Biological correlations in the development of atypical gender identities (2018)

"The expression of gender characteristics that are not stereotypically associated with one's assigned sex at birth is a common and culturally diverse human phenomenon that should not be judged as inherently pathological or negative".[1]

"Gender dysphoria is the distress associated with the experience of one's personal gender identity being inconsistent with the phenotype or the gender role typically associated with that phenotype".[2]

In 2013, the World Health Organisation was advised, in relation to gender identity, to 'abandon the psychopathological model for a model that reflects current scientific evidence'. Accordingly, the new classification 'gender incongruence'[3] is no longer placed under Mental and Behavioural Disorders in the International Classification of Diseases (ICD11). Treatment is based the personal experiences and insights of trans people themselves, including those who have non-binary identifications, as well as on clinical observations of medical practitioners. Even though gender incongruence is no longer classified as a mental illness, most people experiencing it will benefit from mental health support as they may face more social and cultural challenges and barriers than their cisgender (non-trans) counterparts. Clinical interventions are aimed at helping individuals to make informed decisions about how they might overcome the physical and social discomfort they experience.

More is now understood about the biological correlations in the development of gender incongruence, and there is acceptance by many relevant bodies, that these conditions are somatic. it is important to note that medical and scientific findings are often amended and clarified but the right of individuals to appropriate care and respect remains**.** (GIRES *et al.,* 2006).[4]

Gender incongruence may lead to different levels of discomfort, and a variety of outcomes. It is likely that biological pathways will also vary from

1 World Professional Association for Transgender Health, Standards of care (2011).
2 Good practice Guidelines for the assessment and treatment of adults with gender dysphoria, (2013). Available at www.rcpsych.ac.uk/files/pdfversion/CR181.pdf
3 Gender incongruence replaces the old terminology, 'transsexualism'.
4 GIRES *et al*. (2006). Atypical gender development – a review. *International Journal of Transgenderism* 9(1):29–47. https://www.gires.org.uk/atypical-gender-development/

individual to individual, so no single route to the development of identities that are not congruent with the sex assigned at birth, is likely to be identified. The factors which impinge on the pre-natal sex differentiation of genitalia, gonads and brain, are a combination of genetic, hormonal and environmental. Influences on post-natal outcomes will be multifactorial and will depend not only on individual circumstances but on cultural norms and mores. In cultures where allowance is made for gender expressions that are less distinctly either masculine or feminine, the discomfort of those experiencing gender incongruence seems considerably lessened. It is suggested that the likelihood of associated psychological stress may thereby be reduced (Connolly, 2003).[5]

In order to understand the factors that are influential in shaping gender identity, it is helpful to consider the histories of conditions characterised by ambiguous genitalia in the newborn. These are associated with genetic and hormonal anomalies. Accidental damage to the penis neonatally can also give rise to circumstances where a decision may have to be made as to whether to raise a child as a boy or a girl. In the past, faced with such anomalies or accidents, parents accepted the medical viewpoint that early 'corrective' surgery – usually to create a female appearance – followed by raising the child as a girl, would deliver a congruent gender identity despite, in many cases, the underlying XY (male) karyotype. However, the reality was that some rejected their feminine role. Their gender identity resolved independently of genital appearance and the imposed feminine gender expression, despite the persuasive power of these two factors. (Diamond and Sigmundson, 1997; Kipnis and Diamond, 1998; Reiner, 2004; Hines, 2004; Dessens, 2005, Reed and Diamond, 2016)[6,7,8,9,10,11,12] This supports the view

[5] Connolly, P Transgendered Peoples of Samoa, Tonga and India: diversity of psychosocial challenges, coping, and styles of gender reassignment. Paper presented at the *Harry Benjamin International Gender Dysphoria Association Conference*, Ghent, Belgium. September 10–13 (2003).

[6] Diamond, M and Sigmundson HK (1997) Sex reassignment at birth. Long term review and clinical implications. *Archives of Pediatrics and Adolescent Medicine* 151: 298-304.

