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Untangling the most probable role for vitamin D₃ in autism

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ABSTRACT

Recent studies indicate an important role for vitamin D₃ in autism spectrum disorder (ASD), although its mechanism is not completely understood. The most puzzling aspect of ASD is that identical twins, who share identical DNA, do not have 100% concordance rates (~88% for identical and ~31% for fraternal twins). These findings provide major clues into the etiology: ASD must involve an environmental factor present in the prenatal milieu that both identical twins are not always exposed to because they do not always share it (i.e., placentas). Combined with the exponential increasing rates of ASD around the world, these observations suggest a contagious disease is probably transferred to the fetus via the placenta becoming infected by a cervical virus. Vitamin D₃ boosts immune responses clearing viral infections and increases serotonin and estrogen brain levels. Here we review the different roles and untangle the most probable one vitamin D₃ plays in ASD.

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autism spectrum disorder; cervix; cerebral spinal fluids; choroid plexus; estrogen; human papillomavirus; learning disabilities; placenta; prenatal environment; serotonin; vitamin D₃

The most puzzling aspect of autism spectrum disorder (ASD) is that identical twins, who share identical DNA, do not have 100% concordance rates. Identical, monozygotic twins only have concordance rates of ~88%, while fraternal, dizygotic twins have concordance rates of ~31%.^{1,2} These twin observations alone provide clues into the etiology: ASD must involve something present in the prenatal environment that both identical twins are not always exposed to because they do not always share it. Identical twins can share the same placenta and amniotic sac (occurrence ~1%) or they can share the same placenta but not their amniotic sac (occurrence ~69%) or they can have their own placentas and amniotic sacs (occurrence ~30%), while fraternal twins always have their own placentas and amniotic sacs³ (see Fig. 1). The subtle differences between the prenatal environments of identical twins, especially their placentas, might explain why a 100% concordance rate of ASD does not exist for them. Thus, we need to closely examine the prenatal environment of twins.

Prenatal soluble factors

Many soluble factors exist in the prenatal environment that can possibly affect the developing fetus: vitamins, hormones, cytokines, chemicals, alcohol, drugs, medications, etc. A prenatal environment with low levels of vitamin D₃, measured as 25-hydroxyvitamin D₃, was hypothesized to cause ASD.⁴ Recent investigations confirm low maternal 25-hydroxyvitamin D₃ levels during gestation are associated with ASD-related traits in a large population-based sample⁵ and supplementing children with vitamin D₃ improve the signs and symptoms of ASD.⁶ However, although vitamin D₃ treatment is beneficial for improving and possibly preventing some of the symptoms of ASD or even lowering its occurrence, those observations do not prove a causal relationship exists because low 25-hydroxyvitamin D₃ levels are shared between twins in their prenatal environment whether they are identical or not. In fact, any circulating soluble factor like cytokines, medications, alcohol, drugs, or exposure to any chemical in our environment would give a 100% concordance rate

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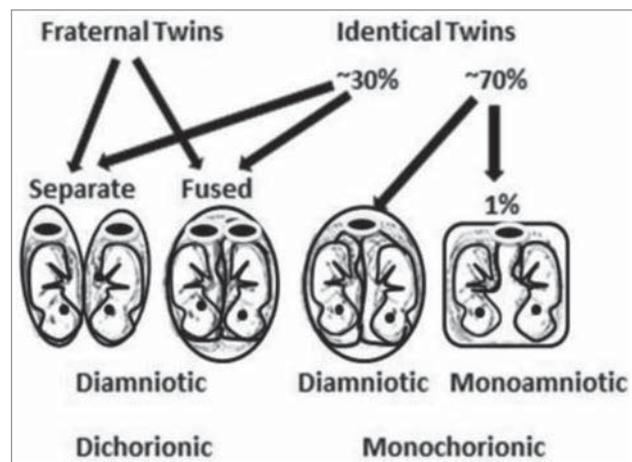


Figure 1. Identical and fraternal twin placenta and amniotic sac possibilities and percent occurrences: shared placentas (monochorionic), separate placentas (dichorionic), shared amniotic sacs (monoamniotic) and separate amniotic sacs (diamniotic). The placenta is represented by an oval with a large dark disc in the middle.

for either identical or fraternal twins, but this is not observed. Thus, something else must be awry that vitamin D₃ somehow differentially affects.

