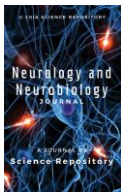

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Review Article

Overwhelming Evidence Transplacental Transmission of Human Papillomavirus Primarily Causes Autism

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ABSTRACT

Because the concordance rate between identical twins is only 88%, an environmental factor must cause autism spectrum disorder (ASD). Furthermore, when identical twins share ASD, it is to varying degrees suggesting different prenatal environments exist, which occurs when identical twins have separate placentas (~30% of the time). Placental inclusions are predictive of ASD along with excessive increases in extra-axial cerebral spinal fluid (CSF) detected by MRI in the brains of 6- and 12-month-old infants later diagnosed at 2 years with ASD. The human papillomavirus (HPV) can infect the trophoblast cells of placentas and transmit to the fetus where it infects the epithelial cells of the choroid plexus, a centrally located lining inside the brain responsible for producing CSF via the *SLC4A10* gene product. HPV causes epigenetic changes, deletions, and duplications of genes, and besides its characteristic methylation patterns, the *SLC4A10* gene was found to be increased in children with ASD. Moreover, male placentas implant close to the cervix (low-lying) three times more often than female placentas paralleling the ASD ratio of ~3:1 (boys to girls). Finally, the Australian HPV vaccination programme that began in 2007 might explain why the 0-4 yr. ASD incidence did not increase from 2010 to 2015.

Introduction

Autism spectrum disorder (ASD) encompasses a wide range of neurological developmental conditions usually characterized by insufficiencies in social interactions and communication abilities. Everything from genetics (including epigenetic changes, copy number variants, somatic mutations, and polymorphisms) to environmental exposures (including low vitamin D levels, vaccinations, chemicals, medications, drugs, and cytokines) and combinations of both have been frantically investigated in a desperate attempt to stop the alarming rate increase. The alarming rate increase was blamed on enhanced public awareness and changes in diagnostic criteria, but the rate of increase in the ASD incidences around the world over the past few decades were shown to be real by the CHARGE study [1, 2]. The rate varies in developed countries around the world from 1 in 27 in Hong Kong to 1 in 3,333 in Poland, and in the United States (U.S.) it may have been as high as 1 in 45 in 2017 [3, 4]. ASD is pandemic and thought to be genetic in origin, but because it increased at exponential rates in all races around the world in recent decades suggests it is primarily due to an environmental factor like a contagious disease.

I Environment Versus Genetics

The best evidence an environmental factor causes ASD is provided by identical twin studies. Identical twins share identical genetics, but they have less than a 100% concordance rate (both have it) for ASD. We expect pairwise concordance rates of 100% for identical twins if ASD is a genetic disorder, but only an 88% pairwise concordance rate exists between identical twins and a 31% pairwise concordance rate exists between non-identical or fraternal twins as shown by a large twin study involving 277 twin pairs [5]. Another study of 366 identical twin pairs demonstrated the proband concordance rate for ASD was as high as ~96%, but the similarity of shared symptoms was low; the authors concluded some non-shared environmental factor during early development caused the broad range of genetic and behavioural differences observed between identical twins [6]. If the etiology of ASD

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was genetic, the concordance rate between identical twins would be 100% and their symptoms would also be 100% identical, but they are not showing ASD is caused by an environmental factor. Twin data including non-identical twins with concordance rates ~31% shows blood-borne substances like alcohol, medications, cytokines, infections, or low prenatal vitamin D levels cannot be the primary cause of ASD because all twins - identical or not - would share that exposure equally and would have a 100% concordance rate and the same degree of symptoms, but this is not the case [7].

Blood-borne viruses like HIV, Herpes simplex virus, cytomegalovirus, and Epstein Barr Virus can infect the mother but cannot be the primary cause of ASD because both non-identical and identical twins would have a 100% concordance rate for those viruses [8-10]. Some infections in utero are associated with an increased risk for ASD and would cause both twins to be concordant, but these types of infections do not explain the discordant rates of ASD between identical twins [11]. The primary cause of ASD must explain why the concordance rate of ASD is less than 100% for identical twins who have identical DNA. The prenatal environment of identical twins is only the same 70% of the time when they share the same placenta (monochorionic); identical twin prenatal environments are different 30% of the time when they have separate placentas and non-identical twins' prenatal environment is always different because they always have separate placentas (dichorionic) [12].