[7] Kipnis K and Diamond M. (1998) Pediatric ethics and the surgical assignment of sex. *Journal of Clinical Ethics*, 9(4) :398-410.

[8] Reiner, WG (2004) Psychosexual development in genetic males assigned female: the cloacal exstrophy experience. In *Child and Adolescent Clinics of North America* (Sex and Gender) Milton Diamond and Alan Yates (eds.) WB. Saunders, Philadelphia 13(3): 657–674.

[9] Hines, M (2004) Brain Gender, New York, Oxford University Press. A very small minority of female individuals with congenital adrenal hyperplasia, who have been raised as girls, choose to live in adulthood as males (estimates range from about 1% to about 3%).

[10] Dessens, AB, Froukje, ME, Slijper, FME, Stenvert, LS, Drop SLS (2005) Gender dysphoria and gender change in chromosomal females with congenital adrenal hyperplasia. *Archives of Sexual Behavior* 34(4):389–397. Dessens found a much higher frequency of individuals within this group who identify comfortably as men: Of 250 raised as girls, 13(5.2%) experienced FtM

that pre-natal sex hormones[13] (and/or direct genetic effects, Dewing et al. 2003)[14] have an indelible impact on brain development which may trigger an inconsistent gender identity that is resistant to social pressures. Given the greater understanding of the impact of these biological factors on the development of gender identity, surgical intervention is now less often undertaken in infancy and is believed by many, to be unethical, since the infant cannot give consent, nor make a choice. In 2015, Malta was the first country to make such surgical interventions unlawful.

It is also the case for those trans people whose gender identity develops in conflict with their genital and other sex characteristics, that societal pressures to conform, whether deliberate or inadvertently imposed, cannot overcome their innate gender identity. It is therefore postulated that divergent brain development in the fetus is the most likely trigger for this dissonance. The scientific evidence for this position continues to grow.

Studies on twins and on other family co-occurrences of severe gender dysphoria, indicate that these are unlikely to be random, and the potential for a genetic link in a subset of these individuals is postulated (Green 2000; Diamond and Hawk, 2003, Diamond 2013)[15,16,17] The comparison between monozygotic and dizygotic twins is especially informative, since the former have a much higher degree of concordance for permanent transition of the gender role: 33% in male monozygotic twins and 23% in female monozygotic twins, compared

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gender dysphoria; of 33 raised as boys, 4 experienced MtF gender dysphoria; therefore, it appears that of the total 283, 42 individuals must be living comfortably as men or uncomfortably as women. These figures do not represent the whole XX, CAH population and, therefore, although interesting should be viewed with caution).

[11] Ochoa, B (1996) Trauma of the External Genitalia in Children: Amputation of the Penis and Emasculation, *Journal of Urology*, 1116.

[12] Reed, T and Diamond, M (2016), Biological Correlations in the development of gender dysphoria, *The Lancet*, June p12-13.

[13] Bao, A-M, Swaab, DF (2011) Sexual differentiation of the human brain: Relation to gender identity, sexual orientation and neuropsychiatric disorders. *Frontiers in Neuroendocrinology* 32:214–226.

