GENETIC TESTING BY SNP ARRAY ANALYSIS IN A GROUP OF ROMANIAN PATIENTS WITH DISORDERS OF SEXUAL DEVELOPMENT

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INTRODUCTION

Disorders of sexual development (DSD) - frequency 1:4.000

- Important long term consequences on psychical and physical health, social, fertility, sexuality
- Etiologic knowledge → the appropriate choice of social sex at the age of the newborn and a proper management at an optimum age

PATIENTS AND METHODS

- 17 patients diagnosed in Clinical Emergency Hospital for Children, Cluj-Napoca
- The evaluation consisted in:
  - A complete clinical picture
  - Hormonal/biochemical investigations
  - Morfological evaluation: Ultrasounds, genitography, IRM or biopsy
  - Caryotype+SRY
  - 21 hydroxylase deficiency (11 mutations CYP21A2/stripassay)
  - SNP array analysis

+other individualised analysis depending on clinical picture

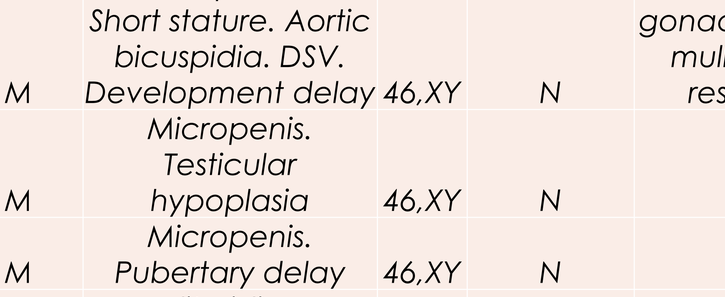
SNP array analysis

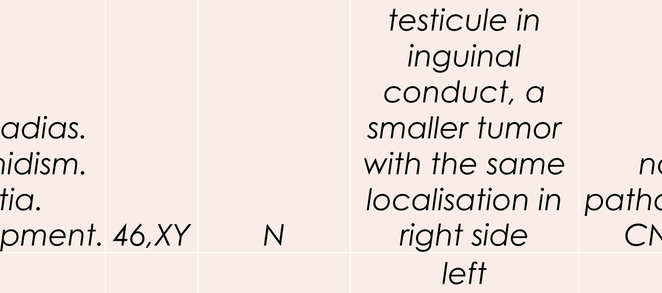
- AND extraction Wizard® Genomic DNA Purification Kit (Promega)
- Infinium OmniExpress-24 BeadChip array
- Image acquisition - iScan System - 700,000 markers - a mean resolution of 5kb
- SNP copy numbers (log R Ratio) and B allele frequencies - Genome Studio 3.0
- CNV analysis: UCSC, DGV, Decipher, and OMIM databases

RESULTS

Patient	Age (yrs)	social gender	phenotype	Karyo type	Hormonal	Ultrasounds	SNP array
p1	10	M	Micropenis. 5th clinodactyly	46,XY	Testo N DHT ↓	N gonads, no mullerian derivates	no pathogen CNV
p2	18	F	clitoridean hypertrophy	46,XX	N	gonads, OGI VN	no pathogen CNV
p3	1	F	Right inguinal hernia. Feminine OGE. 2 aunts maternal line with primary amenhoree	46,XY	N	left gonads in inguinal conduct. Absence muller residus	no pathogen CNV
p4	5	M	Penoscrotal hipospadias. Craniofacial dysmorphism. Blefarophimosis. Short stature. Aortic bicuspidia. DSV. Development delay	46,XY	N	gonads N, no mullerian residus	VOUS CNV SYCE1
p5	7	M	Micropenis. Testicular hypoplasia	46,XY	N		VOUS CNV SYCE1
p6	18	M	Micropenis. Pubertary delay	46,XY	N		CNV dup 16p11.2
p7	1	F	clitoridian hypertrophy	46,XX	17OHP↑	uterus	Del CYP21A2
p8	2	female	penoclitoridian gland, labial hypertrophy fusionated posterior, single meat, no palpable gonads	46,XY	N	no visible gonads	no pathogen CNV
p9	3	M	micropenis. Hypospadias	46,XY	N	no muller residues	no pathogen CNV
p10	20	F	amenoree. Hirsutism. Gonadal dysgenesis	46,XX	N		no pathogen CNV
p11	1	F	clitoris hypertrophy, labial hypertrophy, vaginal and uretral meatus presents, right inguinal hernia	46,XY	T DHT ↑	in inguinal hernia-ovalary tumors with testicule appearance	no pathogen CNV
p12	2	M	proximal hypospadias. Cryptorchidism	46,XY			no pathogen CNV
p13	3	F	gonadal dysgenesis, craniofacial dysmorphisms, short 4th and 5th metacarpals, 5th clinodactyly, SGA, short stature	46,XY	AMH, testo↓	no muller residus	no pathogen CNV
p14	3	M	severe hypospadias	46,XY	N		no pathogen CNV
p15	14	Male	Penian hypospadias. Right cryptorchidism. Ginecomastia. Pubertal development.	46,XY	N	no muller residus, left testicule in inguinal conduct, a smaller tumor with the same localisation in right side	no pathogen CNV
p16	3	Male	Bilateral cryptorchidism. Gonadal dysgenesis	46,XY	LH,FSH ↑↑↑	left scleroatrophic testicule, ecografic, absent right testicule	no pathogen CNV
p17	1	Male	penoscrotal hypospadias. Scrotal bifidity. Testicules in normal position	46,XY	T, DHT↑	normal testicules	no pathogen CNV

Patient	chr	start	stop	size	CNV	Gene	Interpretation
p4	10	135257091	135378802	121711	Dup	SYCE1	VOUS
p5	10	135252347	135378802	126455	Dup	SYCE1	VOUS
p6	16	29595483	30192561	597078	Dup	16p11.2	Pathogenic
p7	6	32005904	32006896	992	Homo del	CYP21A2	Pathogenic





CONCLUSIONS

- 4/17 patients (23%) present pathogenic CNV or probably pathogenic VOUS
- The knowledge of the genetic instruments available allow a better diagnosis in DSD
- A good partenerships endocrinologist-geneticist is also important for a better diagnostic efficiency
- A complete clinical, hormonal and ultrasound assessement in DSD cases is indispensable for the interepretation of genetic results
- We recommend using genetic testing protocols in DSD, and also a good partenerships with the specialised centres in these disorders