Editorial

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Clinical tools in the diagnosis of disorders of sex development: a switch from the hormonal to the genetics laboratory?

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Traditionally, the vast majority of societies around the world have had a binary approach to sex. “Girl or boy?” has typically been the first question about a newborn. This vision deeply rooted in the society has undoubtedly shaped the medical approach throughout times in face of individuals in whom the genetic sex, the sex of the gonads and/or the appearance of the genitalia showed inconsistencies. Yet, it was only in 2005 that experts in the various fields related to these conditions, including paediatricians, endocrinologists, surgeons, geneticists, psychologists and patients’ organisations first met to critically appraise the management of intersex disorders from a broad perspective and reach a consensus on future directions. The “Chicago consensus” set the bases for the use of a new nomenclature by coining the term “Disorders of Sex Development (DSD)” and, more importantly, dealt with critical issues such as the investigation and management of patients with DSD by a multi-disciplinary team, the recommendation on the assignment of a social gender to the newborn considering cultural aspects of the family and the need for prospective studies addressing long-term outcomes [1]. Despite the relatively short time elapsed since then, major scientific and societal changes have occurred, which lead to permanent revisions on the subject [2–4].

One particular issue that has revolutionised the approach of diagnosis of congenital conditions is the advent of high throughput technologies, such as next-generation

sequencing (NGS). Until the first decade of the present century, the candidate-gene approach prevailed, based on the anatomic and hormonal features of the patient with DSD [5]. The molecular diagnosis yield was relatively poor, except for extremely typical conditions such as complete androgen insensitivity syndrome (CAIS), the persistent Müllerian duct syndrome (PMDS) or congenital adrenal hyperplasia (CAH) (Table 1), where pathogenic variants (“mutations”) in the genes respectively encoding the androgen receptor, anti-Müllerian hormone (AMH) or its receptor or the enzyme 21-hydroxylase were found in the majority of the cases. Conversely, the diagnostic efficiency was low in patients with gonadal dysgenesis, partial androgen insensitivity, ovotesticular DSD or non-CAH 46,XX DSD. The use of gene panels in the clinical setting or of the whole exome or whole genome sequencing in the research setting has dramatically increased the attainment of an etiologic diagnosis in patients with DSD [6].

Does this mean the end of the clinical characterisation of patients with ambiguous genitalia or discordance between the aspect of the external genitalia and the karyotype? The availability of NGS is still limited. But even when it will become widespread – following its constant cost reduction –, the interpretation of the big data yielded by exome or genome sequencing will rely on the validation of the underlying pathophysiology. Indeed, one of the major challenges of this technology is its capacity to determine the pathogenicity of the thousands of gene variants detected in one read, and adherence to consensus guidelines produced by professional associations, like the American College of Medical Genetics and Genomics and the Association for Molecular Pathology is warranted [7]. These guidelines stress the importance of both the preanalytical and the postanalytical procedures. In fact, to decide performing NGS a clinical characterisation of the patient is essential, and the deepest the phenotyping, the more efficient the diagnostic yield. Similarly, the finding of variants of unknown significance in unexpected genes can be more easily interpreted when a precise characterisation of the patient has been made, by using anatomical descriptions (clinical, imaging) and hormonal assessments, including sex steroids, AMH and gonadotrophins [8–10]. Achieving a

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Table 1: Genetic aetiologies of Disorders of Sex Development (DSD).

46,XY DSD	Sex chromosome DSD (45,X/46,XY – 46,XX/46,XY – etc.)	46,XX DSD
Gonadal dysgenesis Defects of androgen synthesis (Leydig cell hypoplasia, Steroidogenic defects) Disorders of androgen action (Partial or complete AIS) Disorders of AMH synthesis or action (PMDS)	Gonadal dysgenesis Ovotesticular DSD	Testicular DSD Ovotesticular DSD Excess of androgen synthesis (CAH, Aromatase deficiency)

precise genetic diagnosis leads to a better, personalised medical approach in many cases. However, faced with the impossibility of performing sophisticated genetic analyses, a clinical and endocrine characterisation may be very useful for the first steps in the management of a patient with DSD [8, 9]. Indeed, patients need to be considered case by case, according to their karyotype, age at presentation and appearance of the internal and external genitalia, as well as other non-reproductive features [10]. Furthermore, the contribution made by the progressive introduction of mass spectrometry for the accurate measurement of steroids in serum or urine samples shows the improvement in diagnosis in neonates [11] or in the therapeutic management later in life [12–14].

In conclusion, deep phenotyping by means of anatomic and endocrine characterisation remains essential for the initial diagnosis of DSD with either a 46,XX, 46,XY or other abnormal karyotypes. Enlarged panels of sex steroid measurement by mass spectrometry and massive parallel sequencing of potentially involved genes have come to improve the efficiency in aetiological diagnosis leading to an enhanced personalised medicine approach in DSD.

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