

Homozygous Loss-of-function Mutations in *SOHLH1* in Patients With Nonsyndromic Hypergonadotropic Hypogonadism

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Context: Hypergonadotropic hypogonadism presents in females with delayed or arrested puberty, primary or secondary amenorrhea due to gonadal dysfunction, and is further characterized by elevated gonadotropins and low sex steroids. Chromosomal aberrations and various specific gene defects can lead to hypergonadotropic hypogonadism. Responsible genes include those with roles in gonadal development or maintenance, sex steroid synthesis, or end-organ resistance to gonadotropins. Identification of novel causative genes in this disorder will contribute to our understanding of the regulation of human reproductive function.

Objectives: The aim of this study was to identify and report the gene responsible for autosomal-recessive hypergonadotropic hypogonadism in two unrelated families.

Design and Participants: Clinical evaluation and whole-exome sequencing were performed in two pairs of sisters with nonsyndromic hypergonadotropic hypogonadism from two unrelated families.

Results: Exome sequencing analysis revealed two different truncating mutations in the same gene: *SOHLH1* c.705delT (p.Pro235fs*4) and *SOHLH1* c.27C>G (p.Tyr9stop). Both mutations were unique to the families and segregation was consistent with Mendelian expectations for an autosomal-recessive mode of inheritance.

Conclusions: *Sohlh1* was known from previous mouse studies to be a transcriptional regulator that functions in the maintenance and survival of primordial ovarian follicles, but loss-of-function mutations in human females have not been reported. Our results provide evidence that homozygous-truncating mutations in *SOHLH1* cause female nonsyndromic hypergonadotropic hypogonadism. (*J Clin Endocrinol Metab* 100: E808–E814, 2015)

The diagnosis of hypergonadotropic hypogonadism, also known as primary or gonadal hypogonadism, is based on the clinical finding of absent/delayed or arrested puberty and primary or secondary amenorrhea. Biochemically it is associated with elevated plasma FSH and LH as well as low estradiol levels in females. Failure of normal estradiol and inhibin production by the ovaries causes elevated FSH and LH secretion from the pituitary due to impaired negative feedback on the synthesis of gonadotropins. Hypergonadotropic hypogonadism can occur commonly due to acquired damage of the ovaries (such as surgery, autoimmune diseases, infections, irradiation and chemotherapy) or congenital disorders that affect normal ovarian development and function (1).

Hypergonadotropic hypogonadism may be either syndromic or nonsyndromic. Syndromic hypergonadotropic hypogonadism may be associated with Turner syndrome (45,X), carbohydrate-deficient glycoprotein syndromes (*GALT*) (MIM#230400), pseudohypoparathyroidism type 1a (*GNAS1*) (MIM#103580), progressive external ophthalmoplegia (*POLG*) (autosomal dominant: MIM#157640, autosomal recessive: MIM#258450), autoimmune polyglandular syndrome type 1 (*AIRE*) (MIM#240300), ovarian leukodystrophy (*EIF2B2*) (MIM#603896), ataxia telangiectasia (*ATM*) (MIM#208900), Demirhan syndrome (*BMPR1B*) (MIM#609441), blepharophimosis-ptosis-epicanthus inversus syndrome (*FOXL2*) (MIM#110100) (2), or Perrault syndrome (*PRLTS*) (*HSD17B4*, *HARS2*, *CLPP*, *LARS2*, *C10orf2*) (*PRLTS1*: MIM#233400, *PRLTS2*: MIM#614926, *PRLTS3*: MIM#614129, *PRLTS4*: MIM#615300, *PRLTS5*: MIM#616138) (3–6). Nonsyndromic hypergonadotropic hypogonadism patients are females with 46,XX karyotype and they can have different modes of inheritance. Nonsyndromic hypergonadotropic hypogonadism patients can be classified according to the effects of the related gene defects on the reproductive system, such as: genes affecting steroidogenesis and follicular function (eg, *FSHβ*, *FSHR*, *LHβ*, *LHR*, *NR5A1*, *CYP17*, and *CYP19*), genes having a role in oogenesis (eg, *NOBOX*) or genes affecting folliculogenesis (eg, *BMP15*) (2, 7).