When the placenta implants close to a contaminated cervix, it can become infected with HPV and transmit it to the fetus [13, 14]. Placentas can implant near the cervix (low-lying), but they usually move upward in the uterus during the second or third trimester. Of the low-lying placentas, about 90% clear the cervix area by 32 weeks and about 96% clear the cervix by 36 weeks circumventing placenta previa [15, 16]. Identical twins will be concordant for ASD only if either their shared placenta (70%) is located near the infected cervix and both twins become infected to the same degree with similar symptoms (top of Figure 1) or both non-shared placentas (30%) are near the infected cervix but one is closer to it than the other and becomes more infected than the other with increased ASD symptoms (bottom of Figure 1). The identical twins will be discordant for ASD if only one placenta is near the infected cervix while the other is not (middle of Figure 1). For non-identical twins to be concordant for ASD, both placentas must be close to the infected cervix (top of Figure 2), because if only one placenta is close to the infected cervix, they will be discordant for ASD (bottom of Figure 2). The probability of both identical twin placentas locating close to the cervix is estimated from the non-identical twin concordance rate of 31% [5]. The total concordance rate can be estimated for identical twins by multiplying 31% (probability of both placentas locating near the cervix) by 30% (non-shared placentas) which gives about 10% that is added to 70% (shared placentas locating near the cervix) for an estimated 80% pairwise concordance rate. That is within 10% of the observed 88% concordance rate for identical twins [5] which is acceptable because some smaller studies found lower concordance rates for identical twins. And the fact that males tend to have low-lying placentas three times more often than females, demonstrated by their placenta previa rates, matches the averaged worldwide ratio of boys to girls with ASD (~3:1) [4, 17, 18].

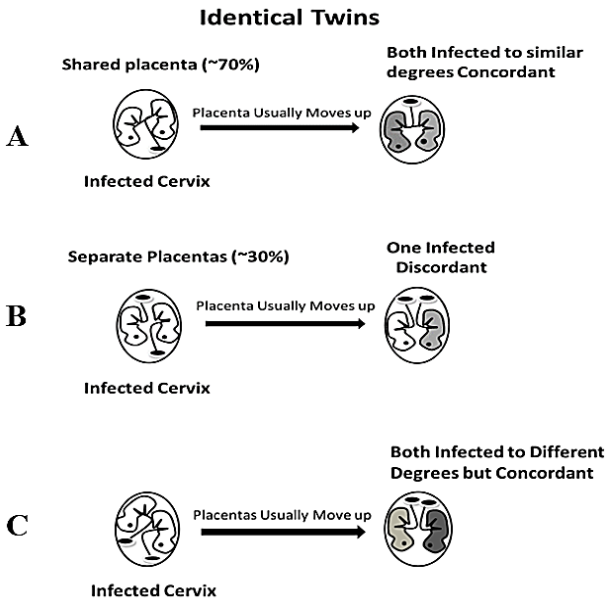

Figure 1: Identical twins have three scenarios for placentas: **A)** 70% shared placentas – concordant, **B)** 30% non-shared or separate placentas and only one is low in the uterus – discordant, and **C)** both separate placentas are low in the uterus and can be infected to different degrees – concordant.

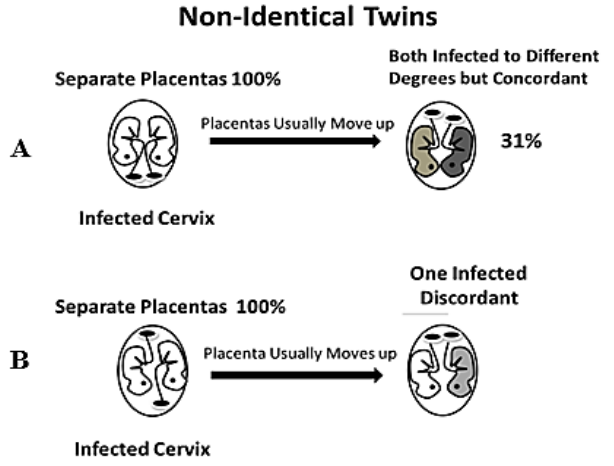

Figure 2: Non-identical twins never share a placenta so they only have two scenarios: **A)** Both placentas are low in the uterus and can be infected to different degrees – concordant (31%), and **B)** only one placenta is low in the uterus – discordant.

