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News, views and comments

Role of Twins in Waardenburg Syndrome: 1916 – present/Twin Research Reviews: MZ Twins' Different Dermatoglyphics; Twins with Sagittal Suture Crainosynostosis; Blood Pressure in Female Twins; MZ Twins' Education and Political Knowledge/Media Reports: Twins Created by Reciprocal In Vitro Fertilization; Reared-Apart Triplets' Limited TV Series; Abducted Twin Infants; Winkelvoss Twins Charged by the Securities and Exchange Commission; Going From 'Me' to 'We'

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Abstract

Waardenburg's syndrome involves deafness accompanied by various visual difficulties. The role of twins in identifying this disorder and advancing understanding of its origins and symptoms is described, beginning in 1916 and continuing to the present. This overview is followed by current research on monozygotic (MZ) twins' different dermatoglyphic features, twins with sagittal suture crainosynostosis, blood pressure in female twins, and MZ twins' education and political knowledge. The final section presents media reports describing controversies surrounding twins created by reciprocal in vitro fertilization, reared-apart triplets' limited TV series, abducted twin infants, the Winkelvoss twins' charges by the Securities and Exchange Commission, and going from 'Me' to 'We'.

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Role of Twins in Waardenburg Syndrome: 1916 – present

When I began studying twins, I came across the work of Dr Petrus Johannes Waardenburg for whom the Waardenburg syndrome has been named. I believe I remembered him largely because he was the father of identical twin daughters. My memory served me well because he was indeed the father of twins. According to the author of his obituary, his twins 'were obviously a great joy to his inquiring mind and enabled him to conduct twin studies on the spot' (Williamson, 1980, p. 224). Other twin researchers have also entered the field because of their personal interest in twinning as a phenomenon, as well as its scientific fascination and significance (Tarnoki et al., 2022).

The twin research contributions of historical figures are important to recall, so I chose to review the life and work of Dr Waardenburg. First, a brief background on the syndrome.

Waardenburg syndrome is a cluster of genetic conditions variously involving hearing loss (e.g., one or both ears), atypical visual characteristics (e.g., eyes of different colors), and distinctive hair features (e.g., hair patches that prematurely turn white or gray). It affects an estimated 1/40,000 people, explaining 2–5% of cases involving congenital hearing loss (MedlinePlus, 2022). The condition was first described by van der Hoeve, in 1916, who observed it in both members of a pair of 14-year-old monozygotic (MZ) female twins; eventually, the condition came to be known as the van der Hoeve-Halbertsma-Waardenburg-Klein syndrome. However, Waardenburg was responsible for associating the congenital deafness with the pigmentary defects of the iris and hair (Williamson, 1980), possibly explaining why the syndrome currently bears his name alone.

Career

Waardenburg enjoyed a career rich in clinical studies, professional accomplishments and scholarly awards. Born in Arnhem, the Netherlands, in 1886, he studied medicine, specialized in ophthalmology, and received his medical degree in 1913. He practiced medicine in Arnhem until 1952, but also served as medical lecturer at the Rijksuniversiteit in Utrecht, secretary of the Netherlands Opthalmological Society, and president of the Netherlands Anthropogenetic Society. In addition, he became an honorary member of several universities, and was awarded the Royal Decoration Order of the Dutch Lion and the Snellen medal; Waardenburg had studied ophthalmology under Professor Snellen in Utrecht. In 1965 he founded the Waardenburg prize

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for research in medical genetics. Waardenburg's scholarship is complemented by his talents as a painter and musician (Williamson, 1980).

Dr Waardenburg passed away in 1979 at age 93, but remained active in research into his late eighties. He rarely relied on a secretary, conducting correspondence, fieldwork, and other activities on this own. He did not lend his name to work he had not verified personally. He was known not just for his intelligence, but also for his kindness and generosity.

