Synthesis of Significant Studies Utilized by Batcher K, Dickinson P, Giuffra J, et al. (2019). *Genes*, 10(6), 435.

The paper by **Batcher et al. (2019)** is primarily a **review and phenotypic analysis** of the two canine FGF4 retrogenes (CFA12 and CFA18). It did not generate all of its conclusions from a single experiment; rather, it synthesized previous genetic, clinical, radiographic, and breed studies.

The paper contains approximately 50 references. Below are the **most important references that form the scientific foundation** for the paper, along with a brief summary of each and why it is important.

Reference	Brief Summary	Importance
Brown EA, Dickinson PJ, Mansour T, et al. (2017). FGF4 retrogene on CFA12 is responsible for chondrodystrophy and intervertebral disc disease in dogs. PNAS.	Discovered the chromosome 12 FGF4 retrogene (CDDY). Demonstrated that it causes chondrodystrophy (shortened limbs) and is strongly associated with IVDD across many breeds.	Landmark discovery establishing the mutation.
Parker HG, VonHoldt BM, Quignon P, et al. (2009). An expressed fgf4 retrogene is associated with breed-defining chondrodysplasia in domestic dogs. Science.	Identified the chromosome 18 FGF4 retrogene responsible for the classic short-legged phenotype in breeds such as Dachshunds and Corgis.	Demonstrated that dogs possess two separate FGF4 retrogenes with different biological effects.
Mogensen MS, Karlskov-Mortensen P, Proschowsky HF, et al. (2011).	Investigated radiographic disc calcification and IVDD risk in Dachshunds, confirming calcified discs as a major predictor of future IVDD.	Helped explain how CDDY increases disease risk.
Jensen VF, Beck S, Christensen KA, Arnbjerg J. (2008).	Showed that radiographic disc calcification is inherited and associated with later IVDD.	Demonstrated the hereditary nature of disc degeneration.
Ball MU, McGuire JA, Swaim SF, et al. (1982).	Early epidemiologic study documenting breed predisposition to IVDD.	Established that certain breeds have markedly increased IVDD risk.

Brisson BA. (2010). Intervertebral Disc Disease in Dogs. Veterinary Clinics of North America.	Comprehensive review of IVDD including pathology, diagnosis, treatment, and genetics known at that time.	Standard clinical review frequently cited in IVDD research.
Bergknut N, Smolders LA, Grinwis GCM, et al. (2013).	Reviewed degeneration of the canine intervertebral disc and the biological mechanisms involved.	Explained why discs degenerate prematurely in chondrodystrophic dogs.
Smolders LA, Bergknut N, Grinwis GCM, et al. (2012).	Examined early disc degeneration in young chondrodystrophic dogs.	Showed degeneration begins well before clinical signs appear.
Hansen HJ (1952).	Classic pathological description of Hansen Type I disc disease in chondrodystrophic breeds.	Foundation of modern understanding of IVDD.
Bergknut N, Egenvall A, Hagman R, et al.	Compared degeneration between chondrodystrophic and non-chondrodystrophic breeds.	Demonstrated markedly earlier degeneration in affected breeds.

Major Conclusions Supported by These References

The references consistently support several conclusions:

1. **The CFA12 (CDDY) FGF4 retrogene causes shortened limbs (chondrodystrophy).**
    - Supported primarily by Brown et al. (2017).
2. **The mutation greatly increases the risk of IVDD.**
    - Supported by Brown et al. (2017), Brisson (2010), Bergknut et al. (2013).
3. **Disc degeneration begins early in life.**
    - Supported by Smolders et al. (2012) and Bergknut et al. (2013).
4. **Not every genetically affected dog develops IVDD.**
    - Penetrance is incomplete; other genetic and environmental factors influence disease expression.
    - Discussed throughout the review by Batcher et al.
5. **Disease severity varies among breeds.**
    - Breed background and modifier genes influence expression.
    - One reason breed-specific studies are needed.

One Important Observation

One point, often overlooked in discussions, but was discussed by Linda, Laurie and me, is that **Batcher et al. do not recommend removing all CDDY-positive dogs from breeding.** Rather, the authors emphasize that the mutation should be considered **as one important component of an overall breeding strategy**, balanced with maintaining genetic diversity and avoiding excessive narrowing of the gene pool. At the same time, the paper reinforces that **the mutation has clear biological effects and warrants careful consideration in breeding decisions.**

Knowing this, we recommended a pause and would not consider a permeant recommendation of this type without breed specific penetrance information. Our (BTCA) approach, must be based on science and there is a big difference between 20 or 30% penetrance and 5 to 10% penetrance. So should our approach. This is supported in population study protocol.

This balance between disease risk and preservation of genetic diversity is consistent with the cautious, evidence-based approach that many veterinary geneticists advocate.