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Association of genetic disorders and congenital malformations with premature ovarian insufficiency: a nationwide register-based study

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STUDY QUESTION: Are genetic disorders and congenital malformations associated with premature ovarian insufficiency (POI)?

SUMMARY ANSWER: A wide range of genetic disorder and congenital malformation diagnoses are associated with POI, especially early onset POI.

WHAT IS KNOWN ALREADY: POI is known to be associated with some genetic disorders, such as Turner syndrome and Fragile X premutation. Multiple genetic syndromes, such as ataxia teleangiectasia and galactosemia, have also been associated with an increased risk of POI, and many of these genetic syndromes manifest with various congenital malformations. In previous studies, a genetic aetiology has been found for 7–15% of POI cases.

STUDY DESIGN, SIZE, DURATION: This population-based study included 5011 women diagnosed with POI in 1988–2017. The data were collected from various national registries and covers women with POI nationwide.

PARTICIPANTS/MATERIALS, SETTING, METHODS: We identified 5011 women diagnosed with POI from 1988 to 2017 from the drug reimbursement registry of the Social Insurance Institution of Finland. Women with surgical POI (bilateral oophorectomy for benign indications) were not included. We selected four population controls per woman with POI matched by month and year of birth and municipality of residence. Diagnostic codes for genetic disorders and congenital malformations (GD/CM) for the cases and controls were searched from the Hospital Discharge Register. Binary logistic regression was used to compare the odds for GD/CM among cases and controls. To minimize bias, for the statistical analyses, we excluded diagnoses which were reported <2 years prior to the index date.

MAIN RESULTS AND THE ROLE OF CHANCE: Of the women with POI, 15.9% (n = 797) had at least one diagnostic code for GD or CM. The odds ratio (OR) for Turner syndrome was 275 (95% CI 68.1–1110), and for other sex chromosome abnormalities, it was 12.7 (95% CI 4.1–39.1). For autosomal single gene disorders, the OR was 16.5 (95% CI 6.2–43.7). Women with POI had a higher odds of having a GD/CM diagnosis in all categories. The OR for GD/CM diagnoses was highest among the youngest POI patients (10–14 years old, OR 24.1, 95% CI 15.1–38.2). The odds of having POI were higher the more GD or CM diagnoses a woman had.

LIMITATIONS, REASONS FOR CAUTION: Some women with POI might not have sought help for their symptoms and therefore remain undiagnosed. Due to the register-based nature of our study, we did not have access to more specific genetic diagnoses than international classification of diseases offers.

WIDER IMPLICATIONS OF THE FINDINGS: GD/CM diagnoses were strongly associated with POI, especially when POI was diagnosed at a young age. The risk of POI was highest in women with multiple GD/CM diagnoses. Early onset POI can be a sign of underlying genetic disorder or congenital anomaly, and this should serve as a reminder for clinicians to consider further examinations. To avoid unnecessary delay in the diagnosis of POI and starting relevant hormone replacement therapy treatment, clinicians should be aware of these associations.

STUDY FUNDING/COMPETING INTEREST(S): Oulu University Hospital financially supported this work. H.S. has received personal grants from the Finnish Menopause Society, Oulu Medical Research Foundation, and Finnish Research Foundation of Gynaecology and Obstetrics. S.S. has received grants from the Finnish Menopause Society, the Finnish Medical Foundation, and the Juho Vainio Foundation. None of the authors have any competing interests to declare.

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Introduction

Premature ovarian insufficiency (POI) means loss of ovarian function before the age of 40 years (Webber *et al.*, 2016). The prevalence of POI at the age of 40 is estimated to be 0.5–1% (Mishra *et al.*, 2017; Golezar *et al.*, 2019; Silvén *et al.*, 2022). The aetiology of POI is heterogeneous and includes autoimmune, iatrogenic, infectious, and genetic causes (Jiao *et al.*, 2017). New technologies, such as next-generation sequencing and whole-exome sequencing, have enhanced progress in identifying genetic causes for POI. A genetic cause is found for 7–50% of patients, although the percentages are likely to be exaggerated due to the poor variant curation in some of the published studies (Bachelot *et al.*, 2009; Jiao *et al.*, 2012, 2017; Shen *et al.*, 2021; Heddar *et al.*, 2022; Rouen *et al.*, 2022; Tucker *et al.*, 2022). Majority of POI cases remain undefined.