Vitamin D₃ – estrogen, serotonin and immune function

The hormonal form of vitamin D₃, 1, 25-dihydroxyvitamin D₃, affects over 200 genes through the vitamin D₃ receptor,⁷ but more importantly it increases estrogen levels in the placenta⁸ and the brain⁹ and is probably necessary for regulating serotonin production.¹⁰ Estrogen brain levels might help to somewhat explain why males are 4 to 5 times more likely to become autistic than females¹¹ because estrogen is extremely important in brain development.¹² Of note, ASD subjects displayed dysregulation of the estrogen receptor beta, aromatase, and estrogen receptor co-activators in the middle frontal gyrus region of their brains.¹³ Racial disparity supports a causal role for estrogen rather than vitamin D₃ in ASD because African-American blacks have lower vitamin D₃ status than whites¹⁴ but instead of having higher incidences of ASD their incidences are actually lower^{15–17} probably because their male's estrogen levels are significantly higher than white males.¹⁸ Estrogen increases the synthesis of tryptophan hydroxylase-2, the rate-limiting enzyme in the production of serotonin,¹⁹ and vitamin D₃ also increases tryptophan hydroxylase-2.¹⁰ Apparently some of the positive effects of vitamin D₃, or 1, 25-

dihydroxyvitamin D₃, on ASD is its ability to raise both estrogen and serotonin levels during fetal brain development.²⁰

Another important biological function of vitamin D₃ is its ability to activate the mother's immune system,²¹ especially T cells²² that remove infected cells and infectious agents like bacteria and viruses in the mother, especially from her cervix. Thus, if ASD is caused by an infectious agent, boosting the immune system with vitamin D₃ might also help to explain its positive effects.

Infectious placental and cervical diseases

The increase in the incidence of ASD is much faster than that predicted from genetic inheritance or from exposure to environmental pollutants²³ but rather displays characteristics of an infectious disease because it is increasing at an exponential rate in the United States (see Fig. 2, plotted from the data in reference 24) and around the world.²⁴ This infectious disease is probably either a bacterium or a virus.²⁵ We can rule out bacterial infections because they would have been noticed on hematoxylin and eosin stained slides of different tissues and would have produced other health problems. So, if it is an infection, it is most likely a viral infection.²⁶ Human immunodeficiency virus was a candidate over two decades ago that did not pan out²⁷ but co-infections are common so that other viruses should be considered. Evidently, the virus that may cause ASD does not cause any obvious symptoms or it would have been discovered years ago.

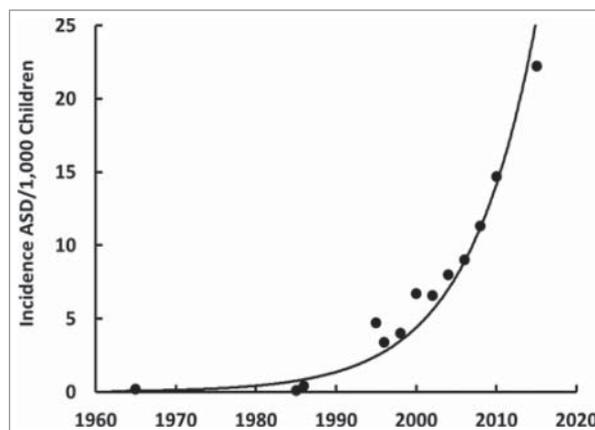


Figure 2. Incidence ASD/1,000 children over time in the United States. Plotted from the data in reference 24. Note that an exponential increase over time for ASD occurs around the world primarily in developed countries.