The most prevalent pandemic cervical infection is the human papillomavirus (HPV) [19]. The exponential increase in the incidence of HPV+ oropharyngeal cancers in the U.S. (Figure 3A) parallels the exponential increase in ASD in the U.S. (Figure 3B) during the same time frame, and in Europe (Sweden) the HPV+ oropharyngeal cancers (Figure 4A) also parallel the exponential increase in ASD (Figure 4B) [20, 21]. Clinicians find HPV in the trophoblast cells of placentas that can transmit HPV to the fetus [13, 14, 22, 23]. Trophoblast inclusions are predictive of ASD and placental abnormalities and preterm births are major risk factors for ASD [24, 25]. Unfortunately, clinicians have not yet tested for HPV in the trophoblast cells with inclusions, but HPV is

known to cause placental abnormalities, preterm births, low birth weights, and spontaneous abortions [26, 27]. The severity of ASD symptoms might depend on the viral load due to the location of the placenta, i.e., how close the placenta embeds near the contaminated cervix, the timing of infection (first trimester or longer), the strain(s) of HPV (e.g., -6, -16, -52, -90, etc.), or some or all of those factors combined which might explain why a broad spectrum of autistic symptoms exists.

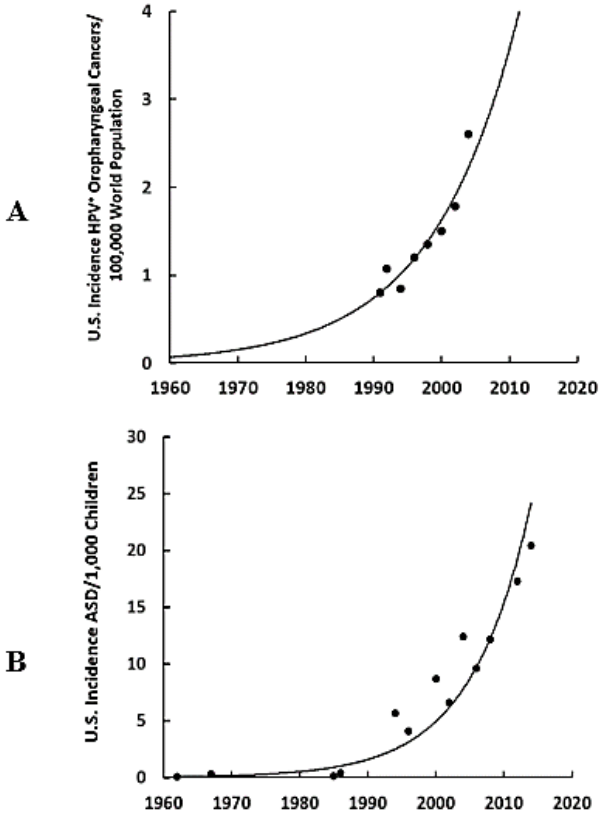

Figure 3: A) Temporal incidence in the U.S. of HPV+ oropharyngeal cancers per 100,000 world population, **B)** Temporal incidence in the U.S. of ASD per 1,000 children. Note that if more than one study existed, the ASD incidences were averaged [21].

II Worldwide Prevalence of Cervical HPV Infection, ASD, and Placenta Previa

The prevalence of HPV infection varies by the mother's age, continent, and region [28]. Older women have a much lower HPV prevalence than younger women of child-bearing age. The continent of Africa (21.1%) had the highest HPV prevalence followed by Europe (14.2%), and North and South America (11.5%; including the regions of Canada, U.S., Greenland, Central and South Americas, and the Caribbean islands), and Asia (9.4%); while Australia was excluded because they have an ongoing HPV vaccination programme. The order of HPV prevalence is Africa (21.1%)> Europe (14.2%) > Americas (11.5%) [N. America (4.7%)] >Asia (9.4%).