Contributions

Waardenburg's contributions to the syndrome are set forth in a seminal paper in which he summarized the clinical details of 14 families and discussed possible genetic underpinnings of the condition (Waardenburg, 1951). The 59 pages include photographs of patients and pedigrees, material that is informative and insightful — but unlikely to appear in current journals, due to participant privacy issues. After explaining Waardenburg's initial interest in the syndrome and his subsequent search for new cases, I will describe some of the concordant MZ twins he studied. A recent case of twins concordant for the condition will also be examined. I will also describe the genetic explanation he offered and compare it with what is known today.

Waardenburg, an ophthalmologist, discovered his first case in the 1940s — an elderly gentleman suffering from congenital deafness, watering eyes and distinct *bilateral dystopia canthi medialis lateroversa*. The bilateral dystopia that caught Waardenburg's attention involves increased distance between the inner angles of the eyelids, displacement of small bones in the eye socket and other atypical visual structures. Waardenburg acknowledged van der Hoeve (1916) as having first described this condition, which was recognized by other investigators in the years that followed. He was intrigued by van der Hoeve's report of both congenital deafness and eye anomalies in the twins, as well as four other cases he discovered in the Netherlands, two other cases in the United States and one case in Switzerland. He also noted concordance in a brother-sister pair. Assisted by five different Dutch institutions, new cases consisting of 13 individuals who were deaf and mute were identified. These patients became the probands for the 14 pedigrees Waardenburg presented in his 1951 paper.

The Original Twins

MZ female twins, known as RS and SS, were first studied by van der Hoeve (1916) at age 14 years. Waardenburg gathered information on them when they were 49; by then, both twins had married men who were also deaf. Waardenburg personally examined the first-born twin (RS), while a colleague examined her twin sister and her sons. The twins' symptoms were similar and consistent with what would be known as Waardenburg's syndrome. Both twins were deaf and mute. Their hair color had turned gray at an early age before turning white. Both twins displayed hypermetropia in which distant objects appear clear, while near objects appear blurry (Medical Dictionary, 2023). They also displayed slight astigmatism, that is, imperfect curvature of the eye that causes blurred distance and near vision (Mayo Foundation, 2023a).

RS's husband had been deaf from birth. The couple had a son who appeared normal, suggesting to Waardenburg that if the deafness in both partners was hereditary then different genes were involved. In contrast, SS's husband's deafness had been acquired. The couple gave birth to one normal son and one son with deafness and other symptoms consistent with Waardenburg's syndrome, such as a patch of white hair. His vision was poor, and like his mother and aunt, he suffered from hypermetropia and astigmatism.

The twins' mother had been married previously, delivering two unaffected sons who would become the twins' half-brothers. In her second marriage to the twins' father, she delivered an unaffected son in addition to the affected twins. The twins' father was deceased but, based on inspection of his portrait, showed increased distance between the eyelids. Waardenburg commented that the two-generation presence of symptoms in this family was consistent with dominant inheritance of the syndrome. He wondered if the twins' early appearance of gray hair and the son's white patch of hair were 'equivalent components' of the condition.

Recent Twin Case

A rare case of infant male twins was presented by medical researchers from Karachi and Quetta, in Pakistan (Masood et al., 2020). The twins met the criteria for one of the four subtypes (WS-II) of Waardenburg's syndrome, that is, white forelock, heterochromia (different colored irises), hearing loss and affected first degree relative(s). The twins were born via vaginal delivery to a consanguineous couple. The twins also had light patches on their skin. Their family pedigree included a paternal uncle who displayed deafness and areas of the skin with reduced pigmentation, similar to those found in the twins. However, the twins' three older brothers were unaffected. The researchers noted that for a child to be affected only one parent had to transmit the relevant gene; this mode of transmission suggests dominant inheritance, except that neither parent was affected. As Masood et al. (2020) indicated, different types of gene mutations, such as insertions and deletions, may explain this syndrome. Furthermore, a recessive form of the condition (WS-II) is recognized, as I explain below.