Which viral infection?

We know viral infections can affect the developing fetal brain from the Zika virus that causes microencephaly. Evidence that ASD might be caused by a virus is obtained from affected children's increased levels of the virally-induced enzyme, alpha-N-acetylgalactosaminidase,²⁸ similar to women with cervical cancer whose enzyme levels are elevated by the Human Papillomavirus (HPV).²⁹

HPV is vertically transmitted from the mother's infected cervix to her placenta and then to her fetus rather than through her blood.^{30,31} Further proof of placental transmission of HPV rather than blood is obtained from the prevalence of HPV DNA, which was found to be considerably lower in newborns (~1.5% or ~1/68) of infected mother's (~30% population of pregnant women).³² Coincidentally, this infection rate matches the incidence of 1 in 68 children with ASD eight years later. HPV is known to infect the trophoblasts of the placenta³³ where inclusions in it have been found to be predictive of ASD.³⁴ Moreover, the discordant rates of identical twins might be explained by the initial location of one of their placentas being juxtapose to the cervix, where HPV infection occurs; a low-lying placenta, which is a fairly common occurrence, moves back up 90% of the time during the second trimester³⁵ and can sometimes take HPV with it. Fraternal twins with only a 31% concordant rate of ASD might be explained by one twin having its placenta in closer proximity to the cervix than the other twin whether or not it moves back up (placenta previa if it remains low). And besides the differences in estrogen levels, the higher male to female ratio of ASD might be explained by the male fetuses' tendency to implant their placentas lower in the uterus during the first trimester, as demonstrated by male fetuses having a higher incidence of placenta previa (the reason is unknown).^{36,37} Twins also have a higher rate of placenta previa than singletons³⁸ and they have a higher rate of ASD as well.^{39,40} Furthermore, cesarean births increase the risk for placenta previa⁴¹ and they also increase the risk for ASD.⁴² Finally, the increase in ASD with increasing age of the mother might be explained by the increasing incidence of placenta previa as women age.⁴³ Thus, timing of HPV infection during pregnancy might be important because HPV probably has to be replicating in the cervix during the first trimester while the placenta

is low-lying in the uterus prior to moving back up;^{44,45} however, if placenta previa occurs or if the infection travels higher into the uterus, then transfer of the infection can occur at any time during pregnancy.

Supporting evidence HPV is the primary infecting agent

Some argue that HPV cannot exist in the brain because it only infects mucosal (alpha genus) or epithelial (beta and gamma genera) cells and those cell types are not present inside the brain. It is true that no mucosal or epithelial cells exist inside the brain, but there is an epithelial lining in the center of the brain known as the choroid plexus that forms the blood-cerebrospinal fluid barrier and is responsible for producing cerebrospinal fluids.⁴⁶ Although the choroid plexus appears to be a small structure, it affects every region of the brain during early embryogenesis and throughout brain development through the production of cerebral fluids;⁴⁷ we now know that every region of the ASD brain is affected to some degree and that there is serious disruption in the central nervous system.⁴⁸ The epithelial cells of the choroid plexus secrete cerebrospinal fluid by unidirectionally transporting sodium, chlorine and bicarbonate from the blood to the ventricles of the brain. The sodium-driven chloride bicarbonate exchanger, or SCL4A10 gene product,⁴⁹ is associated with ASD⁵⁰ and HPV integration into the host genome might lead to duplication of this gene. Disruption in this one gene augments neuronal excitability and synaptic short-term plasticity⁵¹ and might cause complex partial epilepsy and mental retardation.⁵² Although controversial, some studies found HPV in the post-mortem brains of children with focal cortical dysplasia (epilepsy and seizures),⁵³ a condition also associated with ASD.⁵⁴

