Novel synonymous and missense variants in FGFR1 causing Hartsfield syndrome

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Abstract

Hartsfield syndrome is a rare clinical entity characterized by holoprosencephaly and ectrodactyly with the variable feature of cleft lip/palate. In addition to these symptoms patients with Hartsfield syndrome can show developmental delay of variable severity, isolated hypogonadotropic hypogonadism, central diabetes insipidus, vertebral anomalies, eye anomalies, and cardiac malformations. Pathogenic variants in FGFR1 have been described to cause phenotypically different FGFR1-related disorders such as Hartsfield syndrome, hypogonadotropic hypogonadism with or without anosmia, Jackson–Weiss syndrome, osteoglophonic dysplasia, Pfeiffer syndrome, and trigonocephaly Type 1. Here, we report three patients with Hartsfield syndrome from two unrelated families. Exome sequencing revealed two siblings harboring a novel de novo heterozygous synonymous variant c.1029G>A, p.Ala343Ala causing a cryptic splice donor site in exon 8 of FGFR1 likely due to gonadal mosaicism in one parent. The third case was a sporadic patient with a novel de novo heterozygous missense variant c.1868A>G, p.(Asp623Gly).

Keywords

FGFR1, fibroblast growth factor receptor 1, gonadal mosaicism, Hartsfield syndrome, holoprosencephaly
1 | INTRODUCTION

Pathogenic variants in fibroblast growth factor receptor 1 (FGFR1) are associated with a wide phenotypic spectrum including Pfeiffer syndrome (PS; Muenke et al., 1994), Kallmann syndrome (hypogonadotropic hypogonadism 2 with or without anosmia; Dode et al., 2003), Trigonocephaly 1 (Kress, Petersen, Collmann, & Grimm, 2000), Jackson–Weiss syndrome (Roscioli et al., 2000), and Hartsfield syndrome (Simonis et al., 2013). Apart from these hereditary traits, sporadic mosaic variants in FGFR1 are implicated in encephalocraniocutaneous lipomatosis (Bennett et al., 2016) and occur in a wide variety of cancers either by missense variants with resulting gain of function or by chromosome rearrangements (Gallo, Nelson, Meyer, & Donoghue, 2015). FGFR1 is expressed in cranial neural crest cell-derived mesenchyme and plays an important role during embryogenesis by deregulating cell death at early stages of limb initiation (Li et al., 2005; Mason, 2007).

**TABLE 1** | Phenotypic features of HS

| Feature                     | Patient 1 (male) | Patient 2 (female) | Patient 3 (male) |
|-----------------------------|------------------|--------------------|------------------|
| Cranium                     |                  |                    |                  |
| Holoprosencephaly (alobar, semilobar, and lobar) | + (lobar)        | –                  | (+) semilobar    |
| Corpus callosum agenesis/hypoplasia | –                | + (agensis)        | (+) hypoplasia   |
| Microcephaly                | +                | – (third centile)  |                  |
| Craniostenosis              | + (sagittal suture) | –                  |                  |
| Face                        |                  |                    |                  |
| Cleft lip/palate            | –                | –                  | (+) bilateral    |
| Hypertelorism/hypotelorism  | –                | –                  | (–) normal       |
| Eye anomalies               | + (ocular apraxia)| –                  | (–)              |
| Ear anomalies               | –                | –                  | (+)              |
| Hands                       |                  |                    |                  |
| Ectrodactyly                | –                | –                  | (+)              |
| Digit number (right/left)   | (5/5)            | (5/5)              | (3/4)            |
| Syndactyly                  | +                | –                  | (+)              |
| Feet                        |                  |                    |                  |
| Ectrodactyly                | +                | –                  | (+)              |
| Digit number (right/left)   | (6/4)            | (6/5)              | (2/2)            |
| Syndactyly                  | +                | +                  | (+)              |
| Genital anomalies           |                  |                    |                  |
| Micropenis                  | –                | (+)                |                  |
| Hypospadias                 | –                | (–)                |                  |
| Cryptorchidism              | +                | (+)                |                  |
| Metabolism/endocrine system abnormality |                  |                    |                  |
| Hypernatremia               | –                | +                  | Not reported     |
| Gonadotropin deficiency     | Not tested       | Not tested         | Not tested       |
| Diabetes insipidus          | –                | + (central)        | Not reported     |
| Tumoral calcinosis          | –                | –                  | –                |
| Development delay           | + (mild)         | + (mild)           | (+)              |
| Growth retardation          | +                | –                  | (+) up to 2 years|
| Axial hypotonia             | (+)              | –                  | (+)              |
| Other                       |                  |                    |                  |
| Stenosis of the aortic isthmus |                |                    |                  |
| Gastro-oesophageal reflux   |                  |                    |                  |
| Vesicoureteral reflux       |                  |                    |                  |
| Epilepsy                    |                  |                    |                  |
| Severe failure to thrive up to 2 |               |                    |                  |
| Years of age (improved after PEG) |            |                    |                  |
| Swallowing problems (PEG)   |                  |                    |                  |