Here we report four patients diagnosed with nonsyndromic hypergonadotropic hypogonadism, sister pairs from two unrelated consanguineous families. Genomic analysis of these families led to the identification of *SOHLH1* as the critical gene for autosomal-recessive hypergonadotropic hypogonadism. *Sohlh1* was shown previously to be expressed during oogenesis in mice and to play a critical role in early folliculogenesis (8). We now describe phenotypic consequences of loss-of-function mutations of *SOHLH1* in human females.

Methods and Materials

Patients

This study was approved by the institutional review boards at Baylor College of Medicine and University of Washington. Institutional review board–approved informed consent was obtained from all participants (patients and their kindred that took part in the study) prior to enrollment. All subjects were evaluated by one or more pediatricians, endocrinologists, and clinical geneticists. Participants provided venous blood samples, and genomic DNA was extracted from whole blood using the Genra Puregene Blood Extraction Kit based on the manufacturer's protocol (QIAGEN, <http://www.qiagen.com/>).

Sequencing

Genomic DNA from four affected individuals (BAB4619, BAB4620, CF1374.03, and CF1374.04) from the two unrelated families was sequenced and analyzed at Baylor College of Medicine Human Genome Sequencing Center (family HOU1852) (9) and at the King laboratory of the University of Washington (family CF1374). Genomic DNA samples were prepared and sequenced, and variants identified according to previously described protocols (10, 11). Candidate variants identified by exome sequencing were confirmed by Sanger sequencing of all available family members.

Results

Patient characteristics

From family HOU1852, two sisters were referred to the pediatric endocrinology clinic at Marmara University Hospital with primary amenorrhea and lack of secondary sex characteristics at 16.25 and 14.25 years of age, respectively. Further hormonal investigations revealed elevated FSH and LH levels with decreased progesterone concentrations. The estradiol level was low in patient 1 (BAB4619) but patient 2 (BAB4620) had a detectable estradiol level (Table 1). Bone ages for the patients were 12.5 and 12 years, respectively. There was no history of chronic disease, radiation exposure, or chemotherapy. Pelvic ultrasound imaging revealed hypoplastic ovaries (Figure 1) and prepubertal sized uteri in both patients (Table 2). Karyotype analyses were normal and no other significant clinical or dysmorphic features were identified; the patients were clinically diagnosed with nonsyndromic hypergonadotropic hypogonadism. Hormone replacement therapy (HRT) was initiated with estrogen and then cyclic estrogen and progesterone, which resulted in breast development and menstrual cycles in both patients.

From family CF1374, two sisters were referred to the pediatric endocrinology department of Dokuz Eylul University Faculty of Medicine, Izmir, Turkey, with amenorrhea, lack of secondary sex characteristics, and short stature. A detailed clinical description of the family was previously reported (12). At age 15, patient 3 (CF1374.03)

Table 1. Genetic and Hormonal Characteristics of the Patients

Patient	BAB4619	BAB4620	CF1374.03	CF1374.04	Normal Range
Age, y	16.25	14.25	15	12	
<i>SOHLH1</i> allele	c.705delT	c.705delT	c.27C>G	c.27C>G	
Karyotype	46,XX	46,XX	46,XX	46,XX	
FSH, mIU/mL	98.8	109	30.04	59.3	F: 2.5–10.2
LH, mIU/mL	25	24.5	29.44	8.31	F: 1.9–12.5
Estradiol, pg/mL	<5	42	<20	<20	F: 27–122
ACTH test, IV, 250 mcg					
Peak cortisol, mcg/dL	36.3	30.2	–	28.1	3–25
Peak androstenedione, ng/mL	0.78	1.61	–	–	0.22–2.25
Peak 17OH-Progesterone, ng/mL	1.49	–	–	–	1–10
Progesterone, ng/mL	0.24	0.51	–	–	5–20
DHEA-S, mcg/dL	87.8	161	–	–	35–430
Prolactin, pg/mL	11.3	6.35	–	–	F: 2.28–29.2
TSH, mIU/mL	1.6	1.49	3.13	5	0.35–5.6
Urinary reducing substances	Absent	Absent	–	–	

Abbreviation: –, not performed.

had elevated FSH and LH levels with decreased estradiol levels (Table 1). Her height was 152.5 cm (fifth to tenth percentile) and bone age was 12 years. At age 11, patient 4 (CF1374.04) had prepubertal serum gonadotropin levels. Her height was 132.7 cm (fifth to tenth percentile) and her bone age was 10 years. Follow up of this patient at the age of 12 revealed elevated FSH and LH levels with decreased estradiol (Table 1). Pelvic ultrasound imaging revealed an infantile uterus and lack of ovaries (Table 2). Karyotype analyses were normal and no other significant clinical or dysmorphic features were identified. A presumptive clinical diagnosis of nonsyndromic hypergonadotropic hypogonadism was made and estrogen re-

placement therapy was initiated with cyclic progesterone addition by the end of the first year. By the third year of treatment, menstrual cycles for both patients became regular and the height and weight attained were at the 20–50th percentile.