Curiously, papillomas have been found in the choroid plexus of adults and children^{55,56} and tumors have been found in the choroid plexus in children under the age of 2.⁵⁷ Another curious observation is the fact that about 75% of ASD children have gastrointestinal problems including inflammatory bowel disease⁵⁸ and a single layer of epithelium cells very similar to the choroid plexus with similar functions and immune responses exist in the gastrointestinal tract;⁵⁹ vitamin D₃ reduces the symptoms. Furthermore, inflammation of the brain is a hallmark of ASD and inflammatory cytokines are in the cerebrospinal

fluids of affected children.⁶⁰ Microglia cells are the first line of defense to rid the brain of infections resulting in an inflammatory response⁶¹ and differential M2 activation of microglia cells in ASD brains is driven by type 1 interferon responses to damage caused by viral infections.⁶² This inflammatory response continues throughout the lifetime of an ASD individual, probably caused by HPV continually producing virions, and this inflammation might be reduced by vitamin D3.⁶³ Recently, the MRIs of children's brains at 6 or 12 months of age that showed abnormal amounts of cerebrospinal fluid displayed ASD traits at 2 yrs. of age; the more cerebrospinal fluid present, the worse the ASD symptoms were later in life.⁶⁴

Similarities between Cancer and ASD?

If HPV is involved in ASD, we would expect to see many biochemical similarities between cancer and ASD – and we do!⁶⁵ Most importantly, both cancer and ASD share disruptions in the PI3K-Akt-mTOR signaling pathway involving PTEN, FMR1, NF1, TSC1 and TSC2, and both share signal transduction pathways, chromatin remodeling and transcription factors. What is most amazing and specific for HPV in cancer is its E6 activation of mTORC1 signaling⁶⁶ and, coincidentally, mTORC1 and PTEN are also associated with ASD.⁶⁷ The mTOR protein is a serine/threonine kinase involved in brain development mediating signaling pathways crucial for neuronal and glial differentiation and maintenance of the stemness of neural stem cells; abnormalities in its function are associated with ASD, seizures, pediatric brain tumors, learning disabilities, and mental retardation.⁶⁸ Another shared gene between ASD and HPV-induced cancers is UBE3A, which encodes the ubiquitin E3 ligase, E6-AP that degrades p53 and other proteins.^{69,70} If HPV is involved in ASD, we would expect to see a higher incidence of cancers in this population – and we do!^{71,72}

Note here that HPV-16 or –18 might not be the strains that cause ASD; it could be HPV-11 or HPV-58, or one or more, or possibly all of the other 200+ available strains.⁷³ Alternatively, it might be another sexually transmitted infection of the cervix.⁷⁴ Other viruses and infections such as influenza, rubella, cytomegalovirus, parvovirus, Lyme's disease or toxoplasma gondii infection have sometimes been implicated in ASD. However, no correlation between

any viral, bacterial, or parasitic infections could consistently be reliably made with ASD and appeared to be coincidental occurrences; whereas, HPV infection has never been explored probably because it is thought to only cause cancers. And the fact that HPV has been found in adult brain tumors such as glioblastoma multiforme⁷⁵ without any ASD symptoms can be explained by the mode of transmission; the adult becomes infected with HPV via sexual transmission after their brain has developed rather than the fetus that becomes infected with HPV via placentas while their brain is developing. Finally, HPV has also been found in neurons.⁷⁶ Thus, although other infections may sometimes be associated with ASD, HPV appears to be the primary infectious agent.

Do HPV's biochemical and epigenetic fingerprints match ASD's fingerprints?