The order of HPV prevalence does not parallel the order of ASD prevalence found around the world [3]. The ASD rate in Africa was not determined, but in Europe the rate was about 0.681%. The South American, Central American, and Greenland ASD rates were not determined, but they were determined in the U.S. as 1 in 45 (2.22%) and in Canada as 1 in 94 (1.06%). The ASD rate in North America cannot be calculated because the rate was not determined in Greenland but if it is assumed to be similar to Europe's rate (0.681%), North America would be about 1.32%. The ASD rates were only determined in eastern Asia at 1 in 38 (2.63%) in South Korea, 1 in 55 (1.82%) in Japan, and 1 in 435 (0.23%) in China for an average of 1.56%. The order for ASD prevalence is Asia (~1.56%) > N. America (~1.32%) > Europe (~0.681%, excluding southern regions) which is the opposite order of HPV prevalence in similar regions of the world.

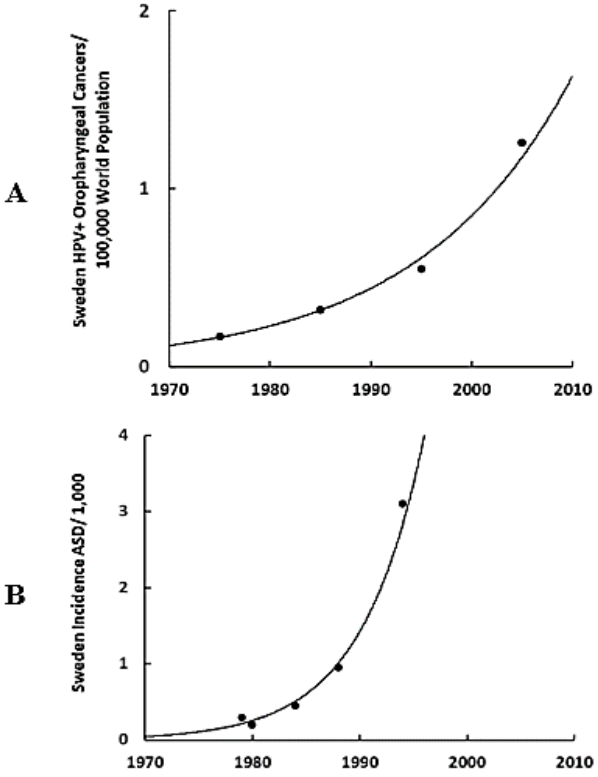

Figure 4: A) Temporal incidence in Europe (Sweden) of HPV+ oropharyngeal cancers per 100,000 world population, **B)** Temporal incidence in Europe (Sweden) of ASD per 1,000 children.

But cervical HPV infection does not predict the rate of ASD, because the placenta cannot get infected unless it is located near the cervix. Thus, placenta previa rates would be the best predictors of ASD because they reflect the rate of placentas implanting low in the uterus where they can become infected by HPV. Up to 30% of placentas can be low-lying in the uterus prior to 6 months gestation but sometime before delivery 90% move higher up in the uterus avoiding placenta previa [29, 30]. The placenta previa rates were found to be the highest in Asia (12.2 per 1000 pregnancies) followed by Europe (3.6 per 1000 pregnancies) and North America (2.9 per 1000 pregnancies) with the lowest rates in Sub-Saharan Africa (2.7 per 1000 pregnancies) [31]. The region of the world can reflect contributions towards placenta previa rates from genetics (race/ethnicity) or something in the environment (e.g., water, food, or chemical exposures). A study in northern California involving different races living in the same location shows genetics plays the largest role in

placenta previa rates [32]. The placenta previa rates correlate well with the ASD rates as the Asians have the highest placenta previa rates of all the races and also have the highest ASD rates in the world, e.g., Hong Kong (1 in 27 or 3.7%), South Korea (1 in 38 or 2.63%), and Japan (1 in 55 or 1.82%). The placenta previa rates parallel the ASD rates: Asians (0.64%) > Native Americans (0.6%) > African Americans (0.44%) > Caucasians (0.36%) > Hispanics (0.34%).