Genetic analyses

Given that all parents were unaffected and neither family had a history of the trait, we hypothesized that the daughters’ hypergonadotropic hypogonadism would be recessively inherited. Given consanguinity of the parents, we also anticipated that the critical allele in each family would be homozygous in both affected sisters. From complete exome sequences of each family, we therefore identified all variants that were homozygous, shared by affected sisters, and with predicted functional effect. Exome sequencing of the two pairs of sisters revealed two different homozygous truncating mutations in *SOHLH1* (Figure 2).

Exome sequencing of the affected sisters (BAB4619 and BAB4620) in HOU1852 yielded average 106× depth of coverage with 92% of targeted bases covered at least 20-fold. The affected sisters were both homozygous for *SOHLH1* c.705delT; p.Pro235fs*4 in exon 6 (NM_001012415; chr9:138,587,065 TA>T [hg19]), which is predicted to result in protein truncation at codon 238. Haplotype block analysis based on single nucleotide polymorphism

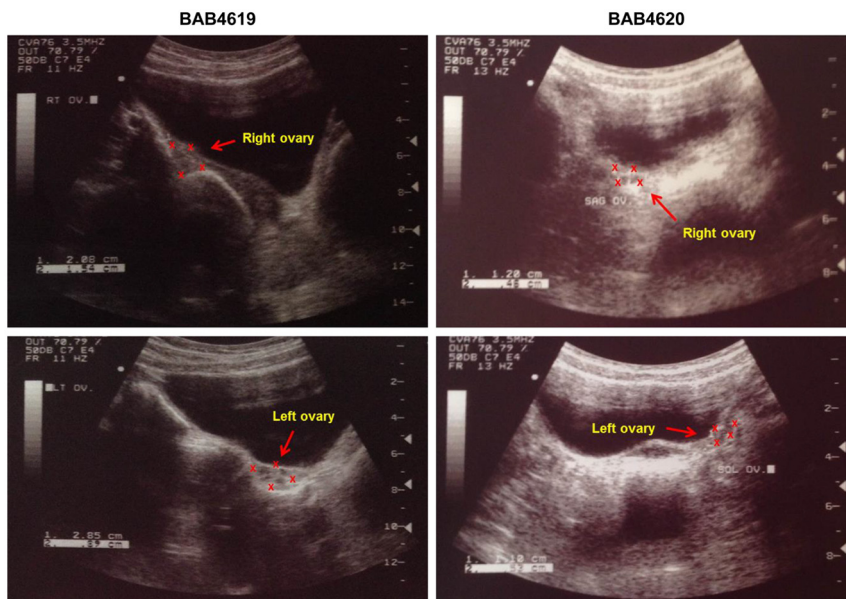


Figure 1. Pelvic ultrasound imaging of the patients (BAB4619 and BAB4620). The red arrows indicate the visualization of the ovaries and the red stars indicate the ovarian boundaries. These images were captured while the patients were under hormone replacement therapy. Note that the ovaries can be visualized but they are still hypoplastic (BAB4619, right: 21 × 15 mm; left: 29 × 9 mm. BAB4620, right: 12 × 5 mm; left: 11 × 5.5 mm).

Table 2. Pelvic Ultrasound and MR Imaging Studies of the Patients

Patient	HRT	Uterus length, cm	Right ovary, mm	Left ovary, mm	Pelvic MRI
BAB4619	Before	2.2	NV	NV	NV bilateral ovaries
	After	7.4	21 × 15	29 × 9	
BAB4620	Before	–	–	–	NV bilateral ovaries
	After	3.7	12 × 5	11 × 5.5	
CF1374.03	Before	–	–	–	NV bilateral ovaries
	After	4.5	10 × 5	NV	
CF1374.04	Before	2.1	NV	NV	NV bilateral ovaries
	After	5.3	NV	NV	
Pubertal normal ranges		3.4–8.8	25–50 × 15–30	25–50 × 15–30	

Abbreviations: HRT, hormone replacement therapy after 9–12 months of low-dose estrogen (0.5 mg 17 β -Estradiol); NV, nonvisualized; –, not performed. Ovaries could be more visible at US after increasing uterine volume with estrogen treatment.

data culled from exome sequencing (ie, B-allele frequency) showed that this identified novel variant was found in an ~10.4-Mb block of absence of heterozygosity (AOH), which was overlapping in both siblings (data not shown).

