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Commentary

Long-term healthcare of people with disorders of sex development: Predictors of pubertal outcomes of partial androgen insensitivity syndrome

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Partial androgen insensitivity syndrome (PAIS) is a relatively common type of 46, XY disorders of sex development (DSD) caused by hypomorphic mutations in the androgen receptor gene (AR) [6]. Patients with PAIS typically present with hypomasculinized external genitalia at birth [6]. The median external masculinization score (EMS) of neonates with PAIS is around 5–7 (typical female- and male-type genitalia correspond to scores 0 and 12, respectively) [5], causing difficulties in sex assignment of many cases. Moreover, PAIS tends to be associated with poor clinical outcomes: PAIS patients more frequently require multiple surgeries and exhibit insufficient masculinization in adulthood than patients with similar genital abnormalities at birth but no AR mutations [5]. Since degrees of pre- and post-natal masculinization are highly variable among PAIS patients [5,6], personalized management is necessary for each case. In this regard, outcome prediction for children with PAIS is essential for the decision-making of clinicians and patients' parents; however, no reliable biomarkers for long-term outcomes of PAIS have been documented.

In *EBioMedicine*, Lek and colleagues introduce their findings about outcome predictors of PAIS [4]. The authors performed a prospective long-term follow-up study on 27 patients with molecularly confirmed PAIS. The authors also investigated the residual activity of each mutant AR protein by *in vitro* assays. The results suggested that the pubertal outcomes of PAIS patients do not parallel to the predicted activities of the mutant proteins. Instead, the outcomes were correlated with EMS at birth. Specifically, all patients with EMS ≥ 5 at birth subsequently exhibited spontaneous puberty and frequently developed normal adult male-type external genitalia, while 33% and 83% of patients with EMS < 5 at birth did not show spontaneous puberty and satisfactory adult genitalia, respectively. These results highlighted the usefulness of EMS as clinical parameters of PAIS. Since EMS can be easily obtained from all neonates suspected to have PAIS, these findings would facilitate decision-making in clinical practice. From the viewpoint of basic research, the paper revealed limitations of current *in vitro* methods in the functional assessment of hypomorphic mutations in *AR*.

In their paper, Lek et al. also pointed out two unsolved issues that need to be addressed in future studies. First, it remains unknown whether blood hormone values can be used as biomarkers for pubertal outcomes of PAIS. In this regard, previous studies have shown that PAIS occasionally underlies testicular dysfunction, in addition to androgen resistance in peripheral tissues [5]. Indeed, elevated blood levels of FSH and/or blunted responses of testosterone to human chorionic gonadotropin stimulation have been reported in multiple patients with PAIS [5]. Testicular dysfunction of these patients was assumed to result from maldescent of the testis or insufficient androgen action in the developing testis [5]. Since testicular dysfunction further attenuates suboptimal masculinization caused by androgen resistance, hormonal evaluation of children with PAIS may provide information about future phenotypes. Second, Lek et al. did not examine somatic mosaicism of AR mutations, which has previously been reported in multiple patients with PAIS [3]. The lack of genotype-phenotype correlation in this cohort may be ascribed to somatic mosaicism, because mosaicism can modify phenotypic severities of the patients. Furthermore, Lek et al. mentioned that current *in vitro* assays may not be sensitive enough to detect mild functional impairment of AR mutations. In this regard, novel methods for the functional assessment of AR mutants, such as quantification of APOD mRNA in genital skin fibroblasts, have recently been developed [2]. In future studies, detection of mosaicism and the use of novel assay methods would help to clarify precise genotype-phenotype correlation of PAIS.

An important issue that also needs to be addressed is psychological outcomes of PAIS patients. Currently, there are no parameters to predict long-term gender identity in children with DSD including PAIS [1]. The lack of reliable predictors for gender development raises difficulty in sex-assignment of neonates. Indeed, PAIS patients have a risk of gender incongruousness in adulthood. In addition, PAIS has been linked to a relatively high risk of gynecomastia, cardiovascular diseases, glucose intolerance, and osteoporosis [5]. Thus, biomarkers for these complications also need to be established.

Altogether, the study by Lek et al. [4] provided useful information for the long-term healthcare of DSD. Yet, further studies are necessary to determine reliable predictors of various health issues of PAIS. To this end, international registries and study groups for DSD have been launched recently (for example, I-DSD registry, https://www.i-dsd.org/) [1]. Such research networks enable scientists to collect longitudinal data of a large number of patients, and are therefore expected to promote personalized management for patients with DSD including PAIS.

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Conflict of interest

The author declares no conflict of interest.

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