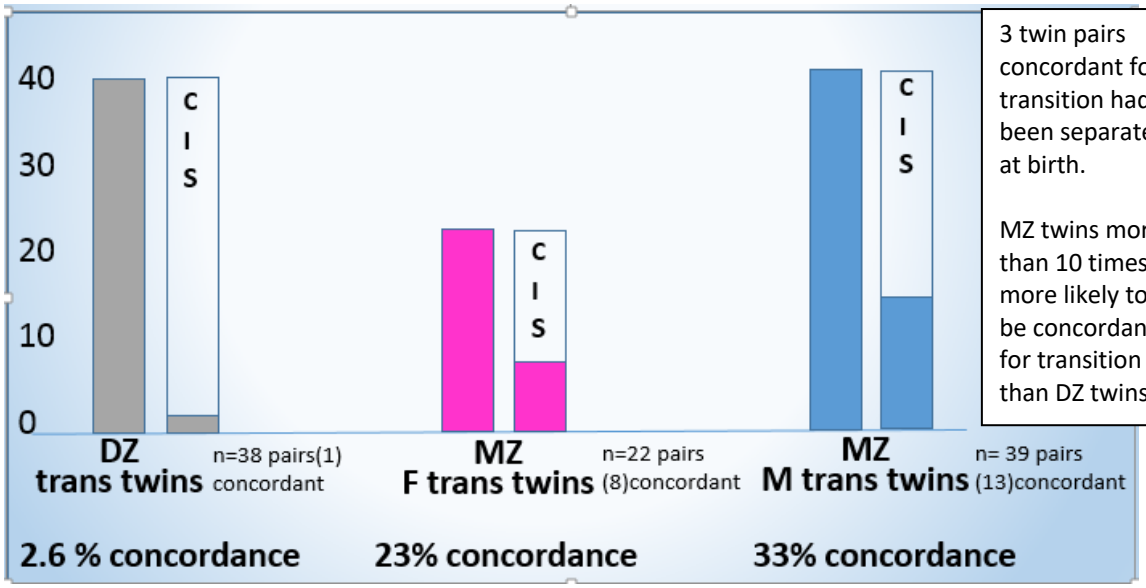
[14] Dewing, P, Shi, T, Horvath, S, Vilain, E (2003) Sexually dimorphic gene expression in mouse brain precedes gonadal differentiation. *Molecular Brain Research* 118:82-90.

[15] Green, R (2000) Family co-occurrence of gender dysphoria: ten sibling or parent-child pairs. *Archives of Sexual Behavior* 29:499-507.

[16] Diamond, M, Hawk, ST. Transsexualism among twins has a high concordance for GID among monozygotic twins and a strong but lesser concordance among dizygotic twins with the effect more noticeable among males than females. Paper presented at the Harry Benjamin International Gender Dysphoria Association Symposium, Ghent, Belgium, September 10–13 2003.

[17] Gooren, LJ, Sungkaew, T, Gilta, EJ (2013) Exploration of functional health, mental well-being and cross-sex hormone use in a sample of Thai male-to-female transgendered persons (kathoeys). *Asian Journal of Andrology*. 15, 280–285

with dizygotic twins where concordance is under 3%. Thus, a strong genetic influence is inferred (Diamond et al, 2013).[18]



A genetic anomaly of repeat polymorphisms in the gene coding for the androgen receptor has been found in two studies on different populations of individuals identifying as women, in contradiction to their male phenotype and karyotype (Henningsson et al, 2005; Hare et al, 2008).[19,20]

A study comparing the DNA of 380 trans women compared with 344 cis-gender men showed that in 12 genes related to hormone signalling, there "were 4 small but significant differences between these groups." It is postulated that these genetic changes alter relevant sex-hormone levels in the brain.[21]

Certain chromosome disorders in those with male phenotype, are associated with a raised incidence of individuals who identify as women (Snaith *et al*., 1991; Diamond and Watson, 2004).[22,23,] Additionally, low

[18] Diamond (2013) Transsexuality among twins. *International Journal of Transgenderism*, 14:1, 24-48.

[19] Henningsson, S., Westberg, L., Nilsson, S., Lundström, B., Ekselius, L., Bodlund, O., Lindstrom E., Hellstrand, M., Rosmond, R., Eriksson., E., Landén, M. (2005). Sex Steroid Related Genes and Male to Female Transsexualism. *Psychoneuroendocrinology* **30**(7), 657-664.

[20] Hare, L, Bernard, P, Sanchez FJ, Baird PN, Vilain E, Kennedy T, Harley, VR. (2008) Androgen receptor repeat length polymorphism associated with male to female transsexualism. *Biological Psychiatry*.