Because of the consanguinity between parents we examined the other AOH regions in these patients. There were 15 other overlapping AOH blocks (>0.5 Mb) that ranged in size from 0.56–16.2 Mb, which in total accounted for

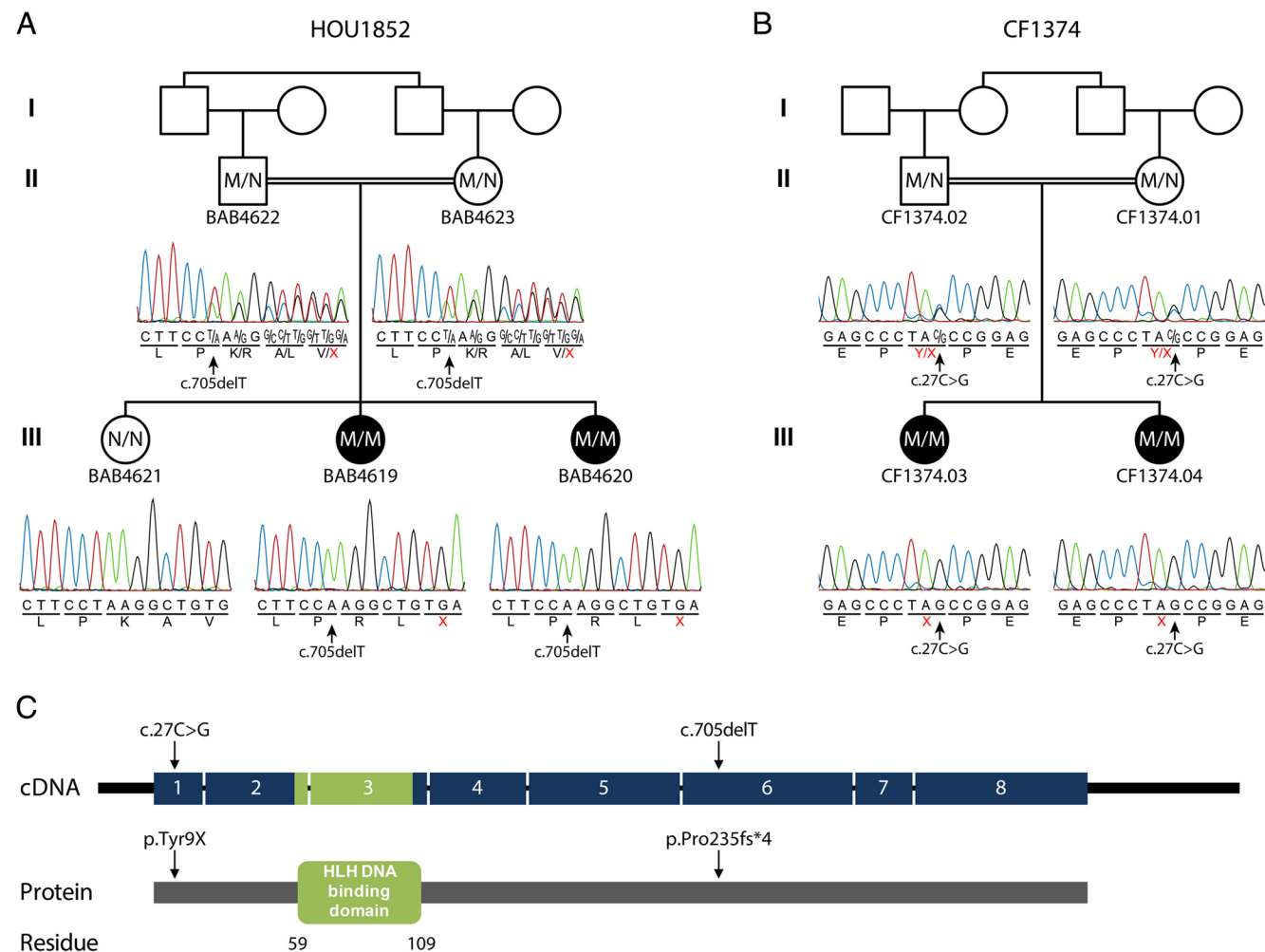


Figure 2. Segregation of *SOHLH1* mutations in families and location of the mutations. A, Affected sisters BAB4619 and BAB4620 in family HOU1852 were homozygous (M/M) for c.705delT allele whereas the parents were heterozygous carriers (M/N) and the unaffected sibling was homozygous for the normal allele (N/N). The c.705delT allele results in a premature stop at residue 238. B, Affected sisters CF1374.03 and CF1374.04 in family CF1374 were homozygous for c.27C>G mutation which corresponds to a premature stop at residue 9. Both parents were heterozygous for this allele. Affected individuals are shown with black filled shapes, the locations of mutations are indicated with arrows and the resulting premature stop codons are shown (red). C, Locations of the loss of function mutations are shown in *SOHLH1* and in the protein encoded by the gene.

~1.5% of the human genome (46 273 916 base pairs). None of these AOH regions included a homozygous-truncating mutation that occurred in both siblings. Both parents were heterozygous and the unaffected sister was homozygous for the normal allele at this *SOHLH1* variant site (Figure 2A).

Exome sequencing of the affected sisters (CF1374.03 and CF1374.04) of family CF1374 yielded median 101× depth of coverage with 94% of targeted bases covered at least 10-fold. The affected sisters were both homozygous for *SOHLH1* c.27C>G; p.Tyr9stop in exon 1 (NM_001012415; chr9:138,591,287 G>C [hg19]) and both parents were heterozygous for this mutation (Figure 2B). The mutation is located in a 2.3-Mb segment between chr9:138,518,010 and chr9:140,777,306 that is shared, homozygous, and identical by descent in the two affected siblings. In the entire exome sequence, this variant in *SOHLH1* was the only truncating mutation that was homozygous and shared by both sisters.