We can obtain evidence that HPV is a risk factor for ASD by looking at its incidence rate, and characteristic biochemical and epigenetic fingerprints. Unlike other sexually contagious diseases, the incidence of HPV infection has been exponentially increasing in the United States (Fig. 3)⁷⁷ like ASD (Fig. 2).²⁴ Meanwhile, vitamin D₃ status has been dramatically decreasing over the last five decades, as shown by the inversely-related parathyroid hormone levels that have decreased nearly ten-fold during the same period.⁷⁸ Vitamin D₃ is important for proper immune function,⁷⁹ especially enabling activated T cells to eliminate virally infected cells²² and to clear viral infections.⁸⁰ Vitamin D₃ also decreases leptin levels⁸¹ that were

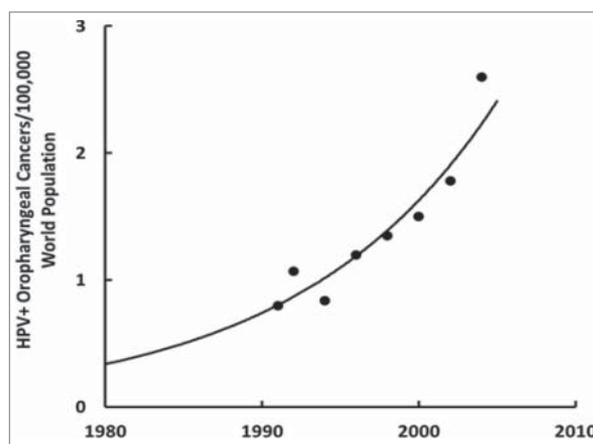


Figure 3. Incidence HPV+ oropharyngeal cancers/100,000 world population over time in the United States. Plotted from the data in reference 77.

found to be higher in ASD children⁸² and older women who have a persistent HPV infection.⁸³ HPV causes preeclampsia, or high blood pressure, in pregnant women⁸⁴ and so does ASD.⁸⁵ Furthermore, ASD children's brains have downregulated estrogen receptor beta in their middle frontal gyrus region¹³ where sexual dimorphisms have been observed¹⁸⁶ and HPV can downregulate estrogen receptor beta,⁸⁷ which in turn can downregulate the vitamin D₃ receptor.⁸⁸ And among the multitudes of HPV's genomic integration sites, one happens to be at 12q13-15⁸⁹ where the vitamin D₃ receptor gene is located;⁹⁰ integration might decrease or annihilate its function. The fact that African-American blacks have lower vitamin D₃ status¹⁴ while they have a higher prevalence of HPV⁹¹ but lower incidences of ASD¹⁵⁻¹⁷ might be explained by their males having significantly higher estrogen levels than white males.¹⁸

Genetic or epigenetic component?

For the most part, ASD cannot be inherited or caused by sporadic genetic mutations because it is increasing at an exponential rate indicating it has a contagious epidemic aspect (Fig. 2); the belief that ASD's exponential increase is due to over diagnosis was laid to rest more than a decade ago by the CHARGE study.⁹² Arguments that epigenetics plays a major role in ASD have been escalating over recent years⁹³ – with little evidence that ASD might begin with a sexually transmitted disease – except noted in the very religious and somewhat isolated Amish community by having a low ASD rate of 1 in 271 children compared with the overall United States having a high ASD rate of 1 in 91 children in 2009.⁹⁴ Because identical twins were 88% and fraternal twins were only 31% concordant for ASD along with an increased rate (10–20 times higher) over the general population's recurrence in siblings,¹ investigators thought ASD was a 'highly' inheritable, genetic disease. As a result, over 800 different predisposition genes have been identified so far with little consensus; these genes are involved in a multitude of different functions: chromatin remodeling, gene transcription regulation, cell growth and proliferation, ubiquitination, and neuronal-specific processes like synaptic activity and organization, dendritic morphology, and axonogenesis.⁹⁵ In addition, copy number variants have been implicated in ASD⁵⁰ but once again like the different infections noted in

some cases of ASD, they were not found to be universal.⁹⁶ Logic dictates that for identical twins to be ~12% discordant in ASD very few genes can be involved in its etiology due to the rare frequency of functional mutations. Some consensus has been reached on a few genetic loci that appear to be recurrently duplicated or deleted such as chromosomal regions 15q11-q13, 16p11 and 22q11; note that region 15q11-q13 encodes for UBE3A, the ubiquitin E3 ligase, E6-AP that degrades p53 and other proteins and is duplicated in ASD⁹⁷ possibly from viral intervention.