The most common genetic disorders (GDs) among women with POI are X-chromosome-related Turner syndrome and Fragile X premutation. Turner syndrome occurs in 1 in 1700–3000 live-born girls. Typical characteristics include short stature, lymphoedema, cardiac disease, renal malformations, and gonadal dysgenesis. (Ranke and Saenger, 2001; Sybert and McCauley, 2004; Bernard *et al.*, 2016). In women with Turner syndrome, only 5–20% have spontaneous menarche, and more than one-third of these women reach menopause within 5 years of menarche (Bernard *et al.*, 2016; Calanchini *et al.*, 2020; Komura *et al.*, 2021). About 50% of the Turner women miss the other X chromosome entirely, but the additional 50% have different karyotypes, such as 45,X/46,XX mosaicism or ring X chromosome (Lin *et al.*, 2019). The variation in karyotypes explains some, but not all, of the wide variety of phenotypes (Huang *et al.*, 2021). Of women who carry the Fragile X premutation, approximately 15–24% are affected by POI (Allen *et al.*, 2021). GDs other than Turner syndrome and Fragile X premutation are found only in a small proportion of POI cases.

Multiple genetic syndromes have been associated with an increased risk of POI. Examples of POI-related syndromes are galactosemia (due to variants in the *GALT* gene), BPES (blepharophimosis, ptosis, epicanthus inversus syndrome, due to genetic variant in *FOXL2*), ataxia-telangiectasia (due to variants in the *ATM* gene), and premature ageing syndromes like Bloom syndrome. Many of these GDs are also associated with various congenital malformations (CM) (Rossetti *et al.*, 2017). A mother's POI is associated with congenital anomalies in children (Fauque *et al.*, 2021), but the prevalence of congenital anomalies in women with POI has not been studied. In our previous register-based study, we found that the risk for POI is significantly increased among first-degree relatives of women with POI, which might indicate a higher prevalence of hereditary aetiology among these patients (Silvén *et al.*, 2022). Among children born in Finland in 2018, 5.2% were diagnosed with major congenital anomaly before the age of 1 year (Kiuru-Kuhlefelt, 2021).

Previous registry population-based studies of women with POI are scarce. Our aim was to assess the associations of genetic disorders and congenital malformations (GD/CM) with POI and, thereby, deepen the understanding of the aetiology of POI by using reliable registry-based data from Finland.

Materials and methods

Study population and design

We identified women with POI in Finland using reimbursement data for hormone replacement therapy (HRT) from the Social Insurance Institution of Finland (SII). Women with POI get 100% reimbursement for HRT until they are 50 years old. Obtaining the reimbursement is a two-step process. First, the treating physician writes a certificate which includes relevant information of the disease and diagnostic testing performed. Second, an expert physician at SII checks for the eligibility of the reimbursement and, if the criteria are met, the woman receives the reimbursement. Reimbursement criteria have changed slightly over time but have always aligned with international criteria for POI. Changes in the reimbursement criteria have been described in detail in our previous article (Silvén *et al.*, 2022). We identified 5011 women with non-surgical POI diagnosed between 1988 and 2017.

Four population controls for each POI case were selected from the Finnish Population Information System of the Digital and Population Data Services Agency, matched by month and year of birth and municipality of residence. The controls had to be alive and living in Finland on the date when the reimbursement was granted for the case (index date). Information from the registries was combined using personal identity codes given to all permanent residents in Finland.

Data collection

Data from the Hospital Discharge Register (HDR) of the Finnish Institute for Health and Welfare, THL were used to find GD/CM

diagnoses of the cases and controls from 1970 to 2017. The included diagnostic codes from the 8th, 9th, and 10th version of International Classification of Diseases (ICD) can be found in Supplementary Table SI. As part of the diagnostic process of POI, women undergo a comprehensive clinical examination and diagnostic tests (e.g. chromosomes and gynaecological ultrasound). Such a diagnostic process increases the likelihood of having a record in the Hospital Discharge Register and the likelihood of having a diagnosis code of GD/CM written in the Hospital Discharge Register record. To minimize bias, for the statistical analyses, we excluded diagnoses which were reported <2 years before the index date. The 2-year cut-off was based on statistical analysis and a clinical estimation of the diagnostic process in POI. For descriptive purposes, we also reported the frequencies of diagnoses in women with POI ever reported to the Hospital Discharge Register.

