus with polymorphic IRS1 factor allele, should be amenable to detection in the mother. In other words, the potential to eventually develop autism, as evidenced by the presence of rs1801123, can be distinguished from a non-SNP form of IRS1 (ASD-free). Noninvasive prenatal testing (NIPT) would preclude the need for riskier amniocentesis to collect testable fetal samples, thus making this assessment available to essentially all gravidas on a routine basis. The women displaying positive results can have their babies tested at birth by other corroborating methods such as the Autism Index [14]. A prospective study, testing insulin-receptor substrate (IRS1) polymorphism, as in cell-free fetal DNA in maternal blood, and the correlation with ASD incidence would be the first step to explore this possible interventional research hypothesis.

This type of prenatal testing is especially important in the case of a woman who has already delivered another child that eventually developed autism. In that situation, the risk is estimated to be 1-in-5, versus 1-in-64 in the general population [18,19]. Using this ratio and the observation that 3,853,000 babies were born in the United States in 2017, this would average out to another 165 children found in America to be affected by this malady EVERY DAY of the year. The urgent need for a means to reduce or eliminate this medical problem requires prompt attention. Putative contemporaneous cofactors entertained thusfar (folate deficiency, major genetic defects, heavy metals, gluten, oxidative stress, and air pollution, for example) have been consistent with a minority of cases but have not resolved the underlying primary cause of autism. To date, IGF deficiency has been the most plausible, encompassing etiological factor which has been proposed to be at the heart of this condition.

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#### Conflict of interest

The author has no conflict of interest.

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#### Appendix A. Supplementary data

Supplementary data to this article can be found online at <https://doi.org/10.1016/j.mehy.2018.11.001>.

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#### Glossary

ASD: Autism spectrum disorder  
 IGF: Insulin-like growth factor  
 IGF-R: IGF receptor  
 IRS: Insulin receptor substrate  
 RS: Rett Syndrome  
 SNP: Single nucleotide polymorphism