

## **Biological correlations in the development of atypical gender identities**

*“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”.<sup>1</sup>*

*“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”.<sup>2</sup>*

In 2013, the World Health Organisation was advised, in relation to gender dysphoria, to ‘abandon the psychopathological model for a model that reflects current scientific evidence’. Accordingly, gender dysphoria, possibly classified as ‘gender incongruence’ will no longer be placed under Mental and Behavioural Disorders in the upcoming ICD11. The clinical observations of medical practitioners, and the personal experiences and insights of trans people themselves, including those who have non-binary identifications, have led to approaches to treatment that rely less on psychiatric interventions, and more on assisting individuals to make informed choices about their lives.

When discussing what is known about biological correlations, 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).<sup>3</sup>

Gender dysphoria is a condition which is experienced to different degrees in different individuals. Given the variety of experiences, and the variety of outcomes, it is likely that etiological pathways will also vary from 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

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<sup>1</sup> World Professional Association for Transgender Health, Standards of care (2011).

<sup>2</sup> Good practice Guidelines for the assessment and treatment of adults with gender dysphoria, (2013). Available at [www.rcpsych.ac.uk/files/pdfversion/CR181.pdf](http://www.rcpsych.ac.uk/files/pdfversion/CR181.pdf)

<sup>3</sup> GIRES *et al.* (2006). Atypical gender development – a review. *International Journal of Transgenderism* 9(1):29–47. Available at [www.gires.org.uk/genderdev.php](http://www.gires.org.uk/genderdev.php)

lessened. It is suggested that the likelihood of associated psychological stress may thereby be reduced (Connolly, 2003).<sup>4</sup>

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 gender role, despite the persuasive power of these two factors. (Diamond and Sigmundson, 1997; Kipnis and Diamond, 1998; Reiner, 2004; Hines, 2004; Dessens, 2005)<sup>5,6,7,8,9,10</sup> This supports the view that pre-natal sex hormones<sup>11</sup> (and/or direct genetic effects, Dewing et al. 2003)<sup>12</sup> 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

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<sup>4</sup> 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).

<sup>5</sup> 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.

<sup>6</sup> Kipnis K and Diamond M. (1998) Pediatric ethics and the surgical assignment of sex. *Journal of Clinical Ethics*, 9(4) :398-410.

<sup>7</sup> 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.

<sup>8</sup> 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%).

<sup>9</sup> 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 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).

<sup>10</sup> Ochoa, B (1996) Trauma of the External Genitalia in Children: Amputation of the Penis and Emasculation, *Journal of Urology*, 1116.

<sup>11</sup> 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.

<sup>12</sup> 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.

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.

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)<sup>13,14,15</sup> 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 with dizygotic twins where concordance is essentially zero. Thus a strong genetic influence is inferred (Diamond et al, 2013).<sup>16</sup> 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).<sup>17,18</sup>

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).<sup>19,20</sup> Additionally, low androgen input to an XY fetus

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<sup>13</sup> Green, R (2000) Family co-occurrence of gender dysphoria: ten sibling or parent-child pairs. *Archives of Sexual Behavior* 29:499-507.

<sup>14</sup> 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.

<sup>15</sup> Gooren, LJ, Sungkaew, T, Giltia, 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

<sup>16</sup> Diamond (2013) Transsexuality among twins. *International Journal of Transgenderism*, 14:1, 24-48.

<sup>17</sup> 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.

<sup>18</sup> 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*.

<sup>19</sup> Snaith, RP, Penhale, S, Horsfield, P (1991) Male to female transsexual with 47 XYY karyotype. *Lancet* 337:557–558.

<sup>20</sup> 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.

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).<sup>21</sup>

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).<sup>22</sup> 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).<sup>23,24</sup> 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).<sup>25</sup>

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).<sup>26</sup> Recent scans of the white matter of the brains of untreated trans men indicate that their neural patterns are masculinised, and appear male in three of the four levels scanned. (Rametti *et al.*, 2011)<sup>27</sup>; 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).<sup>28</sup>

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<sup>21</sup> 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.

<sup>22</sup> Govier, E, Diamond, M, Wolowiec, T, Slade, C (2010). Dichotic listening, handedness, brain organisation and Transsexuality, *International Journal of Transgenderism*, 12(3) 144-154.

<sup>23</sup> Green, R and Young, R (2001) Hand preference, sexual preference, and transsexualism, *Archives of Sexual Behavior* 30:565-574).

<sup>24</sup> 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.

<sup>25</sup> 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.

<sup>26</sup> 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.

<sup>27</sup> 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.

<sup>28</sup> Rametti, G, Carrillo, B, Gómez-Gil, E, Junque, C, Zubiare-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.

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).<sup>29,30,31</sup>

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<sup>29</sup> 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.

<sup>30</sup> 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.

<sup>31</sup> 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.