III Can HPV Infect the Brain?

HPV was found in neurons and in the post-mortem brains of children who had focal cortical dysplasia type IIB (epilepsy and seizures), which is also sometimes associated with ASD [33-36]. Of the five HPV genera (alpha, beta, gamma, mu, and nu), two genera (beta and gamma) can infect epithelial cells [37]. The choroid plexus, which is a centrally located lining inside the brain that produces cerebral spinal fluid (CSF), is comprised of epithelial cells that have the sodium-driven chloride bicarbonate exchanger, *SLC4A10* gene product, required for CSF production [38, 39]. CSF is secreted when *SCL4A10* unidirectionally transports sodium, chlorine, and bicarbonate from the blood to the ventricles of the brain. *SLC4A10* disruption enhances neuronal excitability, modifies synaptic short-term plasticity, and is sometimes associated with complex partial epilepsy and mental retardation [40, 41]. Most importantly, increases in extra-axial CSF at 6 and 12 months of age observed in brain ventricles by MRI were predictive of infants who developed ASD at 2 yrs. of age, and increasing amounts of CSF correlated with increasing severity of ASD symptoms [42]. An increased copy number of the *SLC4A10* gene is associated with ASD and integration of HPV into the genome results in duplications and deletions of genes [43, 44]. More scientific evidence that HPV causes problems in the brain is obtained from the papillomas and tumors of the choroid plexus found in children younger than 2 [45, 46]. The *E6* and *E7* oncogene proteins of HPV caused tumors in the choroid plexus of transgenic mice [38]. Further, neuroinflammation is a hallmark of ASD and can be caused by activation of the neuroglial cells that remove infections in the brain [47, 48]. Moreover, the gut is similar to the choroid plexus, having similar immune functions and a single layer of epithelial cells that HPV can infect [49]. In fact, 75% of ASD children have gastrointestinal diseases like inflammatory bowel disease [50].

IV Evidence of Biochemical and Epigenetic Fingerprints of HPV in ASD Children

Because HPV is involved in cancer, we would expect to find biochemical similarities between ASD and cancer, and indeed they exist (see Table 1 for the following discussion) [51-53]. Both ASD and cancer have disruptions in the PI3K-Akt-mTOR signaling pathway; mTOR serine/threonine kinase mediates signaling pathways required for glial and neuronal differentiation in brain development. mTORC1 signaling is disrupted in ASD and occurs in pediatric brain tumors, seizures, learning disabilities, and mental retardation [54]. mTOR signaling is activated through PTEN in children with ASD and the E6 protein of HPV activates mTORC1 signaling [55, 56]. Clinicians use Rapamycin, which inhibits the mTORC1 pathway, to treat both ASD and cancer [57-59]. More biochemical evidence is obtained from the *UBE3A* gene that encodes the ubiquitin E3 ligase, E6-A, which degrades *p53* (the Guardian of the Genome) and is associated with both ASD and HPV [60, 61].

Table 1: Endpoints in common between HPV and ASD.

Endpoint	HPV	ASD
Placental Inclusions	HPV not tested but viral infections are known to cause inclusions [85]	Predictive of ASD [24]
mTOR	E6 protein activates mTORC1 [56] (Rapamycin used medically to inhibit [59])	mTOR activated [55] (Rapamycin used medically to inhibit [57, 58])
UBE3A	Duplicates gene that degrades *p53* [61] causing genomic instability in cervical cancer [74]	Gene is duplicated in ASD [60, 62] causing genomic instability [75] and cancers
SLC4A10	Duplicates gene [44]	Duplicated gene [62] increases CSF in brain recently related to ASD [42]
Cancer	Causes several types of cancers (including children's choroid plexus brain tumors [46] and papillomas [45])	Increased incidence of cancers in the ASD population [63, 64]
Preeclampsia	Infection increases blood pressure of pregnant women [66]	A known risk factor for ASD [65]
DNA Methylation/ genomic instability	Abnormal in cervical and only HPV+ oropharyngeal cancers [71, 72]/ genomic instability [74]	Identical twins discordant for DNA methylation [70]/genomic instability [75]