The number of women with malformations in the respiratory system, spleen or endocrine glands, CM syndromes due to known exogenous causes, disorders of sexual differentiation or development, and other chromosomal abnormalities were too small to report exact numbers or to analyse in regression models. Due to the Finnish data protection policy, we do not report exact numbers if there are <5 cases or controls in a specific subgroup. However, the approximate numbers are presented in Table I. We excluded women with POI and their controls who had no information in the Hospital Discharge Register (22 women with POI and 539 controls).

Methods

We calculated the odds ratios (ORs) and 95% CIs for GD/CM with binary logistic regression analysis. The analyses were also stratified by age at the index date. In addition, we calculated ORs for one, two, and three or more GD/CM diagnoses in one person.

The data were processed with RStudio and SAS Enterprise guide 7.1, and statistical analyses were performed with IBM SPSS 28.0 (IBM Corp., Armonk, NY, USA). A *P*-value <0.05 was considered statistically significant. The data were analysed and reported in accordance with the STROBE statement.

Study approvals

We obtained approval for this study from the Finnish Institute for Health and Welfare (THL/1973/5.05.00/2019), the Social Insurance Institution (135/522/2018) and the Digital and Population Data Services Agency (VRK 4304-2019-2). Anonymization was done before

Table I Number of chromosomal abnormality and congenital malformation diagnoses among 5011 women with premature ovarian insufficiency (POI) reported in the Hospital Discharge Register during the follow-up period.

	n	%
Genetic disorders		
Turner syndrome	256	5.13
Autosome chromosomal abnormalities	35	0.70
Sex chromosome abnormalities*	44	0.88
Autosomal single-gene disorders	28	0.56
Other chromosomal abnormalities	5	0.10
Congenital malformations of gynaecological organs		
Congenital malformations of the ovary, fallopian tubes and broad ligaments	101	2.02
Congenital malformations of the uterus and cervix	47	0.94
Other congenital malformations of female genitalia	19	0.38
Other congenital malformations		
Skin and mammary gland anomalies	57	1.14
Congenital malformations of the nervous system	31	0.62
Congenital malformations of the eye, ear, face, and neck	84	1.68
Congenital malformations of the circulatory system	120	2.41
Cleft lip and cleft palate	20	0.40
Other congenital malformations of the digestive system	47	0.94
Congenital malformations of the urinary system	42	0.84
Congenital malformations and deformations of the musculoskeletal system	197	3.95
Unspecified congenital malformations	45	0.90
Disorder of sexual differentiation/development	7	0.1
Congenital malformations of the respiratory system	9	0.2
Congenital malformation syndromes due to known exogenous causes	1–4	<0.1
Congenital malformations of spleen or endocrine glands	1–4	<0.1

*Turner syndrome excluded.

analyses; hence, we had no access to identifiable personal data. Due to the registry-based nature of the study, ethics committee approval is not required according to the Finnish policy.

Results

Of the women with POI, 15.9% (n = 797) had at least one GD/CM diagnosis when we included all diagnoses registered in the Hospital Discharge Register from the whole study period (Table I). Of POI cases, 9.6% (n = 479), and 3.5% (n = 675) of the control women, had diagnoses registered more than 2 years before the index date.

Table II reports the numbers of GD/CM diagnoses registered at least 2 years before receiving the reimbursement among the cases and controls as well as the ORs for POI in these diagnostic groups. The OR for Turner syndrome was very high (275, 95% CI 68.1–1110). Also, the odds for sex chromosome abnormalities excluding Turner syndrome (OR 12.7, 95% CI 4.1–39.1) and autosomal single gene disorders (OR 16.5, 95% CI 6.2–43.7) were high, although the number of cases in the data was low. Women with POI had higher odds of having a diagnosis from all other subgroups and in various organs (Table II).

The ORs for GD/CM diagnoses were higher the younger the POI diagnosis was made (Table III). The mean age for POI diagnosis was the youngest, at 15.9 years, among women with Turner syndrome. Of the women diagnosed with Turner syndrome, 52.6% (n = 70) received the right for reimbursement for POI at the age of 10–14 years.

The OR for POI increased with an increasing number of GD/CM diagnoses (Table IV). Since Turner syndrome was the dominating subgroup in our data and carried a very high OR, we also estimated the ORs for numerous GD/CM diagnoses, excluding women with Turner syndrome. Still, the OR for POI increased with an increasing number of diagnoses. In women with three or more diagnostic codes for GD/CM, the OR for POI was 10.4 (95% CI 4.8–22.4), when women with Turner syndrome were excluded.

