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# Genetic Factors in Isolated and Syndromic Esophageal Atresia

\*David Geneviève, †Loïc de Pontual, †Jeanne Amiel, and †Stanislas Lyonnet

**E**sophageal atresia (EA) and tracheoesophageal fistulae (TEF) are frequent congenital malformations (1/3500 births) characterized by a discontinuity of the lumen of the esophagus.

EA/TEF is anatomically divided into 5 subtypes based on the location and type of anastomosis between trachea and esophagus. To our best knowledge, no differences in developmental origin could be identified for each of the 5 subtypes, and no correlation has been established between subtypes of EA and specific genetic disorders. EA is clinically divided into 2 different forms: isolated EA (IEA, 50%) and syndromic EA (SEA, 50%).

Epidemiological studies do not support the existence of strong genetic factors in IEA (1). In IEA, recurrence risk is estimated to 1%, and twin concordance rate is low (2.5%). However, in SEA, first-degree relatives are more likely to present malformations of the VACTERL spectrum (2). In addition, identification of several disease genes involved in SEA, mouse models (3), and chromosomal anomalies (4) argues in favor of genetic factors in EA.

## ISOLATED OESOPHAGEAL ATRESIA

In IEA, the sex ratio is balanced with a mild excess of males (1). Offspring risk studied in IEA patients averages 1%, and the recurrence risk in sibs is low (1/130 affected sib in a series of 79 EA/TEF patients). Very little is known regarding the cause of IEA. To our knowledge, no murine model has been hitherto described.

Maternal exposure to environmental factors has been suspected to be responsible for EA/TEF, namely statins, smoking, exogenous sex hormones, or work in agriculture or horticulture. However, these factors have not been formally identified as risk factors for EA/TEF (5). Taken together, these scarce data do not support strong evidence for heritability of IEA.

## SYNDROMIC ESOPHAGEAL ATRESIA

Frequent syndromes or syndromic association with EA will be discussed in this part. The etiologies of SEA are summarized in Table 1.

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From the \*Département de Génétique, Centre de Référence Maladies Rares Anomalies du Développement et Syndromes Malformatifs Sud-Languedoc Roussillon, Hôpital Arnaud de Villeneuve, CHRU Montpellier, Université Montpellier 1, Faculté de Médecine de Montpellier-Nîmes, Montpellier, and the †Département de Génétique, Hôpital Necker-Enfants Malades, Université Paris-Descartes, Unité INSERM U781, Paris, France.

Address correspondence and reprint requests to Stanislas Lyonnet, Département de Génétique, Hôpital Necker Enfants malades, 149 Rue de Sèvres 75743 Paris Cedex 15, France (e-mail: stanislas.lyonnet@inserm.fr).

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## Materno-fetal Intoxication/Environmental Agents

Maternal-fetal intoxication or environmental agent, namely maternal diabetes, fetal alcohol syndrome, maternal phenylketonuria, and exposure to methimazole (carbimazole), have been described to be responsible for SEA (5).

## Chromosomal Anomalies

Around 6% to 10% of SEA are due to chromosomal anomalies. The majority is represented by trisomies (trisomy 13, 18, 21), whereas a few recurrent chromosomal deletions are observed in patients with EA/TEF and multiple congenital anomaly (MCA) mental retardation (MR) syndromes, namely 13q13-qter, 16q24.1, 17q21.3-q23, and 22q11.2 deletions (4,6).

## VATER/VACTERL Association

EA/TEF is a frequent feature in VACTERL syndrome. The VACTERL association (MIM 214800) is a nonrandom condition including vertebral defects, anal atresia, cardiac defects, tracheoesophagus fistula, and renal and limb (radial ray) defects (2).

Recently, the loss of the *FOX* genes cluster (16q24.1 microdeletion) has been demonstrated to be responsible for a phenotype resembling VACTERL association (6). Furthermore, isolated *FOXF1* mutations are responsible for a syndrome with overlapping features with the VACTERL association including EA/TEF, renal and cardiac malformations, and alveolocapillary dysplasia. In addition, abnormal *ZIC3* polyalanine expansion has been observed in a patient with VACTERL association with heterotaxy (7).

However, the VACTERL association should be considered as a diagnostic only until other genetics disorders mimicking or partly overlapping this condition have been excluded.

## Feingold Syndrome

EA is a frequent feature in Feingold syndrome (FS or oculo-digito-esophago-duodenal syndrome, MIM 164280). This autosomal dominant condition is characterized by gastrointestinal stenosis or atresia (including EA), microcephaly, mild learning disability, and characteristic hands (brachymesophalangy of the 2nd and 5th fingers). The disease is caused by mutations of the *MYCN* gene involved in the regulation of transcription, cell cycle, cell differentiation, and morphogenesis by acting as a downstream target of the *SHH*, *WNT*, *TGF*, and *FGF* signaling pathways (8).