In contrast with the affected homozygous females, heterozygous carriers for these truncating mutations had no recognizable pathologic finding in sexual or gonadal development. In family HOU1852, the mother had normal menarche at age 13 years. She still had regular menstrual cycles at age 41 years and no significant clinical abnormality. In family CF1374, the mother had normal menarche at age 14 years and regular menstrual cycles until natural menopause at age 49 years. Both fathers reported normal histories of pubertal maturation.

Neither of these *SOHLH1* mutations was reported in any public database, including the 1000 Genomes Project (<http://www.1000genomes.org>), the National Heart, Lung, and Blood Institute Exome Sequencing Project (<http://evs.gs.washington.edu/evs/>), The Single Nucleotide Polymorphism Database, or the Exome Aggregation Consortium (<http://exac.broadinstitute.org/>). Nor was either allele identified in our internal database of more than 3000 exomes, including more than 700 persons of Turkish ancestry or in exome data of the Atherosclerosis Risk in Communities study (<https://www2.csc.unc.edu/aric/>). Each mutation seems unique to its family of origin consistent with a Clan Genomics hypothesis (13). *SOHLH1* was fully sequenced in 21 other persons of Turkish ancestry with nonsyndromic hypergonadotropic hypogonadism; no rare damaging variants were identified.

Discussion

Homozygous loss of function mutations in *SOHLH1* were identified in two families with nonsyndromic hypergonadotropic hypogonadism. This condition has also been

described because of mutations in *FSHβ*, *FSHR*, *LHβ*, *LHR*, *NR5A1*, *CYP17*, *CYP19*, *NOBOX*, or *BMP15* (2, 7, 14, 15). *SOHLH1* (Spermatogenesis- and oogenesis-specific basic helix-loop-helix protein 1) contains eight exons and encodes a 328–amino acid basic helix-loop-helix (bHLH) transcription factor with homologs in humans and other placental mammals (8). The protein has an helix-loop-helix DNA-binding domain encoded by exons 2 and 3. Loss-of-function mutations in *SOHLH1* have not previously been associated with any phenotype in human females. The identified frame-shift mutation in our study, c.705delT, in family HOU1852, is located at the sixth exon of the gene resulting in a premature stop codon at residue 238 (Figure 2C) and is likely to be subject to non-sense-mediated decay. In family CF1374, homozygous c.27C>G mutation located at the first exon of the protein and causes a premature stop at residue 9 (Figure 2C).