The fact that few genes are consistently changed but many genes appear to be involved might be explained by epigenetic events influencing multitudes of genetic pathways, which can make ASD appear to be genetic when it is not.⁹⁸ DNA methylation patterns, long non-coding RNAs and microRNAs^{99,100} combined with the persistence of HPV infection might make ASD appear to be genetic because so many genes are affected. In addition, some mothers are not able to clear the virus before having another child, so that reoccurrence in siblings also makes ASD appear to be genetic. Over half the women were still infected with HPV after 2 years,¹⁰¹ which might explain why the spacing between pregnancies of 1 year is 3 times riskier for having a second baby with ASD than 3 years.² Moreover, DNA methylation is significantly different between identical twins discordant for ASD,¹⁰² and is aberrant in cervical¹⁰³ and only in HPV+ not HPV-oropharyngeal cancers.¹⁰⁴ Another deceiving genetic connection is HPV integrating into the host genome at multiple sites (>190), mapped from cervical cancers,¹⁰⁵⁻¹⁰⁷ but note that the integration sites in ASD might differ somewhat from cervical cancer or could be caused by another strain of HPV other than 16 or 18. Integration can result in deletion or duplication of a section of the DNA and considerable genomic instability¹⁰⁸ similar to what is observed in ASD.¹⁰⁹ Besides epigenetic events leading to aberrant gene expression in ASD, some of the point mutations observed might be due to methylation of cytosines leading to deamination that result in transition mutations.¹¹⁰ Finally, because HPV is sometimes found in sperm¹¹¹ but is usually transmitted vertically from the mother's placenta,¹¹² ASD can appear to be genetically transferred when it is not.

Epigenetic fingerprints of ASD and HPV might appear to be smudged sometimes because ASD and

cancer researchers each concentrate on searching for endpoints related to their particular disease, so that they miss the relevant endpoints in each other's diseases; when they both might be looking at opposite sides of the same coin.

HPV strains found in cervical smears

The highest occurring strains of HPV in the uterine cervix associated with developing cervical carcinomas and precancerous lesions from the highest to lowest occurrence are HPV-16, -58, -18, -52, and -56 followed by the low risk strains.¹¹³ This was determined by a PCR-based DNA chip microarray detection method of cervical smears that can assess 22 different strains of HPV including 15 from the high-risk group, HPV-16, -18, -31, -33, -35, -39, -45, -51, -52, -56, -58, -59, -66, -68, -69 and 7 from the low-risk group, HPV-6, -11, -34, -40, -42, -43, -44.¹¹³ It is important to note once again that these strains of HPV are the high- and low-risk groups for cervical cancers and that they might not reflect the same risk for ASD. In addition, multiple strains of HPV might be required to produce ASD. Because Papanicolaou (Pap) smears only detect cancerous cells – not the presence of HPV¹¹⁴ – this PCR method or another HPV detection method should be used in combination with a second, different HPV detection method for confirmation^{115,116} during routine cervical exams. Be aware that other PCR-based methods sometimes detected HPV when this PCR-based microarray chip method did not, which is probably due to differences in their sensitivities.

This difference in sensitivities between detection methods points out how important it is to use multiple detection methods and approaches to find and confirm the existence of HPV, and to use broad spectrum probes before searching for specific strains. Furthermore, amplification of the signal is best because HPV might be missed due to a weak signal.¹¹⁷ Alternatively, HPV might be missed due to the timing of infection or when some observations are performed, which might be critical because HPV can cause opposite biological effects during different phases of its life cycle. For example, in the beginning, HPV uses estrogen and its receptors to make more E6 and E7 proteins, but towards the end of its life cycle, in differentiated cells (and possibly third trimester fetuses), it downregulates estrogen and its receptors¹¹⁸ and increases p16 when

it makes capsid proteins L1 and L2. Thus, it is best to cover both ends of HPV's life cycle.

