A genetic link between gender dysphoria and sex hormone signaling

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Introduction

There is a likely genetic component to gender dysphoria, but association study data have been equivocal. We explored the specific hypothesis that gender dysphoria in transgender women is associated with variants in sex hormone–signaling genes responsible for undermasculinization and/or feminization. Subject-control analysis included 380 transgender women and 344 control male subjects. Associations and interactions were investigated between functional variants in 12 sex hormone–signaling genes and gender dysphoria in transgender women.

Patients were recruited from the Monash Gender Clinic, Monash Health, Melbourne, Australia, and the University of California, Los Angeles. Caucasian (non-Latino) transgender women were recruited who received a diagnosis of transsexualism [Diagnostic and Statistical Manual of Mental Disorders (DSM)-IV) or gender dysphoria (DSM-V)] pre- or postoperatively. Most were receiving hormone treatment at the time of recruitment. Genomic DNA was genotyped for repeat length polymorphisms or single nucleotide polymorphisms.

Results

A difference in median repeat length was identified, with transgender women having a significantly shorter median repeat length (16 TA repeats) for ERα when compared with male control subjects (17 TA repeats; P = 0.03; Table 1).

Table 1. Comparison of Repeat Length Distributions of AR, ERα, ERβ, CYP11A1, CYP1,9 and PGR Repeat Length Polymorphisms

Gene	Male Control Subjects		Transgender Women		Mann-Whitney U Test P Value
	No.	Median	No.	Median	
AR	289	22	327	22	0.31
ERα	567	17	640	16	0.03 ^a
ERβ	580	23	668	23	0.70
CYP11A1	546	4	668	4	0.55
CYP19	580	7	658	7	0.21
PGR	562	18	676	18	0.20

^aStatistically significant at P < 0.05.

Allele frequencies were determined for the five SNPs COMT, CYP17, HSD17B6, SULT2A,1 and STS, and the dichotomous SRD5A2 repeat-length polymorphism (Table 2). A difference between transgender women’s and male control subjects’ allele frequencies was identified in two of the six genes (SRD5A2 and STS).

Table 2. Allele Frequencies of the COMT, CYP17, HSD17B6, SRD5A2, STS, and SULT2A1 Single Nucleotide or Dichotomous Polymorphisms

Gene	Allele	Male Control Subjects		Transgender Women		P Value ^a
		No.	%	No.	%	
COMT	G	303	58.7	356	54.1	0.11
	A	213	41.3	302	45.9	
CYP17	T	354	63.7	384	58.9	0.090
	C	202	36.3	268	41.1	
HSD17B6	T	366	65.6	406	60.2	0.053
	C	192	34.3	268	39.8	
SRD5A2	TA(0)	516	91.5	598	87.7	0.030 ^b
	TA(9)	48	8.5	84	12.3	
STS	G	238	85.9	302	92.1	0.015 ^b
	A	39	14.1	26	7.9	
SULT2A1	T	419	80.9	504	77.5	0.16
	C	99	19.1	146	22.5	

^aThe P value was calculated using the χ^2 test.

^bStatistically significant at P < 0.05.

An association was identified between transgender women and the SULT2A1 homozygous TC genotype (P = 0.009) and the ERα SS genotype (P = 0.035) when compared with male control subjects (Table 3). The ORs indicate that within this population, the likelihood of being transgender increases by 1.61 times (95% CI, 1.13 to 2.31) if an individual possesses the SULT2A1 TC genotype and increases by 1.65 times (95% CI, 1.04 to 2.63) if an individual possesses the ERα SS genotype.

Table 3. Genotype Analysis of the COMT, CYP11A1, CYP17, CYP19, ERα, ERβ, HSD17B6, PGR, SRD5A2, and SULT2A1 Polymorphisms

Gene	Genotype	Male Control Subjects		Transgender Women		P Value (OR; 95% CI) ^a
		No.	%	No.	%	
COMT	GG	85	32.8	100	30.4	0.06 (1.59; 0.98–2.58)
	GA	135	52.1	156	47.4	
	AA	39	15.1	73	22.2	
CYP11A1	SS	89	33.1	124	37.1	0.24 (0.81; 0.57–1.15)
	SL	138	51.3	155	46.4	
	LL	42	15.6	55	16.5	
CYP17	TT	112	40.3	109	33.2	0.097 (1.34; 0.95–1.91)
	TT	130	46.8	170	51.8	
	CC	36	12.9	85	14.9	
CYP19	SS	86	30.3	83	25.2	0.20 (1.36; 0.85–2.16)
	SL	142	50.2	174	52.9	
	LL	55	19.4	72	21.9	
ERα	SS	75	27	103	32.2	0.035 ^b (1.65; 1.04–2.63)
	SL	138	49.6	163	50.9	
	LL	65	23.4	54	16.9	
ERβ	SS	186	65.7	216	64.7	0.81 (1.04; 0.74–1.45)
	SL	85	30	103	30.8	
	LL	12	4.2	15	4.5	
HSD17B6	TT	122	43.7	123	36.5	0.091 (1.53; 0.93–2.51)
	TC	122	43.7	160	47.5	
	CC	35	12.5	54	16	
PGR	SS	81	29.3	106	31.4	0.35 (0.80; 0.50–1.27)
	SL	135	48.9	169	50	
	LL	60	21.7	63	18.6	
SRD5A2	TA(0)/(0)	238	84.4	269	78.4	0.12 (1.42; 0.92–2.18)
	TA(0)/(9)	40	14.2	64	18.7	
	TA (9)/(9)	4	1.4	10	2.9	
SULT2A1	TT	175	67.6	192	58.9	0.009 ^b (1.61; 1.13–2.31)
	TC	69	26.6	122	37.4	
	CC	15	5.8	12	3.7	

Abbreviations: L, long allele; S, short allele.

^aP values, ORs, and 95% CIs were calculated using binary logistic regression. ORs > 1 indicate an increased likelihood of being transgender compared with the reference allele. ORs < 1 indicate a decreased likelihood of being transgender compared with the reference allele.

^bStatistically significant at P < 0.05.

Of possible two-locus gene interactions modeled using binary logistic regression, four interactions were overrepresented in transgender women when compared with male control subjects: AR- ERb, AR-PGR, AR-COMT, and CYP17-SRD5A2 (Table 4). Notably, three of the four interactions involve the long CAG repeats of the AR.

Table 4. ORs and 95% CIs of Statistically Significant Two-Locus Gene Interactions Determined by Binary Logistic Regression Modeling

Two-Locus Gene Interaction ^a	OR ^b	95% CI ^b		P Value ^b
		Lower	Upper	
AR (L) – ERβ (SL)	2.78	1.15	6.70	0.023
AR (L) – PGR (LL)	5.68	1.63	17.95	0.006
AR (L) – COMT (AA)	3.88	1.2	12.56	0.024
CYP17 (A1A2) – SRD5A2(TA(0)/TA(9))	4.09	1.19	14.03	0.025

Conclusion: The results of our study of transgender women support the hypothesis that gender dysphoria has a polygenic basis, involving interactions among multiple genes and polymorphisms that may alter the sexual differentiation of the brain in utero, contributing to the development of gender dysphoria in transgender women.