## Rogers/AEG Syndrome

Rogers syndrome (or anophthalmia-esophageal-genital syndrome, AEG -MIM 600992) is a rare autosomal dominant disorder

TABLE 1. Principal genetic syndromes with esophageal atresia

Environmental agents	Chromosomal anomalies	Malformative associations	(Gene/MIM)	Polymalformative genetic disorders	(Gene/MIM)
Fetal alcohol syndrome	Trisomy 21	VATER/VACTERL association	ZIC3? FOX cluster? (214800)	Feingold syndrome	(MYCN/164280)
Maternal phenylketonuria	Trisomy 13	OAVS spectrum	(Epigenetic anomaly? BPAX1/164210)	Charge syndrome	(CHD7/214800)
Maternal diabetes	Trisomy 18	MURCS	(601076)	AEG syndrome	(SOX2/206900)
Fetal carbimazole syndrome	Del 22q11.2			Fanconi anemia	(FANCA to M/227645)
Adriamycine (animal models)	Del 17q21.3-q23 Del 16q24.1			G syndrome	(MID-1/30000)
				Mitochondrial DNA mutations	
				Bartsocas-Papas/lethal popliteal pterygium syndrome	(263650)
				Fryns syndrome	(229850)

characterized by the association of EA to ocular (anophthalmia, microphthalmia, lens abnormalities, optic nerve malformation), genital, vertebral, and cerebral malformations. Mutations in the *SOX2* gene are responsible for this syndrome.

### CHARGE Syndrome

The acronym CHARGE (MIM 214800) refers to a MCA/MR syndrome characterized by ocular coloboma (C), heart disease (H), choanal atresia (A), retarded growth and/or anomalies of the central nervous system (R), genito-urinary defects and/or hypogonadism (G), and ear anomalies and/or deafness (E). Other diagnostic criteria include semi-circular canal agenesis, which is now regarded as major diagnostic criteria in CHARGE syndrome. EA is observed in between 10% and 17% of patients (9). Mutations in the *CHD7* gene are responsible for this condition.

### Fanconi Anemia

Fanconi anemia (FA) (MIM 227650) is a rare autosomal recessive disorder. FA patients presents with bone marrow failure,

variable MCA (cardiac, renal, and limb malformations), and skin pigmentary changes. Gastrointestinal atresia has been reported in 14% of FA patients. However, EA is a rare feature of FA and is frequently observed with other malformations including the VACTERL association with hydrocephalus (VACTERL+H). Both X-linked and recessive forms of FA/VACTERL+H have been described. The VACTERL phenotype appears to be overrepresented in the FA complementation groups D1, E, and F (10). Mutations in the *FANCB* gene have been recently identified in patients with the X-linked VACTERL+H (11).

EA/TEF is a frequent malformation with heterogeneous etiology. The systematic search for associated features should help to decide whether one is dealing with an IEA or a SEA. This step is essential to recognize known SEA and offer genetic counseling and prenatal diagnosis.

Molecular and cellular mechanisms responsible for EA/TEF remain unknown. However, several genes have been identified among monogenic conditions of EA/TEF providing an *hitherto* unknown clue to the understanding of the physiopathology of this malformation.

DNA damages during development have been suspected as teratogenic events responsible for malformations, and therefore

TABLE 2. Knockout mouse models with EA/TEF

Mouse gene	Human gene	Pathology in human	Main features	EA/TEF
<i>Shh</i>	<i>SHH</i>	Yes	Holoprosencephaly	No
<i>Gli2</i>	<i>GLI2</i>	Yes	Holoprosencephaly	No
<i>Gli3</i>	<i>GLI3</i>	Yes	Greig cephalopolysyndactyly syndrome; Pallister–Hall syndrome.	No
<i>Foxf1</i>	<i>FOXF1</i>	Yes	Alveolar capillary dysplasia and MCA resembling VACTER association	Yes
<i>Noggin</i>	<i>NOGGIN</i>	Yes	Symphalangism with synostosis and brachydactyly type B2	No
<i>Hoxc4</i>	<i>HOXC4</i>	No	—	—
<i>Ttf1</i>	<i>TTF1-NKX2.1</i>	Yes	Brain-lung-thyroid syndrome	No
<i>Pcsk5</i>	<i>PCSK5</i>	Yes	VACTERL association, caudal regression and Currarino syndrome-like malformations	Yes
<i>Sox2</i>	<i>SOX2</i>	Yes	Rogers/AEG syndrome	Yes

EA = esophageal atresia; MCA = multiple congenital anomaly; TEF = tracheoesophageal fistulae.

agents checking DNA damages and regulating DNA repair through cell cycle checkpoints and apoptosis may act as teratogen suppressors (12). DNA damage, either directly or as a result of oxidative stress observed in fetal alcohol syndrome, maternal diabetes, and exposure to adriamycin (13) in combination to the observation of *MYCN* mutations in FS and *FANCD1* mutations in FA, strongly support the view that DNA repair and cell cycle checkpoint genes play a key role in EA.

Developmental genes may also be involved in the pathophysiology of EA. Indeed, several knockout mouse models of developmental genes including mice knocked out for the *sonic hedgehog* pathway genes (*Shh*, *Gli2* and *Gli3*, *Foxf1* – 14) also present with OA (Table 2). Moreover, a direct link between *MYCN* and *SHH* has been observed, suggesting common physiopathological mechanisms between DNA repair/cell cycle checkpoint and development (8). Other knockout mouse models for the *hoxc4*, *Noggin*, *Tcf1*, and *Pcsk5* genes also produced EA (14). However, to our knowledge, no direct link between these genes and human pathologies with EA/TEF has been reported.

At least, abnormal epigenetic control during development may produce EA. This hypothesis is supported by the report of abnormal histone acetylation of *BAXP1* in oculo-auriculo-vertebral syndrome, a rare cause of SEA (15).

It is likely that new genetic tools, such as microarrays and exome sequencing, will contribute to elucidate the etiology of EA/TEF.

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