Discussion

Based on our study, the prevalence of GD/CM diagnoses was higher among women with POI than in the general population. As expected, the risk for POI in women with Turner syndrome was high, but our study shows that various other groups of GDs and CMs also associate with POI. The risk of POI was highest in women with three or more diagnoses of GD/CM, even when women with Turner syndrome were excluded. Women with GD/CM diagnoses received reimbursement for POI at a younger age than women with POI in general. These factors lead our thoughts towards the possibility of a higher prevalence of genetic syndromes among women who experience POI at an early age. Based on our findings, early onset POI should also

Table II The number of chromosomal abnormality and congenital malformation diagnoses among women with premature ovarian insufficiency (POI) and controls.

Diagnostic group	POI women (n = 4989)		Controls (n = 19 492)		OR	95% CI
	n	%	n	%		
Genetic disorders						
Turner syndrome	137	2.75	1–4	<0.03	275	68.1–1110
Autosome chromosomal abnormalities	13	0.26	8	0.04	6.4	2.6–15.4
Sex chromosome abnormalities*	13	0.26	1–4	<0.03	12.7	4.1–39.1
Autosomal single-gene disorders	21	0.42	5	0.03	16.5	6.2–43.7
Congenital malformations of gynaecological organs						
Congenital malformations of the ovary, fallopian tubes, and broad ligaments	38	0.76	33	0.17	4.5	2.8–7.2
Congenital malformations of the uterus and cervix	21	0.42	45	0.23	1.8	1.1–3.1
Other congenital malformations						
Skin and mammary gland anomalies	18	0.36	38	0.19	1.9	1.1–3.3
Congenital malformations of the nervous system	18	0.36	20	0.10	3.5	1.9–6.7
Congenital malformations of the eye, ear, face, and neck	68	1.36	154	0.79	1.7	1.3–2.3
Cleft lip and cleft palate	19	0.38	23	0.12	3.2	1.8–5.9
Other congenital malformations of the digestive system	34	0.68	56	0.29	2.4	1.6–3.7
Congenital malformations of the urinary system	34	0.68	60	0.31	2.2	1.5–3.4
Congenital malformations and deformations of the musculoskeletal system	123	2.47	141	0.72	3.5	2.7–4.4
Unspecified congenital malformations	37	0.74	11	0.06	13.2	6.7–26.0

Odds ratios (ORs) with 95% CIs are calculated for diagnoses registered a minimum of 2 years before the index date.
*Turner syndrome excluded.

Table III Odds ratios (ORs) for chromosomal abnormality or congenital malformation diagnosis by age at premature ovarian insufficiency (POI) diagnosis.

POI diagnostic age	n, POI and genetic disorder or congenital malformation diagnosis (n = 473)	%	n, POI and no genetic disorder or congenital malformation diagnosis (n = 4509)	%	OR	95% CI
10–14	97	20.5	86	1.9	24.1	15.1–38.2
15–19	104	22.0	249	5.5	8.5	6.0–11.9
20–24	42	8.9	212	4.7	5.7	3.5–9.2
25–29	28	5.9	351	7.8	2.0	1.3–3.2
30–34	65	13.7	798	17.7	2.5	1.8–3.4
35–39	137	29.0	2813	62.4	1.4	1.2–1.7

Table IV Odds ratios (ORs) for premature ovarian insufficiency (POI) by the number of chromosomal abnormality and congenital malformation diagnoses.

Number of genetic or congenital malformation diagnoses	POI cases		Controls		OR	95% CI of OR
	n	%	n	%		
Turner syndrome included						
0	4510	90.40	18817	96.54	1.0	Ref.
1	338	6.77	630	3.23	2.2	2.0–2.6
2	96	1.92	36	0.18	11.1	7.6–16.3
≥3	45	0.90	9	0.05	20.9	10.2–42.7
Turner syndrome excluded						
0	4508	92.95	18309	96.56	1.0	Ref.
1	276	5.69	609	3.21	1.8	1.6–2.1
2	43	0.89	35	0.18	5.0	3.2–7.8
≥3	23	0.47	9	0.05	10.4	4.8–22.4

alert clinicians of the higher risk of GD/CM diagnoses and consider further evaluation for these patients.