UBE3A is another consistently duplicated gene in ASD besides *SLC4A10* [62]. Further evidence HPV probably causes ASD is obtained from significantly higher incidences of cancer in the ASD population [63, 64]. Moreover, preeclampsia (high blood pressure) in associated with pregnant women who had an ASD child and an almost 2-fold increase in the risk for developing preeclampsia exists for mothers with HPV infection [65, 66]. Finally, ASD children all had lower vitamin D3 levels, which were only lower in the discordant identical twin who had ASD even though both twins had similar diets and sun exposures [67]. HPV may decrease vitamin D levels by increasing the production of the enzyme alpha-N-acetylgalactosaminidase that was found to be elevated in ASD children [68]. Alpha-N-acetylgalactosaminidase cleaves the sugar moiety from the vitamin D binding protein so that it can no longer bind to and transport vitamin D into the bloodstream. Another detrimental effect of cleaving off the sugar moiety is losing enzymatic conversion to the macrophage-activating factor, which results in suppression of the innate immune response. Vitamin D is also required for T-cell activation and antigen receptor signaling, so that low levels suppress the adaptive immune response as well [69]. Increasing that enzyme, results in suppression of both the innate and adaptive immune responses allowing HPV to escape immune surveillance.

Epigenetic events like DNA methylation of promoters, duplications and deletions of genes, and point mutations can make ASD appear to be

genetic disguising the environmental factor involved. Decreases or increases in the production of gene products occurs when promotors are either hypomethylated or hypermethylated. An abnormal DNA methylation pattern is only found in the identical twin with ASD - not in the discordant twin– and an abnormal DNA methylation pattern is also found in cervical cancer and only in HPV positive not negative oropharyngeal cancers [70-72]. Over 190 sites in the host genome can allow HPV integration that results in duplications and deletions of genes resulting in genomic instability observed in cervical cancers and in ASD [73-75]. Some point mutations found in ASD might be from deamination of methylated cytosines in CpHpG sites (where H = A, C or T) [76].

Another potential genetic indicator was thought to be the higher occurrence of ASD between siblings, but over half the infected women could not clear HPV for 2 years so that another pregnancy during that time could also yield a child with ASD [77]. One year between pregnancies was found to be three times riskier than 3 years between pregnancies for having a second child with ASD [78]. If ASD had a genetic origin, the time between sibling births would not matter. In addition to short spacing times between sibling births (<2 yrs.), long spacing times (>6 yrs.) also increased the risk for having a child with ASD; however, that could be due either to reinfection or to the mother becoming immunosuppressed and HPV becoming reactivated [79, 80]. Vitamin D3 deficiency (and insufficiency) is one way to cause immunosuppression and reactivate HPV [81]. Additionally, gestational vitamin D deficiency and neonatal or combined maternal and neonatal insufficient levels of vitamin D also represent an increased risk for ASD [7, 82].

V Prevention

The best strategy to prevent ASD is for people, especially women, to get HPV vaccinated (3 shots) prior to and even during pregnancy, which was found to be safe, because the mother can supply passive immunity to the neonate and infant [83]. Australia began a free school HPV vaccination programme (quadrivalent HPV-6, -11, -16, -18) for 12-13 yr. girls in 2007 that was extended to boys in 2013. Vaccinated 12–13-year-old girls in 2007 were of child-bearing age in 2015 (20-21 yr.) and some had children 4 yrs. old or younger and an Australian study found no increase in the incidence of ASD from 2010 to 2015 for the 0-4 yr. age group [18]. Besides HPV vaccination, people and children should also increase their vitamin D3 to sufficient blood levels (≥50 nmol/L) to boost their innate and adaptive immune responses and improve their brain health [84].

Conflicts of Interest

None.

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Disclosure

The findings and conclusions in this paper have not been formally disseminated by the Food and Drug Administration and should not be construed to represent any agency determination or policy. The mention of commercial products, their sources, or their use in connection with material reported herein is not to be construed as either an actual or implied endorsement of such products by Department of Health and Human Services.

Abbreviation

ASD: Autism Spectrum Disorder
CSF: Cerebral Spinal Fluid
HPV: Human Papillomavirus
U.S.: United States

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