Studies in mice reveal that *Sohlh1* is expressed during oogenesis and is critical for early folliculogenesis (8). *Sohlh1* transcripts are present in primordial follicles in the newborn ovary and preferentially expressed in primordial oocytes of adult ovaries, but disappear rapidly as the oocytes begin to differentiate to primary and secondary follicles. *Sohlh1* $-/-$ female mice are infertile with atrophic ovaries that lack oocytes; *Sohlh1* $+/-$ females have normal fertility and ovaries. On histological examination, ovaries from newborn wild-type and *Sohlh1* $-/-$ mice showed no apparent differences in morphology or histology, suggesting that embryonic germ cell migration and proliferation is normal in newborn *Sohlh1* $-/-$ females. In contrast, on postnatal day 3, *Sohlh1* $-/-$ ovaries lack primary follicles, suggesting that loss of *Sohlh1* leads to a defect in follicle development during the primordial-to-primary follicle transition (8). *Sohlh1* also apparently plays a role in spermatogonial differentiation, with mutations leading to nonobstructive azoospermia identified in mice, in macaques, and in two human patients (16–19). Recently, known variants of *SOHLH1* were suggested to be potentially associated with secondary amenorrhea in Chinese and Serbian populations (20).

Oogenesis in the human female reproductive system begins with the formation of primordial germ cells in the endoderm during early embryonic life and proceeds in different stages until the secondary oocyte becomes an ovum soon after fertilization with a sperm. Folliculogenesis depends on genetic and hormonal factors. Mouse studies have revealed the transcriptional regulators that affect different stages during oogenesis (21), such as: *Pou5f1* (*Oct4*) and *Nanog* involved in primordial germ cell specification, migration, and mitosis (22–24), *Figla* and *Nobox* effecting meiotic arrest and suppressing male-specific genes (25–29), *Tbp2* affecting the growing follicle

(30), and *Lhx8*, *Foxo3*, *Sohlh1*, and *Sohlh2* together with *Figla* and *Nobox* influencing follicle formation, follicular development, and activation (21, 31, 32). Both *SOHLH1* and *SOHLH2* are expressed in early folliculogenesis but not in secondary follicles while *FIGLA*, *NOBOX*, and *LHX8* are expressed throughout folliculogenesis. This expression pattern suggests that SOHLHs may play important and unique roles in formation, activation, and survival of primordial follicles (8, 21, 33, 34). *SOHLH1* closely interacts with other transcriptional regulatory proteins (ie, *FIGLA*, *NOBOX*, *LHX8*, and *SOHLH2*) that set up a network to coordinate germ cell development (35, 36). Small ovary sizes, very low sex steroids, and absence of the pubertal findings that were displayed in our patients support the importance of *SOHLH1* in ovarian development and function in humans.

In conclusion, the clinical features and the results of genomic analysis of patients with hypergonadotropic hypogonadism, together with findings observed in mouse models, strongly suggest that homozygous loss-of-function mutations in *SOHLH1* cause ovarian dysfunction in humans as well as in mice. Our study will illuminate further the regulation of human reproductive functions especially in familial cases. *SOHLH1* is important to human gonadal development.

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Disclosure Summary: J.R.L. has stock ownership in 23andMe, is a paid consultant for Regeneron Pharmaceuticals, has stock options in Lasergen, Inc, and is a coinventor of multiple United States and European patents related to molecular diagnostics for inherited neuropathies, eye diseases, and bacterial genomic fingerprinting. The Department of Molecular and Human Genetics at Baylor College of Medicine derives revenue from the chromosomal microarray analysis and clinical exome

sequencing offered in the Baylor Miraca Genetics Laboratory (<http://www.bmgl.com/BMGL/Default.aspx>). R.A.G. is interim Chief Scientific Officer of Baylor Miraca Genetics Laboratory. Y.B., S.G., T.Gu., A.A., G.Y., H.U.G., Z.A., S.B.P., T.Ga., M.L., S.T., E.Bob., M.M.A., T.W., E.K., D.P., S.N.J., D.M., A.Be., A.Bu., E.Boe., R.A.G., and M.C.K. have no disclosures relevant to the manuscript.

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