Treatment and prevention options

If HPV is found guilty for being the contributing factor in ASD, the future incidence and current symptoms might be reduced by increasing both the mother's and child's 25-hydroxyvitamin D3 levels to at least 50 ng/mL using adequate amounts of vitamin D3^{119, 120, 121} to raise estrogen and serotonin levels, decrease leptin levels and inflammation, and improve brain function¹²² of the fetuses and children, while clearing existing HPV infections in the mother and children over 18 months of age. In addition, increasing estrogen and tryptophan (for serotonin synthesis) levels might help the brain to develop better. And recently new treatments for ASD target inhibiting the mTOR pathway;¹²³ Rapamycin shows promise for treating ASD¹²⁴ and coincidentally it is also being used to improve clearance during treatment of HPV-positive head and neck cancers.¹²⁵ More importantly, vaccinating mothers prior to and even during pregnancy (found to be safe and provides passive immunity to the neonate and infant)¹²⁶ and giving at least two doses of the nine-valent HPV vaccine to ASD children (over 18 months old when they have a competent immune system) might boost their immune systems to clear HPV and help improve the symptoms in some ASD cases, because the quadrivalent vaccine was found to decrease or eliminate the occurrence of oral and genital warts.^{127,128} However, these current HPV vaccines might not completely protect against the strain(s) of HPV that cause the entire spectrum of autism so that another or other vaccines might have to be developed. For example, along with HPV-16 and -18, HPV-38 has been found in melanomas and are implicated in its etiology.¹²⁹⁻¹³¹ Most importantly, note that the cervical Pap smears only detect cancerous cells and not the presence of HPV, so that it would be wise to include a broad-spectrum HPV test along with routine Pap smears in the future, especially for women who intend to get pregnant or who already are pregnant.

Conclusions

The fact that identical twins, who share identical DNA, do not have 100% concordance rates shows genetics plays a minor role (excluding epigenetic events) and some environmental factor that differs between twins plays a major role in ASD. Because identical twins only share

their placentas about 70% of the time and their concordance rates are only ~88%, an environmental factor probably plays its role through the placenta. Low levels of 25-hydroxyvitamin D₃, or any other soluble factor, cannot be the cause of ASD because if it were, then all twins, identical or not, would be affected but they are not. Thus, the cause of ASD has to be something that vitamin D₃ affects in the environment of the placenta. Based on observations of placenta inclusions, predictive of ASD and indicative of an infection, we proceeded to untangle the major role vitamin D₃ plays in ASD and found it is probably to clear the viral infection that a low-lying placenta picked up from the cervix. The most probable viral infection is HPV because it is the only cervical infection that is increasing at an exponential rate around the world like ASD. HPV can exist in the epithelial lining in the center of the brain known as the choroid plexus that forms the blood-cerebrospinal fluid barrier. The choroid plexus secretes cerebrospinal fluid by unidirectionally transporting sodium, chlorine and bicarbonate from the blood to the ventricles of the brain via the sodium-driven chloride bicarbonate exchanger, or SCL4A10 gene product, which is associated with ASD;⁵⁰ HPV integration into the host genome might lead to duplication of this gene and elimination or disruption of the vitamin D₃ receptor gene. More supporting evidence HPV is involved in ASD is obtained from the epigenetic fingerprints of HPV that match those of ASD, which also makes it appear to be of genetic origin when it is not. The roles of vitamin D₃ in ASD include increasing the brain's estrogen and serotonin levels while decreasing inflammation via decreasing inflammatory cytokines produced by activated microglia cells¹³² and reducing leptin levels. The untangled major role for vitamin D₃ in ASD and most cancers¹³³ is its ability to regulate 291 genes and boost the immune system¹³⁴ in order to clear HPV and other viral infections.

Conflict of interest statement

The authors declare no conflict of interest.

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Author contributions

DEG planned the study, analyzed the data in the literature, and was the primary author. SJM contributed to the scientific discussions and revising the final version.

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