"Phenotype and genotype analysis of a French cohort of 119 patients with CHARGE syndrome"
By: Marine Legendre, Véronique Abadie, Brigitte Gilbert-Dussardier and 44 others!
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AUTHORS AND THEIR CONNECTION TO THE CHARGE SYNDROME FOUNDATION:



This paper lists a total of 47 contributors. These include clinical geneticists from all over France who contributed information from their patients with CHARGE syndrome (CS), molecular geneticists, other clinical specialists and a number of research experts. It takes a team such as this to not only collect (relatively) complete information on 119 individuals with CS but also to synthesize it, compare it with what has been previously published and create a paper that will be useful to so many others around the world. Several of the authors are already known to the CHARGE Syndrome Foundation because they have been publishing and presenting on CS for decades and have presented at conferences in the US and Europe. Others are new to those of us at the Foundation, but are probably well-known to the CS communities in France and Europe. Here are a few of the authors:

Marine Legendre, MD, **PHD** (above, right) is a clinical geneticist at Service de Génétique, CHU [University Hospital Center] de Poitiers, Poitiers, France. Her PhD thesis was on CHARGE syndrome. She worked with Dr. Gilbert-Dussardier in clinical genetics at CHU.

Veronique Abadie, MD, is a professor of pediatrics and coordinator of a certified center involved in CHARGE syndrome in the service de Pédiatrie Générale, Hôpital Universitaire Necker-Enfants Malades, Paris, France.

Stanislas Lyonnet (pictured with his lab in the email blast) is a professor of genetics involved in CHARGE syndrome and research on its molecular bases. He presented at the first International CS Conference.

Frédéric Bilan (above, left) is assistant-professor in genetics, in charge of organizing molecular testing and research on CS.

Brigitte Gilbert-Dussardier (center photo, with some of her team) is a clinical geneticist, professor in genetics, coordinator of a French national program of research on CHARGE syndrome.

SUMMARY OF THE PAPER:

Abstract: CS is a complex genetic disorder most often caused by a genetic mutation in the *CHD7* gene. Current clinical diagnosis can be done by classification of typical, partial, or atypical CS on the basis of major and minor clinical criteria. The published detection rate of a pathogenic variant in the *CHD7* gene varies from 67% to 90%.

We conducted a national study of phenotype (clinical features) and genotype (genetic status) in 119 patients with CS. In addition to a detailed clinical description, patients underwent additional exams when possible: a full ophthalmologic examination, audiometry, temporal bone CT scan, gonadotropin analysis, and olfactory-bulb MRI. All patients had *CHD7* sequencing and MLPA analysis (deletion testing). 107 (90%) of patients had a typical form of CS and 12 (10%) an atypical form [or "CHARGE-like" as other authors call it]. We identified a pathogenic *CHD7* variant in 83% of typical CS cases and 58% of atypical cases. The most frequent features were deafness/semicircular canal hypoplasia (94%), pituitary defect/hypogonadism (89%), external ear anomalies (87%), square-shaped face (81%), and arhinencephaly/anosmia [lack of sense of smell](80%). Coloboma (73%), heart defects (65%), and choanal atresia (43%) were less frequent.

Additional summary: This paper is a comprehensive summary of clinical and molecular findings of more than 100 French individuals with CS of all ages. There were three familial cases: two cases of transmission from a parent with typical CS to a child (one had a pathogenic *CHD7* variant, the other did not) and one case of two children of unaffected parents. Ultrasound anomalies had been noted in about half of the pregnancies.

Table 1 is a comparison of diagnostic criteria for CS by Verloes (2005), updated by Blake (2006), Sanlaville & Verloes (2007), and Hale (2016). Note that the French "atypical" is equivalent to Hale "CHARGE-like." Table 2 lists all 93 individuals who were *CHD7* positive: their clinical features and specific mutations. The text summarizes how many individuals had which feature. Some interesting findings for the *CHD7* positive group include:

- 99% had semicircular canal (SCC – balance organs of inner ear) defects
- 77% had arhinencephaly/anosmia (decreased or absent smell organs/sense of smell)
- 84% had swallowing problems; 70% had facial palsy
- 26% had cerebellar defects – there were a variety of brain changes noted
- 65% had heart defects; 75% had heart or esophagus defects
- 72% had coloboma
- 34% (23/67 tested) had growth hormone (GH) deficiency; 8% were hypothyroid
- 49% had vertebral malformations; 29% had limb abnormalities
- 30% had kidney malformations or abnormalities

Table 3 compares the frequencies of major and minor diagnostic clinical features of the patients with CS. Table 4 lists the frequencies of clinical features in CS cases with or without a pathogenic *CHD7* variant. Figure 1 shows a range of typical CS ear shapes: asymmetric square ears with a triangular concha and without an earlobe. Figure 2 shows the locations of pathogenic *CHD7* variants in CS. Their finding that only seven variants were found more than once confirms that most mutations are private (different in each individual with CS). The text elaborates on the types of variants found (30 frameshift, 25 splice, 24 nonsense, 5 missense, 1 deletion of locus). Table 5 compares the frequency of features in individuals with truncating (shortening of the protein) or non-truncating (changes the shape of the protein) mutations. Figure 3 shows pie charts comparing the types of mutations in those with typical and atypical CS.

Bottom lines – there are many. Here are a few:

1) Hypogonadotrophic hypogonadism (HH) is common and important for predicting growth and puberty***. It should be investigated in patients in the first months of life if CS is suspected***, because it can be treated at expected pubertal age, but biological diagnosis is not possible between age 6 months and puberty.
2) They could not conclude to a phenotype–genotype correlation. That is, the type of mutation (frame-shift, nonsense, etc) does not predict the features seen in a particular individual.
3) The diagnosis remains clinical rather than molecular (based on DNA). Those with a clinical diagnosis but without identifiable pathogenic *CHD7* variant were not significantly different in their features.
4) They agree with Hale et al. (2016) that presence of a pathogenic *CHD7* variant should be a major criterion of the CS diagnosis.
5) They also think that arhinencephaly (brain finding on MRI or CT), present in 80% of patients, should be considered as a criterion.

WHAT DOES THIS MEAN TO FAMILY/PERSON WITH CHARGE?

This paper will likely not directly affect you or your family. It adds tremendously to the overall knowledge of CS – what are the features, how often do each of the features appear, what are the molecular findings of a large cohort of individuals with CS. It confirms that CS still should be a clinical diagnosis, but *CHD7* sequencing is one important criterion in making that clinical diagnosis. It confirms that the presence/lack of *CHD7* variant or type of variant does NOT predict features or outcome. The specific clinical features of each individual are the best predictors of outcome. The most important new information/confirmation is that hypogonadotrophic hypogonadism (HH) and growth hormone deficiency are both COMMON in CS. ***HH should be evaluated before 6 months of age, the only time it can be detected before puberty*** (or lack of puberty!!). They identified GH deficiency in 30% of individuals with CS – as Dr. Blake often says, get an endocrinologist by age three!

Should I read it? Should one of my doctors read it?

Maybe. If you are one of those people who want to know everything about CS, then yes, read it. If you are curious how common various features are, this is a gold mine. It would be even easier to get that information if there were more tables - a lot of the frequency information is only listed in the text. In

terms of genetics literature, this is a very important study, as it collects comprehensive data on more than 100 individuals with CS. If any of the professionals who work with your child are interested in the "statistics of CS" they might be interested in this paper. At least take a look at the tables and figures and appreciate all of the work that went into it.

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