Note: Phenotypic annotation after (Simonis et al., 2013).
Abbreviation: PEG, percutaneous endoscopic gastrostomy.
The clinical entity of Hartsfield syndrome (OMIM #615465) is characterized by the occurrence of holoprosencephaly, ectrodactyly (split-hand/foot malformation), with or without cleft lip and palate. Since the initial clinical report in 1984 by Hartsfield, several other cases have been reported with different possible associated features such as facial dysmorphism, cardiac defects, abnormal genitalia, vertebral anomalies, central diabetes insipidus, growth hormone deficiency, tumoral calcinosis, and hypogonadotropic hypogonadism as well as varying degrees of developmental delay (Hartsfield, Bixler, & DeMyer, 1984; Prasad, Brewer, & Burren, 2016; Simonis et al., 2013; Vilain et al., 2009; Villanueva et al., 2014). The underlying genetic defect was unknown until exome sequencing identified heterozygous or homozygous variants in \( \text{FGFR1} \) (Simonis et al., 2013) in six out of seven affected individuals. To date, more than 200 variants in \( \text{FGFR1} \) have been described (HGMD database, assessed December 2018), however only 17 dominant or recessive loss-of-function variants in 32 individuals have been associated with Hartsfield syndrome (Simonis et al., 2013; Hong et al., 2016; Takagi et al., 2016; Dhamija et al., 2014; Oliver, Menapace, & Cofer, 2017; Metwalley Kalil & Fargalley, 2012; Lansdon et al., 2017; Shi et al., 2016; Table 1). Here, we describe three patients with Hartsfield syndrome from two unrelated families.

## 2 | PATIENTS' MEDICAL REPORTS

We describe two siblings born to healthy, non-consanguineous Swiss parents. Their healthy sister has no reported medical issues and the family history is otherwise unremarkable. Patient 1 (II:1) was born at term after an uneventful pregnancy with a birth weight of 3,195 g (−1.3 SD). He was referred to the genetic department at the age of 18 months with a craniosynostosis of the sagittal suture, ectro- and poly-/syndactyly of both feet, syndactyly of both hands (Figure 1a), cryptorchidism, a single maxillary incisor, as well as global developmental delay. His length at the time of examination was 79 cm (−1.5 SD), his weight 9.6 kg (−1.4 SD), and his head circumference 44 cm (−3.4 SD). During the following years he developed an ocular apraxia and ataxia, mild intellectual disability and was diagnosed with a hypogonadotropic hypogonadism. A cranial MRI at the age of 7 years showed a lobar holoprosencephaly. An echocardiogram and abdominal ultrasound were normal. His younger sister, Patient 2 (II:2), was born at term after an uneventful pregnancy with a birth weight of 2,760 g (−1.6 SD). At the age of 3 weeks, she was referred to the genetic department with poly-/syndactyly of the right foot (Figure 1b) and a stenosis of the aortic isthmus. At the age of 1 month she was diagnosed with a central diabetes insipidus, which was excluded in her brother. A cranial MRI showed agenesis of corpus callosum and colpocephaly. An abdominal ultrasound was normal. She was later diagnosed with mild developmental delay/mild intellectual disability.