Our study has several strengths. The study consisted of a large number of POI women from the nationwide whole-population data, and the follow-up time was 30 years. The diagnoses of POI in our cohort were reliable, as they were made by medical professionals. They were based on HRT reimbursement rights and, hence, evaluated by two independent physicians, one being the treating physician and the other one an expert at SII. None of the diagnoses were based on self-reporting. The relationship between POI and GD/CM has not previously been studied to this extent.

Our study also has some limitations. We only had access to women who had received the right to POI reimbursement. However, it is likely that undiagnosed women with POI are a small minority as we expect that most women seek medical advice in the event of amenorrhoea at a young age. Another limitation is that, due to ICD coding, we could not find more specific genetic diagnoses than those used by the Hospital Discharge Register. We did not have access to karyotypes and do not know if genome sequencing was performed. On the other hand, not every patient with a CM is tested with wide gene panels, particularly as the earliest POI diagnoses in our data were made in the 1980s. Women with suspected POI undergo diagnostic test panels before receiving the diagnosis and reimbursement for HRT. The population controls are unlikely to have a similar extensive evaluation done. To minimize the bias, the focused diagnostic testing and selective reporting to HDR might cause, we included only diagnoses received a minimum of 2 years before the index date in the statistical analyses.

The HDR has diagnoses from hospitals and tertiary clinics, where in Finland women suffering from amenorrhoea are treated, with a few exceptions. Some women with intellectual disabilities are treated primarily in primary health facilities, not in tertiary clinics. Since managing menstruation might be difficult with an intellectual disability, it is often desirable to treat patients with effective hormonal therapy, such as an intrauterine device or the contraceptive pill to achieve amenorrhoea. It is also likely that POI is not considered as a major problem when

patients have severe multisystemic problems or life-threatening conditions. These factors might lead to underdiagnosis of POI in women with disabilities, and it would be interesting to see further studies about the risk of POI in women with GD/CM diagnoses and to see whether POI is indeed more common in this group of women.

Based on our findings, women with GD/CM, especially multiple diagnoses, are at increased risk of POI. To avoid unnecessary delay in the diagnosis of POI and starting relevant HRT treatment, clinicians should be aware of these associations. On the other hand, early onset POI can be a sign of an underlying GD or congenital anomaly, and thus further systematic examinations of these women are recommended.

Supplementary data

Supplementary data are available at *Human Reproduction* online.

Data availability

The data underlying this article will be shared upon reasonable request to the corresponding author.

Authors' roles

All authors participated in planning the study design. P.P. and H.S. performed the data analyses. The article was drafted by H.S., S.M.S., P.P., M.N., and E.P. All authors were involved in commenting and discussing the article.

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Conflict of interest

None of the authors have any conflicts of interest to declare.

References

Allen EG, Charen K, Hipp HS, Shubeck L, Amin A, He W, Nolin SL, Glicksman A, Tortora N, McKinnon B *et al.* Refining the risk for fragile X-associated primary ovarian insufficiency (FXPOI) by FMR1 CGG repeat size. *Genet Med* 2021;**23**:1648–1655.

Bachelot A, Rouxel A, Massin N, Dulon J, Courtillot C, Matuchansky C, Badachi Y, Fortin A, Paniel B, Lecuru F *et al.*; POF-GIS Study Group. Phenotyping and genetic studies of 357 consecutive patients presenting with premature ovarian failure. *Eur J Endocrinol* 2009;**161**:179–187.

Bernard V, Donadille B, Zenaty D, Courtillot C, Salenave S, Brac de la Perrière A, Albarel F, Fèvre A, Kerlan V, Brue T *et al.*; CMERC Center for Rare Disease. Spontaneous fertility and pregnancy outcomes amongst 480 women with Turner syndrome. *Hum Reprod* 2016;**31**:782–788.

Calanchini M, Aye CYL, Orchard E, Baker K, Child T, Fabbri A, Mackillop L, Turner HE. Fertility issues and pregnancy outcomes in Turner syndrome. *Fertil Steril* 2020;**114**:144–154.

Fauque P, De Mouzon J, Devaux A, Epelboin S, Gervoise-Boyer M-J, Levy R, Valentin M, Viot G, Bergère M, De Vienne C *et al.* Do in vitro fertilization, intrauterine insemination or female infertility impact the risk of congenital anomalies in singletons? A longitudinal national French study. *Hum Reprod* 2021;**36**:808–816.