[21] Foreman, M, Hare, L., York, K., Balakrishnan, K., Sánchez FJ., Harte, F., Erasmus, J., Vilain, E., Harley, RV., (2018) *Journal of Clinical Endocrinology and Metabolism.*

[22] Snaith, RP, Penhale, S, Horsfield, P (1991) Male to female transsexual with 47 XYY karyotype. *Lancet* 337:557–558.

androgen input to an XY fetus associated with medication to the pregnant mother is linked with a raised incidence of individuals assigned male at birth, later identifying as women (Dessens *et al.,* 1999).[24]

Cerebral lateralisation of hearing in the non-trans male and female populations is distinct and well-recorded. A study on dichotic hearing in trans individuals found that trans women's hearing is significantly different from non-trans males and, in fact, resembles the cisgender *female* pattern (Govier *et al*., 2010).[25] The same study also confirmed previous studies that demonstrated a marked correlation with non-right-handedness in both trans men and trans women (Green and Young, 2001 Zucker et al, 2001).[26,27] In addition, trans women have been shown to have physiological responses to specific odours that reflect their gender identity, in contradiction to their male karyotype and sex assigned at birth (Burglund et al, 2008).[28]

Three post-mortem studies have been carried out on small cohorts of individuals who, in life, had experienced their gender identity as being incongruent with their phenotype. In these individuals, unlike the control subjects, small nuclei in the brain, known to be sex-dimorphic, have been shown to have neural differentiation in opposition to genital and gonadal characteristics (Zhou *et al*., 1995; Kruijver *et al*., 2000; Garcia-Falgueras and Swaab, 2008).[29]

More recent scans of the white matter of the brains of untreated trans men indicate that their neural patterns are masculinised and appear

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[23] Diamond, M, Watson, LA (2004). Androgen insensitivity syndrome and Klinefelter's Syndrome. In *Child and Adolescent Psychiatric Clinics of North America (Sex and Gender*). Milton Diamond and Alayne Yates (eds); W.B. Saunders, Philadelphia 13(3):623–640.

[24] Dessens, AB, Cohen-Kettenis, PT, Mellenbergh, GJ, van der Poll, NE, Koppe, JG, Boer, K (1999). Prenatal exposure to anticonvulsants and psychosexual development. *Archives of Sexual Behavior* 28:31-44.

[25] Govier, E, Diamond, M, Wolowiec, T, Slade, C (2010). Dichotic listening, handedness, brain organisation and Transsexuality, International Journal of Transgenderism, 12(3) 144-154.

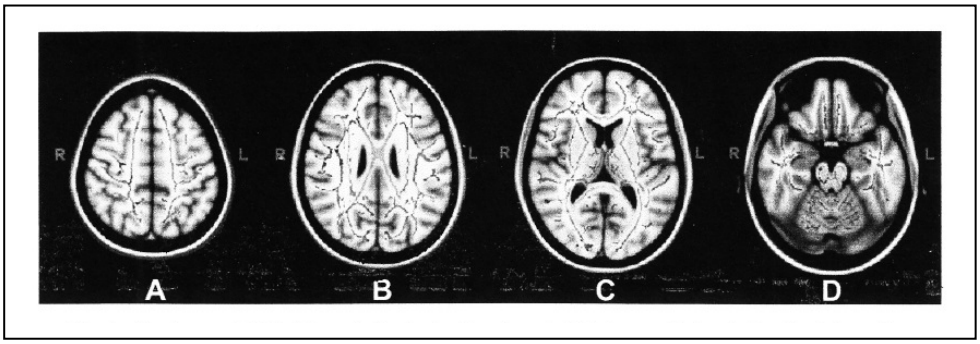
[26] Green, R and Young, R (2001) Hand preference, sexual preference, and transsexualism, *Archives of Sexual Behavior* 30:565–574).