Patient 3 was the first child of a healthy, non-consanguineous couple of Polish ethnicity. Early prenatal ultrasound examination was unremarkable. However at 28 weeks of gestation bilateral cleft lip and palate as well as absence of the cerebellar vermis were diagnosed. The

![FIGURE 1](https://example.com/figure1.png) Clinical presentation and family pedigrees of presented Hartsfield cases. (a) II:1 index patient currently 19 years old. From left to right: Ectro-/syndactyly on both feet, operated syndactyly dig III/IV on both hands, single maxillary incisor in the male patient. (b) II:3 14-year-old affected sister. Syndactyly of the right foot in the female patient. (c) II:1 from left to right: Patient at 8 months of age with bilateral cleft lip and palate and after surgical intervention at 2 years and 3 months of age, facial dysmorphism composed of flat facial profile, high-arched eyebrows, low set, dysplastic ears, and thin vermilion border; top right: X-ray of ectro- and syndactyly of feet; lower row: ectro- and syndactyly of hand and feet. (d) Family pedigree of Patients 1 and 2. (e) Family pedigree of Patient 3 [Color figure can be viewed at wileyonlinelibrary.com]
boy was born at term to a 27-year-old mother by Caesarean section with a birth weight of 2,740 g (−2.1 SD), length of 56 cm (+1.8 SD), and head circumference of 33 cm (−2 SD). His Apgar scores were 9 and 8 (1 and 5 min). Physical examination after birth revealed bilateral cleft lip and palate, ectrodactyly (split-hand/foot malformation), cryptorchidism, microenpenis, and facial dysmorphism composed of flat facial profile, high-arched eyebrows, low set, dysplastic ears, and thin vermillion border (Figure 1c). Ultrasound examination of the brain showed agenesis of the corpus callosum, but failed to detect other structural abnormalities. Brain MRI performed at 7 months of age revealed the presence of semilobar holoprosencephaly. During the first 2 years of life bilateral vesicoureteral reflux and gastroesophageal reflux were observed. The boy presented with a severe failure to thrive and marked retardation of psychomotor development. Due to the difficulties in swallowing and tendency toward food aspiration, he presented with failure to thrive and thus at the age of 2 years undertook percutaneous endoscopic gastrostomy (PEG). At the age of 3 years, the patient was diagnosed with seizure disorder and was initiated on antiepileptic therapy with good control of seizures. Upon last clinical evaluation at the age of 7 years and 4 months, the boy presented with a severe intellectual disability with absent speech. In addition, independent sitting was still not achieved. Cryptorchidism was still present and abdominal ultrasound showed severely hypoplastic testes. His body measurements were as follows: body mass 19.5 kg (−1.32 SD), height 120 cm (−1.08 SD), head circumference 48.5 cm (−3.1 SD). Clinical and radiographic features of Patient 3 are shown in Figure 1c. The family history was unremarkable. Detailed phenotypic observations of all three patients are provided in Table 1.

### 3 | GENETIC INVESTIGATIONS

#### 3.1 | Patients 1 and 2

Genetic testing of Patient 1 revealed a normal karyotype of 46,XY as well as normal results from direct Sanger sequencing of GLI3 (OMIM #165240). In Patient 2, chromosomal microarray analysis (1.4M Roche NimbleGen oligonucleotide CGH array) revealed normal results as well. As the genetic etiology of Hartsfield syndrome was not known at the time of the analyses, the family was included in a trio-whole exome sequencing (WES) approach in 2013 resulting in nonconclusive results. After reevaluating the phenotype and reviewing the literature, the exome data were reanalyzed in particular for FGFR1 and revealed a heterozygous synonymous variant c.1029G>A, p.Ala343Ala located in exon 8 of Patient 1.

Subsequent Sanger sequencing to study familial segregation revealed the identical variant in his affected sister, which was absent in their parents and healthy sister in DNA derived from peripheral blood (Figure 2b). The variant was also excluded in the parental exome data.
at 300x coverage retrospectively. The variant was not reported in public databases (ExAC, gnomAD).