Genetic Transmission

In his 1951 paper Waardenburg indicated that he had initially anticipated finding evidence of recessive inheritance, typical of deaf-mutism. However, he failed to detect consanguinity among his patients' parents. He eventually favored autosomal dominant inheritance, given that it rendered certain data more plausible, but allowed for the possibility of varying degrees of penetrance. He also noted that the condition had a higher frequency among males than females, but ruled out X-linked transmission as either parent could pass on the genetic predisposition to a child. He also noted that recessive forms of deafness exist.

Currently, Waardenburg's syndrome is recognized as an autosomal dominant condition with six genetic mutations that explain why there are four subtypes with unique symptoms (Cleveland Clinic, 2023). Two of the subtypes (WS-II and WS-IV) are associated with recessive inheritance. New cases in an unaffected family may also arise due to a mutation in one family member.

Twin Research Reviews

MZ Twins' Different Dermatoglyphics

Dermatoglyphic features are the pattern types found across individuals' fingers, soles and toes. Both genetic and environmental factors underlie the presence of the arches, loops, and whorls–the three main types of fingerprints — as well as their variations (e.g., tented arch, double loop, double whorl; see Segal, 2017). Fingerprint patterns are mirrored in approximately 25% of MZ twin pairs; even MZ twins do not show identical features. In

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addition, there is a system for counting the number of lines or ridges across the 10 fingers to determine a total ridgecount score. As I note in *Twin Mythconceptions,* 'The entire development process [of fingerprints] is so chaotic that, in the entire course of human history, there is virtually no chance of the same exact pattern forming twice' (Roizen, n.d.).

An interdisciplinary team of researchers recently used genome-wide scans to identify 18 loci associated with pattern type (Li et al., 2022). A variant near *EV11* was found to modify regulatory activity; this variant also affects dermatoglyphic patterning in mice and limb development in humans. It was concluded that human limb development plays a key, albeit indirect, role in fingerprint genesis. Hand proportion was also found to affect various fingerprint patterning characteristics.

Twins with Sagittal Suture Crainosynostosis

A study of twins and nontwins with sagittal suture crainosynostosis (SSC) was undertaken by a research team in the Netherlands (Cinca et al., 2022). The researchers note that prenatal and early postnatal development of the skull is governed chiefly by the cranial sutures (cranial sutures are joints made of fibrous tissue that keep an infant's skull together; see Mayo Foundation, 2023b). The investigators also point out that prenatal fusion of the sutures occurs more commonly in multiple births than in nontwin births. It is generally believed that SSC in twins is caused by constraint, but new data by Cinca et al. (2022) have challenged that wisdom.

Twins with SSC were identified at the Sophia Children's Hospital in Rotterdam. Their prenatal ultrasound scans were examined if available and clear, yielding 26 twins who entered the study. Affected individuals' values were then compared with the reference values of affected nontwins. If only one cotwin in a pair was affected the unaffected twin was also used for comparison. It was concluded that SSC in twins and nontwins can be explained by the same disruptive processes in suture development, rather than by constraint as had been suspected for twins. Hopefully, these new data will encourage rethinking of the detection and management of this condition. Additional information about twins with SSC can be found in one of my previous articles; see Segal (2021a).

Blood Pressure in Female Twins

Researchers in the UK have noted the relationship between aortic stiffness and blood pressure, but the direction of causality has remained uncertain (Keehn et al., 2023). In an effort to bring clarity to this situation, these investigators assessed aortic stiffness and mean arterial pressure in a sample of 2037 female twins, most of whom were from intact pairs. A subset of 947 twins had undergone repeated measurement. It was determined that contemporaneous mean blood pressure, rather than measurement history, is more strongly linked to the progression of arterial stiffness. It was also observed that prior arterial stiffness was associated with mean arterial pressure. Collectively, these findings demonstrate bidirectionality between blood pressure and arterial stiffness. The suggestion that reducing blood pressure may mitigate arterial stiffness and hypertension was raised.

