

## **A Gene, MMP12, which encodes a Metalloprotease is Responsible for nearly 6% of Patients with Congenital Heart Defects and Heterotaxy**

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**Introduction:** Heterotaxy results from a failure to establish normal left-right asymmetry early in embryonic development. As a consequence, the normal positioning of thoracic and abdominal organs is disturbed with eventually complex cardiovascular malformations. Several genes were already associated with heterotaxy but the vast majority of heterotaxy cases remain elusive.

**Method:** Whole exome sequencing was performed in a family with a pair of dizygotic twins suffering from congenital heart defects and heterotaxy. In a second step, a cohort of 264 index cases with either heterotaxy (extracardiac and/or cardiac laterality defects such as dextrocardia or transposition of the great arteries; n = 154) or non-heterotaxy Congenital Heart Defects (CHDs) such as isolated tetralogy of Fallot or common arterial trunk (n = 110) was sequenced after HaloPlex target enrichment of the MMP21 gene.

**Results:** Patient 1, a girl, had interrupted IVC with azygous continuation, partial APVR, unbalanced AVC, cleft anterior mitral valve leaflet, hypoplastic LV, dextrocardia, common mesentery and polysplenia. Patient 2, a boy, had left SVC draining to coronary sinus, secundum ASD, abnormal atrioventricular connection, subarterial VSD, right aortic arch with mirror image branching, and PDA. Patient 1 died shortly after birth from haemodynamic failure. Whole exome sequencing of this affected dizygotic twins led to the identification of rare, compound heterozygous mutations in MMP21 (NM\_147191.1): c.677T>C, p.Ile226Thr (paternally inherited) and c.1203G>A, p.Trp401\* (maternally inherited). The cohort of 264 index cases included 25 syndromic cases in which heterotaxy or CHDs were associated with one or more other anomalies (for example, anal atresia, vertebral anomalies or cleft palate) and comprised 117 familial and 147 sporadic cases, with 34 index cases born to consanguineous parents. We identified nine cases with rare, biallelic MMP21 variations predicted to affect protein function; all variations were confirmed by Sanger sequencing and segregated with heterotaxy or other laterality defects and complex CHDs

**Conclusion:** Overall, the penetrance of laterality defects in our series was very high (>90%) in comparison to that observed for Primary Ciliary Dyskinesia (~50%). On the basis of the above findings, MMP21 mutations account for 5.9% of non-syndromic heterotaxy cases.