Golezar S, Tehrani FR, Khazaei S, Ebadi A, Keshavarz Z. The global prevalence of primary ovarian insufficiency and early menopause: a meta-analysis. *Climacteric* 2019;**22**:403–411.

Heddar A, Ogur C, Da Costa S, Braham I, Billaud-Rist L, Findlinki N, Beneteau C, Reynaud R, Mahmoud K, Legrand S *et al.* Genetic landscape of a large cohort of Primary Ovarian Insufficiency: new genes and pathways and implications for personalized medicine. *eBioMedicine* 2022;**84**:104246.

Huang AC, Olson SB, Maslen CL. A review of recent developments in Turner syndrome research. *J Cardiovasc Dev Dis* 2021;**8**:138.

Jiao X, Qin C, Li J, Qin Y, Gao X, Zhang B, Zhen X, Feng Y, Simpson JL, Chen Z-J. Cytogenetic analysis of 531 Chinese women with premature ovarian failure. *Hum Reprod* 2012;**27**:2201–2207.

Jiao X, Zhang H, Ke H, Zhang J, Cheng L, Liu Y, Qin Y, Chen Z-J. Premature ovarian insufficiency: phenotypic characterization within different etiologies. *J Clin Endocrinol Metab* 2017;**102**:2281–2290.

Kiuru-Kuhlefelt S. *Synnynnäiset epämuodostumat 2018: Epämuodostumien esiintyvyydessä ei merkittäviä muutoksia*, OSF Statistical Report, Vol. 36, 2021. https://www.julkari.fi/bitstream/handle/10024/143270/Synnynn%C3%A4iset%20ep%C3%A4muodostumat%202018.pdf?sequence=5&isAllowed=y.

Komura N, Mabuchi S, Sawada K, Nishio Y, Kimura T, Komura H. Subsequent menstrual disorder after spontaneous menarche in Turner syndrome. *Clin Endocrinol (Oxf)* 2021;**95**:163–168.

Lin AE, Prakash SK, Andersen NH, Viuff MH, Levitsky LL, Rivera-Davila M, Crenshaw ML, Hansen L, Colvin MK, Hayes FJ *et al.* Recognition and management of adults with Turner syndrome: from the transition of adolescence through the senior years. *Am J Med Genet A* 2019;**179**:1987–2033.

Mishra GD, Pandeya N, Dobson AJ, Chung H-F, Anderson D, Kuh D, Sandin S, Giles GG, Bruinsma F, Hayashi K *et al.* Early menarche, nulliparity and the risk for premature and early natural menopause. *Hum Reprod* 2017;**32**:679–686.

Ranke MB, Saenger P. Turner's syndrome. *Lancet* 2001;**358**:309–314.

Rossetti R, Ferrari I, Bonomi M, Persani L. Genetics of primary ovarian insufficiency. *Clin Genet* 2017;**91**:183–198.

Rouen A, Rogers E, Kerlan V, Delemer B, Catteau-Jonard S, Reznik Y, Gompel A, Cedrin I, Guedj A-M, Grouthier V *et al.* Whole exome sequencing in a cohort of familial premature ovarian insufficiency cases reveals a broad array of pathogenic or likely pathogenic variants in 50% of families. *Fertil Steril* 2022;**117**:843–853.

Shen J, Qu D, Gao Y, Sun F, Xie J, Sun X, Wang D, Ma X, Cui Y, Liu J *et al.* Genetic etiologic analysis in 74 Chinese Han women with idiopathic premature ovarian insufficiency by combined molecular genetic testing. *J Assist Reprod Genet* 2021;**38**:965–978.

Silvén H, Savukoski SM, Pesonen P, Pukkala E, Gissler M, Suvanto E, Niinimäki M. Incidence and familial risk of premature ovarian insufficiency in the Finnish female population. *Hum Reprod* 2022;**37**: 1030–1036.

Sybert VP, McCauley E. Turner's syndrome. *N Engl J Med* 2004;**351**: 1227–1238.

Tucker EJ, Tan TY, Stark Z, Sinclair AH. Genomic testing in premature ovarian insufficiency: proceed with caution. *Biol Reprod* 2022; **107**:1155–1158.

Webber L, Davies M, Anderson R, Bartlett J, Braat D, Cartwright B, Cifkova R, de Muinck Keizer-Schrama S, Hogervorst E, Janse F *et al*. ESHRE Guideline: management of women with premature ovarian insufficiency. *Hum Reprod* 2016;**31**:926–937.