[27] Zucker, K.J., Beaulieu, N., Bradley, S.J., Grimshaw, G.M., Wilcox, A. (2001). Handedness in Boys with Gender Identity Disorder. *Journal of Clinical Child Psychology and Psychiatry* 42,767-776.

[28] Burglund H, Lindstrom P, Dhejne-Helmy C, Savic I. Male-to-female transsexuals show sex-atypical hypothalamus activation when smelling odorous steroids. Cerebral Cortex 2008; 18(8): 1900-8.

[29] Zhou, J-N, Swaab, DF, Gooren, LJ, Hofman, MA (1995) A sex difference in the human brain and its relation to transsexuality. *Nature,* 378:68–70. This evidence was cited by Professor Louis Gooren of the University Hospital, Vrije Universiteit of Amsterdam, in his affidavit to the court in Bellinger v Bellinger, TLR 22-11-2000.

male in three of the four levels scanned. (Rametti et al, 2011)[30]; white matter in the brains of untreated trans women, is shown to be feminised and significantly different from both male and female controls at all four levels scanned (Rametti *et al* 2011).[31]



White matter microstructure in trans men before cross-sex hormone treatment. A diffuser tensor imaging study.

Recent studies using MRI scans on brain activation patterns in adolescents who experience gender dysphoria, were found to be more aligned with their gender identity than their birth sex: those assigned female resembled male controls, those assigned male resembled female controls.[32]

Considered in the context of the other research, cited above, these brain studies on both grey and white matter, support the paradigm that the neurobiology of the brain is an important element in the development of gender dysphoria. (Zhou *et al*., 1995; Kruijver *et al*., 2000; Garcia-Falgueras and Swaab, 2008). [33,34, 35]

[30] Rametti, G, Carrillo, B, Gómez-Gil, E, Junque, C, Segovia, S, Gomez, A, Guillamon, A. (2011). White matter microstructure in female to male transsexuals before cross-sex hormonal treatment. A diffusion tensor imaging study, *Journal of Psychiatric Research* 45 199–204.

[31] Rametti, G, Carrillo, B, Gómez-Gil, E, Junque, C, Zubiarre-Elorza, L, Segovia, S, Gomez, A, Guillamon, A. (2011). The microstructure of white matter in male to female transsexuals before cross-sex hormonal treatment. A DTI study. *Journal of Psychiatric Research*, 1- 6.

[32] Bakker J, et al (2018 May)Liege University and the Center of Expertise on Gender Dysphoria, VU University Medical Center, the Netherlands, European Society of Endocrinology https://www.ese-hormones.org/media/1506/transgender-brains-are-more-like-their-desired-gender-from-an-early-age.pdf

[33] Zhou, J-N, Swaab, DF, Gooren, LJ, Hofman, MA (1995) A sex difference in the human brain and its relation to transsexuality. *Nature,* 378:68–70.

[34] Kruijver, FPM, Zhou, J-N, Pool, CW, Hofman, MA, Gooren, LJ, Swaab, DF (2000) Male to female transsexuals have female neuron numbers in a limbic nucleus. *The Journal of Endocrinology & Metabolism* 85(5):2034–2041.

[35] Garcia-Falgueras, A and Swaab, DF (2008) A sex difference in the hypothalamic uncinate nucleus: relationship to gender identity, *Brain: a journal of neurology* 131(12):3132-3146.

The research provides compelling evidence that biological factors predispose the development of incongruent gender identities in some individuals.

"However, people experiencing gender incongruence, including those who are gender dysphoric might have one, more than one, or none of these markers. Therefore, these indicators cannot be used diagnostically. The only valid route to understanding a person's gender identity is to listen to them. Whatever our scientific understandings, the needs of transgender people should be met on the basis of universally recognised human rights". (Reed and Diamond, 2016)[36]

[36] Reed, T and Diamond, M, (2016) Biological correlations in the Development of Gender Identity. The Lancet: Transgender Health, pp12-13.