MZ Twins' Education and Political Knowledge

Past researchers have reported a positive association between education and political knowledge, an issue recently revisited by a Danish team (Weinschenk et al., 2021). In their article, the researchers cited an earlier study of discordant MZ twins from the United States showing that, after removing familial factors shared by MZ twins raised together, the correlation between education and political knowledge was small and not statistically significant, suggesting confounding of variables. An attempt at replicating the Weinshenk at al. (2021) study with twins from the Danish Twin Registry at the University of Southern Denmark was undertaken. A survey administered in 2019 yielded complete data from 190 MZ twin pairs. Results were consistent with those of the 2021 twin study, affirming that the link between education and political knowledge is small and nonsignificant.

Media Reports

Twins Created by Reciprocal In Vitro Fertilization

Reciprocal in vitro fertilization (IVF) is a situation in which the egg(s) of a (typically) gay female are extracted, fertilized in a laboratory, and implanted into the womb of her partner. This process is also called co-maternity (Margarelli, 2021). A case that attracted national attention in Israel several years ago is still timely, with implications for current family law in the United States. Smadar and Hadas Peker-Nir had hoped to enlarge their family, but Hadas could not carry a pregnancy (Yaron, 2018). It was decided to use her eggs and, once fertilized, implant them into Smadar's womb. The Israeli government would not allow this, so the couple had the procedure performed in Cyprus.

Unfortunately, the twin infants, born in 2017, required considerable medical care, such that the couple failed to meet the 90-day deadline for Hadar's formal parenthood request; the court did not recognize her as a parent because, despite her genetic connection to the twins, she did not gestate them. Instead, the court suggested that Hadar adopt the children, which is a long difficult process. The case finally settled in favor of the family when a female judge ordered the state to recognize Hadar as the twins' parent and to pay the couple 3000 shekels (approximately $850 USD) in damages. The legalities of reciprocal IVF vary across states in the United States, as well as between countries (Resolve, 2023).

Reared-Apart Triplets' Limited TV Series

The actor Ben Stiller is slated to play the reared-apart identical triplets in a televised adaptation of the 2018 documentary film, *Three Identical Strangers* (Gallagher, 2023). I published an in-depth investigation, *Deliberately Divided* (Segal, 2021b), of the study in which the triplets and several sets of identical twins were adopted apart and secretly studied for years. None of the twins' and triplets' adopted parents were told by the adoption agency, Louise Wise Services, that they were raising a 'singleton twin'. The chance reunions of the triplets and twins directed attention to this controversial — and unethical — study and the two psychiatrists and staff behind it.

Abducted Twin Infants

In the last issue of *Twin Research and Human Genetics*, I discussed an unfortunate incident in which infant male twins in Ohio had been abducted from a car while their mother was purchasing a pizza (Segal, 2023). One twin was recovered the same day, the other twin three days later. In a sad turn of events, one of the six-month-old twins passed away after police officers responded to an emergency telephone call saying the baby was not breathing. An autopsy has been scheduled (Associated Press, 2023).

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Winkelvoss Twins' Charges by the Securities and Exchange Commission

Tyler and Cameron Winkelvoss, the heads of the cryptocurrency lender Genesis Global Capital and the cryptocurrency exchange Gemini Trust, were cited for unregistered securities (*Orange County Register*, 2023). The twins did not immediately respond to these charges, but found them 'disappointing' (p. A-14). The Winkelvoss twins are well known for their professional rowing competitions and failed social platform collaboration with Mark Zuckerberg of Facebook during their years as Harvard University students (Olympics.com, 2023).

Going From 'Me' to 'We'

American culture values individuality and independence, so using collectives such as 'we' and 'us' may be disquieting for some individuals (Leibowitz, 2023). In an insightful *New York Times* column, Leibowitz referenced her husband and his identical twin, noting that 'Twins, especially identical twins, offer an interesting counterpoint to this emphasis' (p. 7). She writes of identical twins' commonality, partnership and shared identity, all of which are evident in the research literature (Segal, 2017). I take exception (and I believe she does, as well) to the views of several experts she cites who believe that healthy twin relationships come from separating and/or downplaying twinship, such as dressing twins differently, placing them in different bedrooms and never calling them 'twins'.

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