To investigate the consequences of this variant on transcript level, RNA was extracted and reverse transcribed (RT) from patient and control-derived fibroblasts using routine protocols. Resulting cDNA was analyzed for FGFR1 splice variants by the use of primers located within the coding sequence of the FGFR1 gene (GenBank: NM_023110.2) in exon 5 (fwd 5’-GCTGCCAAGACA GTGAAGTT-3’) and in exon 10 (rev 5’-TCATGGATGCACTGGA GTCA-3’). Resulting amplicons were separated by agarose gel electrophoresis. The RT-PCR from two healthy individuals, Control 1 and Control 2, resulted in a single amplicon of 804 bp corresponding to the FGFR1 reference sequence (Figure 2d). Two independent samples of Patient 1-derived fibroblasts, carrying the sequence alteration c.1029G>A in FGFR1, revealed two bands. Sanger sequencing confirmed that this variant generated a novel cryptic splice donor site in exon 8 of FGFR1 (Figure 2d). The synonymous mutation activates a cryptic splice site shortening exon 8 by 51 bp (in-frame), which is predicted to shorten the extracellular domain of FGFR1 by 16 amino acids.

This supports the synonymous substitution c.1029G>A as cause for the Hartsfield phenotype observed in Patient 1. According to the recommendations of the American College of Medical Genetics and Genomics (Richards et al., 2015), the FGFR1 variant c.1029G>A, p. Ala343Ala is classified as pathogenic (fulfilling criteria PS2, PS3, PM2, PP1, PP3).

3.2 | Patient 3

Initial genetic testing revealed a normal karyotype of 46XY as well as normal chromosomal microarray analysis (1.4M Roche NimbleGen oligonucleotide CGH array). Subsequent Sanger sequencing revealed the heterozygous FGFR1 missense variant c.1868A>G, p.(Asp623Gly), which was subsequently confirmed to be de novo with parental segregation analysis by Sanger sequencing (Figure 2c). The variant was predicted to be damaging to the protein function by the common bioinformatic algorithms used for pathogenicity assessment (Ioannidis et al., 2016). Additionally, the variant was not annotated in ExAC, gnomAD, EVS, or dbSNP databases, as well as 200 ethnically matched control chromosomes. However, a substitution within the same amino acid position leading to a aspartic acid to tyrosine p.(Asp623Tyr) instead of glycine has been described in another case of Hartsfield syndrome (Simonis et al., 2013). According to the recommendations of the American College of Medical Genetics and Genomics (Richards et al., 2015), the FGFR1 variant c.1868A>G, p.(Asp623Gly) is classified as likely pathogenic (fulfilling criteria PM1, PM2, PM5, PM6, PP1, PP3).

4 | DISCUSSION

Here we report a novel de novo synonymous pathogenic variant in FGFR1, which was found in two siblings (Patients 1 and 2), and a novel de novo missense variant in a sporadic case (Patient 3). Gonadal

### Table 2: Reported cases of Hartsfield syndrome caused by FGFR1 pathogenic variants

| Variant     | Gender | Inheritance | Domain          | References                      |
|-------------|--------|-------------|-----------------|---------------------------------|
| c.494T>C p.(Leu165Ser) | M      | Recessive⁸  | IgII            | Simons et al. (2013)            |
| c.572T>C p.(Leu191Ser) | M      | Recessive⁸  | IgII            | Simons et al. (2013)            |
| c.758A>C p.(His253Pro) | M      | Dominant    | IgIII           | Takagi et al. (2016)            |
| c.1029G>A p.(Ala343=) | M/F    | Dominant    | IgIII           | This report                     |
| c.1454G>T p.(Gly485Val) | n.r.   | Dominant    | TK              | Dubourg et al. (2016)           |
| c.1459G>T p.(Gly487Asp) | M      | Dominant    | TK              | Lansdon et al. (2017)           |
| c.1460G>A p.(Gly487Asp) | M      | Dominant    | TK              | Hong et al. (2016)              |
| c.1468G>C p.(Gly490Arg) | M      | Dominant    | TK              | Simons et al. (2013) and Dubourg et al. (2016) |
| c.1604T>A p.(Met535Lys) | n.r.   | Dominant    | TK              | Hong et al. (2016)              |
| c.1687G>T p.(Asp623Tyr) | F      | Dominant    | TK              | Simons et al. (2013)            |
| c.1868A>G p.(Asp623Gly) | M      | Dominant    | TK              | This report                     |
| c.1869G>C p.(Asp623Tyr/Glu) | n.r.   | Dominant    | TK              | Hong et al. (2016) and Simons et al. (2013) |
| c.1880G>C p.(Arg627Thr) | M/F    | Dominant    | TK              | Dhamija et al. (2014), Keaton et al. (2010), and Oliver et al. (2017) |
| c.1883A>G p.(Asn628Ser) | M      | Dominant    | TK              | Prasad et al. (2016)            |
| c.1884T>G p.(Asn628Lys) | M      | Dominant    | TK              | Simons et al. (2013)            |
| c.1921G>A p.(Asp641Asn) | F      | Dominant    | TK              | Hong et al. (2016)              |
| c.1934C>T p.(Ala645Val) | M      | Dominant    | TK              | Palumbo et al. (2019)           |
| c.2174G>A p.(Cys725Tyr) | M      | Dominant    | TK              | Simons et al. (2013)            |

Note: Annotation reference sequence NM_023110 (ENST00000447712.6) and Uniprot protein sequence P11362-1. The bold value indicates the variant in this report.

Abbreviations: #, refers to homozygous variants; AB, acidic box; IgII, immunoglobulin-like 2 domain; n.r., not reported; TK, tyrosine kinase domain.
mosaic or somatic mosaicism including germ cells is assumed in the affected siblings.

The knowledge of the genetic basis of Hartsfield syndrome is relatively recent and is attributed to both heterozygous and homozygous loss-of-function variants in FGFR1 (Simonis et al., 2013). Most pathogenic variants in FGFR1 causing Hartsfield syndrome are located within the intracellular kinase domain, whereas only four pathogenic variants, including the synonymous variant in this report, are located in one of the three immunoglobulin-like domains in the extracellular region (Figure 2a and Table 2). Several of the known pathogenic variants within the tyrosine kinase domain of FGFR1 have been recently demonstrated to result in dominant-negative effects altering normal signaling in zebrafish (Hong et al., 2016). Whether variable receptor signaling alterations could account for the differing phenotypic findings in Kallmann syndrome compared to Hartsfield syndrome remains to be discovered. Recently, a patient with a de novo variant in the third immunoglobulin-like domain of FGFR1 has been associated with Hartsfield syndrome (Takagi et al., 2016). In our patient with the de novo variant in the third immunoglobulin-like domain of FGFR1, analyses of transcripts from fibroblasts of Patient 1 revealed abnormal splicing through creation of a cryptic splice donor site. Patients 1 and 2 had differing phenotypic presentations with respect to brain and limb malformations despite carrying the same de novo variant. This might potentially be explained by modifying factors resulting in differing splicing efficiency caused by a disrupted exonic splice enhancer motif.

Loss-of-function variants in FGFR1 are associated with a wide phenotypic spectrum and identical variants may present with a variable phenotype attributed to incomplete penetrance and variable expressivity (Simonis et al., 2013). Interestingly, Patient 3 p.- (Asp623Gly) showed a more severe phenotype than a previously reported case p.(Asp623Tyr; Simonis et al., 2013), suggesting differing pathogenic mechanism dependent on the substituted amino acid at that position.

The WES data from DNA extracted from leukocytes of both parents of Patients 1 and 2 showed a normal sequence at this position with a coverage of approximately 300-fold, each. Thus, we assume gonadal mosaicism of this variant in one of the parents or alternatively somatic mosaicism including germ cells. Gonadal mosaicism has previously been reported in a case affected by Hartsfield syndrome (Dhamija et al., 2014; Shi et al., 2016). Herein, we report a second family with gonadal mosaicism in Hartsfield syndrome and emphasize that such genetic constellations should be taken into consideration when counseling clinically unaffected parents regarding their potential recurrence risk.

ACKNOWLEDGMENTS

The authors are indebted to the families participating in this study. This work was supported by the Swiss National Foundation [to C.B.J. and C.C.], the Novartis Foundation for Medical-Biological Research (to C.B.J.), and the Polish National Science Centre (UMO-2016/22/E/NZ5/00270 [to A.J.]).

CONFLICT OF INTEREST

The authors declare no potential conflict of interest.

ETHICS STATEMENT

Informed consent was obtained from all participating individuals and/or their parents.

AUTHOR CONTRIBUTIONS

All authors have reviewed and approved the final manuscript.

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How to cite this article: Courage C, Jackson CB, Owczarek-Lipska M, et al. Novel synonymous and missense variants in FGFR1 causing Hartsfield syndrome. Am J Med Genet Part A. 2019;179A:2447–2453. https://doi.org/10.1002/ajmg.a.61354